Contents

HORMONE CLASSIFICATION 2
THYROID 5
Thyroid gland (anatomy) 7
Physiology 8
Thyroid function tests 12
Hypothyroidism in pregnancy 18
Hyperthyroidism in pregnancy 21
Graves disease in pregnancy 22
Hyperthyroidism and Thyroid Storm 24
Amiodarone induced thyrotoxicosis 30
ANTI-THYROID MEDICATIONS 35
THYROID STORM 37
Euthyroid Sick Syndrome 42
THYROID HORMONE RESISTANCE SYNDROMES 45
Hypothyroidism 46
Management of Thyroid Nodules 49
Management of Differentiated Thyroid cancer 59
CALCIUM METABOLISM AND BONE RELATED PROBLEMS 67
Primary hyperparathyroidism (PHPT) 76
Hungry Bone Syndrome 82
Hypoparathyroidism 91
UROLITHIASIS 98
DEXA Scans 98
➤➤ PAGET' DISEASE OF BONE 114
LIPID METABOLISM --- LIPIDOLOGY 119
REPRODUCTIVE ENDOCRINOLOGY 133
MALE HYPOGONADISM 149
Approach to the patient with Gynecomastia 165
DIABETES PATHOPHYSIOLOGY AND MANAGEMENT 183
HYPOGLYCEMIA 201
Gestational Diabetes 210
ADRENAL DISORDERS 248
Adrenal Vein Sampling 259
NON CLASSICAL ADRENAL HYPERPLASIA 272

PITUITARY DISORDERS 291
Acromegaly 299
Diabetes Insipidus 334
SODIUM DISORDERS : FOCUS ON SIADH (PROF. VERBALIS) 348
OBESITY 354
MULTIPLE ENDOCRINE NEOPLASIA (MEN) 365
PART II - BOARD REVIEW 377

PART I - CLINICAL NOTES
ENDOCRINOLOGY, DIABETES and METABOLISM
Scrap Book Notes by @AUCHUS

HORMONE CLASSIFICATION

Hormonal action : autocrine, paracrine or endocrine

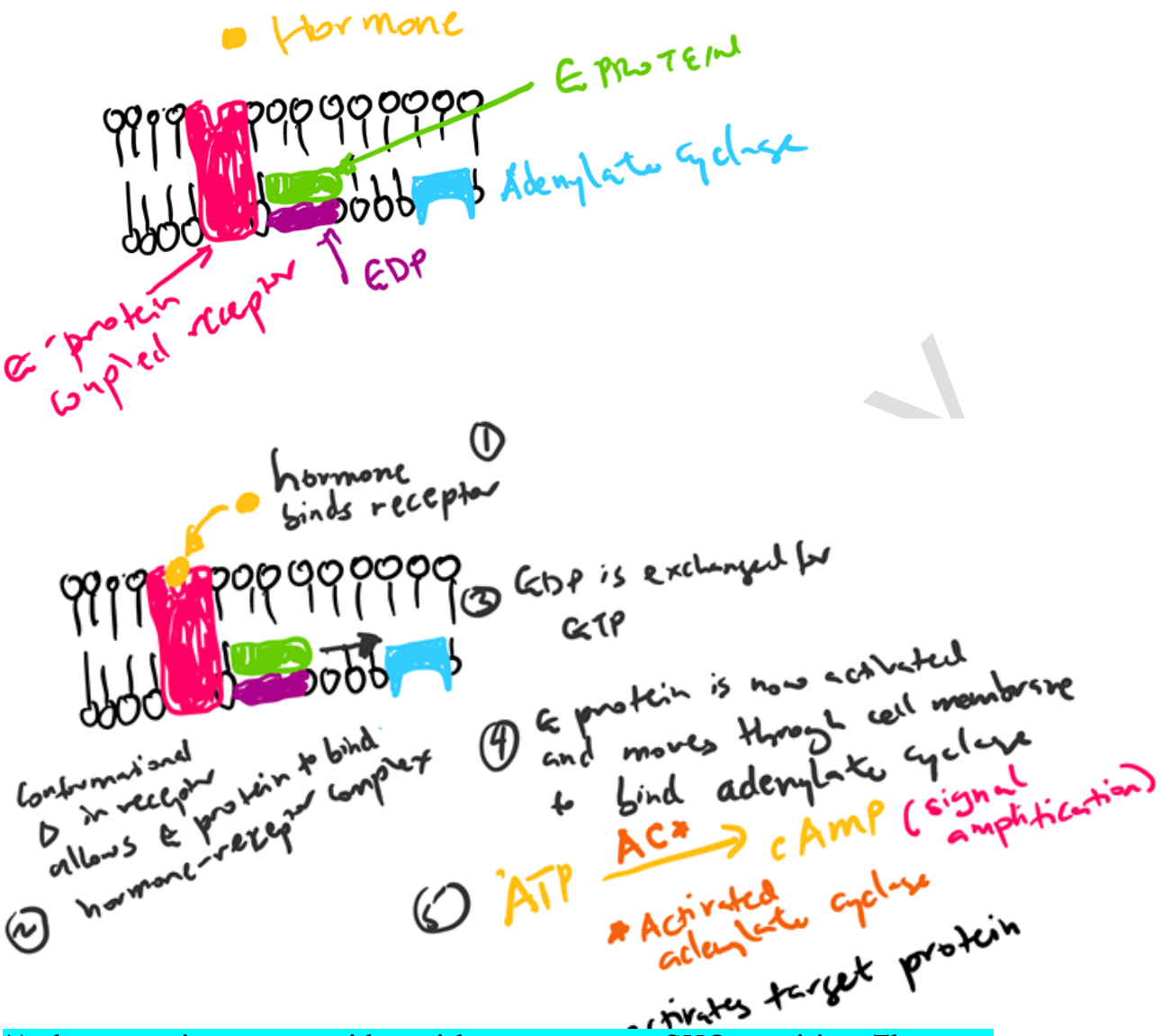
Hormones are classified as peptides, steroids and amines.

Peptide hormones

- Most hormones are peptides, including hormones from hypothalamus, pituitary, pancreas and placenta
- Vary in size from large to small
- Made in the Rough ER (preprohormone) > Golgi apparatus (prohormone post cleavage) > packaged into secretory vesicles and released by exocytosis
- They are released into circulation unbound to carrier proteins and as such are subject to degradation by proteases. Short half life!**
- Peptide hormones are water soluble and cannot cross cell membranes easily.
- They bind to cell surface receptors. Post receptor binding action involves secondary messengers.

Mechanism of action of peptide hormones

1. Coupling of peptide hormone (first messenger) to cell surface receptors generating secondary messengers.
2. Cascade of reactions leading to changes in phosphorylation state



** glycoproteins are peptides with one or more CHO moeities. They are generally more stable and last longer in circulation than peptides.
NB: Due to inactivation by gastric acid and peptidases, peptides are not given orally.

Hypothalamus	• Corticotropin releasing hormone CRH • Growth hormone releasing hormone GHRH • Gonadotropin releasing hormone GnRH • Thyrotropin releasing hormone TRH
Anterior pituitary	• Adrenocorticopric hormone ACTH • Follicle stimulating hormone FSH • Luteinizing hormone

	• Growth hormone • Thyroid stimulating hormone • prolactin
Posterior pituitary	• Antidiuretic hormone • oxytocin
Pancreatic islets	• Glucagon, insulin, somatostatin
Calcium regulating hormone	• Parathyroid hormone, calcitonin
Placenta	• Human chorionic gonadotropin • Human placental lactogen
Gonad	• inhibin
liver	• Insulin like growth factor 1

Steroid hormones[1]

- Derived from cholesterol
- Lipid soluble
- Attached to carrier proteins
- Can be given orally and are lipid soluble.
- Can cross all membranes and enter cells to bind to intracellular receptors (cytoplasm and nucleus)
- Intracellular receptors have hormone binding and DNA binding domains. Hormone-receptor complex binds directly to DNA and alters the rate of initiation of gene transcription. The target binding site on the target gene is called HRE (Hormone response element)

Primary response genes : altered transcription of genes binding hormone-receptor complex directly. Changes occur within 30mins
Secondary response genes: hormone receptor complex binds to primary response genes, initiating protein synthesis, the protein products then bind to secondary response genes and initiate transcription. This process takes hours or days.

Adrenal cortex	Aldosterone Cortisol Dehydroepiandrosterone progesterone

[1] "...memory recalls the tortures of fear, while foresight anticipates them" -- Seneca

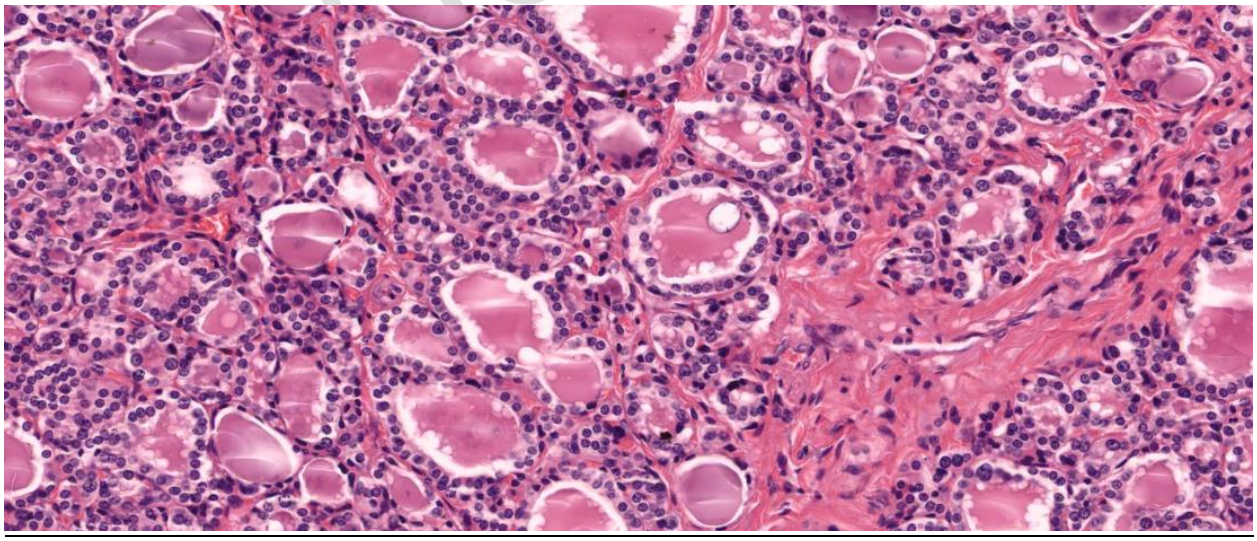
Gonad	Dehydroepiandrosterone Progesterone Testosterone Dihydrotestosterone estradiol
kidney	Calcitriol (1,25 hydroxy vit d)

Amine Hormones

Derived from amino acids tyrosine and tryptophan
Thyroid hormone and behave similar to steroid hormones
Catecholamines act similar to peptide hormones

Adrenal medulla	Epinephrine and norepinephrine (derived from tyrosine residue)
Thyroid	triiodothyronine and thyroxine (derived from tyrosine)
Nonendocrine glands	Melatonin from pineal gland (tryptophan derivative) Serotonin for CNS and GI tract (tryptophan derivative)

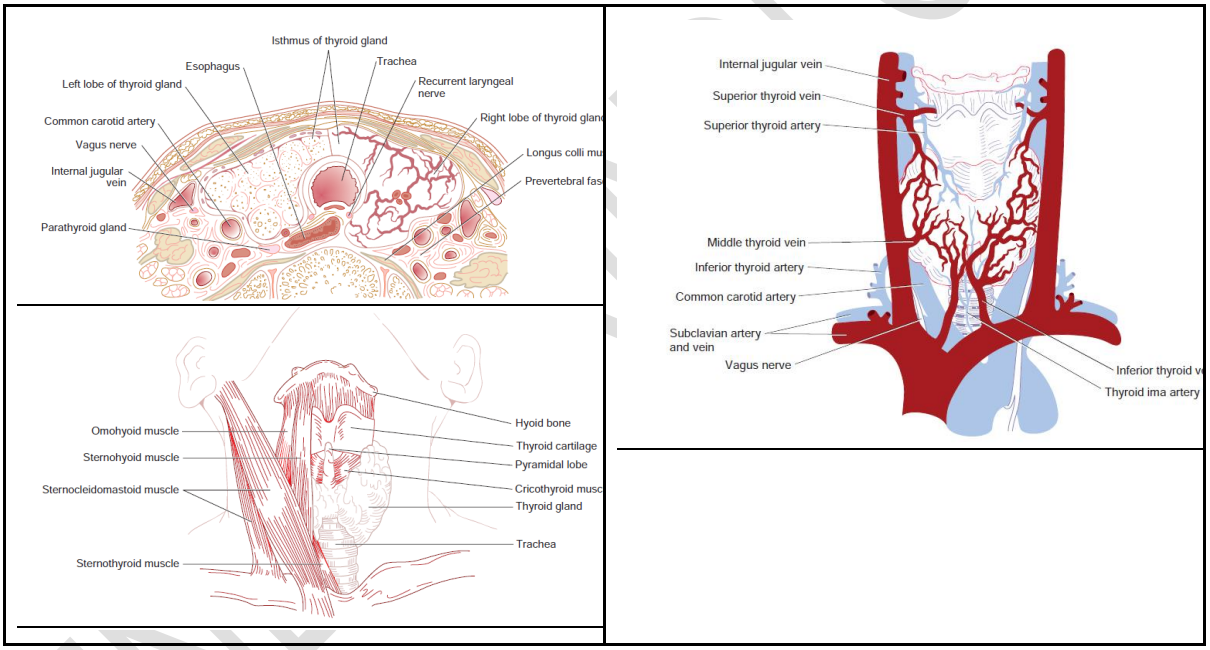
THYROID



Thyroid Disorders	**15%** of Exam
Hyperthyroidism	3.5%
Graves' disease	
Toxic adenoma and multinodular goiter	
Inappropriate thyroid-stimulating hormone (TSH) syndromes	
TSH-secreting tumor	
Thyroid hormone resistance syndromes	
Artifactual TSH "derangements"	
Thyrotoxicosis with low radioactive iodine uptake	
Thyroiditis	
Factitious, accidental, and iatrogenic thyrotoxicosis	
Iodine-induced	
Struma ovarii	
Complicated thyrotoxicosis	
Subclinical hyperthyroidism	
Hypothyroidism	2.5%
Primary	
Secondary	
Subclinical hypothyroidism	
Complicated hypothyroidism	
TSH resistance in pseudohypoparathyroidism	
Therapy	
Nontoxic solitary nodules and multinodular goiter	3%
Fine-needle aspiration and cytology interpretation	
Roles of ultrasonography and radionuclide scanning	
Treatment	
Surgery	
Levothyroxine suppression	
Radioactive iodine	
Chemotherapy and other treatments	
Thyroid cancer	3.5%
Well-differentiated epithelial thyroid cancers	
Hürthle cell cancer	
Anaplastic cancer	

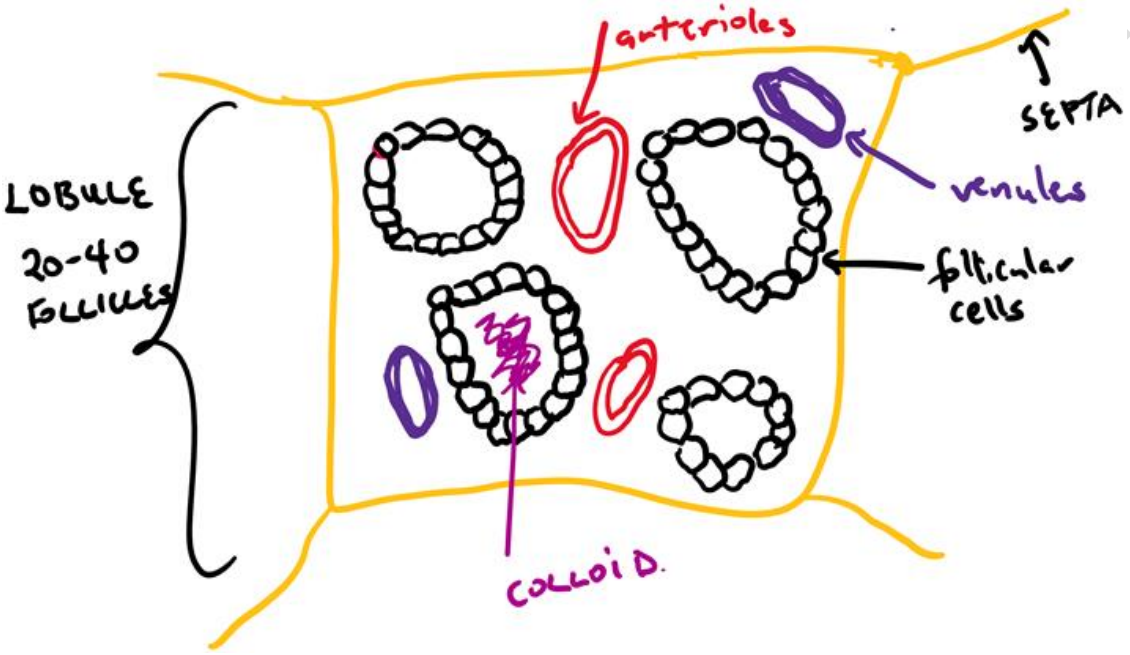
Lymphoma	
Medullary cancer	
Thyroid test abnormalities without thyroid disease	<2%
Euthyroid hypothyroxinemia	
Euthyroid hyperthyroxinemia	
Effect of drugs on thyroid function tests	
Euthyroid sick syndrome	
Thyroid hormone antibodies	
Antibody interferences with TSH measurement	
Thyroid changes in pregnancy	<2%
Hypothyroidism	
Hyperthyroidism	
Thyroid nodule and cancer	

Thyroid gland (anatomy)



- 15 to 20g in an average adult
- Anterior to trachea and inferior to the cricoid cartilage at the level of C5 to T1
- Right and left lobes with an inteconnecting isthmus. Accesory lobe from the isthmus is the pyramidal lobe
- Arterial supply : paired superior thyroid arteries from the external carotid artery and inferior thyroid arteries from the thyrocervical trunk.
- Venous drainage : superior and middle drain the thyroid venous plexus into the internal jugular vein and inferior thyroid veins drain into the brachiocephalic vein
- Lymphatic drainage is variable but is drained by superficial and deep cervical lymph nodes.

- Surrounded by a thin fibrous capsule which invaginates into the parenchyma, forming septa. Septations divide the gland into numerous lobules each containing 20-40 follicles.
- Each follicle is composed of a ring of cuboidal epithelial cells that surround a central repository of colloid.
- Interspersed between the follicles are C cells or parafollicular cells derived from neural crest cells.
- Thyroid is derived from the foramen cecum (an epithelial proliferation) at the base of the tongue.
- By week 7 of embryologic development, the thyroid gland would have migrated from its initial position at the posterior pharynx through the thyroglossal duct to its permanent adult anatomic location in the anterior neck.



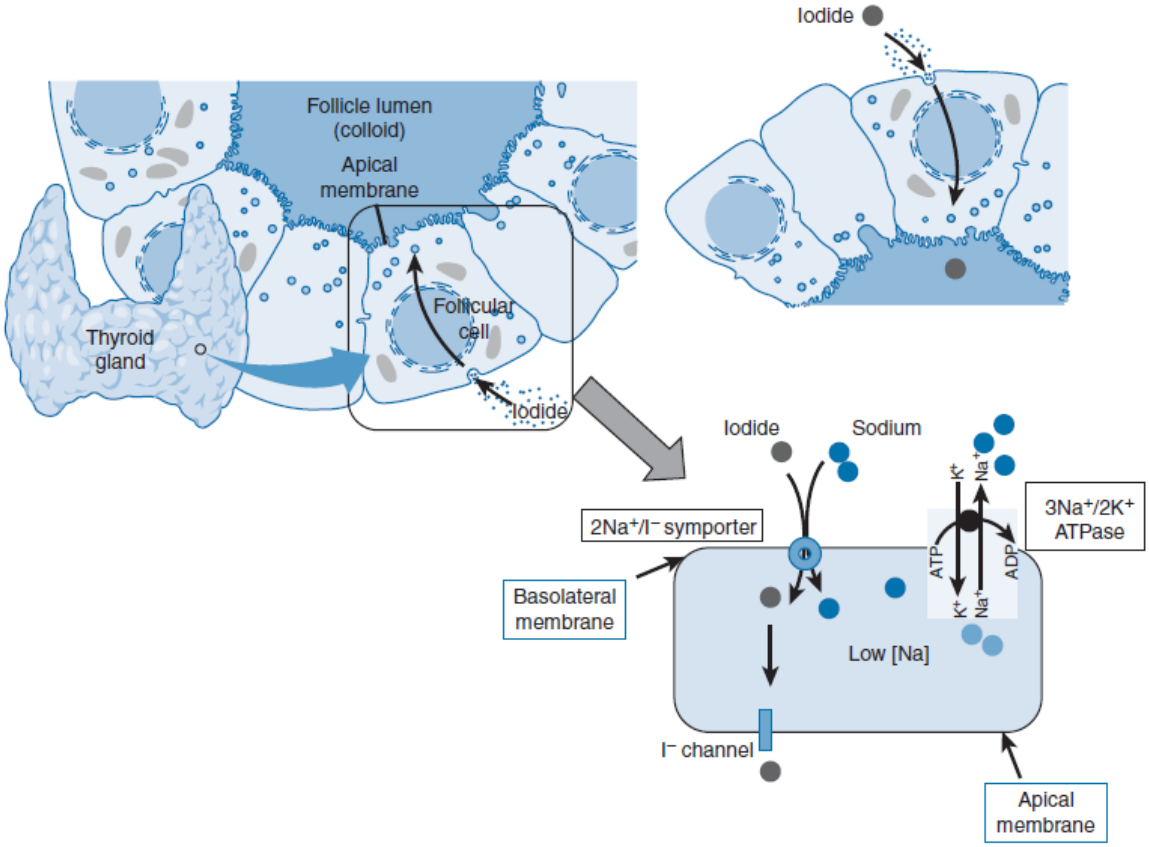
[2]

Physiology

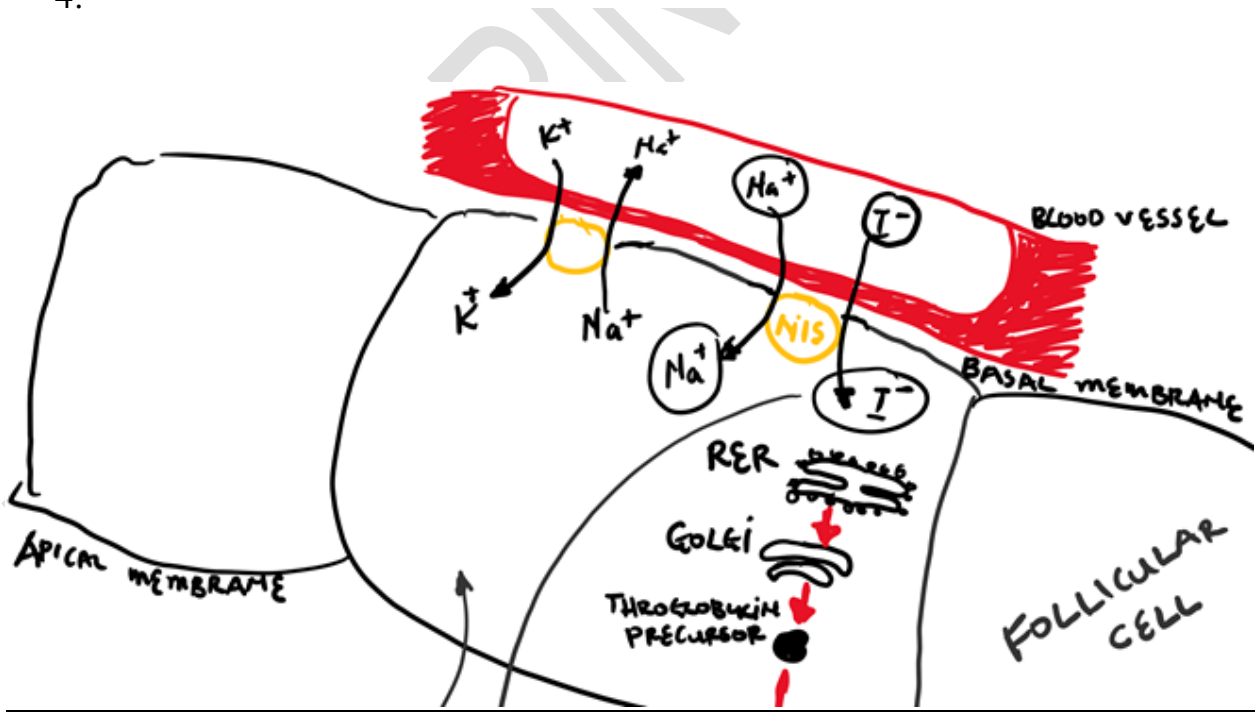
Thyroid hormone synthesis

1. Adequate thyroid hormone synthesis - approximately 1g of iodine per week is needed to ensure adequate thyroid hormone synthesis
2. Iodine is absorbed through the GIT and travels through the bloodstream bound to serum albumin. At the thyroid gland, the **basal Na-Iodide symport transports iodide into the follicular cell.** (the process involves concentrating it to 30x the blood level)
3. It is transported to the apical membrane where it is oxidized with **H2O2 by an apical peroxidase enzyme** where it becomes highly reactive.

[2] **Commit yourself only when you can and must. And when you speak, assert only that which you know**

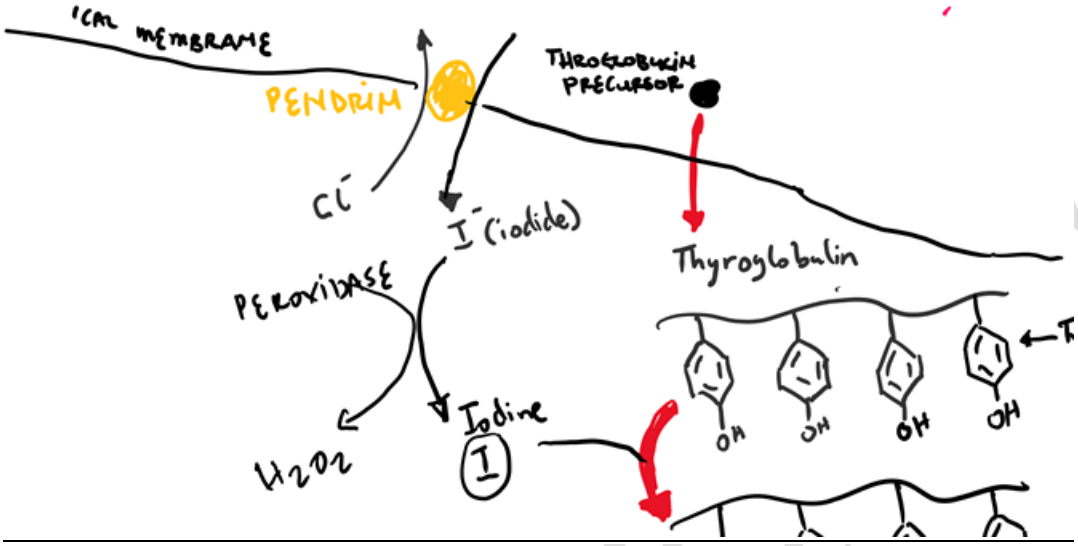


4.



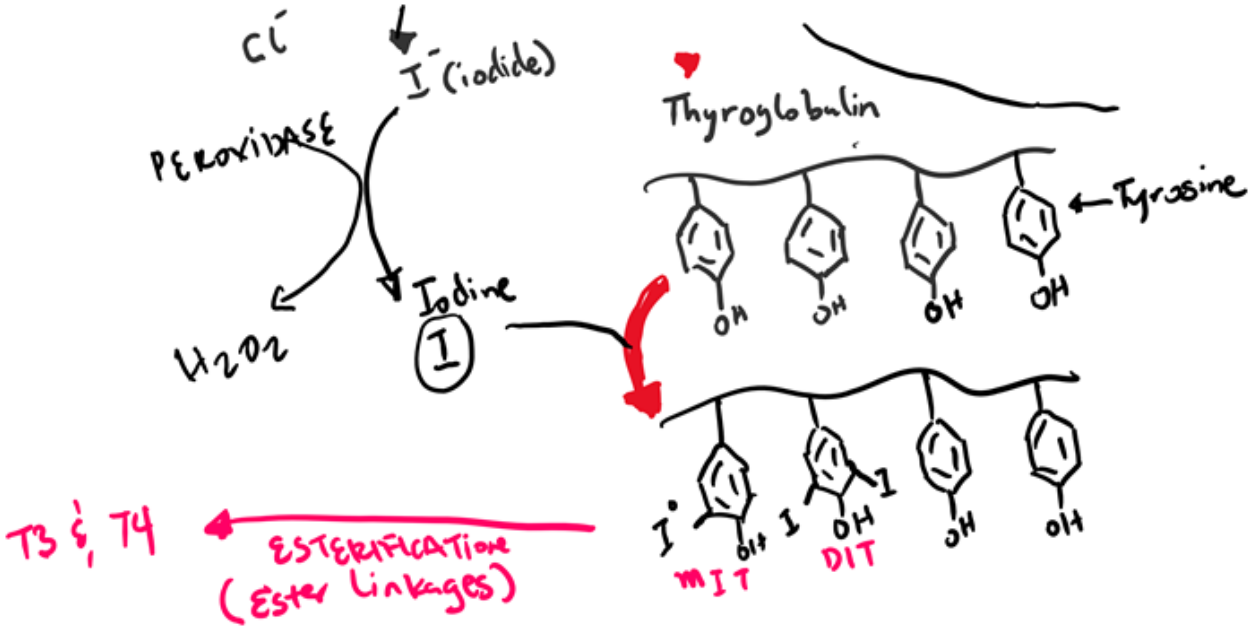
4. The second step involves production of **thyroglobulin - a glycoprotein which forms the backbone for thyroid hormone synthesis.** It is synthesized in the rough endoplasmic reticulum and modified by the golgi apparatus.

5. It is transported to the apical membrane. At the apical membrane **thyroglobulin and the oxidized iodine combine in an organification reaction via the iodinase enzyme**. This forms a thyroglobulin glycoprotein with multiple iodinated tyrosine amino acids. (Monoiodotyrosine and diiodotyrosine)



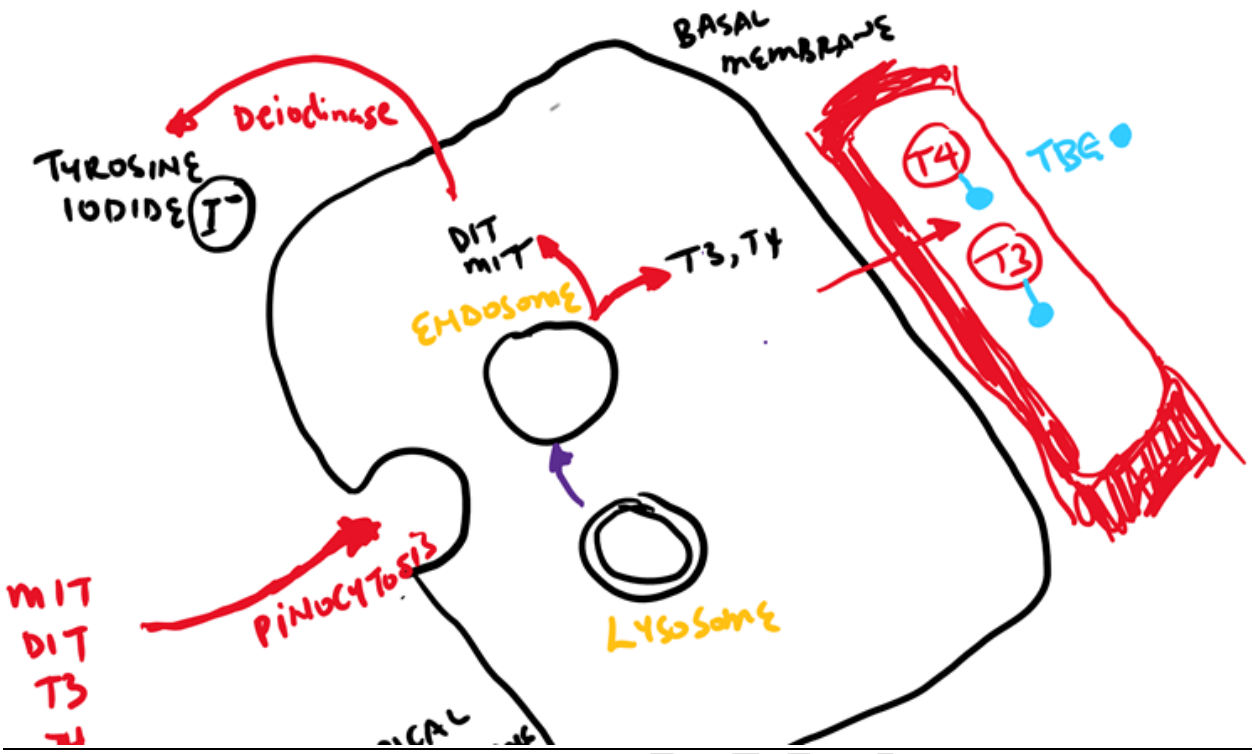
6. The **iodotyrosines are further coupled by ester linkages.** Coupling of MIT and DIT forms triiodotyronine T3 and coupling of 2 DITs forms tetraiodotyronine T4.

7. The thyroid gland stores large amounts of thyroid hormone in the colloid matrix in the form of iodinated thyroglobulin.



8. When there is need for thyroid hormone, **thyroid epithelial cells ingest colloid by endocytosis from their apical borders.** Colloid laden endosomes fuse with lysosomes. Proteases within the lysosomes break down the iodinated thyroglobulin into T3 and T4, which diffuse htrough the basement membrane directly into the blood stream.

9. The thyroid produces 20x more T4 than T3, but T3 is the more active form of the hormone and produces majority of the clinical effects. T4 is peripherally converted to T3 by removing one iodine molecule via a deiodinase enzyme from a T4 molecule.



Thyroid function tests

TSH levels are elevated in even very mild primary hypothyroidism and are suppressed to <0.1 μU/mL in even very mild hyperthyroidism. Therefore, a normal plasma TSH level excludes hyperthyroidism and primary Hypothyroidism.

Because even slight changes in thyroid hormone levels affect TSH secretion, abnormal TSH levels are not specific for clinically important thyroid disease. *Changes in plasma TSH lag behind changes in plasma T4, and TSH levels may be misleading when plasma T4 levels are changing rapidly*, as during treatment of hyperthyroidism, or in the first few weeks after changes in the dose of thyroxine.

Thyroglobulin (Tg), the precursor of thyroid hormones, is a glycoprotein synthesized only by thyroid follicular cells. Most thyroglobulin is broken down within the thyroid to release T4 and T3, but a small amount enters the circulation Intact.x

An assay for antithyroglobulin antibodies should always be done in conjunction with the thyroglobulin assay, since the presence of such antibodies renders the thyroglobulin assay useless.

Wolff-Chaikoff Effect

- Excess iodide actually inhibits three steps in thyroid hormone production: **iodide trapping**, **thyroglobulin iodination (the Wolff-Chaikoff effect)**, and **thyroid hormone release**
- Inhibitory action is transient and escapes after 10--14days
- Autoregulatory effect of iodide -- insulates physiologic thyroid function from short term fluctuations in iodine intake.
- If the thyroid gland is affected by autoimmune thyroiditis or certain inherited forms of dyshormonogenesis, it may be incapable of escaping from iodide-induced inhibition of gland function --- > **leading to hypothyroidism!!!**

***

Jod-Basedow Effect

- **Iodide load** can induce hyperthyroidism
- Occurs in px with MNG or Graves(Basedow's) Disease
- Rarely in normal thyroids.

Thyroid hormone transport

Both thyroid hormones circulate in blood bound to plasma proteins; only **0.04% of T4** and **0.4% of T3** are unbound or free

- thyroxine-binding globulin (TBG)
- transthyretin, formerly called thyroxine-binding prealbumin (TBPA)
- albumin

Why plasma protein binding?

- iodothyronines-- poorly soluble in water.
- large circulating thyroid hormone pool with a stable 7-day plasma half-life

Congenital TBG deficiency

- X-linked recessive trait ; M >>> F
- Despite low circulating total T 4 and T 3 levels in affected individuals, free hormone levels are normal -- CLINICALLY EUTHYROID
- Associated with congenital corticosteroid-binding globulin deficiency

Congenital TBG excess

- **Elevated total T4 and T3 concentrations** in blood, but normal

free hormone levels
- Euthyroid clinical state

Causes of TBG Excess

- Pregnancy
- Estrogen-secreting tumors
- Estrogen therapy

Increased **sialic acid content of the TBG molecule** -- decreased metabolic clearance

Causes of decreased TBG

- Major systemic illness

TBG effect -- cleavage by leukocyte proteases and reduced binding affinity for the
thyroid hormones

Transthyretin (Thyroxine-Binding Prealbumin)

- Its affinity for T 4 is 10-fold greater than for T 3.
- The dissociation of T4 and T3 from transthyretin is rapid, so that transthyretin is a source of readily available T4

Congenital elevation of TPBA

- Increased affinity of transthyretin binding for T4 can occur as a heritable condition
- elevated total T4 but a normal free T4

*Ectopic production -- pancreatic and hepatic tumors (euthyroid hyperthyroxinemia)

Albumin

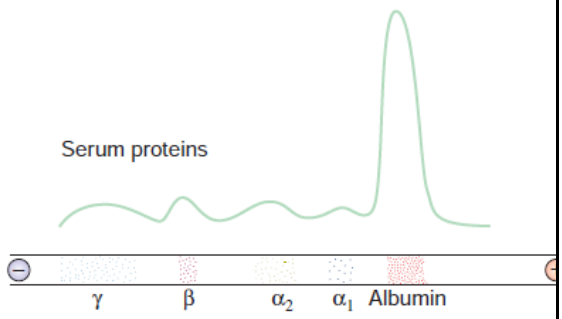
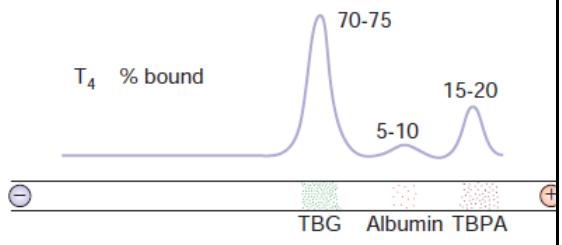
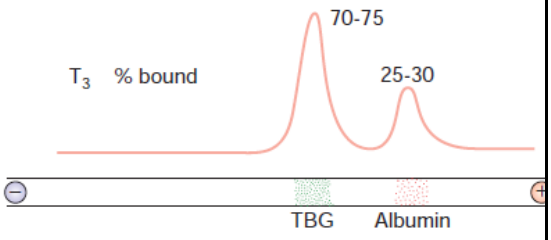
Albumin binds to T 4 and T 3 with lesser affinity than TBG or transthyretin, but its high plasma concentration results in its transport of 15% of circulating T4 and T3 .

Rapid thyroid hormone dissociation rates from albumin make it a major source of free

hormone to tissues

⊕ **Hypoalbuminemia** -- as occurs in nephrosis or cirrhosis, is associated with a low total T 4 and T 3 , but the free hormone levels are normal.

Familial dysalbuminemic hyperthyroxinemia
• Autosomal dominant inherited disorder • 25% of albumin exhibits a higher than normal T4 -binding affinity **An elevated total T4 level but a normal free T4 concentration and euthyroidism.** ** Because these albumin variants do not bind the thyroxine analogs used in many free T4 immunoassays, they may falsely report elevation of the free T 4 in affected individuals.

Paper electrophoretic pattern of serum proteins	
Radioactive T4 was added to serum and was then subjected to paper Electrophoresis. The peaks represent the mobility of radioactive T4 bound to different serum proteins	
Radioactive T3 was added to serum and subjected to paper electrophoresis. The peaks indicate the relative distribution of protein-bound radioactive T3 .	

Causes of abnormal serum thyroxine determinations in euthyroid individuals

Euthyroid Hyperthyroxinemia
↑ Plasma protein binding
  ↑ Thyroxine-binding globulin (TBG)
    Inherited
    Estrogen effect (pregnancy, estrogen therapy)
    Hepatitis
    Drugs: tamoxifen, 5-fluorouracil, clofibrate, methadone, heroin
  ↑ Transthyretin binding
    Inherited
    Paraneoplastic production by hepatic and pancreatic tumors
  ↑ Albumin binding
    Inherited (familial dysalbuminemic hyperthyroxinemia)
↓ T_4-to-T_3 conversion[a]
  Systemic illness
  Medications: amiodarone, radiocontrast agents, glucocor-ticoids, propranolol
Thyroxine therapy in hypothyroidism[a]
Generalized resistance to thyroid hormone[a]
  Anti-T_4 antibody (assay interference)

Euthyroid Hypothyroxinemia

- ↓ Thyroxine-binding globulin
  - ↓ TBG production
    - Inherited
    - Androgens
    - Drugs: danazol, L-asparaginase
  - ↑ TBG clearance
    - Nephrotic syndrome
    - Severe liver disease
    - Protein-losing gastroenteropathy
- Systemic illness[b]
- Medications
  - Exogenous thyromimetic compounds (T_3 [Cytomel])[b]
  - Phenytoin and carbamazepine[b]
  - Iodine deficiency (with normal serum T_3)[b]

[a]Both total and free T_4 elevated.

[b]Both total and free T_4 low.

Decreased conversion of T4 to T3

1. Fetal life
2. Caloric restriction
3. Hepatic disease
4. Major systemic illness
5. Drugs
   - PTU
   - Glucocorticoids
   - Propranolol (mild effect)
   - Iodinated x-ray contrast agents (iopanoic acid, iopate sodium)
   - Amiodarone
6. Selenium deficiency

<u>Thyrotroph Pseudotumor</u>

If a patient presents with a pituitary macroadenoma on CT scan but has inconsistent prolactin levels (here < 100 ng/mL) and hypothyroid symptoms, check a TSH to rule out a **thyrotroph pseudotumor.**

Prolactinoma >1cm should have a serum prolactin level of **>200ng/ml**

- *Pituitary pseudotumor (pituitary thyrotroph hyperplasia) caused by unrecognized and untreated hypothyroidism has been described as a rare condition, mostly in adults. Hormonal testing shows low thyroxine and high TSH levels, hyperprolactinemia.*
- *An intrasellar mass on MRI. Homogeneous contrast enhancement --- pituitary hyperplasia.*
- *Therapy with L-thyroxine results in rapid improvement of the clinical signs, normalization of the hormone levels, and resolution of the pituitary hyperplasia on MRI.*
- *In children, prolonged unrecognized primary hypothyroidism might be accompanied by growth deficiency and pubertal disharmony. Pituitary hyperplasia should be sought in these cases*

Hypothyroidism in pregnancy

- Patients with preexisting hypothyroidism may require up to 50% increase in dose of levothyroxine
- Dose adjustment required as early as 4th week of gestation Monitor TSH q4weekly

Thyroid hormone is critical for fetal brain development, and several changes occur in maternal thyroid function during pregnancy. **TBG and total T4 levels rise early in pregnancy** (The higher reference range of serum total T 3 and T 4 in pregnancy
is due to estrogen-mediated rise in thyroid-binding globulin) . Chorionic gonadotropin is homologous to TSH, and very
high levels in the first trimester stimulate the TSH receptor, causing a transient fall in TSH levels by stimulating T4 secretion. The mother usually remains euthyroid, but rarely she develops a transient clinical hyperthyroidism, often associated with hyperemesis gravidarum.[3]

The **placenta contains high levels of type 3 deiodinase (D3)**, which inactivates T4 and severely limits T4 transfer from mother to fetus.
Nevertheless, some T4 crosses the placenta and is important for early fetal brain development. In mothers with preexisting hypothyroidism, increased T4 metabolism by placental D3 means that their levothyroxine dose must usually be increased to maintain euthyroidism. Urinary iodine excretion increases, and in areas of iodine deficiency, it becomes more difficult for the thyroid to maintain adequate hormone secretion, with development of a transient goiter. If the iodine deficiency is too severe, the fetus receives inadequate thyroid hormone, and endemic cretinism results.

Possible mechanisms for increased requirements
- Increased TBG
- Weight gain

[3] Jod is German for iodine; Carl Adolph von Basedow was one of the first physicians to describe hyperthyroidism.

- Increase T4 pool size
- Increase transplacental transfer of T4[4]

Thyroid hormone physiology in pregnancy

- Hormones that cross the placenta are TRH and T4
- Maternal TRH plays an important role in the growth and development of fetal hypothalamo–pituitary–thyroid (HPT) axis
- T4 is necessary for fetal neural growth and development, particularly during the first trimester (fetal HPT axis starts functioning after 12 weeks of intrauterine life).
- Deiodinase type 3 is expressed in placenta and modulates availability of free T 4 ; thereby preventing overexposure of thyroid hormones to the fetus.fetus.6
- Iodine is the most important molecule which freely crosses placenta as syncytiotrophoblasts express sodium iodide symporter (NIS).
- **TSH receptor antibody (TRAb)** which includes thyroid stimulating immunoglobulin (TSI) and TSH-binding inhibitory immunoglobulin (TBII) can also cross placenta.
- Antithyroid drugs like carbimazole, methimazole, and propylthiouracil can cross placenta and may result in fetal goiter and hypothyroidism and can rarely cause "thionomide embryopathy."
- In addition, levothyroxine also crosses placenta.

Reason for varying TSH goals per trimester

- Human placental HCG (a glycoprotein) shares homology with TSH. it stimulates the thyroid gland directly due to specificity spillover. Excess circulating thyroid hormone therefore inhibits endogenous TSH (through negative feedback inhibition)

- The clinical significance of this alteration is that median TSH is low in all trimesters as compared to nonpregnant women and especially so in the first trimester due to peak hCG levels.

****During pregnancy, placental hCG starts rising by the 3rd week, peaks by 12th week, and progressively declines thereafter**

Comparison of overt and subclinical hypothyroidism in pregnancy

Subclinical hypothyroidism	**Overt hypothyroidism**
TSH values above the trimester-specific reference range** with normal free T4.	TSH value above the reference range but <10 µIU/ml with a low free T4.

[4] It must be confessed that the practice of medicine among our fellow creatures is often a testy and choleric business

	TSH >10 µIU/ml irrespective of free T4 level.

** reference range for TSH during **first trimester is 0.1–2.5 µIU/ml, second trimester 0.2–3.0 µIU/ml,** and **third trimester 0.3–3.0 µIU/ml.**

➽⊕**previously recommended TSH cut point of 2.5 mIU/L , a higher cutoff value of 4.0 mIU/L was recently proposed in the ATA's 2017 revisions**

SCH in pregnancy -- should we treat (current lack of consensus)
1. The Endocrine Society recommends therapy in all pregnant women presenting with SCH, irrespective of autoimmunity status (either TPOAb+ or TPOAb−) 2. American Thyroid Association (ATA) supports treatment only for a specific subgroup of women with SCH who are TPOAb+(SCH-TPOAb+)

Monitoring of thyroid hormone levels in pregnancy (clinicopathophysiology)

During pregnancy, total T4 is increased as thyroxine-binding globulin (TBG) starts rising by 6–8 weeks and remains elevated throughout the pregnancy because of estrogen-mediated increased production and decreased clearance due to sialylation. Therefore, estimation of free T 4 is preferred during pregnancy.

Free T4 should be estimated by equilibrium dialysis as other available methods lack precision.

Management of subclinical hypothyroidism in pregnancy

- Treatment of subclinical hypothyroidism during pregnancy is associated with favorable maternal outcome.
- Effect of maternal subclinical hypothyroidism on fetal neurocognitive development is not so clear.
- Isolated TPO positivity does not warrant treatment if the trimester specific TSH ranges are within the expected reference.
- Use of selenium to lower TPO levels is NOT RECOMMENDED

Preconception TSH goals in hypothyroidism

The recommended TSH level in a nonpregnant individual with hypothyroidism is 0.4–4.1 µIU/ml. However, when a woman is planning pregnancy, **TSH should be targeted <2.5 µIU/ml** as TSH even in the upper normal range (2.5–4.1 µIU/ml) is considered as relative hypothyroidism for a pregnant female during first trimester.

Patients receiving therapy for overt/subclinical hypothyroidism prior to conception

should be advised to increase the dose of levothyroxine by 30–50% at 4–6 weeks of gestation

Management of hypothyroidism in the general population

Levothyroxine replacement therapy for hypothyroidism	
Initial dose	• **Low dose** (25-50 µg QD): Elderly, heart disease patients • **Full replacement dose** (75-125 µg QD): Young healthy patients
Dose adjustments	• Increase dose **every 6 weeks** until TSH is within normal range
Maintenance therapy	• Monitor TSH* every **6-12 months**
Conditions requiring higher doses	• Malabsorption (eg, celiac disease) • Drugs that interfere with absorption (eg, iron, calcium) • Drugs that increase thyroxine metabolism (eg, phenytoin, carbamazepine, rifampicin) • Obesity • Pregnancy • Overt proteinuria

*Monitoring with free T_4 is not necessary unless TSH is unreliable (eg, central hypothyroidism). Total T_3 levels are generally not useful for diagnosis or monitoring of levothyroxine therapy.

Hyperthyroidism in pregnancy

- Pregnant women may normally become mildly thyrotoxic during the first trimester of pregnancy due to Beta HCG stimulation of the thyroid gland.
- To avoid fetal hypothyroidism, treatment goal is to keep pregnant hyperthyroid patients borderline thyrotoxic
- No treatment for transient hcg mediated hyperthyroidism or hyperemesis gravidarum hyperthyroidism. They both resolved by 14-18 weeks gestation with minimal complications

Utility of suppressed TSH in pregnancy

- TSH value less than the trimester-specific lower reference range is said to be suppressed, and possibility of thyrotoxicosis should be considered.
- Small percentage of normal pregnant women and women with multiple pregnancies may have TSH <0.01 µIU/ml

Subclinical hyperthyroidism	**Gestational thyrotoxicosis**

Normal free T4 with a suppressed TSH *	Suppressed TSH with elevated free T4**

* Graves' disease may only have T3 toxicosis
** Molar pregnancy or Graves' disease.

Subclinical hyperthyroidism during pregnancy **does not require treatment** as it is not associated with adverse maternal or fetal outcome because serum free T4 levels are within the normal range.

Graves disease	**Gestational thyrotoxicosis**
Not self limiting, requires antithyroid drugs.	Transient, self-limiting, non-autoimmune hyperthyroidism. Usually manifests between 10 to 16 weeks of gestation.*
prior history of thyroid disease, presence of goiter, infiltrative orbitopathy, and TRAbs positivity	<< Absence of these features

* If gestational thyrotoxicosis is associated with severe nausea, vomiting, weight loss, and ketonemia/ketonuria, it is called as **gestational thyrotoxicosis with hyperemesis gravidarum.**

Graves disease in pregnancy

Natural history during pregnancy

Women with Graves' disease experience exacerbation of symptoms during the first trimester, and there is a gradual improvement during the second and third trimester.

- The initial aggravation is related to hCG-mediated increased thyroid hormone production
- Increase in TBG and suppression of autoimmunity by rising estradiol, progesterone, and cortisol levels leads to reduction in severity of disease in second and third trimester. *(reduction in TRAb titer and decrease in requirement of antithyroid drugs during the second and third trimester)*
- After delivery there may be aggravation of disease due to sudden decline in placental steroids and reactivation of autoimmunity.

Patients with *subclinical, asymptomatic or mild overt hyperthyroidism* due to Graves disease also do not require treatment.

- Monitor TSH every 4-6 weeks
- Thionamides (PTU or Methimazole) are preferred in symptomatic patients with moderate to severe overt hyperthyroidism due to Graves disease.
- Beta blockers(atenolol) can be used for hyperadrenergic symptoms
- **TRAb, thyrototropin receptor antibodies** are typically measured in pregnant patients with **Graves disease during 20-24weeks** to **predict risk of fetal thyrotoxicosis**. TRAb titers > 3x ULN
-

Thyroid-stimulating immunoglobulins (TSIs) are autoantibodies to the TSH receptor that mimic the stimulatory effect of TSH on thyroid growth and hormone production, and cause hyperthyroidism in Graves' disease. Measurement of these antibodies is seldom needed to make this diagnosis, which is usually obvious on clinical grounds. **Its primary use is in pregnant women with a history of**
Graves' disease treated by radioactive iodine or thyroidectomy. These patients may still have high levels of TSI, which can no longer produce hyperthyroidism in the mother, but can cross the placenta and cause neonatal hyperthyroidism. Assay of TSI in the third trimester has some value in predicting this rare complication.

Neonatal thyrotoxicosis due to maternal Graves' disease is almost always transient and abates within 3–12 weeks with disappearance of TRAbs.
If neonatal thyrotoxicosis does not ameliorate within 3–6 months, alternate diagnosis like McCune–Albright syndrome and TSH receptor-activating mutation should be considered

- Patients with Graves' disease often have exacerbation of symptoms in the postpartum period due to withdrawal of estrogen and progesterone
- Increased risk of postpartum thyroiditis, usually between 8 and 24 weeks postpartum, and present with symptoms of new-onset/worsening thyrotoxicosis

Beta blockers results in IUGR and hypoglycemia
PTU results in **hepatotoxicity**
MMI is contraindicated in first trimester due to risk of aplasia cutis, tracheoesophageal fistula and choanal atresia

Preconception planning in patients with Graves Disease
Be rendered euthyroid prior to conception.

1. Women who are euthyroid on maintenance doses of antithyroid drugs can safely proceed for pregnancy.

2. **drug-naïve** or **toxic on antithyroid drugs** or **euthyroid on higher doses of antithyroid drugs** should be considered for ablative therapy prior to conception

NB: After radio-ablation, conception should be avoided for the next 6 months for optimizing levothyroxine therapy.
Surgery preferred over radio-ablation as the level of TRAbs may increase and remain so for up to
1 year post radio-ablation, while after surgery the levels decline faster.

5

Major drug interactions of levothyroxine	
↓ levothyroxine absorption	• Bile acid binding agents (e.g., cholestyramine) • Iron, calcium, aluminum hydroxide • Proton pump inhibitors, sucralfate
↑ TBG concentration	• Estrogen (oral), tamoxifen, raloxifene • Heroin, methadone
↓ TBG concentration	• Androgens, glucocorticoids • Anabolic steroids • Slow-release nicotinic acid
↑ thyroid hormone metabolism	• Rifampin • Phenytoin • Carbamazepine

Hyperthyroidism and Thyroid Storm

Serum TSH measurement has the highest sensitivity and specificity of any single blood test used in the evaluation of suspected hyperthyroidism and should be used as an **initial screening test**

A radioactive iodine uptake should be performed when the clinical presentation of thyrotoxicosis is not diagnostic of GD; a thyroid scan should be added in the presence of thyroid nodularity.

A radioactive iodine uptake (RAIU) is indicated when the diagnosis is in question (except during pregnancy) and distinguishes causes of thyrotoxicosis having elevated or normal uptake over the thyroid gland from those with near absent uptake

The RAIU will be near zero in patients with painless, postpartum, or subacute thyroiditis, or in those with factitious ingestion of thyroid hormone or recent excess iodine intake

[5] Longevity is a vascular question

The radioiodine uptake may be low after exposure to iodinated contrast in the preceeding 1–2 months or with ingestion of a diet unusually rich in iodine such as seaweed soup or kelp***

*** When exposure to excess iodine is suspected (e.g., when the RAIU is lower than expected), but not well established from the history, assessment of **urinary iodine concentration may be helpful.**

Thyroglobulin is released along with thyroid hormone in subacute, painless, and palpation thyroiditis, whereas its release is suppressed in the setting of exogenous thyroid
hormone administration

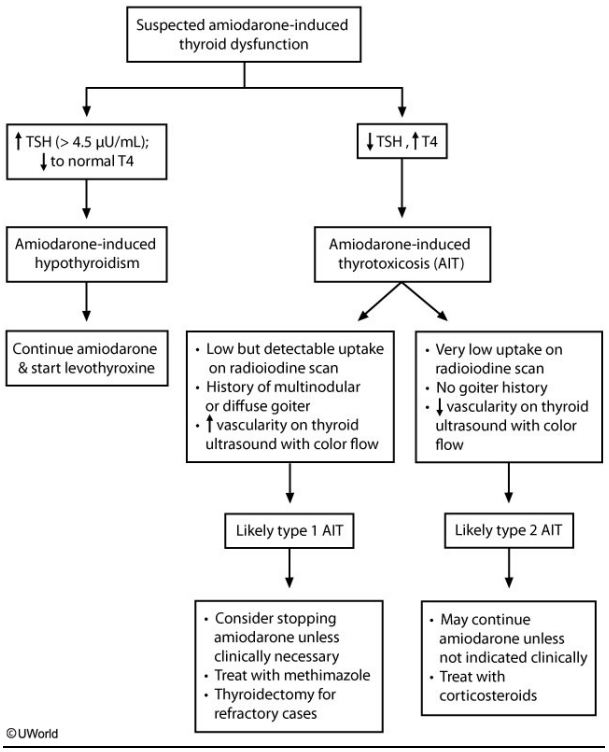
**factitious ingestion of thyroid hormone can be distinguished from other causes of thyrotoxicosis by a low serum thyroglobulin level and a near-zero RAIU

** patients with antithyroglobulin antibodies, which interfere with thyroglobulin measurement, an alternative but not widely available approach is **measurement of fecal T4**

TABLE 3. CAUSES OF THYROTOXICOSIS

Thyrotoxicosis associated with a normal or elevated radioiodine uptake over the neck[a]
GD
TA or TMNG
Trophoblastic disease
TSH-producing pituitary adenomas
Resistance to thyroid hormone (T_3 receptor mutation)[b]
Thyrotoxicosis associated with a near-absent radioiodine uptake over the neck
Painless (silent) thyroiditis
Amiodarone-induced thyroiditis
Subacute (granulomatous, de Quervain's) thyroiditis
Iatrogenic thyrotoxicosis
Factitious ingestion of thyroid hormone
Struma ovarii
Acute thyroiditis
Extensive metastases from follicular thyroid cancer

[a]In iodine-induced or iodine-exposed hyperthyroidism (including amiodarone type 1), the uptake may be low.
[b]Patients are not uniformly clinically hyperthyroid.
T_3, triiodothyronine.



Common forms of thyroiditis

Type	Hashimoto's	Subacute lymphocytic	Subacute granulomatous
Etiology	Autoimmune	Autoimmune	Viral
Clinical presentation	Goiter, hypothyroidism	Thyrotoxicosis followed by hypothyroidism (usually in postpartum patients)	Thyrotoxicosis followed by hypothyroidism
Thyroid pain/ tenderness	Absent or minimal	Absent or minimal	Moderate to severe
Anti-TPO	Present	Present	Absent
ESR	Normal	Normal	Elevated
RAIU	Variable	Low	Low
Treatment	Levothyroxine	Beta-blockers if symptomatic	Beta-blockers, NSAIDs & glucocorticoids in severe cases
Prognosis	Permanent hypothyroidism	Recovery in most patients	Recovery in most patients

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*** Hashimoto's --- chronic lymphocytic thyroiditis

Table 13. Causes of Drug-Associated Thyrotoxicosis

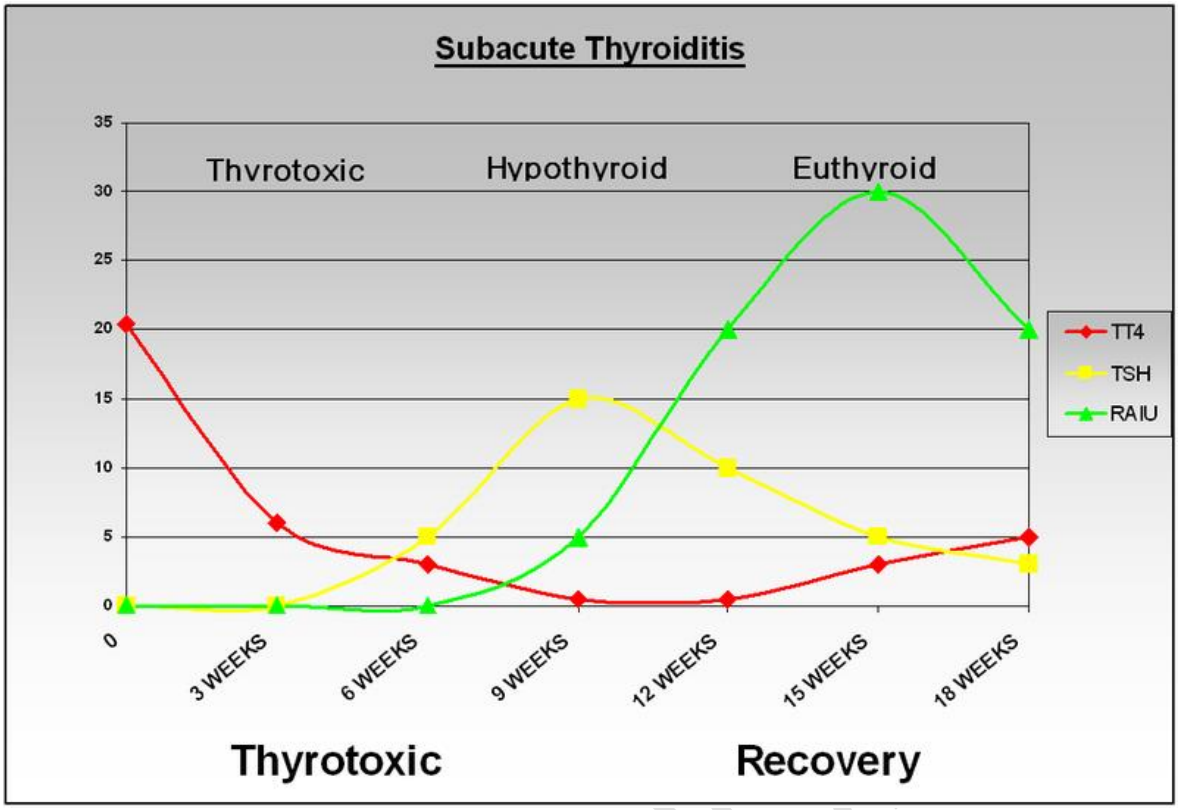
Drug	*Mechanism(s)*	*Timing of onset following initiation of the drug*	*Therapy*
Amiodarone	Iodine induced (type 1)	Months to Years	Supportive care[a] Antithyroid drugs; perchlorate[b] Surgery
	Thyroiditis (type 2)	Often > 1 year	Supportive care[a] Corticosteroids Surgery
Lithium	Painless thyroiditis	Often > 1 year	Supportive care[a] Antithyroid drugs
Interferon α	Painless thyroiditis; GD	Months	Supportive care[a] Antithyroid drugs and/or radioactive iodine (GD only)
Interleukin-2	Painless thyroiditis; GD	Months	Supportive care[a] Antithyroid drugs and/or radioactive iodine (GD only)
Iodinated contrast	Underlying thyroid autonomy	Weeks to months	Antithyroid drugs
Radioactive iodine, early	Destruction	1–4 weeks	Observation; if severe, administer corticosteroids
Radioactive iodine for TMNG, late	GD	3–6 months	Antithyroid drugs Repeat radioactive iodine Surgery

[a]Supportive care may include beta-adrenergic blockers during the thyrotoxic stage and levothyroxine if hypothyroidism develops.
[b]Not available in the United States.

Table 14. Unusual Causes of Thyrotoxicosis

Disorder	*Diagnosis*	*Primary management*
TSH-producing adenoma	Pituitary MRI, alpha-subunit to TSH ratio	Surgical removal
Struma ovarii	Radioiodine uptake over pelvis	Surgical removal
Choriocarcinoma	Elevation in the absence of pregnancy	Surgical removal
Thyrotoxicosis factitia (surreptious LT_4 or LT_3)	Absence of goiter; suppressed thyroglobulin	Psychosocial evaluation
Functional thyroid cancer metastases	Whole-body radioiodine scanning	Radioiodine ablation, embolization and/or surgical removal

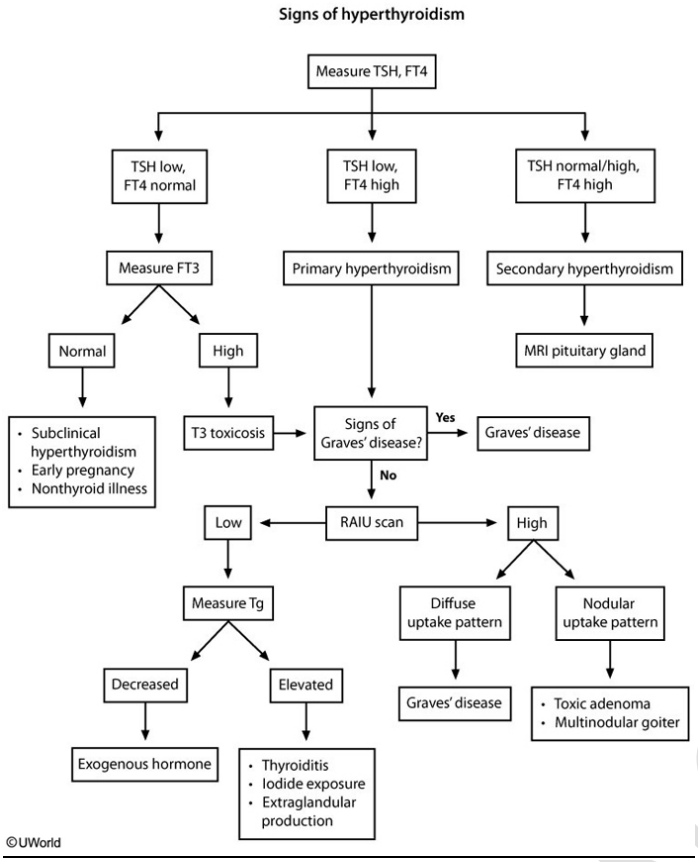
Parameter	Painless thyroiditis	Graves' disease
Etiology	Preformed thyroid hormone release	Excess thyroid hormone formation
Symptom onset	1-2 months, usually no exophthalmos	Gradual onset, exophthalmos usually present
Goiter	Usually mild to none	Usually present
Thyroglobulin level	High	High
RAIU scan	Low iodine uptake	Markedly increased uptake



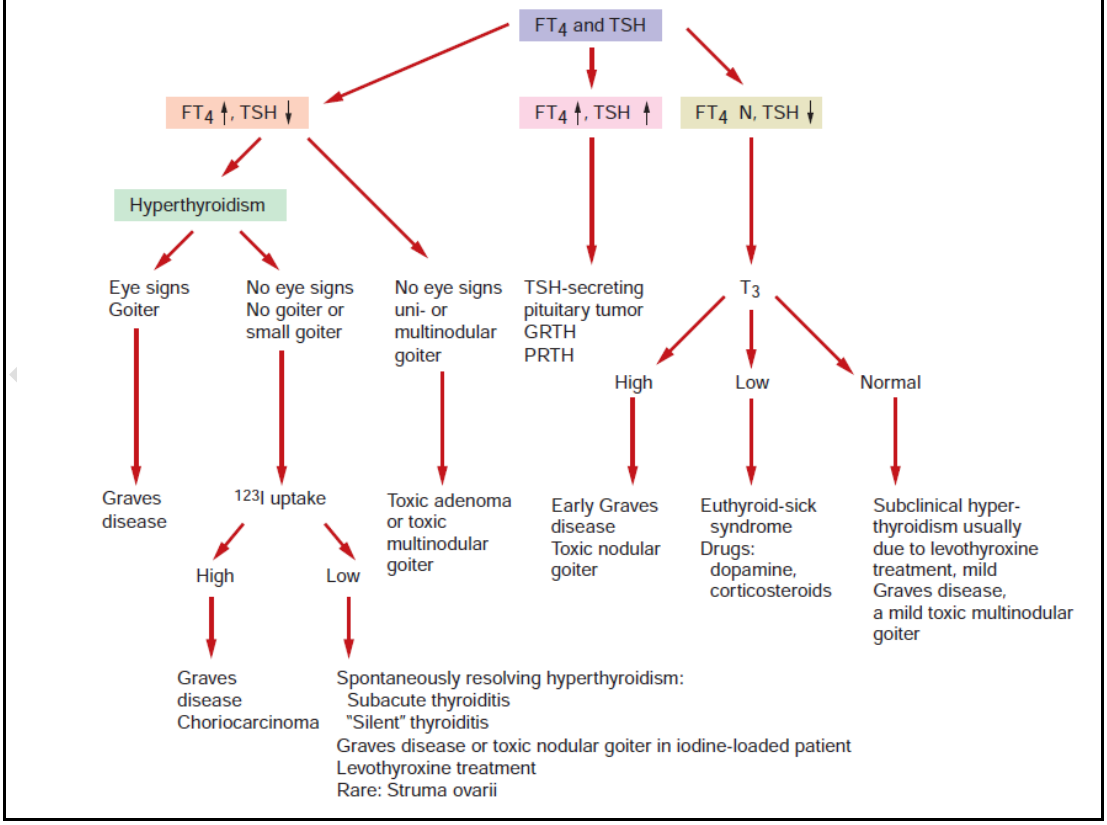
Differential diagnosis of thyrotoxicosis with low radioactive iodine uptake
• Painless thyroiditis (silent thyroiditis, lymphocytic thyroiditis, subacute lymphocytic thyroiditis & postpartum thyroiditis) • Subacute (de Quervain's) thyroiditis (subacute granulomatous thyroiditis) • Iatrogenic (eg, lithium, amiodarone, iodine, interferon alpha, interleukin-2) • Factitious ingestion of levothyroxine (T4) &/or triiodothyronine (T3) • Struma ovarii • Acute thyroiditis • Extensive thyroid cancer metastases

6

[6] "Graves disease? Well, she either has that or she has seen the devil" -- AM



Differential diagnosis of hyperthyroidism

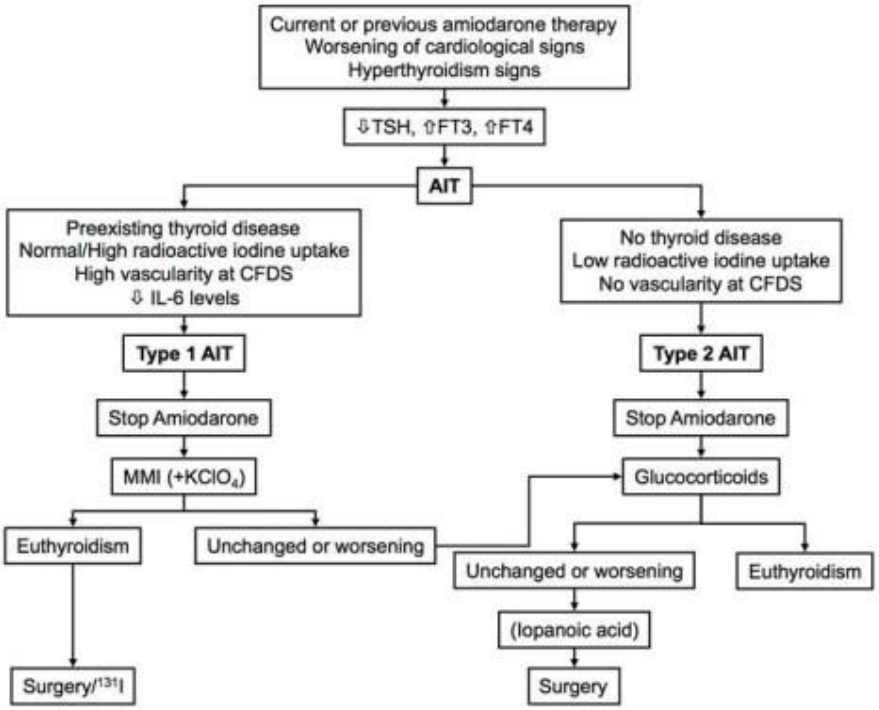


Amiodarone induced thyrotoxicosis

	Type 1	**Type 2**
Underlying thyroid disease	Yes	No
24 hr iodine uptake	Low-Normal-Increased	Absent
Vascularyty at Echo-color Doppler ultrasound	Increased	Absent
T4/t3 ratio	Usually <4	Usually >4
TgAb / TPOAb	Generally present	Normally absent
Circulating interleukin-6	Low - Normal	High – Normal

Treatment of Amiodarone Induced Thyrotoxicosis

- Mild AIT may spontaneously resolve in about 20% of the cases.
- Type 1 AIT should be treated with high doses of thioamides (20-40 mg/day of methimazole; or 400-600 mg/day of propylthiouracil) to block the synthesis of thyroid hormones
- **Once thyroid hormones are back to normal, definitive treatment of the hyperthyroidism should be considered**
- If thyroid uptake is sufficient (>10%) radioactive iodine can be used. Thyroid surgery is a good alternative.
- If thyrotoxicosis worsens after initial control, a mixed form type1-type 2 should be considered, and treatment for type 2 AIT should be started.
- Type 2 AIT can be treated with **prednisone**, starting with an **initial dose of 0.5-0.7 mg/kg body weight per day**, and the treatment is generally continued for three months. If a worsening of the toxicosis occurs during the taper, doses should be increased again. Thioamides are generally not useful in type 2 AIT.



Familial dysalbuminemic hyperthyroxinemia (FDH)
• An autosomal dominant disorder in which there is an abnormal albumin molecule with increased affinity forT4, but not T3. • Thyroid-binding protein electrophoresis performed in the presence of radiolabeled T4 may be used to confirm these diagnoses

Euthyroid hyperthyroxinaemia: term that describes various conditions, most of them related to thyroid hormone binding protein disorders in which serum total (but not free) T4 and T3 concentrations are elevated in the absence of hyperthyroidism

- **elevations in thyroxine-binding globulin (TBG) or transthyretin (TTR)**
- **Familial hyperthyroxinemic dysalbuminemia** (caused by an abnormal albumin with high binding T4 capacity)
- occasional TBG excess associated with pregnancy or estrogen administration, hepatitis, or drugs such as narcotics, amiodarone and high-dose propranolol.

Box 1 Causes of elevated total T4 with non-suppressed thyroid stimulating hormone (TSH)

- Raised serum binding proteins
- Familial dysalbuminaemic hyperthyroxinaemia
- Anti-iodothyronine/anti-TSH antibodies
- Non-thyroidal illness (including acute psychiatric disorders)
- Neonatal period
- Iatrogenic: thyroxine replacement therapy, drugs (for example, amiodarone, heparin)
- TSH secreting pituitary tumour
- Resistance to thyroid hormone

Symptomatic management - Beta blockers

- elderly patients with symptomatic thyrotoxicosis
- Thyrotoxic patients with resting heart rates in excess of 90 bpm
- coexistent cardiovascular disease
- All patients with symptomatic thyrotoxicosis

- propranolol,atenolol, metoprolol
- Non selective beta blocker like nadolol for bronchospastic disease/raynauds
-

TABLE 4. BETA-ADRENERGIC RECEPTOR BLOCKADE IN THE TREATMENT OF THYROTOXICOSIS

Drug	*Dosage*	*Frequency*	*Considerations*
Propanolol[a]	10–40 mg	TID-QID	Nonselective beta-adrenergic receptor blockade Longest experience May block T_4 to T_3 conversion at high doses Preferred agent for nursing mothers
Atenolol	25–100 mg	QD or BID	Relative beta – 1 selectivity Increased compliance
Metoprolol[a]	25–50 mg	QID	Relative beta – 1 selectivity
Nadolol	40–160 mg	QD	Nonselective beta-adrenergic receptor blockade Once daily Least experience to date May block T_4 to T_3 conversion at high doses
Esmolol	IV pump 50–100 μg/kg/min		In intensive care unit setting of severe thyrotoxicosis or storm

Each of these drugs has been approved for treatment of cardiovascular diseases, but to date none has been approved for the treatment of thyrotoxicosis.
[a]Also available in once daily preparations.
T_4, thyroxine.

I-131 RADIOIODINE THERAPY

- Females planning a pregnancy in the future (in more than 4–6 months following radioiodine therapy

- Increased surgical risk
- Contraindications to thionamides
- Previous neck surgery/irradiation

THIONAMIDE THERAPY

- High likelihood of remission (eg. females, mild disease, small goiters, negative or low titer TRAb)
- Elderly,limited life expectancy,unable to follow radiation safety regulations
- Previously operated or irradiated necks.
- Lack of access to a high-volume thyroid surgeon
- Moderate to severe Graves ophthalmopathy.

SURGERY

- Symptomatic compression or large goiters(80 g)
- relatively low uptake of radioactive iodine
- thyroid malignancy is documented or suspected (e.g., suspicious or indeterminate cytology)
- large nonfunctioning, photopenic, or hypofunctioning nodule
- coexisting hyperparathyroidism requiring surgery
- females planning a pregnancy in <4–6 months (i.e., before thyroid hormone levels wouldbe normal if radioactive iodine were chosen as therapy)especially if TRAb levels are particularly high; and patients with moderate to severe active GO.

Contraindications to a particular modality as treatment for Graves' hyperthyroidism:

- **131I therapy**: Definite contraindications include pregnancy, lactation, coexisting thyroid cancer, or suspicion of thyroid cancer, individuals unable to comply with radiation safety guidelines and females planning a pregnancy within 4–6 months.
- **ATDs:** Definite contraindications to long-term ATD therapy include previous known major adverse reactions to ATDs.
- **Surgery:** substantial comorbidity such as cardiopulmonary disease, end-stage cancer, Pregnancy is a relative contraindication and should only be used in this circumstance, when rapid control of hyperthyroidism is required and antithyroid medications cannot be used.

*** **Thyroidectomy** is best avoided in the first and third trimesters of pregnancy because of teratogenic effects associated with anesthetic agents and increased risk of fetal loss in the first trimester and increased risk of preterm labor in the third

TREATMENT OPTIONS

Preparation of patients with GD for 131I therapy

- **extremely symptomatic** or have **free T4 estimates 2–3 times the upper limit** of normal) should be treated with **beta-adrenergic blockade** prior to radioactive iodine therapy
- **Pretreatment with methimazole** prior to radioactive iodine therapy for GD should be considered in patients who are at increased risk for complications due to worsening of hyperthyroidism.
- Medical therapy of any comorbid conditions should be optimized prior to administering radioactive iodine
- **MMI should be discontinued 3–5 days before the administration of radioactive iodine**, restarted 3–7 days later, and generally tapered over 4–6 weeks as thyroid function normalizes
- Sufficient radiation should be administered in a single dose (typically 10–15 mCi)
- A **pregnancy test should be obtained within 48 hours** prior to treatment in any female with childbearing potential who is to be treated with radioactive iodine

- Propylthiouracil (PTU) treatment before 131I increases the radioresistance of the thyroid
- **special diet is not required** before radioactive iodine therapy, but excessive amounts of iodine, including iodine-containing multivitamins, should be avoided for at least 7 days. A low-iodine diet may be useful for those with relatively low RAIU to increase the proportion of radioactive iodine trapped

Conception planning post RAI ablation

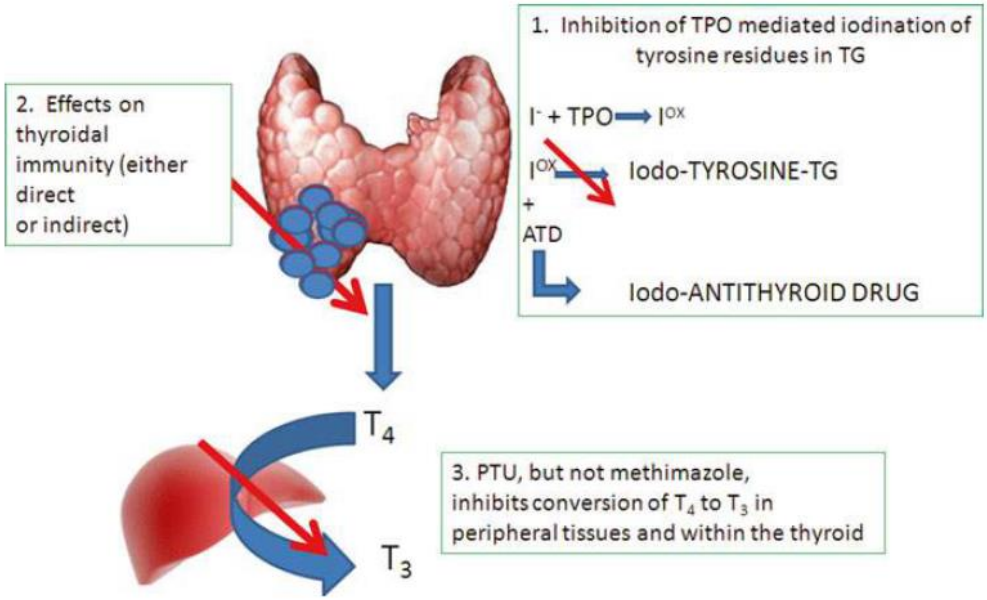
- Women delay 4-6months
- Men delay 3-4months for turnover of sperm production

Other reproductive considerations

- Fetuses exposed to I-131 after the 10th week of gestation may be born athyreotic, with increased risk of reduced intelligence and/or cancer.
- RAI must be delayed for at least 6 weeks after lactation stops to ensure that the radioactivity will no longer be actively concentrated in breast tissue.

Hypothyroidism may occur from 4 weeks on, but more commonly between 2 and 6 months

ANTI-THYROID MEDICATIONS



MECHANISM OF ACTION

- inhibit the thyroid peroxidase (TPO)-mediated iodination of thyroglobulin (Tg), and thereby the synthesis of thyroid hormones, T4 and T3
- The mechanism likely involves TPO-mediated iodination of the drugs themselves, with the drugs competing for oxidized iodine with the normal biosynthetic pathway
- drugs inhibit the TPO mediated intramolecular coupling reaction, whereby iodotyrosines are linked to form the iodothyronines T4 and T3.
- In addition to this primary mechanism of action, PTU, but not MMI, decreases T4 to T3 conversion in peripheral tissues and in the thyroid gland itself, by inhibiting type I deiodinase. It does not inhibit Type 2 deiodinase found in the brain and pituitary
- ATD therapy may have immunosuppressive effects, either indirectly or directly

Methimazole should be used in virtually every patient who chooses antithyroid drug therapy for GD.

Exceptions to methimazole
• First trimester of pregnancy where methimazole is contraindicated. • Thyroid storm • Minor reactions to methimazole

Side effects of thionamides

• pruritic rash, jaundice, acholic stools or dark urine, arthralgias, abdominal pain, nausea, fatigue, fever, or pharyngitis.
alerted to stop the medication immediately and call their physician when there are symptoms suggestive of agranulocytosis or hepatic injury

Dose initiation	1. MMI 10-20mg daily to restore euthyroidism 2. PTU 50-150mg q12h or q8h
Maintenance	1. MMI 5-10mg daily 2. PTU 50mg q12h or q8h
Side effects of methimazole	• Hepatotoxicity (cholestatic/hepatocellular rarely) • Aplasia cutis in babies • MMI embroyopathy first trimester exposure - choanal and esophageal atresia • Arthropathy and lupus like syndrome
Side effects of PTU	• Antineutrophil cytoplasmic antibody positive small vessel vasculitis • Fulminant hepatic necrosis requiring transplant • Rare agranulocytosis • Arthropathy and lupus like syndrome

	PTU	Methimazole
Minor reactions		
Fever, rash, GI distress	1–5 %	1–5 % (dose-related)
Major reactions		
Agranulocytosis	0.2–0.3 %	0.2–0.3 % (dose related)
ANCA positive vasculitis	<1 %, can occur after years of therapy. Predilection for Asians	Rare
Hepatotoxicity	1 % mild; ? 0.1–0.01 % potential life-threatening hepatocellular damage	Rare; primarily cholestatic

The appropriate initial dose of ATD in Graves' disease depends on the biochemical and
clinical severity of the disease. PTU has a less favorable pharmacokinetic profi le and more side effects, and it should only be used in special situations.

relative activity of the two drugs is about 1:20, or in other words 5 mg MMI once daily has about the same effect as 50 mg PTU twice daily

Dose initiation based on biochemical severity
• MMI **30 mg results >2–3 times** the upper reference limit • **20 mg a day** if function tests are **>1.5–≤2** times the upper reference limit • **5–10 mg** per day if test results are **≤1.5** times upper reference limit

Contraindications to starting thionamides
• Baseline ANC <500 /mm3 • Liver transaminase enzyme levels elevated more than fivefold the ULN.

If methimazole is chosen as the primary therapy for GD, the medication should be continued for **approximately 12–18 months, then tapered or discontinued if the TSH is normal at that time.**

Measurement of TRAb levels prior to stopping antithyroid drug therapy is suggested, as it aids in predicting which patients can be weaned from the medication, with normal levels indicating greater chance for remission.

Definition of remission in the setting of thionamide therapy
• **normal serum TSH, FT4, and T3 for 1 year after discontinuation of ATD therapy.** • 20%–30% of patients will have a lasting remission after 12–18 months of medication • TFTs 1–3-month intervals for 6–12 months to diagnose relapse early

THYROID STORM

A multimodality treatment approach to patients with thyroid storm should be used, including beta-adrenergic blockade, antithyroid drug therapy, inorganic iodide, corticosteroid therapy, aggressive cooling with acetaminophen and cooling blankets, volume resuscitation, respiratory support and monitoring in an intensive care unit.

Precipitants of thyroid storm in a patient with previously compensated thyrotoxicosis

- abrupt cessation of antithyroid drugs
- thyroid, or nonthyroidal surgery in a patient with unrecognized or inadequately treated thyrotoxicosis
- acute illnesses unrelated to thyroid disease
- radioactive iodine therapy or exposure to iodine from the use of iodine-containing contrast agents (px with illnesses unrelated to thyroid dx)

Clinical features of thyroid storm	
Precipitating factors	• Thyroid or non-thyroid surgery • Acute illness (eg, trauma, infection), childbirth • Acute iodine load (eg, iodine contrast)
Clinical presentation	• Fever as high as 40-41.1 C (104-106 F) • Tachycardia, hypertension, congestive heart failure, cardiac arrhythmias (eg, atrial fibrillation) • Agitation, delirium, seizure, coma • Goiter, lid lag, tremor, warm & moist skin • Nausea, vomiting, diarrhea, jaundice
Treatment	• Beta blocker (eg, propranolol) to ↓ adrenergic manifestations • PTU followed by iodine solution (SSKI) to ↓ hormone synthesis & release • Glucocorticoids (eg, hydrocortisone) to ↓ peripheral T4 to T3 conversion & improve vasomotor stability • Identify trigger & treat, supportive care

PTU = propylthiouracil; **SSKI** = potassium iodide.

Table 5. Point Scale for the Diagnosis of Thyroid Storm

Criteria	Points	Criteria	Points
Thermoregulatory dysfunction		**Gastrointestinal-hepatic dysfunction**	
Temperature (°F)		Manifestation	
99.0–99.9	5	Absent	0
100.0–100.9	10	Moderate (diarrhea, abdominal pain, nausea/vomiting)	10
101.0–101.9	15	Severe (jaundice)	20
102.0–102.9	20		
103.0–103.9	25		
≥104.0	30		
Cardiovascular		**Central nervous system disturbance**	
Tachycardia (beats per minute)		Manifestation	
100–109	5	Absent	0
110–119	10	Mild (agitation)	10
120–129	15	Moderate (delirium, psychosis, extreme lethargy)	20
130–139	20	Severe (seizure, coma)	30
≥140	25		
Atrial fibrillation			
Absent	0		
Present	10		
Congestive heart failure		**Precipitant history**	
Absent	0	Status	
Mild	5	Positive	0
Moderate	10	Negative	10
Severe	20		

Scores totaled	
>45	Thyroid storm
25–44	Impending storm
<25	Storm unlikely

Source: Burch and Wartofsky, 1993 (21). Printed with permission.

Table 6. Thyroid Storm: Drugs and Doses

Drug	Dosing	Comment
Propylthiouracil	500–1000 mg load, then 250 mg every 4 hours	Blocks new hormone synthesis Blocks T_4-to-T_3 conversion
Methimazole	60–80 mg/day	Blocks new hormone synthesis
Propranolol[a]	60–80 mg every 4 hours	Consider invasive monitoring in congestive heart failure patients Blocks T_4-to-T_3 conversion in high doses Alternate drug: esmolol infusion
Iodine (saturated solution of potassium iodide)	5 drops (0.25 mL or 250 mg) orally every 6 hours	Do not start until 1 hour after antithyroid drugs Blocks new hormone synthesis Blocks thyroid hormone release
Hydrocortisone	300 mg intravenous load, then 100 mg every 8 hours	May block T_4-to-T_3 conversion Prophylaxis against relative adrenal insufficiency Alternative drug: dexamethasone

[a]May be given intravenously.

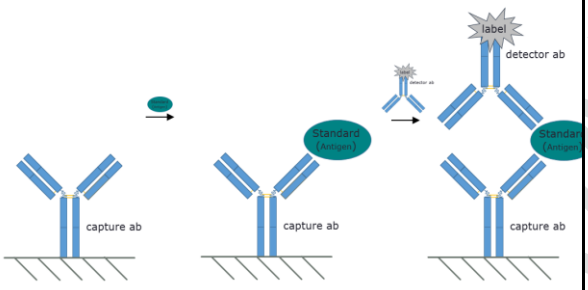
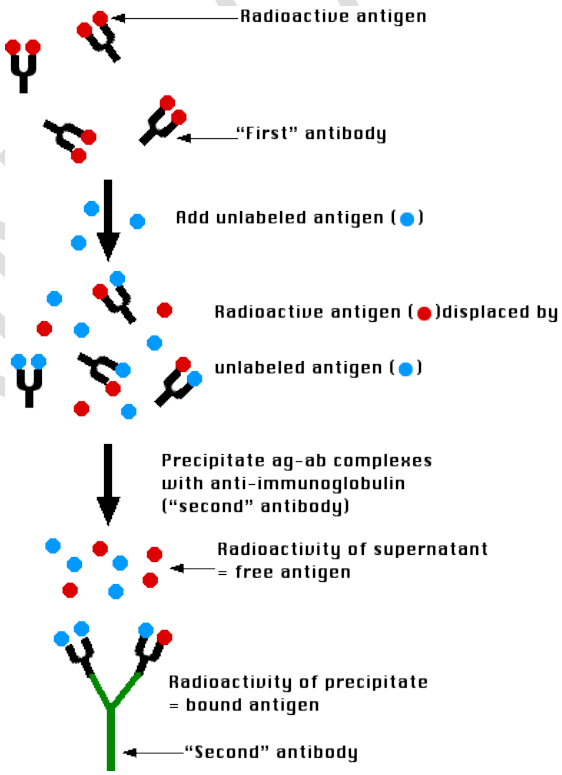
- *Important to note for supportive care: **Acetaminophen** should be used instead of **aspirin** since the latter can increase serum free T4 and T3 concentrations by interfering with their protein binding.*

- Bile acid sequestrants may also be of benefit in severe cases to decrease enterohepatic recycling of thyroid hormones.
    - Cholestyramine (4 g orally four times daily)
- A patient who is unable to take a Thionamides; thyroidectomy is the treatment of choice. This should not be delayed more than 8 to 10 days given Wolff Chaikoff effect.

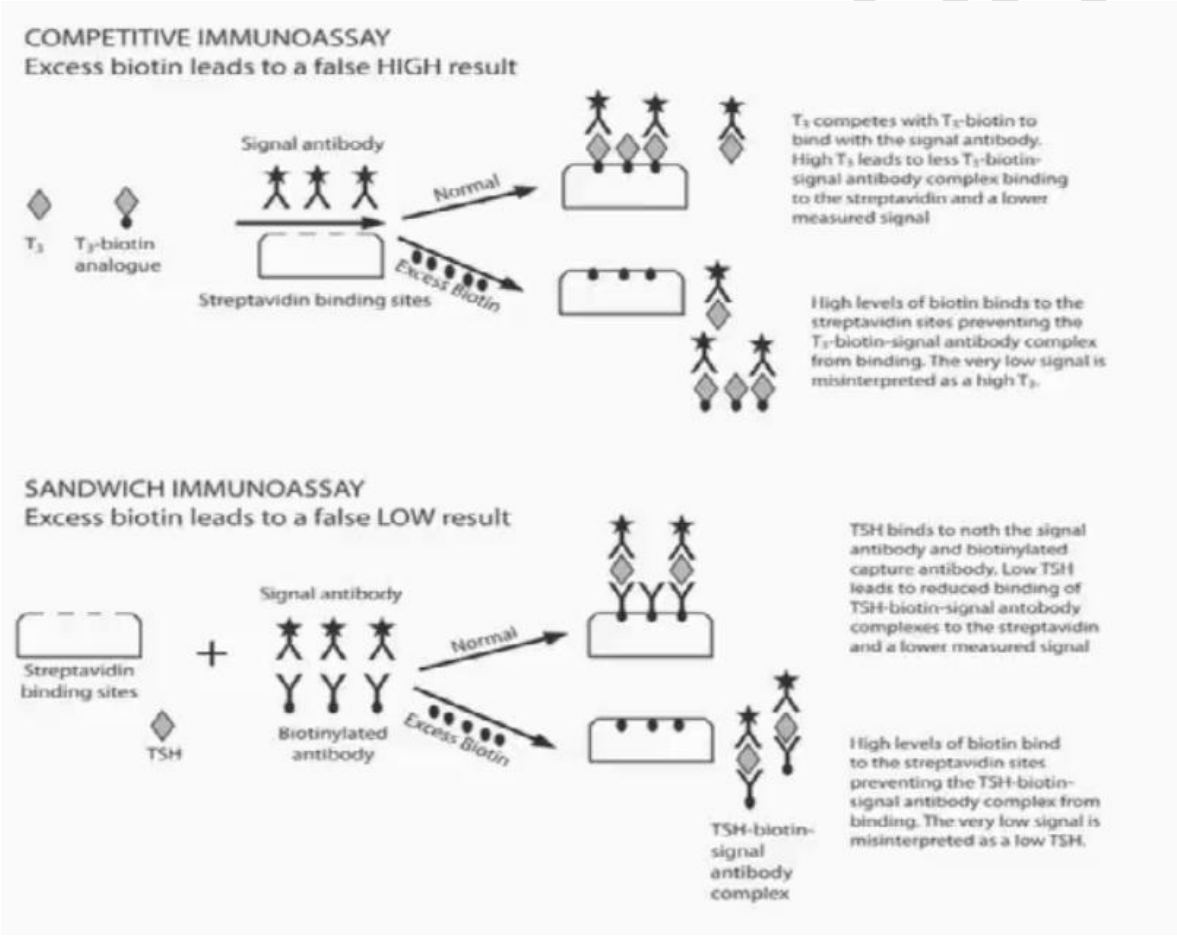
THYROID FUNCTION TESTS!

⊕ **A National Academy of Clinical Biochemistry** guideline specifies that sensitivity, or **lower limit of detection, for TSH assays should be less than 0.02 mU/L**. It is better to assess and compare TSH assays by this quantitative criterion rather than marketing terms such as third generation or ultrasensitive

Two sorts of immunoassays used to measure TSH (and T4 and T3) in serum samples: immunometric assays (IMA) and radioimmunoassay (RIA)

Immunometric assay (IMA)	**Radioimmunoassay (RIA)**
A Sandwich assay  1) An antibody (usually a mouse monoclonal antibody) directed against one epitope on the TSH molecule. 2) This antibody is bound to a solid matrix. 3) Second monoclonal TSH antibody that binds another TSH epitope is labeled with a **detectable marker**, which can be a **radioisotope**, a **colorimetrically quantifiable enzyme**, or a **fluorescent or chemiluminescent tag** 4) *The concentration of TSH, which links the solid state and labeled antibodies*, is proportionate to the intensity of signal emitted by the marker once unbound second antibody has been separated	 1) A small amount of a TSH tracer, to which a radioactive molecule has been linked, competes for binding to first antibody (eg, a rabbit antihuman TSH polyclonal antibody) 2) antibody-bound TSH, both in the sample and the tracer, is separated from the free tracer in the supernatant using one of several techniques: a

off ** Some of these assays are biotinylated.	second antibody directed against the first (eg, goat antirabbit immunoglobulin antibody), polyethylene glycol, or staphylococcal protein A. 3) the concentration of TSH in the sample is inversely proportionate to tracer activity. **In general, TSH RIAs are less sensitive and less widely employed than IMA**s.



Competitive Assay = falsely high
Sandwich Assay = falsely low

Equilibrium dialysis
Equilibrating a serum sample with buffer across a membrane with pores that permit passage only of unbound T 4 ; then the dialysate is assayed for its T4 concentration, from which the serum concentration can be

derived.

- Considered the gold standard for free T4 determination
- It is cumbersome
- Relatively expensive
- Not widely available.

Causes of inappropriate serum TSH concentration

Clinical hyperthyroidism
TSH-secreting pituitary adenoma
Isolated pituitary resistance to thyroid hormone
Clinical hypothyroidism
Central (pituitary or hypothalamic) hypothyroidism
Preceding TSH suppression (eg, recently treated hyperthyroidism)
Clinical euthyroidism
Systemic illnesses (↓ during acute phase, ↑ during recovery)
Generalized resistance to thyroid hormone (compensated)
Assay interference
Anti-TSH antibodies
Anti-mouse immunoglobulin antibodies
Drugs: dopamine, dobutamine, glucocorticoids

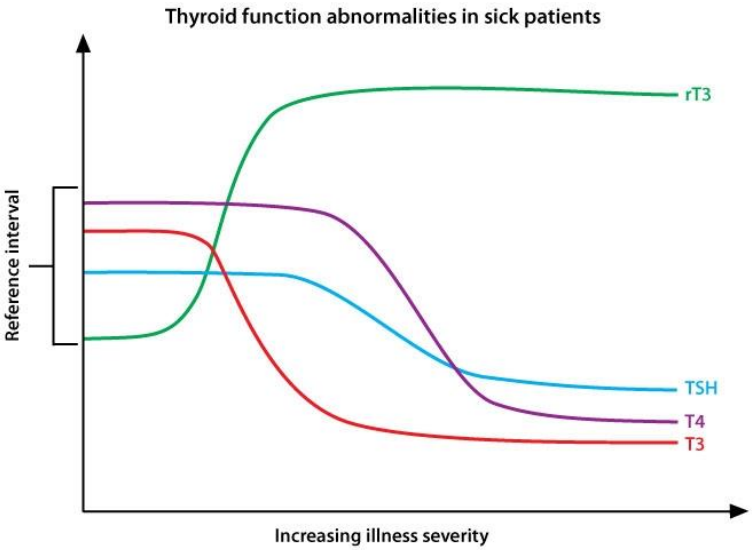
[a]"Inappropriate" refers to disruption of the usual reciprocal relationship between serum TSH and free thyroid hormone concentrations.

Euthyroid Sick Syndrome

-Low T3 due to acute illness is usually due to suppressed conversion of T4 to T3

- In the setting of low TSH, measuring T3 (active thyroid hormone!) levels can differentiate b/n hyperthyroidism (high T3, T3 toxicosis) and ESS (low T3)

Thyroid function normalizes after recovery



Non thyroidal illness

1. 5-deiodination of T4 declines --> leading to decreased T3 production
2. 5-deiodination of T4 to inactive reverse T3 is increased
3. A pattern of thyroid testing that suggests thyroid dysfunction.

- The most common thyroid function pattern during nonthyroidal illness is **reduced T3 level**, **elevated reverse T3 level**, **variable FT4 level**, and **relatively normal or decreased TSH level**, depending on the severity of illness (figure 1)
- During recovery from illness, the TSH level may increase temporarily, sometimes overshooting the normal range, because both FT4 and T3 levels return to baseline values, which may mimic subclincal hypothyroidism***.

***Clinical case -- 60y/o M with HIV/AIDS TSH of 9.98, FT3 1.7 (low) and FT4 (lower limit of normal)

▲ Diagnosis of recovery phase of euthyroid sick syndrome and not subclinical hypothyroidism.

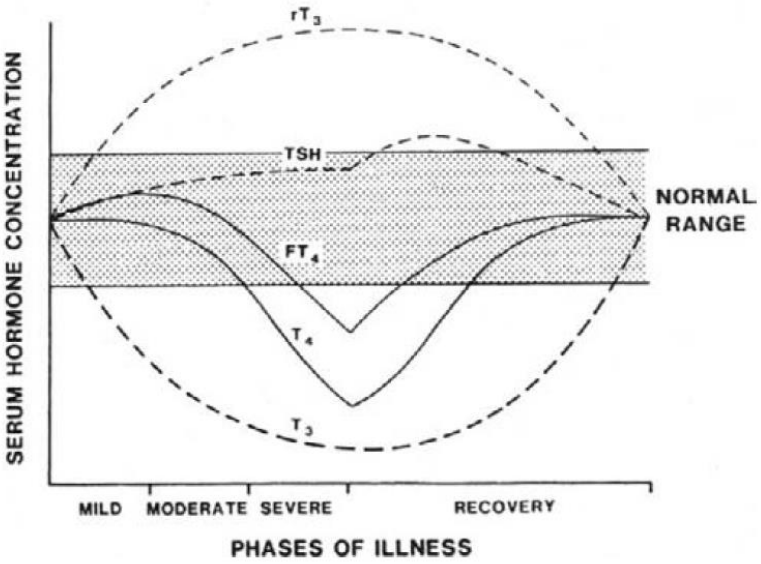


Figure 1. Thyroid function testing during nonthyroidal illness ("euthyroid sick syndrome"). Reprinted from *The Thyroid Gland: A Practical Clinical Treatise* [31], with permission.

Table 1. Clinical syndromes involving decreased thyroid hormone levels.

Condition	TSH level	FT_4 level	T_3 level	Comment(s)
Overt hypothyroidism	↑↑	↓	↓	May be associated with anti-TPO
Subclinical hypothyrodism	↑	N	N	More common during HAART; usually asymptomatic; rarely associated with anti-TPO in HIV-infected patients; health care providers should also consider recovery from nonthyroidal illness
Isolated low FT_4	N	↓	N	More common during HAART; usually asymptomatic and of unclear significance; health care providers should also consider nonthyroidal illness
Central hypothyrodism	↓	↓	↓	Very rare; when it occurs, symptoms of dysfunction in other endocrine systems are usually present (pan-hypopituitarism or hypothylamic dysfunction)
Nonthyroidal illness	N/ ↑	N/ ↓	↓	Occurs during severe acute illness or cachexia as a result of down-regulation of conversion of T_4 to T_3

NOTE. Anti-TPO, anti-thyroid peroxidase; FT_4, free thyroxine; N, normal; TSH, thyrotropin; T_3, tri-iodothyronine; ↑, increase; ↑↑, marked increase; ↓, decrease.

Causes of low TSH & low free T_4	
Condition	**Findings**
Central hypothyroidism	• Usually ↓TSH, ↓free T_4, Low-normal to ↓T_3 • Clinical features of hypothyroidism • Evidence of other pituitary hormonal deficiencies
Subclinical thyrotoxicosis	• ↓TSH, normal to ↓ free T_4, ↑T_3 levels • Typically seen in patients taking T_3 thyroid supplements & toxic multinodular goiter • Radioactive iodine uptake & scan may be helpful
Euthyroid sick syndrome	• Sick hospitalized patients • Normal to ↓TSH, normal to ↓free T_4, & ↓T_3 • ↑Reverse T_3; normal TSH response to TRH • Treatment with levothyroxine not useful
Medications	• May suppress TSH with low-to-normal T_4 • Examples: Dopamine, high-dose glucocorticoids, octreotide

TRH= thyrotropin-releasing hormone.

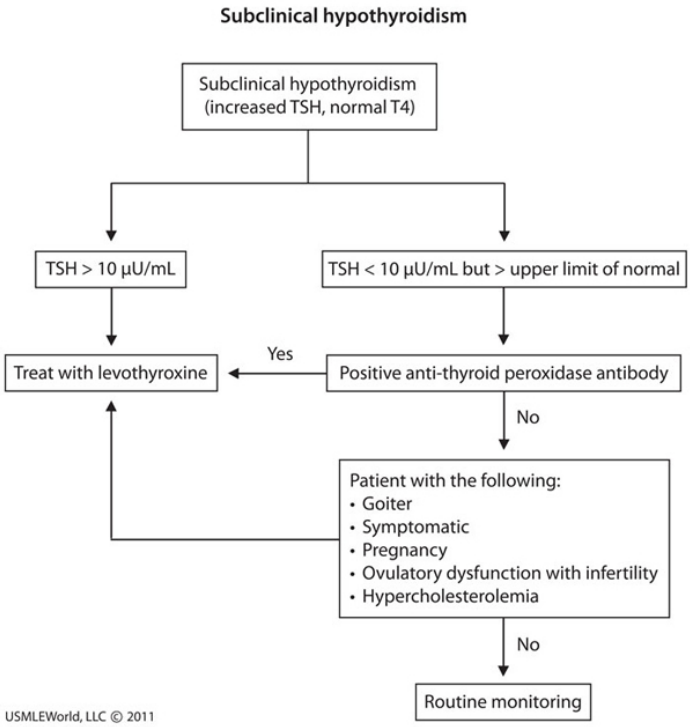
Central hypothyroidism
central (hypothalamic or pituitary) hypothyroidism have **serum FT4 levels that are low or low-normal**, with **serum TSH values that are usually low**, but may also be **inappropriately normal or rarely mildly elevated (up to 10 mIU/L)**
secretion of an abnormally glycosylated form of TSH which is less biologically active, but has normal immunoreactivity

THYROID HORMONE RESISTANCE SYNDROMES

generalized resistance to thyroid hormones (GRTH)	**Selective pituitary resistance to thyroid hormones (PRTH)**
- **Inheritance is autosomal dominant.** - **familial syndrome** of deaf mutism, stippled epiphyses, goiter - Elevated T4 , FT4 , T3 , and	- Symptoms of mild hyperthyroidism, goiter, elevated serum T4 and T3 , and normal or elevated serum TSH -

normal or elevated TSH. *Dynamic tests to distinguish generalized resistance to thyroid hormones from TSH-secreting adenomas usually reveal a fall in TSH with T3 administration* *pituitary MRI fails to demonstrate a pituitary tumor* In fact, some patients are erroneously thought to have Graves disease and undergo inappropriate therapy with radioiodine or surgery. administration of thyroid hormones may be necessary to correct defects in growth or mental development	

Hypothyroidism



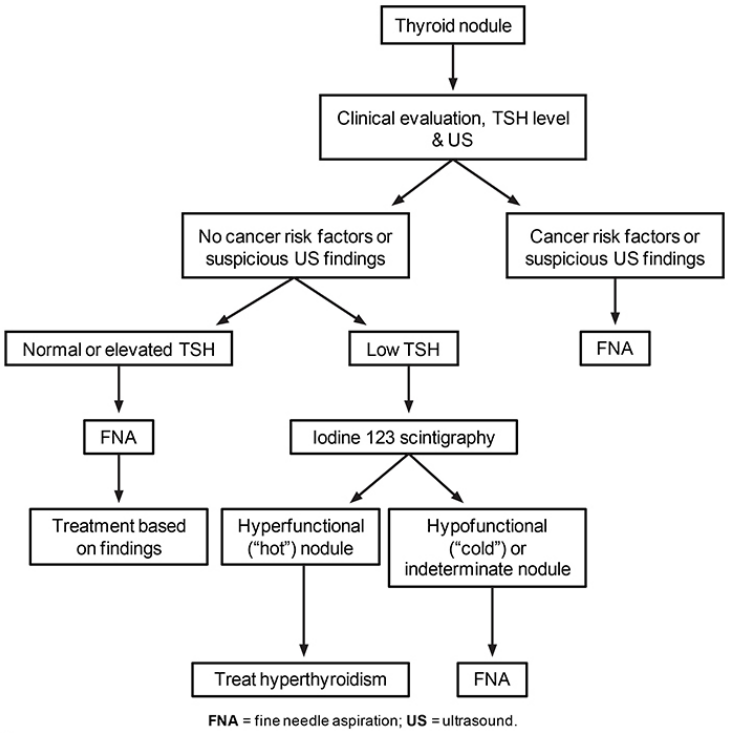
Recovery from Hyperthyroidism
• Patients who have been treated for hyperthyroidism and are in the recovery phase may show persistently suppressed serum TSH concentrations for several months, even when thyroid hormone (FT4, T3) levels have normalized. • Recovering from thyrotoxicosis caused by thyroiditis.

Riedel Thyroiditis

Definition	Cause	Clinical symptoms	PE	Diagnosis	Tx
Rare fibrotic condition that results in destruction of the thyroid and overgrowth of progressively fibrosing connective tissue that may invade surrounding structures. No robust epidemiologic data; incidence 0.06% to 0.98%; more common in women between 30 and 50 Can be associated with other fibrosing processes such as sclerosing cholangitis, pancreatitis, mediastinitis, lacrimal fibrosis, orbital fibrosis and fibroinflammatory lesions of head and neck.	Unclear	Dysphagia, dyspnea, hoarseness, aphonia	firm mass "rock hard" in thyroid associated with compressive symptoms; initially concerning for malignancy given consistency Primary hypothyroidism and anti TPO Ab are present in most pts Clinical evaluation: thyroid function and calcium status sicne can impact parathyroid glands	Histopathologically Disease usually progressive bu may stabilize spontaneously or sometimes regress. High proportions of IgG4-plasma cells have been observed histologically, not always; no reported IgG4 serum elevation	High dose steroids improvement seen reducing size of inflammatory mass Tamoxifen - 2nd lin - proposed MOA: induction of autocrine secretion TGF-beta 1 and the potential inhibition fibroblastic functio Surgery - includes debulking limited t isthmusectomy to relieve constrictive pressure to total thyroidectomy if compression symptoms are seve

Management of Thyroid Nodules

Indications for FNA
- Suspicious ultrasound findings or cancer risk factors
- Normal or elevated TSH require FNA
- Low TSH should undergo iodine 123 thyroid scintigraphy (cold or indeterminate nodules require FNA)



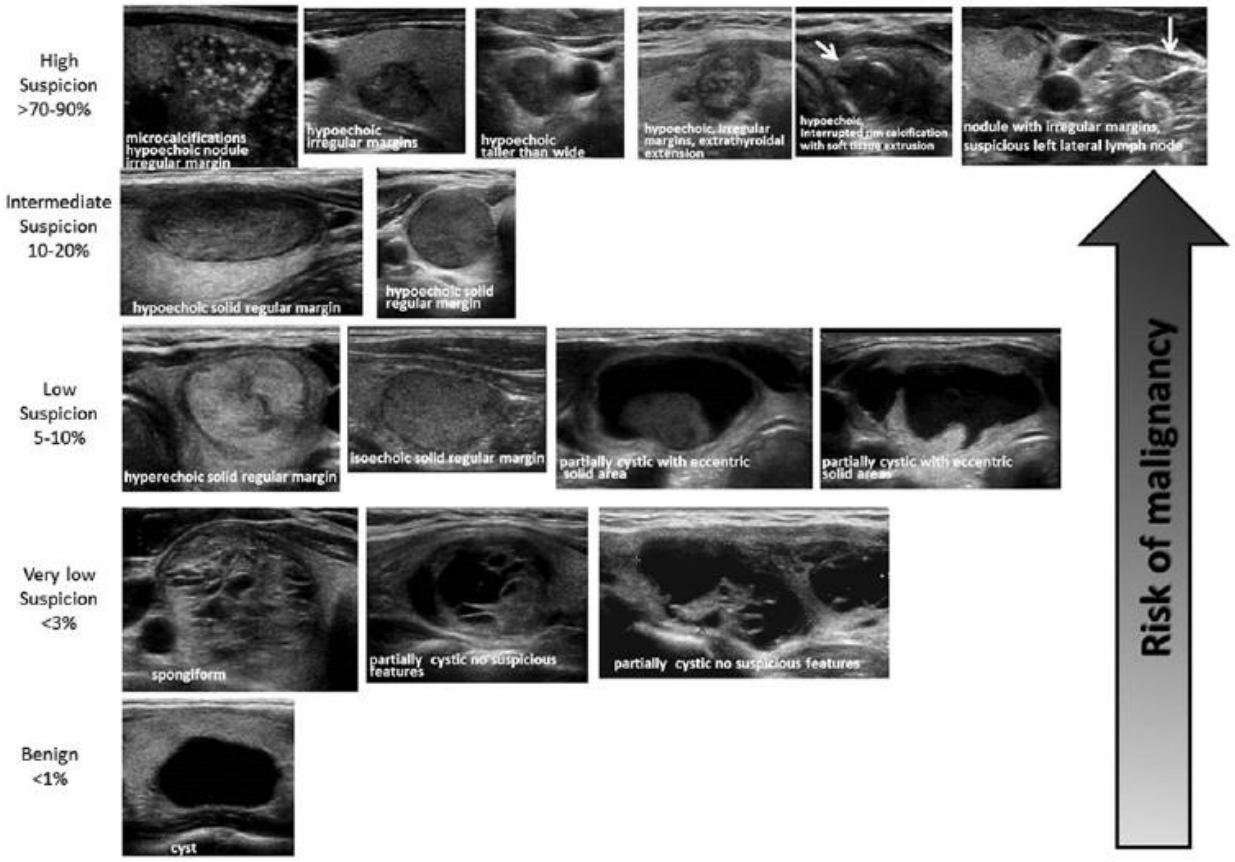


FIG. 2. ATA nodule sonographic patterns and risk of malignancy.

tips for thyroid nodules

1. Previously biopsied nodule with stable findings on size and echopattern does not need to be biopsied
2. Risk of malignancy in a nodule that has previously been found to have benign cytology is approximately 1-3%
3. Follow up USG in 12 months if there is no evidence of malignancy
4. **Diagnostic thyroidectomy** if surveillance is unacceptable by patient due to anxiety.

Table 6. Sonographic Patterns, Estimated Risk of Malignancy, and Fine-Needle Aspiration Guidance for Thyroid Nodules

Sonographic pattern	*US features*	*Estimated risk of malignancy, %*	*FNA size cutoff (largest dimension)*
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule ***with*** one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE	>70–90[a]	Recommend FNA at ≥1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins ***without*** microcalcifications, ETE, or taller than wide shape	10–20	Recommend FNA at ≥1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, ***without*** microcalcification, irregular margin or ETE, or taller than wide shape.	5–10	Recommend FNA at ≥1.5 cm
Very low suspicion	Spongiform or partially cystic nodules ***without*** any of the sonographic features described in low, intermediate, or high suspicion patterns	<3	Consider FNA at ≥2 cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1	No biopsy[b]

Table 8. The Bethesda System for Reporting Thyroid Cytopathology: Diagnostic Categories and Risk of Malignancy[a]

Diagnostic category	*Estimated/predicted risk of malignancy by the Bethesda system, %*[a]	*Actual risk of malignancy in nodules surgically excised, % median (range)*[b]
Nondiagnostic or unsatisfactory	1–4	20 (9–32)
Benign	0–3	2.5 (1–10)
Atypia of undetermined significance or follicular lesion of undetermined significance	5–15	14 (6–48)
Follicular neoplasm or suspicious for a follicular neoplasm	15–30	25 (14–34)
Suspicious for malignancy	60–75	70 (53–97)
Malignant	97–99	99 (94–100)

TABLE 11. ATA 2009 RISK STRATIFICATION SYSTEM WITH PROPOSED MODIFICATIONS

ATA low risk	Papillary thyroid cancer (with all of the following): • No local or distant metastases; • All macroscopic tumor has been resected • No tumor invasion of loco-regional tissues or structures • The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) • If ^{131}I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan • No vascular invasion • Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in largest dimension)[a] Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer[a] Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion[a] Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including *BRAF*^{V600E} mutated (if known)[a]
ATA intermediate risk	Microscopic invasion of tumor into the perithyroidal soft tissues RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Papillary thyroid cancer with vascular invasion Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension[a] Multifocal papillary microcarcinoma with ETE and *BRAF*^{V600E} mutated (if known)[a]
ATA high risk	Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE) Incomplete tumor resection Distant metastases Postoperative serum thyroglobulin suggestive of distant metastases Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension[a] Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)[a]

[a]Proposed modifications, not present in the original 2009 initial risk stratification system. See sections [B19]–[B23] and Recommendation 48B.

TABLE 13. CLINICAL IMPLICATIONS OF RESPONSE TO THERAPY RECLASSIFICATION IN PATIENTS WITH DIFFERENTIATED THYROID CANCER TREATED WITH TOTAL THYROIDECTOMY AND RADIOIODINE REMNANT ABLATION

Category	*Definitions*[a]	*Clinical outcomes*	*Management implications*
Excellent response	Negative imaging ***and either*** Suppressed Tg <0.2 ng/mL[b] ***or*** TSH-stimulated Tg <1 ng/mL[b]	1%–4% recurrence[c] <1% disease specific death[c]	An excellent response to therapy should lead to an early decrease in the intensity and frequency of follow up and the degree of TSH suppression
Biochemical incomplete response	Negative imaging ***and*** Suppressed Tg ≥1 ng/mL[b] ***or*** Stimulated Tg ≥10 ng/mL[b] ***or*** Rising anti-Tg antibody levels	At least 30% spontaneously evolve to NED[d] 20% achieve NED after additional therapy[a] 20% develop structural disease[a] <1% disease specific death[a]	If associated with stable or declining serum Tg values, a biochemical incomplete response should lead to continued observation with ongoing TSH suppression in most patients. Rising Tg or anti-Tg antibody values should prompt additional investigations and potentially additional therapies.
Structural incomplete response	Structural or functional evidence of disease With any Tg level With or without anti-Tg antibodies	50%–85% continue to have persistent disease despite additional therapy[e] Disease specific death rates as high as 11% with loco-regional metastases and 50% with structural distant metastases[a]	A structural incomplete response may lead to additional treatments or ongoing observation depending on multiple clinico-pathologic factors including the size, location, rate of growth, RAI avidity, ^{18}FDG avidity, and specific pathology of the structural lesions.
Indeterminate response	Nonspecific findings on imaging studies Faint uptake in thyroid bed on RAI scanning Nonstimulated Tg detectable, but <1 ng/mL Stimulated Tg detectable, but <10 ng/mL ***or*** Anti-Tg antibodies stable or declining in the absence of structural or functional disease	15%–20% will have structural disease identified during follow-up[a] In the remainder, the nonspecific changes are either stable, or resolve[a] <1% disease specific death[a]	An indeterminate response should lead to continued observation with appropriate serial imaging of the nonspecific lesions and serum Tg monitoring. Nonspecific findings that become suspicious over time can be further evaluated with additional imaging or biopsy.

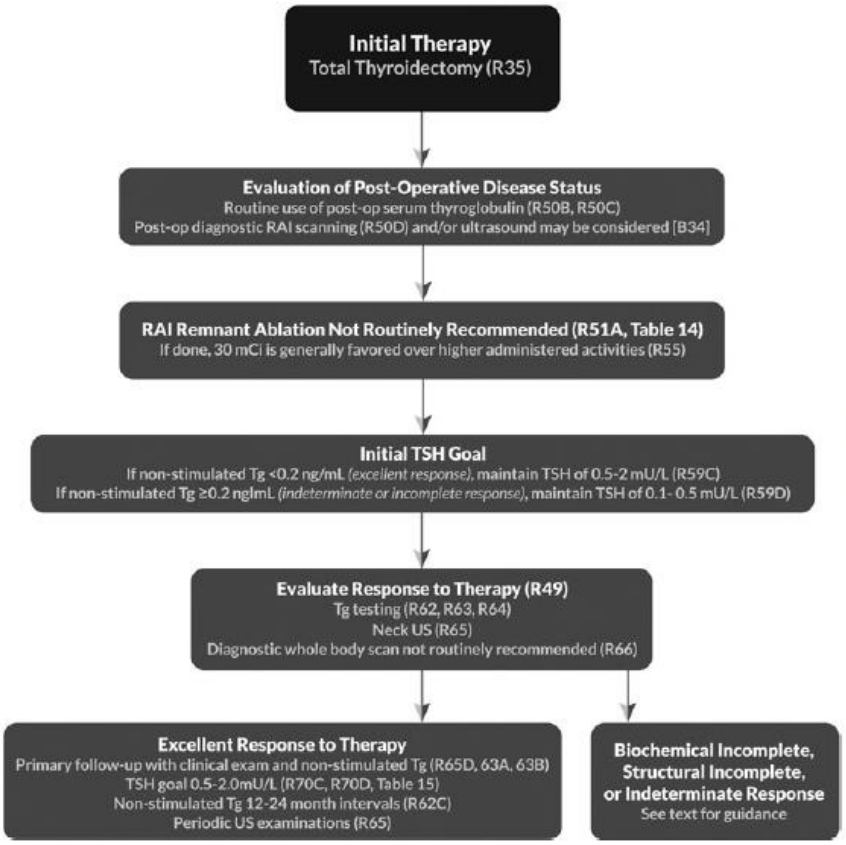


FIG. 5. Clinical decision-making and management recommendations in *ATA low-risk* DTC patients that have undergone total thyroidectomy. R, recommendation in text.

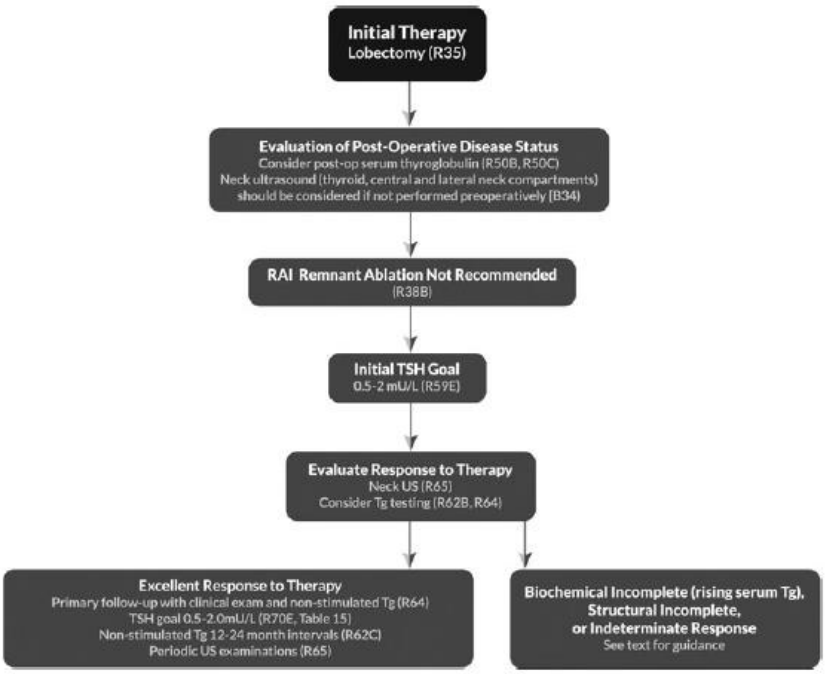


FIG. 6. Clinical decision-making and management recommendations in *ATA low risk* DTC patients that have undergone less than total thyroidectomy (lobectomy or lobectomy with isthmusectomy). R, recommendation in text.

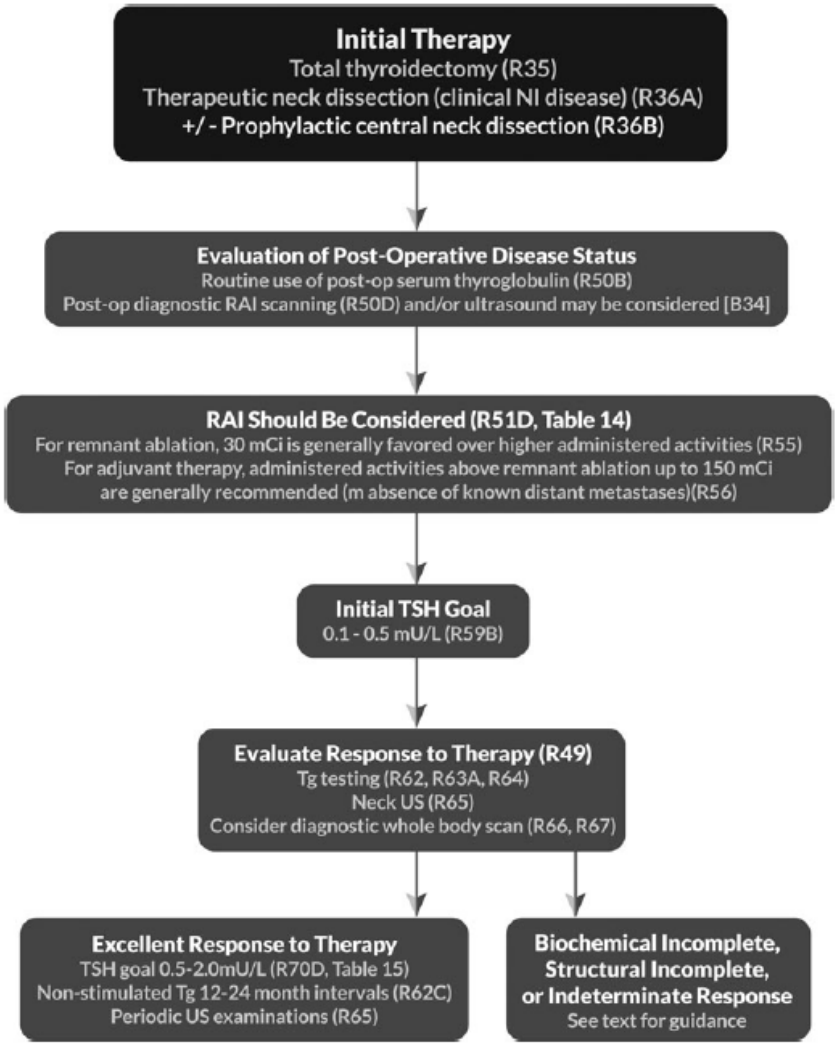


FIG. 7. Clinical decision-making and management recommendations in *ATA intermediate risk* DTC patients that have undergone total thyroidectomy. R, recommendation in text.

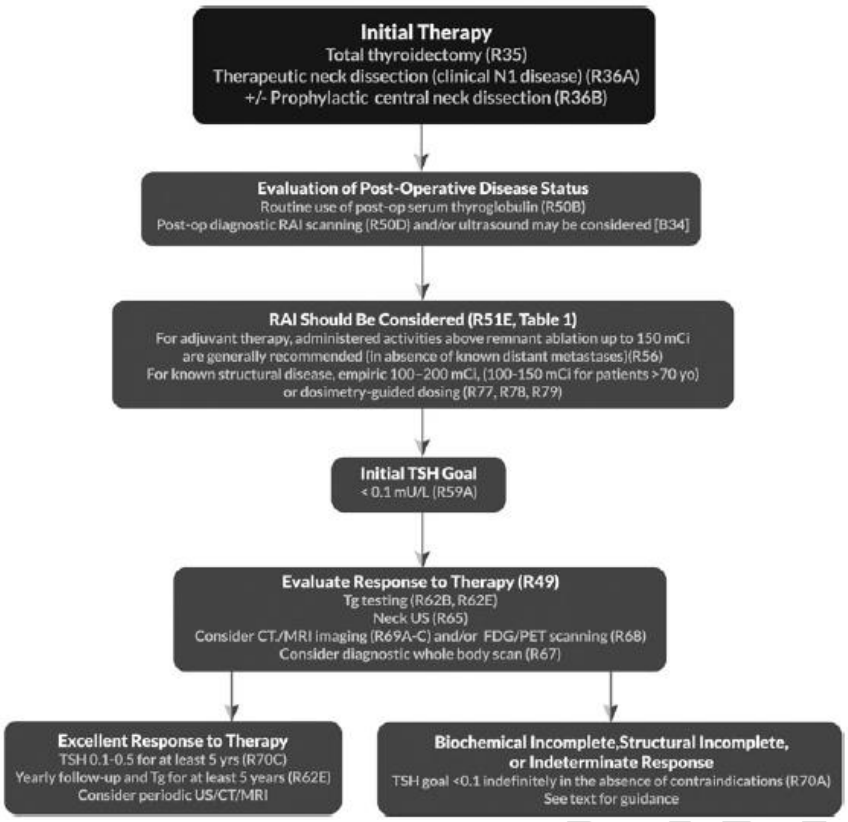


FIG. 8. Clinical decision-making and management recommendations in *ATA high risk* DTC patients that have undergone total thyroidectomy and have no gross residual disease remaining in the neck. R, recommendation in text.

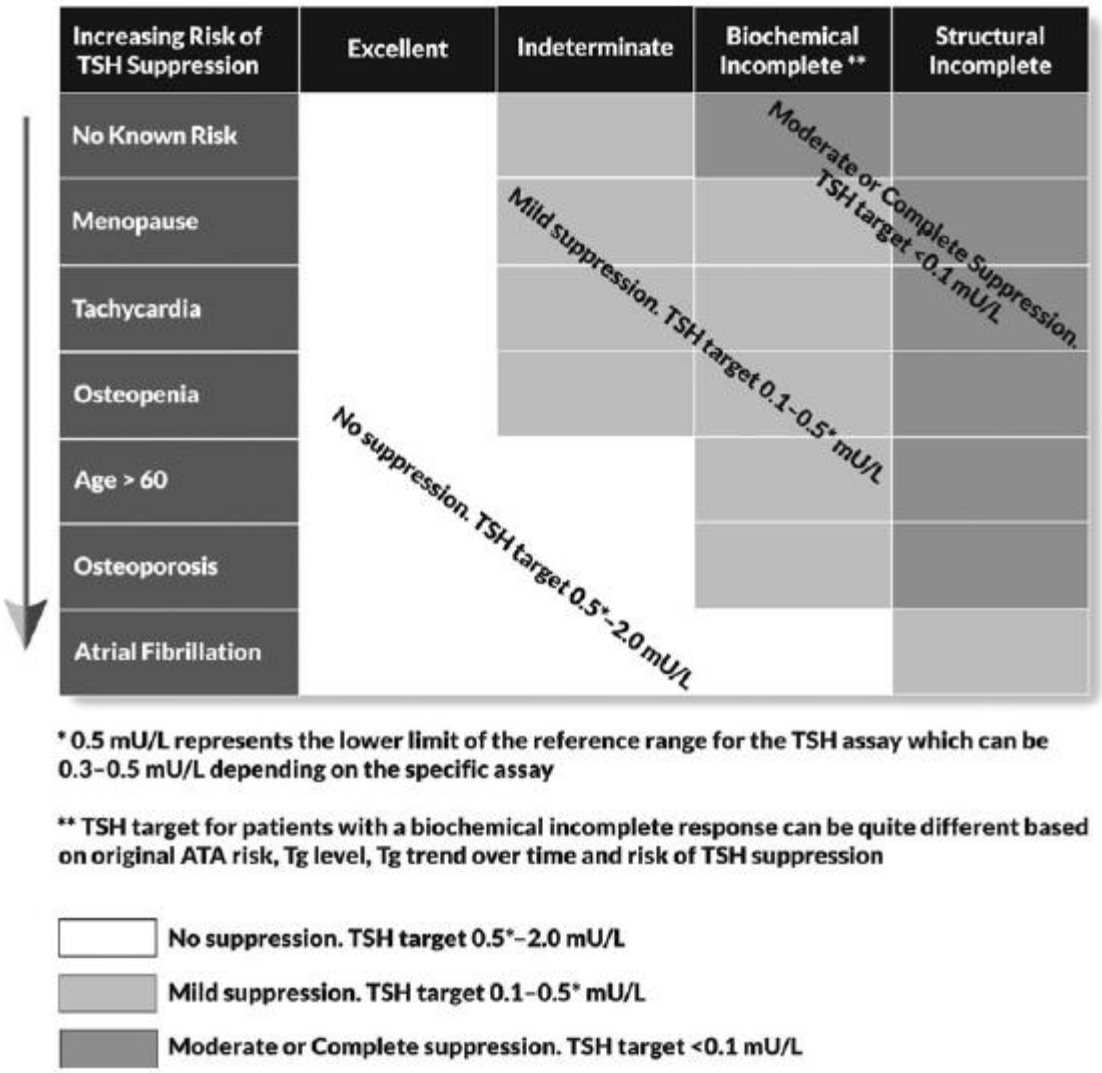


TABLE 16. FACTORS TO REVIEW WHEN CONSIDERING KINASE INHIBITOR THERAPY[a]

Factors favoring kinase inhibitor therapy	*Factors discouraging kinase inhibitor therapy*
Imminently threatening disease progression expected to require intervention and/or to produce morbidity or mortality in <6 months (e.g., pulmonary lesions or lymphadenopathy likely to rapidly invade airways, produce dyspnea, or cause bronchial obstruction). Symptomatic disease (e.g., exertional dyspnea, painful unresectable adenopathy), not adequately addressable using directed therapy. Diffuse disease progression as opposed to focal progression (e.g., in multiple lung metastases, as opposed to a few growing lesions)	Comorbidity including • Active or recent intestinal disease (e.g., diverticulitis, inflammatory bowel disease, recent bowel resection) • Liver disease • Recent bleeding (e.g., ulcer/GI bleed) or coagulopathy • Recent cardiovascular event(s) (e.g., CVA, MI) • Recent tracheal radiation therapy (this is associated with increased risks of aerodigestive fistula with kinase inhibitor therapy) • Cachexia/low weight/poor nutrition • Poorly controlled hypertension • Prolonged QTc interval/history of significant arrhythmia (includes ventricular and bradyarrhythmias) • Untreated brain metastases (controversial) • Recent suicidal ideation (suicide has been reported in depressed patients receiving TKIs) Life expectancy based upon other comorbidities estimated to be too brief to justify systemic therapy

[a]Bone metastases are often poorly responsive to kinase inhibitor therapy (see Bone-Directed Agents in section [C47]).
GI, gastrointestinal; CVA, cerebrovascular accident; MI, myocardial infarction; TKI, tyrosine kinase inhibitor.

TABLE 17. POTENTIAL TOXICITIES AND RECOMMENDED SCREENING OR MONITORING APPROACHES IN PATIENTS STARTED ON KINASE INHIBITOR THERAPY

Toxicity	*Recommended screening/monitoring*
Hypertension	Frequent blood pressure monitoring, most critical during the first 8 weeks of therapy; if hypertension is induced, therapy should be individualized to patient response • Note: effective and expeditious management of hypertension is critical - and may reduce potential for cardiotoxicity. If antihypertensive therapy is needed, calcium channel blockers (e.g., amlodipine) may be most effective.
Cutaneous/mucocutaneous toxicities	Careful patient reporting of rash/mouth sores, patient awareness and education related to increased potential for photosentization/sunburn.
Hepatotoxicity	Serial assessment of alanine serum transferase (AST), alkaline phosphatase and bilirubin - most critical during the first 8 weeks of therapy • Note: dose reduction of kinase inhibitor therapy is commonly required due to hepatic toxicity
Cardiotoxicity	ECG pretherapy and frequently during therapy • Hold (or do not initiate) kinase inhibitor therapy if QTc >480 ms Echocardiogram: elective, but recommended in any patient with cardiac history and especially important in patient with hypertension, symptoms consistent with congestive heart failure or coronary artery disease and in patients receiving sunitinib
Hypothyroidism	TSH should be assessed frequently, with levothyroxine dosage altered in response to rising TSH if observed
Nephrotoxicity	Serial serum creatinine, urine analysis with protein determination,
Hematological toxicities	Serial CBC/diff
Pancreatitis	Serial amylase
Teratogenicity	Pretherapy pregnancy testing and effective contraception in women and men of childbearing potential

CBC, complete blood count; ECG, electrocardiography.

Thyroseq genetic mutation testing

BRAF-V600E	RAS
• PTC classic • PTC tall cell • LN metastasis • Angioinvasion • Distant metastasis	• PTC Follicular variant • NB: **20% of RAS positive tumors** have angioinvasion will therefore need total thyroidectomy

Improving FNA accuracy

Patient factors	• Sex • Age • Ethnicity • Family history • History of radiation
Tumor characteristics	• Size • USG characteristics
Immunocytochemical markers	• Galectin-3 • Hector Battifora mesothelial cell antibody

	(HBME-1)
Genetic markers	• Gene expression analysis • Somatic mutation, gene rearrangements • microRNAs

Noninvasive follicular thyroid neoplasms with papillary-like features (NIFTP)

- PTC FV totally encapsulated without capsular or vascular invasion
- Requires histopathology for diagnosis, a surgical disease
- Not benign but low recurrence rate, likely <1% within the first 15years.

[7]

Management of Differentiated Thyroid cancer

CLASSIFICATION — Thyroid follicular epithelial-derived cancers are divided into three categories:

- Papillary cancer – 85 percent
- Follicular cancer – 12 percent
- Anaplastic (undifferentiated) cancer – <3 percent

[7] One of the first duties of the physician is to educate the masses not to take medicines.

Differentiated and anaplastic thyroid carcinoma TNM staging AJCC UICC 2017

Primary tumor (T)	
Papillary, follicular, poorly differentiated, Hurthle cell and anaplastic thyroid carcinoma	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤2 cm in greatest dimension limited to the thyroid
T1a	Tumor ≤1 cm in greatest dimension limited to the thyroid
T1b	Tumor >1 cm but ≤2 cm in greatest dimension limited to the thyroid
T2	Tumor >2 cm but ≤4 cm in greatest dimension limited to the thyroid
T3	Tumor >4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a	Tumor >4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
T4	Includes gross extrathyroidal extension
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size
NOTE: All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest tumor determines the classification).	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No evidence of locoregional lymph node metastasis
N0a	One or more cytologically or histologically confirmed benign lymph nodes
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1	Metastasis to regional nodes
N1a	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease.
N1b	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups				
Differentiated				
When age at diagnosis is...	**And T is...**	**And N is...**	**And M is...**	**Then the stage group is...**
<55 years	Any T	Any N	M0	I
<55 years	Any T	Any N	M1	II
≥55 years	T1	N0/NX	M0	I
≥55 years	T1	N1	M0	II
≥55 years	T2	N0/NX	M0	I
≥55 years	T2	N1	M0	II
≥55 years	T3a/T3b	Any N	M0	II
≥55 years	T4a	Any N	M0	III
≥55 years	T4b	Any N	M0	IVA
≥55 years	Any T	Any N	M1	IVB
Anaplastic				
When T is...	**And N is...**	**And M is...**	**Then the stage group is...**	
T1-T3a	N0/NX	M0	IVA	
T1-T3a	N1	M0	IVB	
T3b	Any N	M0	IVB	
T4	Any N	M0	IVB	
Any T	Any N	M1	IVC	

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Surgical approach considerations

Tumor <1 cm without extrathyroidal extension and no lymph nodes	a thyroid lobectomy is preferred except - clinically evident thyroid cancer in the contralateral lobe - previous history of head and neck radiation - strong family history of thyroid cancer - imaging abnormalities that will make follow-up difficult)
Tumor 1 to 4 cm without extrathyroidal extension and no lymph nodes	total thyroidectomy or thyroid lobectomy
Tumor ≥4 cm, extrathyroidal extension, or metastases	Total thyroidectomy is recommended
Any tumor size and history of childhood head and neck radiation	Total thyroidectomy

Who receives post operative thyroid hormone replacement?

Lobectomy	• For low-risk patients whose initial surgery was a lobectomy, we do not begin thyroid hormone (T4) immediately postoperatively • measure serum TSH six weeks after surgery and determine the need for T4 based upon the TSH and evaluation of postoperative disease status.
Total thyroidectomy	T4 (usually 1.6 to 2 mcg/kg per day) can be started immediately postoperatively in the following patients: • ATA low and intermediate-risk patients who are unlikely to need radioiodine scanning or ablation • Selected ATA intermediate and high-risk patients in whom radioiodine scanning and ablation will be done using recombinant human TSH (rhTSH [thyrotropin alfa]).

The long-term TSH goals depend upon structural and biochemical response to initial therapy, which is determined by ongoing assessment and risk stratification.

- For patients in whom **radioiodine scanning and ablation will be done using thyroid hormone withdrawal** (typically ATA high-risk patients), short-term thyroid hormone replacement can be **initiated postoperatively with T3**, **25 mcg two to three times daily**. After two to three weeks, T3 is discontinued and imaging is performed once the patient's serum TSH concentration is above 25 to 30 mU/L.
- Another alternative is simply to withhold any thyroid hormone therapy until the patient's serum TSH concentration is above 30 mU/L.

Initial Risk Assessment

1. presence or absence of persistent disease
2. risk for recurrent disease should be assessed

serum thyroid-stimulating hormone (TSH) and a **non-stimulated serum thyroglobulin (Tg)** about **four to six weeks after thyroidectomy** or **lobectomy** in order to better define the postoperative disease status.

American Thyroid Association (ATA) guidelines that the optimal cutoff value for either a stimulated or non-stimulated postoperative Tg four to six weeks after surgery is not clearly established we expect non-stimulated Tg values of:

- <5 ng/mL after a total thyroidectomy
- <30 ng/mL after thyroid lobectomy

ATA risk stratification system to estimate risk of persistent/recurrent disease

Low risk	Intermediate risk	High risk
Papillary thyroid cancer with all of the following present:	**Any of the following present:**	**Any of the following present:**
▪ No local or distant metastases	Microscopic invasion into the perithyroidal soft tissues	Macroscopic tumor invasion
▪ All macroscopic tumor has been resected	Cervical lymph node metastases or ^{131}I avid metastatic foci in the neck on the post-treatment scan done after thyroid remnant ablation	Incomplete tumor resection with gross residual disease
▪ No invasion of locoregional tissues	Tumor with aggressive histology or vascular invasion (aggressive histologies include tall cell, insular, columnar cell carcinoma, Hürthle cell carcinoma, follicular thyroid cancer, hobnail variant)	Distant metastases
▪ Tumor does not have aggressive histology (aggressive histologies include tall cell, insular, columnar cell carcinoma, Hürthle cell carcinoma, follicular thyroid cancer, hobnail variant)	Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension*	Postoperative serum thyroglobulin suggestive of distant metastases
▪ No vascular invasion	Multifocal papillary thyroid microcarcinoma with extrathyroidal extension and *BRAF* V600E mutated (if known)*	Pathologic N1 with any metastatic lymph node ≥3 in largest dimension*
▪ No ^{131}I uptake outside the thyroid bed on the post-treatment scan, if done		Follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion)*
▪ Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in largest dimension)*		
Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer*		
Intrathyroidal, well-differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion*		
Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including *BRAF* V600E mutated (if known)*		

ATA: American Thyroid Association; ^{131}I: iodine-131.
* Proposed modifications, not present in the original 2009 initial risk stratification system.

SUBSEQUENT MANAGEMENT BASED ON RISK CLASSIFICATION

Thyroid hormone suppression — After initial thyroidectomy, whether or not radioiodine therapy is administered, thyroid hormone T4 therapy is required in most patients to prevent hypothyroidism and to minimize potential thyroid-stimulating hormone (TSH) stimulation of tumor growth

initial thyroid hormone suppression is based upon risk of disease recurrence

Low ATA risk	• **detectable serum thyroglobulin (Tg)** levels (with or without remnant ablation) serum TSH initially can be maintained between **0.1 and 0.5 mU/L** • patients who have **undetectable serum Tg levels** (with or without remnant ablation) or **who were treated with lobectomy**, TSH can be maintained in the mid to lower half of the reference range **(0.5 to 2.0 mU/L**
ATA intermediate risk	serum TSH initially can be maintained between **0.1 and 0.5 mU/L.**
ATA high risk	serum TSH initially **should be less than 0.1 mU/L.**

RADIOIODINE THERAPY

- Radioiodine is administered after thyroidectomy in patients with differentiated thyroid cancer to ablate residual normal thyroid tissue (remnant ablation)
- provide adjuvant therapy of subclinical micrometastatic disease
- provide treatment of clinically apparent residual or metastatic thyroid cancer

Low risk	In the absence of a proven benefit on either **disease-free survival or recurrence**, we do not routinely administer radioiodine for remnant ablation to patients with low-risk disease • unifocal tumors <1 cm without other high-risk features

	• multifocal cancer when all foci are <1 cm in the absence of other high-risk features • presence of small-volume regional lymph node metastases (less than five lymph nodes measuring less than 2 mm)
Intermediate risk	We suggest postoperative radioiodine ablation to selected intermediate-risk patients • microscopic invasion into the perithyroidal soft tissue • clinically significant lymph node metastases outside of the thyroid bed • vascular invasion • Aggressive histologic subtypes such as tall cell, columnar cell, insular, or poorly differentiated histologies.
High risk	_postoperative radioiodine ablation to patients with high-risk disease • patients with distant metastases • macroscopic tumor invasion • incomplete tumor resection with gross residual disease.

High dose radiodine

- Breast cancer risk, ovarian or reproductive
- Sialoadenitis (taste tends to return)
- High dose I-131 increases lung fibrosis (especially with lung metastasis, especially with miliary fibrosis)
- Avoid if there is large residual thyroid tissue. (risk of fibrosis due to large remnant tissue, especially if 20-30% residual tissue, skin necrosis, avoid by doing a pretreatment uptake)

Dosimetry is defined as maximally tolerated radioactive iodine exposure. Conventional protocol 30-100mCi.

NB: Tall cell variant PTC tends not to be radioiodine avid.

MONITORING RESPONSE TO TREATMENT

Dynamic risk stratification

At each follow-up visit, patients are classified as having one of the following clinical outcomes

- **Excellent response** – No clinical, biochemical, or structural evidence of disease.
- **Biochemical incomplete response** – Abnormal Tg or rising Tg antibody values in the absence of localizable disease.

- **Structural incomplete response** – Persistent or newly-identified locoregional or distant metastases.
- **Indeterminate response** – Nonspecific biochemical or structural findings that cannot be confidently classified as either benign or malignant. This includes patients with stable or declining antithyroglobulin (anti-Tg) antibody levels without definitive structural evidence of disease.

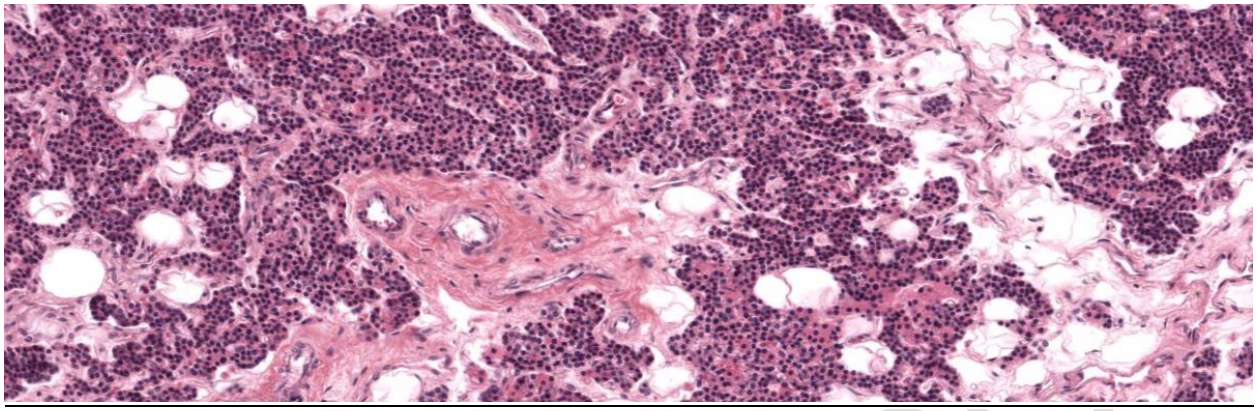
follow-up diagnostic whole-body scanning one year after radioiodine ablation is not required in low and intermediate-risk (with lower-risk features) patients

Table 2. Characteristics of Sporadic Medullary Thyroid Carcinoma, MEN2A, and MEN2B.*

Disease	Associated Phenotype	Mutations†	Clinical Characteristics
Sporadic MTC	None	*RET* (in approximately 50%), *HRAS*, *NRAS*, or *KRAS* (in 0 to 43%)[68]; rarely mutations in *KIT* or *MET*or fusions of *RET* or *ALK*[69,70]	*RET* M918T associated with more aggressive MTC than *RAS*[71]
MEN2A			
Classical	Pheochromocytoma (in 20 to 50%) and hyperparathyroidism (in 12 to 30%)	95% of *RET* mutations occur in exon 10 (codon 609, 611, 618, or 620) or exon 11 (codon 634)	Pheochromocytoma occurs in 30 to 50% of patients with *RET* mutations in exon 11[72] and in 15% of those with *RET* mutations in exon 10; hyperparathyroidism occurs in 30% of patients with *RET* mutations in exon 11 and in <12% of those with *RET* mutations in exons other than 11[73]
With Hirschsprung's disease	Hirschsprung's disease	*RET* mutation in exon 10 at codon 620 (in 50%) and less often at codon 618, 609, or 611[74]	MEN2A in 2 to 5% of patients with Hirschsprung's disease[75]
With cutaneous lichen amyloidosis	Cutaneous lichen amyloidosis	Usually *RET* mutation in codon 634[76]	In approximately 30% of patients with MEN2A; may precede onset of medullary thyroid carcinoma[76]
Familial MTC	None	Broad range of *RET* mutations	Appears to be less aggressive than the MTC associated with classical MEN2A
MEN2B	Typical facies, marfanoid habitus, medullated corneal nerves, and aerodigestive tract ganglioneuromatosis	*RET* M918T mutations in more than 95%, and *RET* A833F in the remainder	*RET* M918T associated with more aggressive MTC than *RET* A833F[77]

* MEN2A denotes multiple endocrine neoplasia type 2A, and MEN2B multiple endocrine neoplasia type 2B.
† Patients with sporadic MTC have somatic *RET* mutations, whereas patients with MEN2A or MEN2B have germline *RET* mutations.

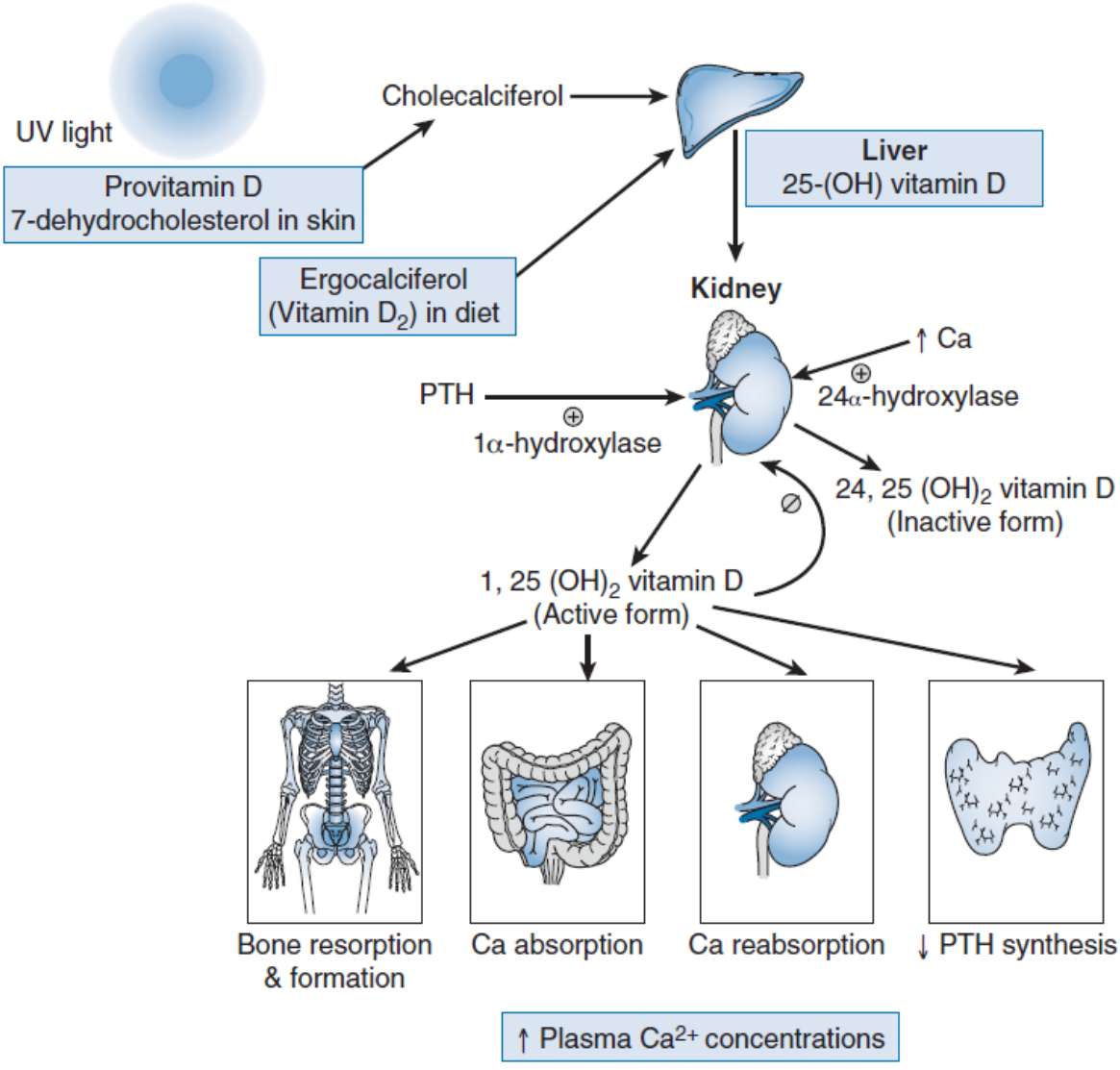
CALCIUM METABOLISM AND BONE RELATED PROBLEMS



Calcium and Bone Disorders	**15%** of Exam
Hypercalcemia	3%
Parathyroid hormone-mediated	
Primary hyperparathyroidism	
Familial hypocalciuric hypercalcemia	
Lithium-induced	

Non–parathyroid hormone–mediated	
Hypercalcemia of malignancy	
Milk-alkali syndrome	
Sarcoidosis, tuberculosis, and other granulomatous diseases	
Vitamin D intoxication	
Post-rhabdomyolysis	
Adynamic bone disease	
Myeloma	
Acute adrenal insufficiency	
Vitamin A	
Hypocalcemia	2.5%
Hypoparathyroidism	
Parathyroid hormone (PTH) resistance	
Hypomagnesemia	
Hyperphosphatemia	
Celiac disease	
Hypocalcemia (general)	
Osteoporosis	4%
In female	
In male	
Post-transplantation and glucocorticoid-induced	
Renal, hepatic, and gastrointestinal disease–related	
Paget's disease of bone	<2%
Hypovitaminosis D	<2%
Dietary deficiency	
Limited sun exposure	
Malabsorption	
Liver failure	
Renal insufficiency	
Vitamin D–dependent rickets types I and II	
Vitamin D–resistant rickets	
Drug-induced	
Bone disease	
Nonskeletal disorders	
Osteomalacia and rickets	<2%
Chronic hypophosphatemia	
Inhibitors of mineralization	
Renal osteodystrophy	<2%
Nephrolithiasis	<2%
Osteogenesis imperfecta and bone dysplasias	<2%
Fibrous dysplasia and other dysplastic syndromes	<2%

Calciphylaxis	<2%
Hypophosphatemia	<2%
Renal losses	
Gastrointestinal malabsorption	
Internal redistribution	



regulators of renal 1α-hydroxylase activity

- enzyme 1α-hydroxylase is expressed in proximal convoluted tubule and
  converts 25 (OH)D to active form 1,25(OH) 2 D (calcitriol).
- Renal 1α-hydroxylase activity is **stimulated** by PTH, hypophosphatemia, hypocalcemia, GH, estrogen, and prolactin
- inhibited by FGF23, 1,25(OH)2D, hypercalcemia, hyperphosphatemia, and drugs like glucocorticoids and ketoconazole.

Parathyroid Hormone

- PTH is produced by the chief cells of the parathyroid glands. Chief cells have CaSRs on their surface which sense extracellular concentrations of calcium
- PTH interacts with receptors on osteoblasts that result in cytokine release. The cytokines then activate osteoclast activity. This results in release of calcium and phosphate from bone
- At the DCT, PTH causes loss of Phosphate and increase Calcium reabsorption
- Stimulates activity of 1a-hydroxylase in the kidney resulting in conversion of inactive 25-OH vitamin D3 (calcidiol) to active 1,25-dihydroxyvitaminD3 (calcitriol).
- PTH increases intestinal absorption of Ca and Phos.

Vitamin D

- Soluble prohormone produced in the skin by the effect of sunlight. 7-dehydrocholesterol is converted to vitamin D3 (cholecalciferol)
- Increases calcium and phosphate absorption from the gut

Calcitonin

- Secreted by parafollicular c cells of the thyroid gland in response to an increase in extracellular calcium. It suppresses osteoclastic activity

Magnesium

- Necessary for PTH synthesis and secretion

Fibroblast growth factor FGF-23

- Expressed in bone and connective tissue and inhibits renal tubular phosphate transport by acting mainly in the proximal convoluted tubule.
- It acts in association with its co-receptor α-Klotho and inhibits the translocation of intracellular sodium phosphorus cotransporter (NaPi-2a and 2c) to the cell membrane in proximal convoluted tubule, resulting in phosphaturia.
- inhibits renal 1α-hydroxylase activity, thereby decreasing intestinal phosphate reabsorption and preventing conversion of calcidiol to calcitriol.

Osteoblasts/osteoclasts

- Osteoclasts are activated via the receptor activator of nuclear factor kappa-B ligand (RANKL).

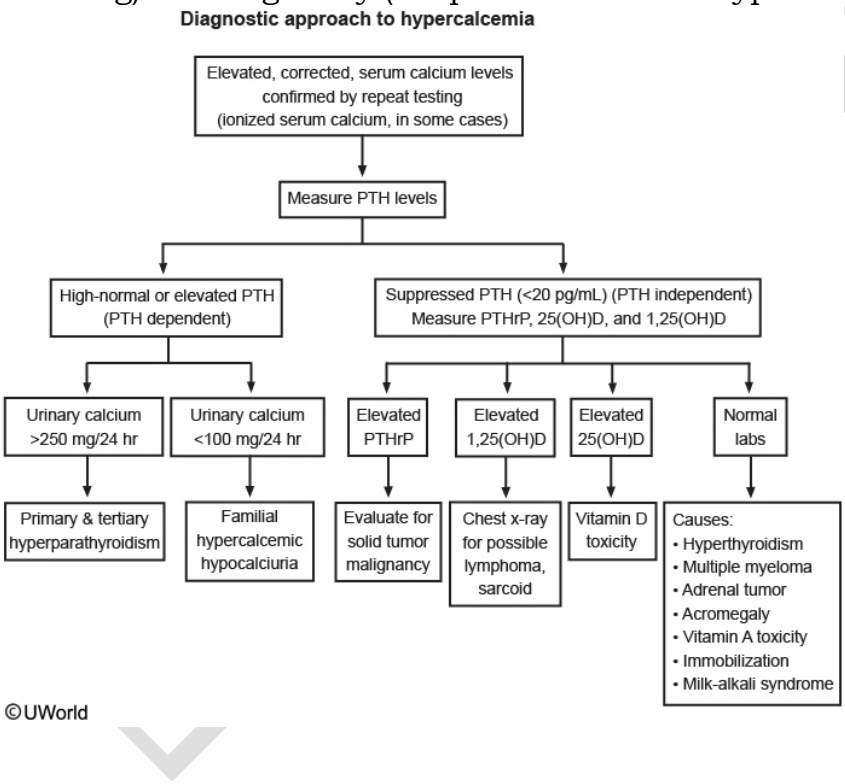
- Osteoclastic activity is triggered via the osteoblasts surface bound RANKL activating osteoclasts surface-bound receptor activator of nuclear factor kappa B (RANK).

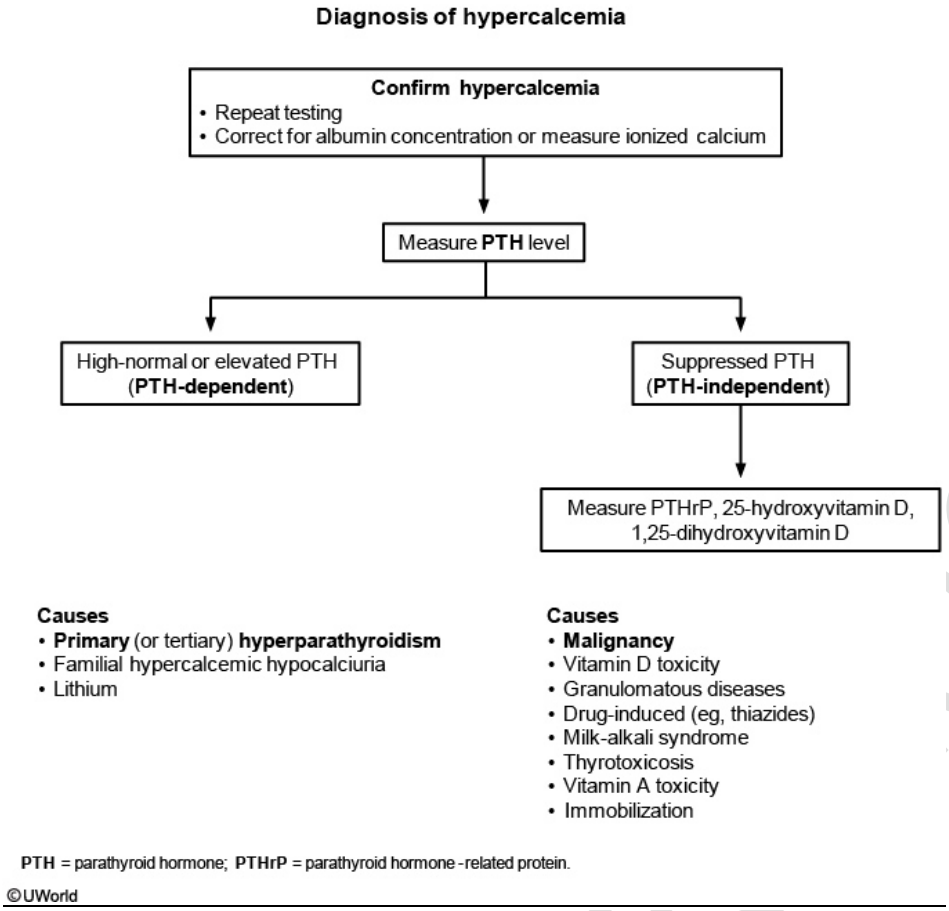
Hypercalcemia

Serum calcium level above the reference range is considered as hypercalcemia. The reference range for serum calcium is based on the data derived from healthy subjects and is dependent on age, vitamin D status, and analytical method.

Pseudo-hypercalcemia is characterized by increased total serum calcium with normal ionized calcium. This is seen in patients with severe dehydration and paraproteinemia (e.g., multiple myeloma) and is due to increased protein binding.

Over 90% of patients with hyperCa have either PHPT (in the clinic, incidental finding) or malignancy (hospitalization with hypercalcemic symptoms)





familial hypocalciuric hypercalcemia

- autosomal dominant disorder characterized by hypercalcemia, hypocalciuria, and normal or mildly elevated PTH.
- inactivating mutation of calcium-sensing receptor (CaSR) at both thick ascending limb of loop of Henle and parathyroid gland.***
- Hypercalcemia is usually mild and is present since birth. Therefore, any child with hypercalcemia should be evaluated for FHH
- Chondrocalcinosis, premature vascular calcification, pancreatitis, andgallstone disease may rarely be seen in patients with FHH
- Rarely, biochemical profile mimicking FHH is seen in adults harboring autoimmune disorders and is due to the presence of anti-CaSR antibodies
- Majority of patients do not require any treatment and inadvertent parathyroid surgery has not yielded any benefi t

Parameters	HHM	Osteolytic metastasis
Prevalence	80%	20%
Mechanism	Circulating PTHrP	Cytokines, chemokines, and local PTHrP
Serum calcium	Elevated	Elevated
Serum phosphate	Low	Normal
Serum PTH	Low	Low
Malignancy	Squamous cell cancer	Lymphoma, multiple myeloma

*** In normal physiology, activation of CaSR result in excretion of calcium at renal tubular level
and inhibits secretion of PTH from parathyroid gland.

Granulomatous disorders causing hypercalcemia	
Noninfectious	**Infectious**
• Sarcoidosis • Berylliosis • Crohn's disease • Eosinophilic granuloma • Granulomatosis with polyangiitis • Lymphomas	• Tuberculosis • Leprosy • Coccidioidomycosis • Histoplasmosis • *Pneumocystis carinii* pneumonia

granulomatous diseases associated with hypercalcemia

- increased 1α-hydroxylase activity, decreased degradation of 1,25-OHD 3 , and
  secretion of PTHrP and bone-resorbing cytokines like IL-6 from granulomatous
  Lesions.
- Increased 1α-hydroxylase activity and decreased degradation of 1,25-OHD 3 in the macrophage are mediated by interferon-Ɣ secreted from
  Granulomas.
- Treatment includes glucocorticoids (prednisolone 0.5–1 mg/kg/day) and specifi c therapy for the underlying disease.
- Glucocorticoids inhibit **1α-hydroxylase activity** and **decrease the secretion of cytokines** from the granulomatous lesions

Malignancy-associated hypercalcemia		
Cause	**Tumor**	**Mechanism**
PTHrP production (**80%** of malignancy-induced hypercalcemia)	• Squamous cell cancers (eg, lung, head, neck, esophagus) • Renal & bladder cancer • Ovarian & endometrial cancer • Breast cancer	Activation of PTH receptor, excessive bone resorption
1,25(OH)2 vitamin D production	• Lymphomas (all types)	Excessive gut absorption of calcium
Bone metastasis	• Breast cancer • Multiple myeloma • Lymphomas	Release of local factors (eg, cytokines) to stimulate bone resorption
Ectopic PTH production (very rare)	• Variable	Bone resorption

PTH = parathyroid hormone; **PTHrP** = parathyroid hormone-related protein.

Parameters	**PTH**	**PTHrP**
Structure	84 amino acids	139–173 amino acids
Expression	Post-natal life	Fetal life
Receptor	PTH/PTHrP	PTH/PTHrP
Effect on 1α-hydroxylase	Stimulates	No action
Effect on urinary calcium reabsorption	Increase	Increase
Actions	Endocrine	Autocrine, paracrine, and endocrine
Physiological role	Bone remodeling	Fetal chondro-osteogenesis Placental calcium transport

Parameters	**PTH-mediated hypercalcemia**	**PTHrP-mediated hypercalcemia**
Disorder	Hyperparathyroidism	HHM
Presentation	Insidious	Rapid
Serum calcium	Mild to moderate hypercalcemia	Severe hypercalcemia
Serum phosphate	Low	Low
Alkaline phosphatase	Elevated	Normal
Bone turnover		
Formation	Stimulates	No effect
Resorption	Stimulates	Stimulates

No formula is available for correcting high albumin, globulin or myeloma proteins in the setting of a measured calcium level.

Evaluate neurological status and EKG for acute hypercalcemia patients.

Parathyroid carcinoma is not curable by surgery or radiation therapy.(in these cases a mean serum calcium of 12mEq is reasonable in a refractory state)

Treatment options for hyperCa

Calcitonin
- Approved by FDA. increases calcium urinary excretion.
- Not effective beyond 48hrs due to tachyphylaxis.
- Skin sensitivity

- Rapid within 4-6hrs reduction in serum levels by decreasing bone resorption
- Good choice for cancer with severe hypercalcemia, Calcium >14mg/dl
- Not helpful in granulomatous diseases (elevated calcitriol levels and increased calcium absorption)

Cinacalcet (sensipar)
- A calcium mimetic drug that acts on calcium sensing receptors on parathyroid cells to decrease secretion of parathyroid hormone
- **Only effective in primary or tertiary hyperparathyroidism**
- **Parathyroid carcinoma. 30mg daily up to 90mg qid.**
- **Risk of tachyphylaxis due to tolerance**
- **LFT impairment**
- **Risk of hypocalcemia.**

Aggressive fluid hydration
- Followed by calcitonin and bisphosphonates. Furosemide should be avoided post hydration due to risk of electrolyte imbalance
- Only effective for mild hypercalcemia.
- Limited use in cardiac and renal disease.
- Should be discontinued if patient develops edema

Bisphosphonates
- Decrease calcium levels in the setting of excessive bone resorption
- Avoid in renal failure
- Risk of osteonecrosis of the jaw
- Reduced dose based on level of hypercalcemia.

Glucocorticoids
- Decrease calcitriol production

Dialysis
- Applicable to patients with renal failure or severe heart failure.

Denosumab
MAB binds to RANK-ligand on osteoblasts. Thus preventing activation of osteoclast surface bound RANK.
120mg SQ q4weekly

Management of hypercalcemia	
Severe (calcium >14 mg/dL) or symptomatic	**Short-term (immediate) treatment** • Normal saline hydration plus calcitonin • Avoid loop diuretics unless volume overload (heart failure) exists **Long-term treatment** • Bisphosphonate (zoledronic acid)
Moderate (calcium 12–14 mg/dL)	• Usually no immediate treatment required unless symptomatic • Treatment is similar to that for severe hypercalcemia
Asymptomatic or mild (calcium <12 mg/dL)	• No immediate treatment required • Avoid thiazide diuretics, lithium, volume depletion & prolonged bed rest

Causes of hypophosphatemia
Internal redistribution • Increased insulin secretion (especially refeeding malnourished patients) • Acute respiratory alkalosis (stimulates glycolysis) • Hungry bone syndrome (after parathyroidectomy) **Decreased intestinal absorption** • Chronic poor intake • Aluminum or magnesium-containing antacids (bind phosphate) • Steatorrhea or chronic diarrhea **Increased urinary excretion** • Primary and secondary hyperparathyroidism • Vitamin D deficiency (↓GI absorption, ↑urinary excretion) • Primary renal phosphate wasting syndromes • Fanconi syndrome

Primary hyperparathyroidism (PHPT)

Indications for parathyroidectomy in PHPT

- T score < - 2.5SD at lumbar spine, hip and distal radius
- Age < 50years
- Serum calcium >1mg/dl above normal limits
- Creatinine clearance <60mL/min

Primary hyperparathyroidism (PHPT) is a metabolic bone disease characterized

by hypercalcemia, hypophosphatemia, and inappropriately elevated PTH due to autonomous production of parathormone by a parathyroid adenoma, hyperplasia or rarely, carcinoma.

Classical clinical pentad	" stones (renal stone disease), bones (osteitis fibrosa cystica, fracture), abdominal groans (gallstone disease, pancreatitis, acid peptic disease), psychiatric moans (mood disorders), and fatigue overtones (myalgia, myopathy)."
Unusual presentation	• Rickets • distal renal tubular disorders • facial asymmetry • proptosis, anemia, and recurrent pancreatitis

The **skeletal tissue** is composed of **cortical** and **cancellous bone** in varying Proportions.

The adult human skeleton is composed of 80% cortical bone and 20% cancellous bone.

- The vertebra is composed of cortical and cancellous bone in a ratio of 25:75.
- This ratio is 50:50 in the femoral head
- Distal radius is 95:5

mild PHPT	anabolic effect on cancellous bone and resorptive effect on cortical bone
severe PHPT	deleterious effects both on cortical and cancellous bone

Table 1. Hereditary States of Hyperparathyroidism.

Disorder	Responsible Gene	Pathogenic Mechanism	Associated Clinical Features
MEN type 1*	*MEN1, CDKN1B*	Loss-of-function mutation	Pituitary and gastroenteropancreatic tumors; less frequently, adrenal tumor, facial angiofibroma, collagenoma, and lipoma
MEN type 2A	*RET*	Gain-of-function mutation	Medullary thyroid cancer, pheochromocytoma, cutaneous lichen amyloidosis
Hyperparathyroidism–jaw tumor syndrome	*CDC73* (formerly known as *HRPT2*)	Loss-of-function mutation	Fibromas in the mandible or maxilla, renal and uterine tumors, increased rate of parathyroid carcinomas (15–20%)
Familial hypocalciuric hypercalcemia	*CASR*	Loss-of-function mutation	Rare pancreatitis, relative hypocalciuria (24-hr urinary calcium:creatinine ratio, <0.01)
Neonatal severe primary hyperparathyroidism	*CASR*	Loss-of-function mutation	Life-threatening condition with marked hypercalcemia, hypotonia, and respiratory distress
Familial isolated hyperparathyroidism	*MEN1, CDC73, CASR, CDKN1B*	Loss-of-function mutation	Lack of the specific features of the other syndromic forms

* Multiple endocrine neoplasia (MEN) type 1, a syndrome associated with a *CDKNB1* gene mutation, is also referred to as MEN type 4.[11]

skeletal manifestations of PHPT

Osteitis fibrosa cystica (OFC) is the protean skeletal manifestation of hyperparathyroidism of any etiology
characterized by increased osteoclast activity resulting in bone resorption (cystica) followed by fibrosis
Radiological features of OFC

- subperiosteal phalangeal bone resorptionAcrosteal resorption of terminal phalanx
- **brown tumors** (trabecular portion of long bones,pelvis, rib, jaw, and rarely in vertebrae)
- **"salt and pepper"** appearance of skull
- bone cysts
- osteopenia and increased risk of fractures.

****** brown tumors**

- Brown tumor is a severe form of OFC. It commonly occurs in the trabecular portion of long bones, pelvis, ribs, and mandible.
- lytic lesion on X-ray
- it is not a tumor but represents hemorrhage into a cystic lesion, and the brown color is a result of hemosiderin deposition.
- Brown tumor associated with PHPT usually heals after curative parathyroidectomy, but rarely may require surgery if it persists >6 months after curative surgery.

Clinical Pearl

Epulis is a swelling situated on gingiva or alveolar mucosa. In the context of PHPT, epulis is a bony swelling arising from maxilla or mandible

Normocalcemic/eucalcemic primary hyperparathyroidism

Features	**Normocalcemic primary hyperparathyroidism** is a biochemical entity characterized by normal total and ionized serum calcium and consistently elevated PTH levels, after **exclusion of secondary causes of hyperparathyroidism.**
	a *forme fruste* of PHPT.
Mechanism	• target tissue resistance to PTH • rise in PTH which precedes the development of hypercalcemia during evolution of PHPT
Secondary causes	*These may mask hypercalcemia* 1. **vitamin D deficiency** 2. reduced eGFR 3. Hypoalbuminemia 4. use of **loop diuretics** 5. **idiopathic hypercalciuria** 6. gastrointestinal disorders associated with calcium **malabsorption** (celiac disease, chronic pancreatitis, and bariatric surgery), 7. **prior bisphosphonate therapy**.

[8]

Parameters	MEN1-related PHPT	Sporadic PHPT
Age of onset	20–25 years	>50 years
Male/female	1:1	1:3
Phenotypic markers	Facial angiofibromas (85%) Collagenomas (70%) Lipomas (30%)	Absent
Hypercalcemia	Mild	Mild to severe
Imaging	Usually normal	Single adenoma (85%)
Pathology	Hyperplasia	Adenoma
Carcinoma	Almost never	<1%
Surgery	$3^{1/2}$ gland excision	Adenoma excision
Outcome	High risk for hypoparathyroidism and recurrent/persistent disease	Usually curative, low risk for hypoparathyroidism

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PHPT with concurrent vitamin D deficiency	**Secondary hyperparathyroidism due**

[8] I do not know what is going on in her foot, but she has parathyroid disease in the neck

	to vitamin D deficiency
• **high normal to elevated serum calcium** • low phosphate • inappropriately elevated PTH (>20 pg/ml)	• **low to low-normal calcium** • Hypophosphatemia • markedly elevated PTH and alkaline phosphatase
• fragility fracture • **recurrent renal stone disease** • gallstone disease, and pancreatitis	• rickets/osteomalacia • pseudofractures

Features suggestive of parathyroid carcinoma
• Presence of a palpable neck mass • Recurrent laryngeal nerve involvement • Cervical lymphadenopathy • Serum calcium >14 mg/dl • Serum PTH >1,000 pg/ml

Hyperparathyroidism–jaw tumor syndrome (HPT–JT) is an autosomal dominant disorder characterized by fi bro-osseous tumors of mandible and/or maxilla with primary hyperparathyroidism.

Modality	Advantages	Disadvantages
Ultrasonography	Structural scan Highly sensitive (72–85%) in experienced hands for solitary adenoma Inexpensive and noninvasive Reproducible No radiation exposure	Operator dependent Decreased accuracy in smaller adenoma (<1 cm), ectopic gland, and obese individuals Falsely positive in the presence of coexisting thyroid nodule and lymph nodes
^{99m}Tc-sestamibi	Functional scan Sensitivity to localize single adenoma-68–95% If combined with SPECT-CT sensitivity for single adenoma –88–93%	Not easily available Expensive False positivity with thyroid nodule, Hurthle cell adenoma, lymph nodes

Clinical Pearl

- **theoretical risk** of hypercalcemia and hypercalciuria with vitamin D repletion in patients of PHPT with concurrent vitamin D deficiency
- **vitamin D supplementation** may be associated with significant reduction in serum PTH and probably **reduce the risk of postoperative hungry bone syndrome**.
- In patients with severe hypercalcemia (>12 mg/dl), vitamin D supplementation should be avoided.

- useful in patients of PHPT with severe hypercalcemia
- severe bone disease (as they are at higher risk of hungry bone syndrome postoperatively)
- those who opt for medical treatment.

Parathyroidectomy (operative considerations)

Table 2. Guidelines for the Treatment of Asymptomatic Primary Hyperparathyroidism.

Variable	Criteria for Surgery*	Surveillance without Surgery
Serum calcium level	>1.0 mg/dl (0.25 mmol/liter) above upper limit of normal range	Annually
Creatinine clearance (calculated)†	Reduced to <60 ml/min	Annually
Bone mineral density	T score less than −2.5 at any site,‡ previous fragility fracture, or both	Every 1–2 yr (three sites)
Age	<50 yr	Not applicable

* Surgery should also be recommended for patients in whom surveillance is not feasible.
† The estimated glomerular filtration rate (milliliters per minute per 1.73 m^2 of body-surface area) should be calculated from the serum creatinine concentration, demographic characteristics (age, sex, and race or ethnic group), and other serum measurements (e.g., blood urea nitrogen and albumin concentrations) according to the following equation: $170 \times (\text{serum creatinine in mg per deciliter})^{-0.999} \times (\text{blood urea nitrogen in mg per deciliter})^{-0.170} \times (\text{serum albumin in g per deciliter})^{0.318} \times (\text{age in years})^{-0.176} \times (0.762 \text{ if patient is female}) \times (1.180 \text{ if patient is black})$. Equation is from Eastell et al.[35]
‡ Sites were the lumbar spine, total hip, femoral neck, and distal third of the radius. According to the International Society for Clinical Densitometry, z scores instead of T scores should be used in evaluating bone mineral density in premenopausal women and men younger than 50 years of age.

Turbo PTH assay is a method which allows **rapid estimation of serum PTH** and is used intraoperatively to confirm successful excision of abnormal parathyroid gland(s).

Miami criterion: is used for **defining the success of parathyroidectomy.**

- It includes >50% reduction in serum PTH levels 10 min after excision of suspected abnormal gland as compared to the highest pre-incision or pre- excision serum PTH level.

- The accuracy of intraoperative PTH (IOPTH) in predicting cure in solitary adenoma is 97%, while 58% in those with multiglandular disease.

Etiology of hypocalcemia post surgery
• hungry bone syndrome, • transient hypoparathyroidism • Hypomagnesemia • Permanent hypoparathyroidism. • prior bisphosphonate therapy • severe vitamin D deficiency

Hungry Bone Syndrome

Presentation	• "increased appetite of bone"for calcium and phosphorus • sudden decrease in osteoclastic activity with continued osteoblast activity driving the influx of calcium and phosphorus into bone.
Biochemical panel* **	• Hypocalcemia • Hypophosphatemia • Hypomagnesemia • raised alkaline phosphatase

	• hypocalciuria
Causes	• **Parathyroidectomy** for hyperparathyroidism (primary/secondary/tertiary) • **rickets/osteomalacia** who are replaced with vitamin D alone without calcium • **untreated severe hyperthyroidism** following thyroid surgery • **correction of metabolic acidosis** in patients with renal tubular acidosis • **after administration of antiresorptive therapy** in patients with osteoblast metastasis (e.g., carcinoma prostate). • **Cushing's syndrome** may also develop HBS after curative surgery
Predictors of HBS	• age (>60 years) • postmenopausal status • vitamin D deficiency • severe bone disease (osteitis fibrosa cystica, high ALP) • high preoperative serum calcium and PTH • large parathyroid adenoma (>5 cm).
Prevention	• Prior use of bisphosphonate reduces ther isk of HBS by causing osteoclast apoptosis, thereby preventing the crosstalk between osteoblast and osteoclasts. • preoperative vitamin D replacement in vitamin D-defi cient individuals with mild hypercalcemia

***prerequisite for development of HBS is measurable levels of PTH which is required for bone remodeling, as HBS does not occur in patients who develop hypoparathyroidism.

Medical Management of PHPT

- adequate hydration
- avoid the use of thiazide diuretic and prolonged immobilization.
- **Dietary calcium** should **not be restricted.**

Modality of treatment	Mechanism of action	Effect on calcium	Effect on BMD
Estrogen, selective estrogen receptor modulator (raloxifene)	Promotes osteoclast apoptosis Antagonizes the action of PTH at receptor level Inhibits cytokine (IL-1, IL-6, and TNF-α)-mediated osteoclast resorption	Modest decline (0.5–1 mg/dl)	Improvement in spine and hip BMD
Bisphosphonates	Potent inhibitors of osteoclastogenesis and prevents bone resorption	Transient reduction in serum calcium	Improvement in spine and hip BMD
Cinacalcet	Calcimimetic	Normalizes serum calcium	No effect
Non-calcemic vitamin D analogues (24 oxo-calcitriol)	Directly suppresses PTH	Modest	No effect

Evaluation of calcium and bone disorders in the setting of renal disease

Hypocalcemia is common in patients with renal failure	• due to decreased renal 1α-hydroxylase activity • vitamin D deficiency • Hyperphosphatemia • PTH resistance • poor oral intake.
Hypercalcemia in patients with renal failure	• Overzealous treatment with calcium and calcitriol • Tertiary hyperparathyroidism • adynamic bone disease • milk–alkali syndrome.

Secondary Hyperparathyroidism

Primary mechanism	• **Progressive loss of renal mass** resulting in decreased glomerular filtration rate. • This leads to hyperphosphatemia and **reduced renal 1α-hydroxylase activity** and consequently hypocalcemia • All these metabolic abnormalities act as **strong stimuli for PTH secretion and parathyroid gland proliferation**, resulting in secondary hyperparathyroidism
Other proposed mechanisms	• skeletal PTH resistance (due to PTH receptor downregulation) • bioinactive PTH fragments (acting as PTH antagonists) • uremic toxins • Intrinsic abnormalities within parathyroid gland, particularly alterations in set point or expression of CaSR also contribute to secondary hyperparathyroidism

Tertiary hyperparathyroidism

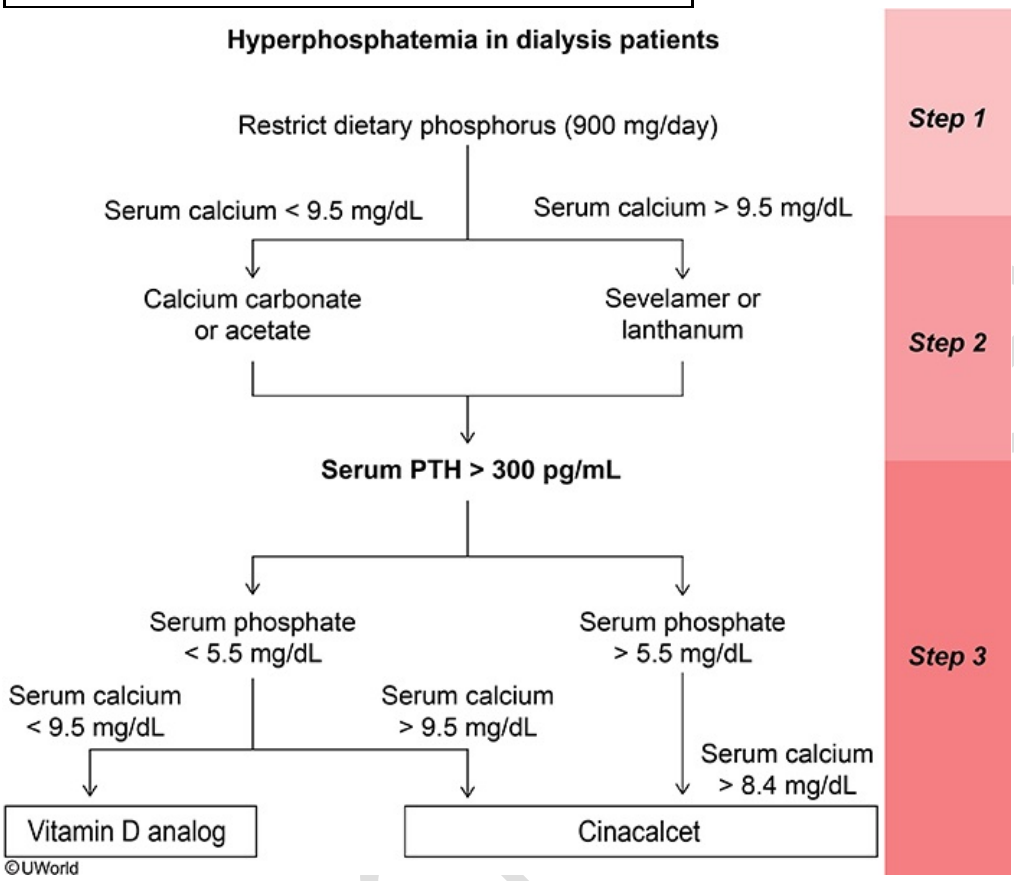
Tertiary hyperparathyroidism is characterized by **autonomous hypersecretion** of PTH leading to hypercalcemia and is invariably a sequel of long- standing undiagnosed/untreated secondary hyperparathyroidism.

1. Parathyroid hyperplasia involving all four glands is a consistent feature in these patients
2. 20% of these patients may additionally have a single or double adenoma.

Chronic hypocalcemia, hyperphosphatemia, low 1,25(OH)2D, and alteration in the set point of calcium-sensing receptor. These stimuli lead to secondary hyperparathyroidism

causes of tertiary hyperparathyroidism
• Chronic kidney disease (CKD) • Vitamin D deficiency • Phosphate supplementation without calcitriol

- Hypophosphatemic osteomalacia
- Pseudohypoparathyroidism type 1b (this is a zebra!).



Treatment of secondary / tertiary hyperparathyroidism associated with CKD

- Serum calcium and phosphorus should be maintained in the reference range
- calcium phosphorus product should be maintained <55.
- If these measures fail to achieve the defined targets of PTH
- calcimimetics (cinacalcet) or parathyroidectomy should be considered.

indications of parathyroidectomy in CKD

- Persistently high **iPTH >800 pg/ml**
- **Sustained hypercalcemia (>11 mg/dl)** and

hyperphosphatemia despite optimal medical management.
- **Calciphylaxis** with iPTH >500 pg/ml
- Presence of fragility fracture
- Refractory pruritus

*** Excision of three to three and a half parathyroid glands is preferred as opposed to total parathyroidectomy, to avoid the risk of recalcitrant hypocalcemia.

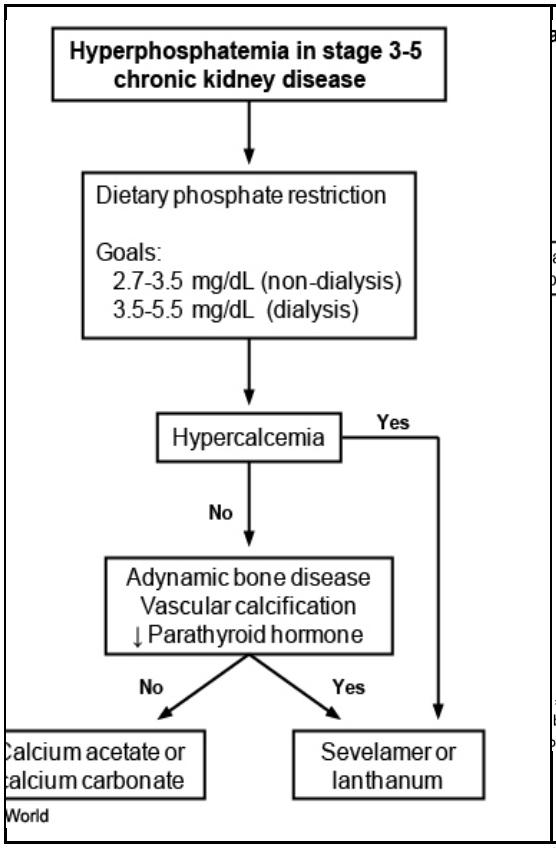
CKD–MBD denotes chronic kidney disease–mineral and bone disorder. It refers to abnormalities of mineral metabolism, metabolic bone disease, and/or metastatic calcification in a patient with chronic kidney disease.

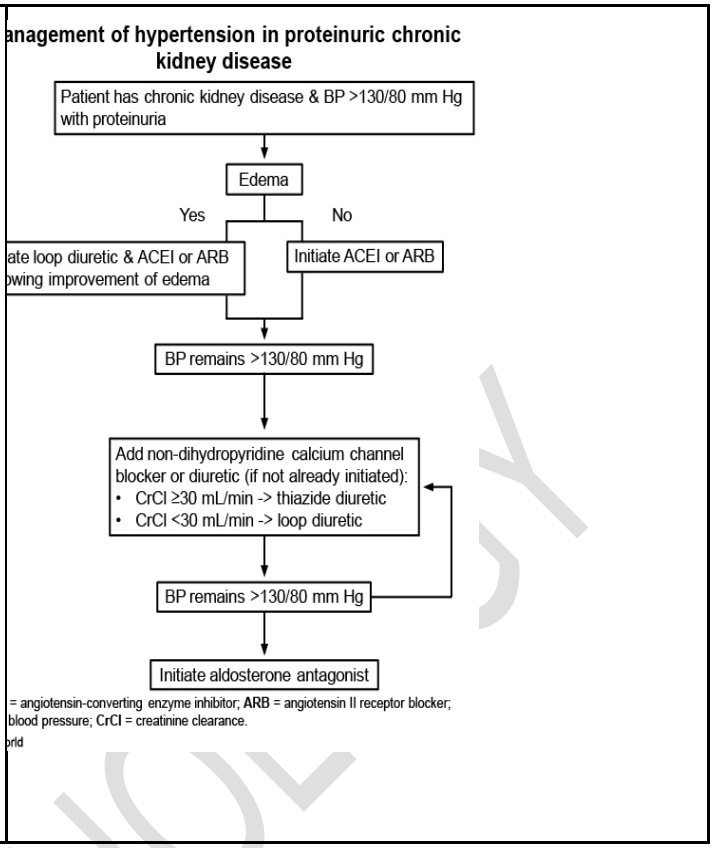
Renal osteodystrophy (ROD) refers to the metabolic bone disease associated with CKD. It is a constellation of osteitis fi brosa cystica, osteomalacia, and adynamic bone disease, with varying combinations as a consequence of CKD

mechanisms	• Decreased renal 1α-hydroxylase activity • PTH resistance • increased FGF23 • concurrent vitamin D deficiency • altered calcium phosphate solubility product • poor oral calcium intake
Differential bone turnover	may be associated with a high, normal, or low bone turnover.
Clinical manifestations	1. **high turnover state** is due to elevated PTH and manifests as **osteitis fibrosa cystica** 2. **adynamic bone disease** is a **low bone turnover state** due to inappropriately suppressed PTH. 3. **osteomalacia** is associated with **normal bone turnover.**

adynamic bone disease

What is it?	Adynamic bone disease is characterized by suppressed bone remodeling due to low PTH (<50 pg/ml)
etiology	overzealous treatment with calcitriol and calcium-containing phosphate binders and is commonly seen in patients on dialysis.
Biochemical presentation	• **Hypercalcemia** with **low iPTH.** Hypercalcemia is a result of reduced influx of calcium from circulation into bone due to decreased bone remodeling, consequent to low PTH.
Clinical presentation	• bone pain • fragility • Fracture • metastatic calcification.
Treatment	• **discontinuation of calcitriol and calcium- contacting phosphate binders** with restriction of oral calcium to 2 g/day • **recombinant PTH** may be useful in refractory cases. • **Bisphosphonates are contraindicated** as bone remodeling is already suppressed.





PSEUDOHYPOPARATHYROIDISM

- Genetic disorder of target-organ unresponsiveness to PTH.
- Biochemically, it mimics hormone-deficient forms of hypoparathyroidism, with hypocalcemia and hyperphosphatemia, but the PTH level is elevated.
- There is a markedly blunted response to the administration of PTH

Pathophysiology	**PHP type 1A** • Loss of function of one allele (haploinsufficiency) of the gene encoding the stimulatory G protein alpha subunit, (Gs alpha or GNAS). • *Produce only 50% of the normal levels of the alpha subunit of the heterotrimeric Gs , which couples the PTH receptor to adenylyl cyclase* • Resistance to TSH, LH, and FSH occurs fairly commonly **PHP type IB** • Resistance to PTH but no somatic phenotype (ie, AHO), and levels of G s alpha protein in red blood cell or fibroblast membranes are normal.

	• It does not involve mutations in the coding region of GNAS. • epigenetic defects in GNAS are present that cause the differentially methylated region at exon A/B to lose its imprinting
Genetics	**PHP type IA** • autosomal dominant trait. GNAS1 allele is maternally derived, the resulting offspring will have PHP; if the mutant GNAS1 allele is paternally derived (and therefore silenced), the resulting offspring will have PPHP

Pseudohypoparathyroidism type 1B	Pseudohypoparathyroidism type 1A
• **Isolated resistance to PTH** • **Hypocalcemia, hyperphosphatemia, and secondary hyperparathyroidism**	• **Albright hereditary osteodystrophy (AHO)** • All features of type 1B + characteristic somatic phenotype

Characteristic somatic phenotype
• short stature, round face, short neck, obesity, brachydactyly(short digits) • shortened metatarsals, subcutaneous ossifications,and often reduced intelligence • metacarpals—affected digits have a dimple, instead of a knuckle, when a fist is made. • Primary hypothyroidism is frequently seen. Less commonly, these patients have abnormalities of reproductive function oligomenorrhea in females and infertility in males due to primary hypogonadism

Pseudopseudohypoparathyroidism
Inherit the somatic phenotype of AHO without any disorder of calcium metabolism; this state, which mimics PHP

Chronic Hypocalcemia

The pivotal mechanisms involved in chronic hypocalcemia include impaired **intestinal absorption of calcium**, **suppressed bone resorption,** and increased **renal loss of calcium** and are the consequence of **impaired secretion/action of PTH and/or calcitriol**.

Etiology and their manifestations in chronic hypocalcemia

chronic kidney disease	High serum phosphate in the presence of chronic hypocalcemia
hypoparathyroidism	Low serum PTH in the presence of high phosphate and low calcium
pseudohypoparathyroidism	High serum PTH with high phosphate, low calcium, and normal serum creatinine
vitamin D deficiency/resistance.	Low serum phosphate in the presence of normocalcemia/hypocalcemia.

Hypoparathyroidism

The most common cause of hypoparathyroidism is inadvertent injury to parathyroid glands during thyroid surgery.

Congenital	Acquired
Polyglandular endocrinopathy type 1 (AIRE gene mutation)	Post-surgical
Polyglandular endocrinopathy type 2	Neck irradiation
Infiltrative diseases Hemochromatosis Wilson's disease	Anti-CaSR antibodies
Parathyroid transcription factor defects DiGeorge syndrome (TBX1 gene mutation) Hypoparathyroidism, deafness, and renal dysplasia syndrome (GATA3 gene mutation)	
PTH gene mutations	
Activating CaSR gene mutations	

Enamel hypoplasia, cataract, and basal ganglia calcification in a patient with hypoparathyroidism suggest the presence of long-standing untreated disease with onset during childhood.

Table 1. Diagnosis and Evaluation of Hypoparathyroidism

Hypocalcemia (albumin-adjusted) confirmed on at least two occasions separated by at least 2 weeks.
PTH concentration, by second- or third-generation immunoassay, that is undetectable or inappropriately low (ie, <20 pg/mL) in the presence of hypocalcemia on at least two occasions.
Phosphate levels in the upper normal or frankly elevated range (helpful but not mandatory).
After neck surgery, chronic hypoparathyroidism is established only after 6 months.

Table 2. Evaluation of Hypoparathyroidism

Family history: History of hypoparathyroidism or other endocrine deficiency disease
Personal history: Previous anterior neck surgery, other endocrine disease
Physical examination
Ectopic calcifications (eg, eyes)
Signs of previous neck surgery
Chvostek's or Trousseau's sign
Nail beds for fungal infection
Mucosal candidiasis
Range of joint motion
Skin for vitiligo
Biochemical evaluation (after the diagnosis has been made)
Phosphate
Magnesium
25-hydroxyvitamin D
1,25-dihydroxyvitamin D
BUN/creatinine
24-hour urine for creatinine clearance or eGFR, calcium excretion, and biochemical stone risk profile
Target organ imaging
X-ray (skull)
Renal ultrasound or computed tomography scanning
BMD by dual-energy x-ray absorptiometry
Genetic studies: If a genetic basis is suspected (young age, family history, multiple endocrine gland failure)

Abbreviation: BUN, blood urea nitrogen.

Clinical manifestations of hypoparathyroidism

hypocalcemia	neuromuscular irritability, tetany, refractory seizures, pseudotumor cerebri, and rarely heart failure
Hyperphosphatemia	metastatic calcification and may present as cataract

	and basal ganglia calcification
Low PTH	decreased bone remodeling and manifests as increased BMD with low bone turnover markers
Other clinical clues	• mucocutaneous candidiasis and concurrent autoimmune endocrine disorders particularly adrenal insufficiency during childhood • childhood- onset adrenal insufficiency, treatment with hydrocortisone may unmask underlying hypoparathyroidism.

Table 3 Symptoms patients should be informed to allow for early detection of hypo- or hypercalcaemia.

Organ System	Hypocalcaemia	Hypercalcaemia
CNS	Depression Irritability Confusion or disorientation Seizures	Weakness Headache Drowsiness Confusion or disorientation Poor memory Reduced concentration
Neuromuscular	Numbness and tingling (paraesthesia) in circumoral and acral areas (fingers and toes) Spasms/twitches Cramps	Muscle weakness
Cardiovascular	Fast, slow or uneven heart rate Symptoms of congestive heart failure	Fast, slow or uneven heart rate Hypertension
Gastrointestinal	Abdominal cramps	Loss of appetite Nausea/vomiting Abdominal pain Constipation
Renal		Polyuria Dry mouth and or increased thirst
Respiratory	Shortness of breath Wheezing Throat tightness	

soft tissue calcification of hypoparathyroidism and hyperparathyroidism

The fundamental basis of soft tissue calcification in patients with a disorder of mineral homeostasis is elevated calcium phosphate solubility product (>55 mg 2 /dl2).

Disorder	Sites of calcification
Primary hyperparathyroidism	Renal pelvicalyceal system, small vessels, pancreas, periarticular tissues, pericardium, endometrium
Secondary hyperparathyroidism (CKD-related)	Medium–small vessels, skin, soft tissue like heart and lung
Hypoparathyroidism	Basal ganglia, cerebellum, cerebrum, lens
Pseudohypoparathyroidism	Basal ganglia, cerebellum, cerebrum, lens

*** Calcification of interosseous membrane is pathognomonic of fluorosis. However, it is also seen in patients with osteogenesis imperfecta type V and rarely in patients with hypoparathyroidism

reversible hypoparathyroidism?

- The crucial defect in the pathogenesis of reversible hypoparathyroidism is transient suppression of PTH secretion

- Dysmagnesemia is associated with decreased PTH secretion due to activation of CaSR and interferes with PTH action; this is reversible with normalization of serum magnesium

Hypomagnesemia	• chronic alcohol intake • Malnutrition • Malabsorption • renal tubular disorders • uncontrolled diabetes • total parenteral nutrition or loop diuretics
Hypermagnesemia	• magnesium salts as cathartics, antacids, or tocolytics
Critical illness	• interleukins increase the expression of CaSR on parathyroid gland and reduces PTH secretion which improves after recovery of underlying illness.

Treatment of hypoparathyroidism

Impractical because of daily injections and higher cost. Further, to sustain normocalcemia PTH has to be administered twice daily.

- Therefore, calcium and calcitriol supplementation remain the mainstay of treatment in patients with hypoparathyroidism

1. Calcium is supplemented at doses of 1–9 g/d and calcitriol 0.25–2 µg per day in divided doses
2. Calcitriol is preferred over alfacalcidol (1α-(OH)D) because of its shorter duration of action that enables rapid reversal in the event of iatrogenic hypercalcemia
3. Addition of thiazides may reduce the risk of renal stone by reducing calcium excretion and helps to normalize serum calcium
4. In those who are vitamin D deficient, replacement with cholecalciferol may decrease the requirement of calcitriol and calcium.
5. Calcilytic agents may be useful in those who have a defect in CaSR
6. Phosphate binder like calcium carbonate is advised in patients with severe hyperphosphatemia to normalize the solubility product

Monitoring during treatment

Aims of treatment in a patient with hypoparathyroidism are resolution of symptoms and prevention of long-term complications.

Biochemical targets

1. maintenance of serum calcium in the low–normal range
2. serum phosphate in the high–normal range
3. calcium phosphate solubility product <55 mg 2 /dl 2
4. urinary calcium <300 mg/day

Reasons for above targets

- efforts to raise serum calcium to normal range might exacerbate hypercalciuria due to lack of PTH
- If 24-hr urinary calcium excretion exceeds 250 mg, addition of thiazides and low salt intake should be considered.
- serum calcium, phosphate, creatinine, and urinary calcium should be measured weekly at initiation of treatment to titrate the doses and once in 3 months later on.
- *Serum PTH monitoring is not required.*

universal screening for vitamin D deficiency recommended prior to vitamin D replacement

Ideally, screening for vitamin D deficiency should be done prior to vitamin D replacement. However, vitamin D deficiency is rampant and is an independent risk factor for fracture; therefore, in routine clinical practice, it should be supplemented without screening.

Table 5 Drug therapy and diseases may interfere with calcium homeostasis and necessitate changes in monitoring and therapy.

Drug/disease	Mechanism	Possible adverse effects in HypoPT	Action
Loop diuretics	Increased urinary calcium losses	May aggravate hypercalciuria and lower serum calcium levels	Avoid if possible
Thiazide diuretics	Decreased urinary calcium losses	May increase serum calcium levels	May be used in a patient with HypoPT (see section 'Treatment')
Systemic glucocorticoids	Decreased intestinal calcium absorption and increased urinary calcium losses	May cause hypocalcaemia	Avoid if possible
Antiresorptive drugs	Decreased bone turnover	May cause hypocalcaemia	Rarely needed, as HypoPT is a state of (very) low bone turnover
Proton pump inhibitors	May cause hypomagnesaemia	May lower serum calcium levels and cause symptoms similar to hypocalcaemia	Avoid if possible – otherwise magnesium supplements as needed
Chemotherapy: cisplatin, 5-fluorouracil, and leucovorin	May cause hypomagnesaemia	May lower serum calcium levels and cause symptoms similar to hypocalcaemia	Magnesium supplements, as needed
Cardiac glycosides (e.g. digoxin)	Hypercalcaemia may predispose to digoxin toxicity Hypocalcaemia may reduce the efficacy of digoxin	Arrhythmias	Avoid if possible. If needed, close monitoring by a cardiologist
Diarrhea/gastrointestinal disease	May reduce intestinal absorption of calcium and vitamin D	May cause hypocalcaemia	Close monitoring of serum calcium levels with dose adjustments as needed
Changes in (correction of) acid–base balance[a]	The affinity of calcium to bind to proteins in serum is highly pH dependent – only the free fraction in physiological active	Correction of metabolic acidosis may cause hypocalcaemia Correction of metabolic alkalosis may cause hypercalcaemia	
Immobilization	Increased bone resorption. In healthy individuals, PTH and 1,25-dihydroxyvitamin D levels are suppressed	May cause hypercalcaemia	

[a]Changes in the free (ionized) fraction of serum calcium (Ca^{2+}) cannot be monitored by measuring total calcium levels. Many laboratories report serum Ca^{2+} levels adjusted to a neutral pH value (7.4), which does not reflect the actual serum Ca^{2+} level in a patient with disturbances in acid–base balance. If so, patients may have symptoms despite (apparently) normal calcium levels and Ca^{2+} levels at actual pH should be requested.

indications of calcitriol therapy

Calcitriol {1,25(OH) 2 D 3 } is synthesized from 25(OH)D 3 by the enzyme 1α-hydroxylase, which is present in proximal convoluted tubule of kidney.

• chronic kidney disease, hypoparathyroidism, pseudohypoparathyroidism, hypophosphatemic osteomalacia, and renal tubular acidosis
• patients with primary hyperparathyroidism who develop hungry bone syndrome or hypoparathyroidism postoperatively also require treatment with calcitriol.
• vitamin D-dependent rickets, type 1 (inactivating mutations of 1α-hydroxylase) and type 2 (vitamin D receptor defects)
• Elderly subjects (>70 years) may also require calcitriol supplementation for their bone health, as there is a decline in 1α-hydroxylase activity with advancing age due to progressive decline in eGFR **

*** evidence is not conclusive for prevention of osteoporosis

Table 2 Vitamin D metabolites in the management of chronic hypoparathyroidism[a].

Medication	Typical dose	Time to onset of action (days)	Time to offset of action (days)
Calcitriol ($1,25(OH)_2D_3$)	0.25–2.0 μg once or twice daily	1–2	2–3
Alfacalcidiol[b] ($1\alpha(OH)D_3$)	0.5–4 μg once daily	1–2	5–7
Dihydrotachysterol[b]	0.3–1.0 mg once daily	4–7	7–21
Vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol)[c]	25 000–200 000 IU daily	10–14	14–75

[a]Derived from Shoback (4).
[b]Alfacalcidiol and dihydrotachysterol are rapidly activated in the liver to $1,25(OH)_2D$ and 25(OH) dihydrotachysterol.
[c]These compounds could be used in a setting where active vitamin D metabolites are not available and/or too expensive.

Table 5. Indications for Considering the Use of rhPTH (1-84) in Hypoparathyroidism

1. Inadequate control of the serum calcium concentration (this could be due to intercurrent illness, compliance, absorption, or intrinsic changes in requirements that are beyond facile correction with calcium and active vitamin D)
2. Oral calcium/vitamin D medications required to control the serum calcium or symptoms that exceed 2.5 g of calcium or >1.5 μg of active vitamin D or >3.0 μg of the 1-α vitamin D analog
3. Hypercalciuria, renal stones, nephrocalcinosis, stone risk, or reduced creatinine clearance or eGFR (<60 mL/min)
4. Hyperphosphatemia and/or calcium-phosphate product that exceeds 55 mg^2/dL^2 (4.4 $mmol^2/L^2$)
5. A gastrointestinal tract disorder that is associated with malabsorption
6. Reduced quality of life

Natpara (rhPTH 1-84) REPLACE TRIAL

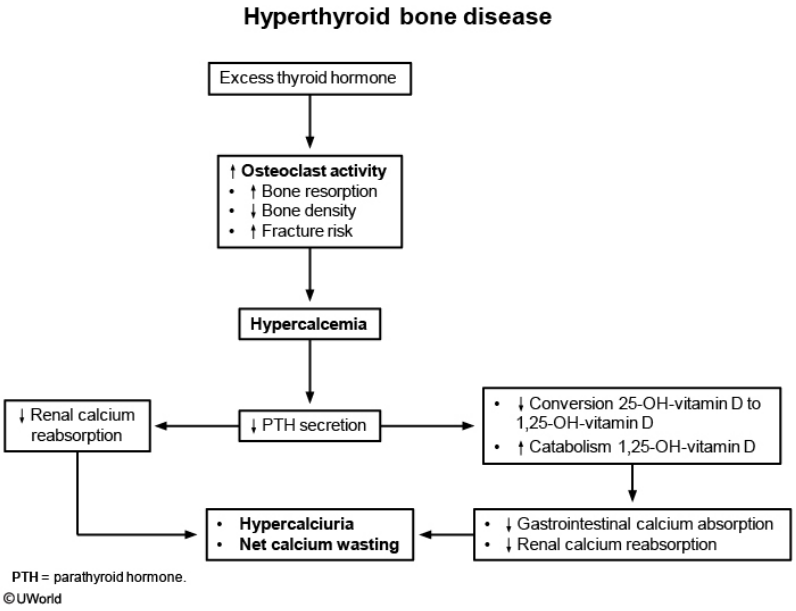
- No difference in adverse or serious adverse events between rhPTH and placebo
- Hypercalcemia can occur, usually within the first few months of therapy, and is easily corrected.
- There is data for safety through 6 years of use.

NATPARA initiation guidelines

- Discuss risk and benefits of natpara (osteosarcoma risk in rats,approved since 2002; Osteosarcoma risk dependent on dose and duration of therapy)
- Enrol patient in the NATPARA **Risk evaluation and mitigation strategy (REMS) program**
- rhPTH (1-84) 50mcg SC daily into alternate thigh. Assistance with mixing medication and administering. Thigh absorption is > abdomen
- Decrease either oral calcium or calcitriol by 50% when starting rhPTH(1-84)
- Monitor serum calcium every 3-7days with adjustments of calcium/calcitriol
- The dose of NATPARA may be increased in increments of 25 mcg every four weeks up to a maximum daily dose of 100 mcg if serum calcium cannot be maintained above 8 mg/dL without an active form of vitamin D and/or oral calcium supplementation

Contraindications to Natpara use

- Pagets disease of bone
- Unexplained elevations of alkaline phosphatase
- Pediatric and young adult patients with open epiphyses
- Hereditary disorders predisposed to osteosarcoma
- Prior history of beam or implant radiation therapy involving the skeleton.
- Concurrent bisphosphonate and natpara use is not recommended



UROLITHIASIS

Stone Type	Dietary Intervention	Mechanism
Calcium	Decreased sodium intake	→ decreased calcium excretion in kidney
	Increased calcium intake	→ decreased oxalate absorption in GI tract
	Increased fluid intake	→ increased urine flow, decreased solute concentration
	Increased fruit & vegetable intake	→ increased citrate excretion in kidney
	Reduced animal protein	→ decreased acid load and urinary calcium excretion
	Increased citrate intake	→ binds urinary calcium to inhibit stone formation

DEXA Scans

In clinical practice, BMD measurements are widely used to diagnose osteoporosis and
measurement in bone mass are commonly used as a surrogate for fracture risk

BMD is the measured parameter, and allows the calculation of the **bone mineral content (BMC)** in grams and the **two-dimensional projected area in cm2 of the bone(s)** being measured; thus the units of BMD are g/cm2. *The BMD values (in g/cm2) are not used for diagnosing osteoporosis.*

Instead, a working group of the WHO proposed to define **osteoporosis** on the basis of the T-score (which is the difference between the measured BMD and the mean value of young adults, expressed in standard deviations (SD) for a normal population of the same gender and ethnicity)

The T-score is calculated using the formula:
(patient's BMD - young normal mean)/SD of young normal.

For example, if a patient has a BMD of 0.700 g/cm2, the young normal mean is 1.000 g/cm2, and the young normal standard deviation is 0.100 g/cm2, then this patient's T-score would be (0.700 - 1.000)/0.100, or –0.300/0.100, or –3.0

Diagnosis	*T-score*
Normal	>–1.0
Osteopenia	<–1.0, >–2.5
Osteoporosis	<–2.5
Severe osteoporosis	<–2.5 plus fragility fractures

WHO. Osteoporosis classification (only postmenopausal women and men over 50)

DXA scanners use two X-ray energies in the presence of three types of tissue (bone mineral, lean tissue and adipose tissue), there are considerable errors arising from the inhomogeneous distribution of adipose tissue in the human body

DXA technology can measure virtually any skeletal site, but clinical use has been concentrated on the lumbar spine, proximal femur, forearm, and total body

Peripheral DXA systems, portable and less expensive than full table systems, are more frequently used as screening and early risk assessment tools; they cannot be used for treatments follow-up.

Sites of bone mineral density measurement

Where to measure?	ISCD recommends obtaining BMD measurements of the **posteroanterior spine** and **hip**
Where not to measure	• lateral spine and Ward's triangle region of the hip • sites overestimate osteoporosis and results can be a false-positive.
femur (neck or total hip)	**Optimum for predicting risk of hip fracture**

Spine	Optimum site for monitoring response to treatment

Osteoporosis is defined as "a [silent] skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality"

The **T-score is defined as the SD of an individual's BMD from the mean value for healthy young white women**. Although the WHO diagnostic criteria were not intended to serve as thresholds for treatment decisions, they are often used for this purpose.

Table 5
2016 AACE Diagnosis of Osteoporosis in Postmenopausal Women

1. T-score –2.5 or below in the lumbar spine, femoral neck, total, and/or 33% (one-third) radius
2. Low-trauma spine or hip fracture (*regardless of BMD*)
3. Osteopenia or low bone mass (T-score between –1 and –2.5) **with** a fragility fracture of proximal humerus, pelvis, or possibly distal forearm
4. Low bone mass or osteopenia and high FRAX® fracture probability based on country-specific thresholds

Table 4
World Health Organization Criteria for Classification of Osteopenia and Osteoporosis

Category	T-score
Normal	–1.0 or above
Low bone mass (osteopenia)[a]	Between –1.0 and –2.5
Osteoporosis	–2.5 or below

[a] Fracture rates within this category vary widely. The category of "osteopenia" is useful for epidemiology studies and clinical research but is problematic when applied to individual patients and must be combined with clinical information to make treatment decisions.

Table 6
Assessment for Fracture Risk and Osteoporosis in Postmenopausal Women

- Medical history and physical examination to identify:
  - Prior fracture without major trauma (other than fingers, toes, skull) after age 50
  - Clinical risk factors for osteoporosis
    - Age ≥65
    - Low body weight (<57.6 kg [127 lb])
    - Family history of osteoporosis or fractures
    - Smoking
    - Early menopause
    - Excessive alcohol intake (≥3 drinks daily)
  - Secondary osteoporosis
  - Height loss or kyphosis
  - Risk factors for falling
  - Patient's reliability, understanding, and willingness to accept interventions
- Lateral spine imaging with standard radiography or vertebral fracture assessment in patients with unexplained height loss, self-reported but undocumented prior spine fractures, or glucocorticoid therapy equivalent to ≥5 mg prednisone daily for 3 months or more
- Bone mineral density measurements in those at increased risk for osteoporosis and fractures and willing to consider pharmacologic treatment if low bone mass is documented:
  - All women ≥65 y of age
  - Younger postmenopausal women
    - With a history of fracture(s) without major trauma
    - Starting or taking long-term systemic glucocorticoid therapy
    - With radiographic osteopenia
    - With clinical risk factors for osteoporosis (low body weight, cigarette smoking, family history of spine or hip fractures, early menopause, or secondary osteoporosis)
- In women who are candidates for pharmacologic therapy, laboratory evaluation to identify coexisting conditions that may contribute to bone loss and/or interfere with therapy

Women with hip fracture have an **increased mortality of 12 to 20%** during the following 2 years. More than **50% of hip fracture survivors are unable to return to independent living**; many require long-term nursing home care

FRAX® predicts the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, humerus, or forearm).

Postmenopausal women aged 50 years or older with osteopenia (T-score between –1.0 and –2.5) with a 10-year probability ≥3% for hip fracture or ≥20% for major osteoporotic fracture in the U.S. or above country-specific threshold) are recommended to consider osteoporosis treatment

BONE DENSITOMETRY
• The T-score represents the number of SDs from the normal young-adult mean values • Z-score represents the number of SDs from the normal mean value for age-, race- or ethnicity-, and sex-matched control subjects
• T-scores are used for diagnostic classification in postmenopausal women. • Z-scores are recommended for premenopausal women, with a Z-

score –2.0 or lower defined as “below the expected range for age” and >–2.0 as “within the expected range for age.”

- Postmenopausal women with very low Z scores often have secondary osteoporosis and should undergo comprehensive evaluation to identify the causes.

THE ISCD OFFICIAL POSITION

STATE THAT VERTEBRAL IMAGING IS INDICATED WHEN THE T-SCORE IS < -1.0 AND ONE OR MORE OF THE FOLLOWING IS PRESENT:

- Woman age ≥ 70 years or man age ≥ 80 years
- Historical height loss > 4 cm (1.5 inches)
- Self-reported but undocumented prior vertebral fracture
- **Glucocorticoid therapy equivalent to ≥ 5 mg of prednisone or equivalent per day for ≥ 3 months**

** *VFA is a method for imaging the thoracic and lumbar spine by DXA for the purpose of detecting vertebral fracture deformities.*

Table 7
Risk Factors Included in FRAX®

Country of residence
Ethnicity (US models only—white, black, Hispanic, and Asian)
Age (accepts ages between 40 and 90 y)
Sex
Weight (kg) and height (cm) used to calculate body mass index; a converter from English to metric units is provided within the FRAX® tool
Family history (either parent with a hip fracture)
Personal history of fragility fracture, including radiographic vertebral fracture
Glucocorticoid use (prednisolone ≥5 mg daily for 3 mo or longer, current or past)
Rheumatoid arthritis (confirmed diagnosis)
Smoking (current)
Alcohol use (>3 units daily)
Secondary osteoporosis[a] (specifically mentioned are type 1 diabetes, osteogenesis imperfect in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause, chronic malnutrition or malabsorption and chronic liver disease)
BMD[b]. Either T-score or femoral neck BMD can be entered. The model also works without BMD.

Table 9 Indications for Bone Mineral Density Testing
All women ≥65 years old
All postmenopausal women
With a history of fracture(s) without major trauma
With osteopenia identified radiographically
Starting or taking long-term systemic glucocorticoid therapy (≥3 mo)
Other peri- or postmenopausal women with risk factors for osteoporosis if willing to consider pharmacologic interventions
Low body weight (<127 lb or body mass index <20 kg/m^2)
Long-term systemic glucocorticoid therapy (≥3 mo)
Family history of osteoporotic fracture
Early menopause (<40 years old)
Current smoking
Excessive alcohol consumption
Secondary osteoporosis

Table 10 Bone Mineral Density Measurements: Potential Uses in Postmenopausal Women
Screening for osteoporosis
Establishing the severity of osteoporosis or bone loss in patients with suspected osteoporosis (e.g., patients with fractures or radiographic evidence of osteopenia)
Determining fracture risk—especially when combined with other risk factors for fractures
Identifying candidates for pharmacologic intervention
Assessing changes in bone density over time in treated and untreated patients
Enhancing acceptance of, and perhaps adherence with, treatment
Assessing skeletal consequences of diseases, conditions, or medications known to cause bone loss

Lateral spine imaging with standard radiography or VFA with DXA is indicated when T-score is <–1.0 and 1 or more of the following is present:

- Women aged ≥70 years or men aged ≥80 years
- Historical height loss >4 cm (>1.5 inches)
- Self-reported but undocumented prior vertebral fracture
- Glucocorticoid therapy equivalent to ≥5 mg prednisone or equivalent per day for ≥3 months

In patients with unexplained height loss or back pain, thoracic and lumbar spine radiography or VFA by DXA is indicated.

Table 11
Causes of Secondary Osteoporosis in Adults

Endocrine or metabolic causes	Nutritional/GI conditions	Drugs	Disorders of collagen metabolism	Other
Acromegaly	Alcoholism	Antiepileptic drugs[a]	Ehlers-Danlos syndrome	AIDS/HIV[a]
Diabetes mellitus	Anorexia nervosa	Aromatase inhibitors	Homocystinuria due to cystathionine deficiency	Ankylosing spondylitis
Type 1	Calcium deficiency	Chemotherapy/ immunosuppressants	Marfan syndrome	Chronic obstructive pulmonary disease
Type 2	Chronic liver disease	Depo-Provera	Osteogenesis imperfect	Gaucher disease
Growth hormone deficiency	Malabsorption syndromes/ malnutrition (including celiac disease, cystic fibrosis, Crohn's disease, and gastric resection or bypass)	Glucocorticoids		Hemophilia
Hypercortisolism	Total parenteral nutrition	Gonadotropin-releasing hormone agents		Hypercalciuria
Hyperparathyroidism	Vitamin D deficiency	Heparin		Immobilization
Hyperthyroidism		Lithium		Major depression
Hypogonadism		Proton pump inhibitors		Myeloma and some cancers
Hypophosphatasia		Selective serotonin reuptake inhibitors		Organ transplantation
Porphyria		Thiazolidinediones		Renal insufficiency/ failure
Pregnancy		Thyroid hormone (in supraphysiologic doses)		Renal tubular acidosis
				Rheumatoid arthritis
				Systemic mastocytosis
				Thalassemia

Abbreviations: AIDS = acquired immunodeficiency syndrome; GI = gastrointestinal; HIV = human immunodeficiency virus; GI = gastrointestinal.
[a] Phenobarbital, phenytoin, primidone, valproate, and carbamazepine have been associated with low bone mass.

Table 12
Laboratory Tests to Consider in Detecting Secondary Osteoporosis

Complete blood cell count
Serum chemistry, including calcium, phosphate, total protein, albumin, liver enzymes, alkaline phosphatase, creatinine, and electrolytes
24-h collection for calcium, sodium, and creatinine excretion (to identify calcium malabsorption or hypercalciuria)
Serum 25-hydroxyvitamin D

Additional tests if clinically indicated might include (but not limited to):
Serum intact parathyroid hormone concentration for possible primary or secondary hyperparathyroidism
Serum thyrotropin
Tissue transglutaminase antibodies for suspected celiac disease
Serum protein electrophoresis and free kappa and lambda light chains for suspected myeloma
Urinary free cortisol or other tests for suspected adrenal hypersecretion
Serum tryptase, urine N-methylhistidine, or other tests for mastocytosis
Bone marrow aspiration and biopsy to look for marrow-based diseases
Undecalcified iliac crest bone biopsy with double tetracycline labeling
- Recommended for patients with bone disease and renal failure to establish the correct diagnosis and direct management
- May be helpful in the assessment of patients with the following:
  - Suspected osteomalacia or mastocytosis when laboratory test results are inconclusive
  - Fracture without major trauma despite normal or high bone density
  - Vitamin D-resistant osteomalacia and similar disorders to assess response to treatment

Genetic testing for unusual features that suggest rare metabolic bone diseases

Secondary Osteoporosis evaluation (MAYO CLINIC)

- CBC
- Chemistry group (calcium,phos, Cr, LFTs, ALP)
- 24hr urinary calcium, sodium, creatinine **(idiopathic hypercalciuria is defined as >4mg/kg in women and >4.5mg/kg in men without cause)**
- TSH
- SPEP
- Testosterone (men)

- 25-OH vitamin D level
- PTH
- Bone turnover markers in non-responders (beware of recent fracture related increases)
- Based on clinical presentation > see above.

Table 14 Measures for Prevention of Falls
Anchor rugs
Minimize clutter
Remove loose wires
Use nonskid mats
Install handrails in bathrooms, halls, and long stairways
Light hallways, stairwells, and entrances
Encourage patient to wear sturdy, low-heeled shoes
Recommend hip protectors for patients who are predisposed to falling
Keep all items within reach and avoid using stepstools

Table 15 Recommendations Regarding Lifestyle Issues
Ensure adequate calcium intake
Ensure adequate vitamin D intake
Consume a balanced diet
Regularly perform weight-bearing and balance exercises
Avoid tobacco use
Limit alcohol consumption
Take measures to avoid falls
Consider use of hip protectors

Table 16
Drugs Approved by the US Food and Drug Administration for Prevention and Treatment of Postmenopausal Osteoporosis[a]

	Postmenopausal osteoporosis	
Drug	**Prevention**	**Treatment**
Alendronate (Fosamax)	5 mg PO daily 35 mg PO weekly	10 mg PO daily 70 mg PO weekly[b] 70 mg + D[c]
Calcitonin (Miacalcin, Fortical)	—	200 IU intranasally once daily, or 100 IU SQ qod
Denosumab (Prolia)	—	60 mg SQ every 6 mo
Estrogen (multiple formulations)	Multiple regimens	—
Ibandronate (Boniva, generic form)	2.5 mg PO daily 150 mg PO monthly	2.5 mg PO daily 150 mg PO monthly 3 mg IV every 3 mo
Raloxifene (Evista)	60 mg PO daily	60 mg PO daily
Risedronate (Actonel, Atelvia, generic form)[a]	5 mg PO daily 35 mg PO weekly 150 mg PO monthly	5 mg PO daily 35 mg PO weekly 150 mg PO monthly
Teriparatide (Forteo)	—	20 µg SQ daily
Zoledronic acid (Reclast, generic infusion form)	5 mg IV every 2nd y	5 mg IV once yearly

Abbreviations: IV = intravenous; PO = per os; qod = every other day; SQ = subcutaneous.
[a] Please review the package inserts for specific prescribing information.
[b] Fosamax 70 mg is available as both a tablet and a unit dose liquid. Alendronate (generic Fosamax) is available.
[c] Fosamax Plus D is a tablet containing 70 mg of alendronate and 2,800 IU or 5,600 IU of vitamin D for weekly administration.
[d] Risedronate 150 mg once monthly tablet is available.

Table 17 Summary of Evidence for Fracture Risk Reduction			
	Fracture risk reduction		
Drug	Vertebral	Nonvertebral	Hip
Alendronate (Fosamax) (197 [EL 1; RCT])	Yes	Yes	Yes
Calcitonin (Miacalcin, Fortical) (177 [EL 1; RCT])	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Denosumab (Prolia) (198 [EL 1; RCT])	Yes	Yes	Yes
Ibandronate (Boniva) (173 [EL 1; RCT], 204 [EL 1; RCT])	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Raloxifene (Evista) (178 [EL 1; RCT])	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Risedronate (Actonel, Atelvia) (174 [EL 1; RCT], 175 [EL 1; RCT])	Yes	Yes	Yes
Teriparatide (Forteo) (180 [EL 1; RCT, partial blinding], 203 [EL 2; RCCS])	Yes	Yes	No effect demonstrated[a]
Zoledronic acid (Reclast) (189 [EL 1; RCT])	Yes	Yes	Yes
[a] The lack of demonstrable effect at these sites should be considered in the context that the studies may not have been adequately powered.			

BISPHOSPHONATES

Mechanism of action	• Bind to hydroxyapatite in bone at sites of active bone remodeling • Reduce activity of bone resorbing osteoclasts • Should be taken after an overnight fast, swallowed with a full glass of water. 30min wait after ingestion prior to other meds/food. • **Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial**
Precautions	• Active esophageal disease (achalasia,stricture, dysmotility) • Inability to remain upright for 30-60minutes • **potential GI malabsorption** (e.g., gastric bypass procedures, celiac disease, Crohn's disease, infiltrative disorders, etc.) • formulation of **risedronate (Atelvia®)** can be taken with or after food and, because the delayed-release coating • reduced kidney function (**GFR <30 mL/min for risedronate and ibandronate** or **<35 mL/min for alendronate and zoledronic acid**)
Side effects	• fever and muscle aches— a flu-like illness—lasting several days • Osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFFs)

DENOSUMAB

Mechanism of action	• human **monoclonal antibody** that prevents r**eceptor activator of nuclear factor kappa-B**

(Xgeva®)	**ligand (RANKL)** from binding to its receptor • reducing the **differentiation of precursor cells into mature osteoclasts** and decreasing the function and survival of activated osteoclasts •
precautions	• **Calcium deficiency**, **vitamin D deficiency**, and **secondary hyperparathyroidism** should be corrected prior to initiating denosumab treatment to avoid precipitating hypocalcemia • **When treatment with denosumab was stopped after 2 years, BMD decreased to baseline values by 12months. No "DRUG HOLIDAY"** • **Up to 10 years of therapy efficacy and safety data**

RALOXIFENE

Mechanism of action	• Raloxifene is approved by the FDA for prevention and treatment of postmenopausal osteoporosis, as well as for the reduction of risk of breast cancer in women with postmenopausal osteoporosis or at high risk of breast cancer • SERM
Precautions	• Contraindicated for women of child bearing potential, history of venous thromboembolism • Loss of skeletal benefits after stopping.
Efficacy	• **Raloxifene has been shown to reduce the risk of spine fracture** , but neither nonvertebral nor hip fracture efficacy has been demonstrated • reduction in breast cancer was seen in an osteoporosis trial with raloxifene • raloxifene is **not indicated** for the treatment of invasive breast cancer, for reduction of the risk of recurrence of breast cancer, or for reduction of the risk of noninvasive breast cancer.
Side effects	• **Venous clots** • **Menopausal symptoms (hot flashes, night sweats)**

TERIPARATIDE

Mechanism of action	• Recombinant human PTH(1-34)—is considered an "anabolic" agent • approved by the FDA for initial treatment of women

	with postmenopausal osteoporosis who are at high risk of fracture or have failed or been intolerant of previous osteoporosis therapy • Teriparatide is also approved for treatment of **glucocorticoid-induced osteoporosis**.
efficacy	• Teriparatide has been shown to reduce the risk of vertebral and nonvertebral fractures in women with postmenopausal osteoporosis • **whether teriparatide protects against hip fracture is unknown.** *Teriparatide dramatically increases BMD in the spine but has little effect on BMD in the hip or forearm.*
Side effects	• Side effects of teriparatide are *mild and transient* and include **nausea, orthostatic hypotension** (which usually does not necessitate discontinuation of the drug, occurs in association with the first few doses, and responds to assumption of a recumbent posture), and **leg cramps.** • **Hypercalcemia, usually mild, asymptomatic, and transient, has been observed but is not common** • occurrence of **osteosarcomas** in 1 strain of rats treated with very high doses (3-50 times higher than the human equivalent dose), starting at 2 weeks of age, and continued for their lifetimes (approximately 75 human-year equivalents)
contraindications	• patients at **increased risk of osteosarcoma** (those with Paget disease of bone, open epiphyses, a history of irradiation involving the skeleton, or an unexplained elevation of alkaline phosphatase level of skeletal origin)
	• When stopped, bone density declines quickly during the following year, although fracture reduction may persist for 1 or 2 years • Alendronate, ZA or denosumab after discontinuation

MONITORING OF THERAPY

Age-related bone loss	begins in the fifth decade of life, occurs at an average rate of 0.5 to 1.0% per year
Menopause-related bone loss	begins 3 to 5 years before the last menstrual period and continues for 3 to 5 years after the

	cessation of menses, occurs at an average rate of 1 to 2% per year
• patients on treatment • **baseline evaluation near a fracture intervention threshold**	BMD testing every 1 to 2 years is often appropriate. (Individualized,recently postmenopausal state etc)

Table 18
ONJ and AFF: Definitions and Diagnostic Criteria (269 [EL 4; consensus NE], 273 [EL 4; review NE], 318 [EL 2; RCCS])

(ONJ)	The presence of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a healthcare professional
(AFF)	The fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare
	Major features (at least 4 of 5) • The fracture is associated with minimal or no trauma, as in a fall from a standing height or less • The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur • Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex • The fracture is noncomminuted or minimally comminuted • Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")
	Minor features (none required) • Generalized increase in cortical thickness of the femoral diaphyses • Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh • Bilateral incomplete or complete femoral diaphysis fractures • Delayed fracture healing
Abbreviations: AFF = atypical femur fracture; ONJ = osteonecrosis of the jaw.	

Management of AFF

- Diagnosis is by conventional xray, ct or bone isotope scan is often helpful**. A DXA application has also been developed.**
- Always check opposite femur for similar lesion
- Surgery for all complete and most incomplete fractures (often have persistent pain, delayed healing or progress to complete fractures)
- Indication for anabolic therapy is unclear or unproven
- Prudent to stop antiresorptives

What is ONJ?

Drug related ONJ is defined as exposed bone in the oral cavity for a minimum of 8 weeks (after identification by a healthcare provider) in patients on antiresorptive therapy in the absence of prior local radiation therapy and in the absence of other causes of odontogenic etiology.

Associated with bisphosphonates and denosumab.

Risk factors for osteonecrosis of the jaw
Osteoporosis setting ● Antiresorptive treatment, glucocorticoids,anemia, dental extraction **Oncology setting** ● Antiresorptive therapy, chemotherapy, age, dental extraction, dentures, diabetes, hyperthyroidism, anemia, male gender, dialysis, smoking, glucocorticoids

Bisphosphonate holidays : who are initially at high risk and remain at high risk receive a treatment duration of 10 years for an oral bisphosphonate or 6 years for IV zoledronic acid

For **lower risk patients**, a drug holiday can be considered after 5 years of stability on oral bisphosphonates or 3 years on IV zoledronic acid

*** No other treatment is needed during the bisphosphonate "holiday" for lower-risk patients but for higher-risk patients, teriparatide or a weaker antiresorptive drug such as raloxifene might be appropriate.
The optimal duration of a "bisphosphonate holiday" has not been established

A post hoc analysis of results from Fracture Intervention Trial (FIT) Long Term Extension (FLEX) Trial of 10 versus 5 years of alendronate assessed the influence of fracture status and T-score on treatment effect. Higher-risk women (those with T-score ≤–2.5) who stopped treatment had nearly twice as many nonvertebral fractures: 21 (28%) versus 16 (15%) with continued treatment

Anabolic agents (new therapies)
Abaloparatide
- An analog of PTHrp
- It amplifies PTH anabolic effects more than resorptive effects
- Increase LS and total hip BMD at 12months more than teriparatide in head to head trials (18months duration, abaloparatide vs placebo ACTIVE trial)

Romosozumab
- Humanized anti-sclerostin therapy
- FRAME trial (12 months duration, placebo vs romosozumab)

Use of sequential therapy
Teriparitide >> denosumab

NB: switching from denosumab to teriparatide is not recommended. DATA switch trial
Decrease in total hip bone density and distal third radius in the first 6-12months after stopping denosumab.

Rapid bone remodeling : after stoppage of denosumab. Augmented by teriparatide.
Reasonable approach of given both together instead.

In the DATA switch trial, denosumab after teriparatide however increased lumbar spine and total hip BMD - and reversal of the decreased with teriparatide in the distal third of radius.

***

1) Except for possible use of denosumab and teriparatide, beginning anabolic and anti-remodeling agents at the same time has little or no advantage over monotherapy
2) Sequential use of bisphosphonates or denosumab after teriparatide results in progressive increased in BMD
3) Use of teriparatide after bisphosphonate is effective - but switching from denosumab to teriparatide results in marked increase in remodeling and loss of cortical BMD.

Anabolic therapy : beyond postmenopausal osteoporosis

States of impaired bone formation
• Long term glucocorticoid therapy (superiority of teriparatide vs alendronate) • Idiopathic osteoporosis of young adults • Immobilization • Adynamic bone disease in chronic renal failure • eating disorders • Genetic disorders of bone formation (teriparatide increases BMD in adults with osteogenesis imperfecta) • Impaired fracture healing.

FAILURE OF THERAPY.

Treatment change strategy in nonresponders

- A weaker antiresorptive is replaced by a more potent drug in the same class
- An oral agent is replaced by an injectable drug
- A strong antiresorptive is replaced by an anabolic agent.

IOF criteria to change osteoporosis therapy.

- **2 or more fragility fractures**
- **One fragility fracture** and no reduction in turnover markers and/or a significant decreased in BMD

- No significant decrease in PINP or BCTX and a significant in BMD
- **Fractures of the hand, skull, feet and ankle are not considered fragility fractures!!**

Risk factors for treatment failure

- Lower baseline SF-36 frailty score
- 2 or more falls in past 12months
- Prior fracture at baseline

The four Fs of fracture failure

1. Food (low BMI)
2. Falls
3. Fracture (prior)
4. Frailty with older age

\+ PLUS 2 more Fs

Forget medication and Secondary **Factors**.

Bone healing

specific physiological events of the healing callus including > inflammation > chondrogenesis > and ossification

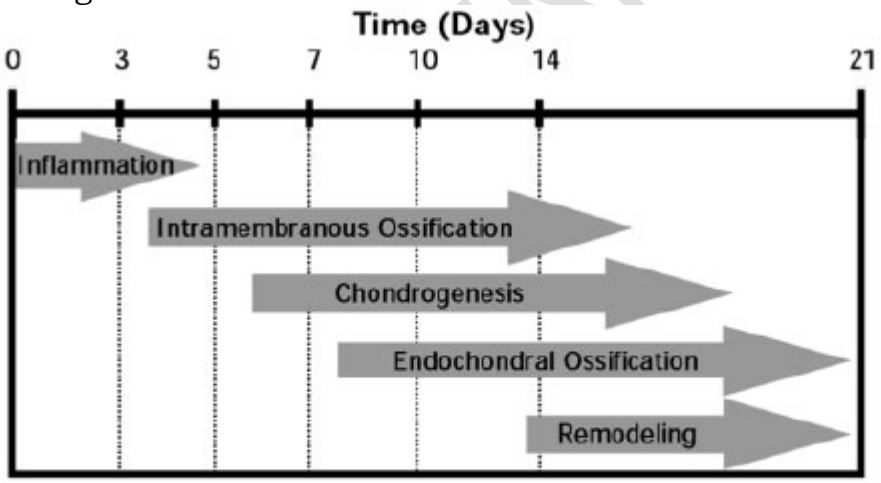


FIG. 1. **Time line showing the interdependent central physiologic processes occurring during the progression of the healing fracture callus.** Each of the *arrows* indicates the approximate starting time and duration of each process.

- Bisphosphonates are preferentially deposited at sites of fracture.
- Best overall efficacy if given >2 weeks after fracture repair.

Denosumab does not appear to worsen healing outcomes irrespective of timing.

Fractures and anti-remodeling agents

- Potent anti-remodeling agents do not impair fracture healing when initiated after fractures.
- Potent anti-remodeling agents improve BMD, prevent bone loss at fracture site and reduce fractures.
- Consider giving potent anti-remodeling medications >2weeks and up to 12weeks after a fragility fracture (denosumab or zoledronic acid)

NB: Many patients who sustain fragility fractures do not receive appropriate osteoporosis therapy.

Table 2. Drugs Approved by the Food and Drug Administration for the Treatment and Prevention of Osteoporosis.*

Drug Class and Agent	Method and Frequency of Administration	Type of Fracture Risk Reduction	Side Effects	Approved Use for Osteoporosis
Bisphosphonates†				
Alendronate	Oral: 35–70 mg/wk	Vertebral, nonvertebral, hip	Common: esophagitis, musculoskeletal symptoms; rare: ONJ, atypical femur fractures	Treatment and prevention
Risedronate	Oral: 35 mg/wk or 150 mg/mo (in a single dose or in two 75-mg doses on consecutive days)	Vertebral, nonvertebral, hip	Common: esophagitis, musculoskeletal symptoms; rare: ONJ, atypical femur fractures	Treatment and prevention
Ibandronate	Oral: 150 mg/mo; intravenous: 3 mg every 3 mo	Vertebral	Common: first-dose (intravenous) reaction, esophagitis, musculoskeletal symptoms; rare: ONJ, atypical femur fractures	Treatment and prevention
Zoledronic acid	Intravenous: 5 mg/yr	Vertebral, nonvertebral, hip	Common: acute-phase response (most often after first dose),‡ musculoskeletal symptoms; rare: ONJ, atypical femur fractures	Treatment and prevention
Biologic: denosumab	Subcutaneous: 60 mg every 6 mo	Vertebral, nonvertebral, hip	Common: cellulitis or skin reactions; rare: ONJ, atypical femur fractures	Treatment
Anabolic: teriparatide	Subcutaneous: 20 μg/day	Vertebral, nonvertebral	Common: nausea, leg cramps; rare: hypercalcemia, osteosarcoma§	Treatment
Calcitonin¶	Intranasal: 200 IU/day	Vertebral	Nasal congestion	Treatment
SERM: raloxifene	Oral: 60 mg/day	Vertebral	Venous thromboembolism, hot flashes, leg cramps, nausea	Treatment and prevention
Estrogens‖			Venous thromboembolism, increased risk of breast cancer and cardiovascular disease	Prevention
Conjugated equine estrogen	Oral: 0.15–1.25 mg/day	Vertebral, nonvertebral, hip		
17β-estradiol	Oral: 0.5–1.0 mg/day; transdermal: 0.025–0.10 mg 2 times/wk	No data from randomized trials		
Ultra-low-dose 17β-estradiol	Oral: 0.014 mg/day	No data		

KEY CLINICAL POINTS

POSTMENOPAUSAL OSTEOPOROSIS

- Fractures and osteoporosis are common, particularly among older women, and hip fractures can be devastating.
- Treatment is generally recommended in postmenopausal women who have a bone mineral density T score of –2.5 or less, a history of spine or hip fracture, or a Fracture Risk Assessment Tool (FRAX) score indicating increased fracture risk.
- Bisphosphonates (generic) and denosumab reduce the risk of hip, nonvertebral, and vertebral fractures; bisphosphonates are commonly used as first-line treatment in women who do not have contraindications. Teriparatide reduces the risk of nonvertebral and vertebral fractures.
- Osteonecrosis of the jaw and atypical femur fractures have been reported with treatment but are rare. The benefit-to-risk ratio for osteoporosis treatment is strongly positive for most women with osteoporosis.
- Because benefits are retained after discontinuation of alendronate or zoledronic acid, drug holidays after 5 years of alendronate therapy or 3 years of zoledronic acid therapy may be considered for patients at lower risk for fracture.

Prevention of steroid-induced osteoporosis

▪ General measures
  ▪ Use lowest possible steroid dose for shortest duration
  ▪ Topical steroids preferred over oral/enteral steroids
  ▪ Daily weight-bearing exercises
  ▪ Stop tobacco & excessive alcohol use
  ▪ Fall prevention
▪ Calcium & vitamin D
▪ Bisphosphonates (eg, alendronate, risedronate)
▪ Parathyroid hormone (eg, teriparatide) as second-line agent for severe osteoporosis

- All **men Age >50 years** and **postmenopausal women** taking more than **7.5mg per day of prednisone** for an **anticipatated course >3 months** should be started on bisphosphonates as initial therapy. Alendronate and Risedronate preferred
- Parathyroid hormone (teriparatide) is second line agent in patients who cannot tolerate bisphosphonates
- **10 year fracture risk > 20%** regardless of anticipated dose or duration of glucocorticoid.

NB: Evidence for men age <50years and premenopausal women is limited and care should be individualized.

➤➤ PAGET' DISEASE OF BONE

Clinical features of Paget's disease	
Signs & symptoms	• Majority of patients are asymptomatic • **Skull:** Deformity with enlargement, hearing loss, dizziness • **Spine & pelvis:** Bone pain, spinal stenosis, nerve compression • **Long bones:** Bowing deformities with ↑ fracture risk • **Bone tumors:** Osteosarcoma, giant cell tumors (usually benign)
Laboratory & imaging findings	• Elevated serum & bone-specific ALP • Bone markers may or may not be elevated with active disease (eg, PINP, CTx, NTx & urinary hydroxyproline). • Calcium & phosphorus are usually normal; may be elevated with fracture or immobilization. • Plain radiographs show osteolytic or mixed lytic/sclerotic lesions.
Diagnosis	• Combination of radiographic findings & elevated ALP • No additional bone turnover tests or imaging is required for diagnosis. • **Bone scan** is more sensitive than x-ray & is helpful to document the extent & locations of skeletal involvement.
Treatment	• **Bisphosphonates** are the preferred treatment.

ALP = alkaline phosphatase; **CTx** = C-telopeptide; **NTx** = N-telopeptide; **PINP** = procollagen type I N propeptide.

Paget's disease of bone (osteitis deformans) is a chronic benign disorder of bone that affects one or several bones

Evolution of pagetic bone disease….

Focal increase in bone resorption by very large osteoclasts

↓

Increased osteoblastic activity producing high rate of bone formation (less organized than normal bone)

↓

final burned-out phase in which bone cell activity is markedly reduced and the bone structure is abnormal, with **chaotic lamellar bone interspersed with woven bone**.

Etiology and epidemiology

- Family member with disorder in 5%
- Autosomal dominant transmission pattern with incomplete penetrance
- Mutations in the gene producing sequestosome 1 increases susceptibility (including other multiple genes are involved in osteoclast biology)
- chronic paramyxovirus infections
- Paget's disease affects both men and women, with an apparent small male predominance

9

Clinical features of Paget's disease of bone

- Mainly asymptomatic
- Incidental finding (bone radiographs or bone scans or ALP on multiphasic chemistry panel)
- Skeletal deformity (frequently affected bones include the pelvis, vertebrae, skull, femur and tibia)
- Bowing of tibia or fibula (begins proximally and advances distally)
- Increased warmth over affected bone (increased blood flow)
- Bone pain (late finding, minority of patients)
- Fractures are termed "chalk-stick" or "banana" fractures because they are transverse and reflect the poor quality of the collagen matrix.
- **Osteosarcomas** (1%, px with multipe bones involved)
- **Benign giant cell tumors**
- **Hearing loss** (cochlear damage, not CNVIII compression)
- Hydrocephalus. Paraplegia, quadriplegia, and other symptoms of spinal stenosis are rare
- **Cardiac output** can increase with widespread and active skeletal lesions, but heart failure is unusual
- **Hypercalcemia** is an unusual complication resulting when patients

[9] "I never sleep…"

with more generalized skeletal disease are immobilized

** **Clinical Practice pearl** ** Sudden localized pain in a physically disabled femur or tibia requires an urgent x-ray to exclude an extending transverse fracture.

Table 1. Symptoms and Complications of Paget's Disease of Bone (18, 21)

System	Complication
Musculoskeletal	Bone pain
	Bone deformity
	Osteoarthritis of adjacent joints
	Acetabular protrusion
	Fractures
	Spinal stenosis
Neurological	Hearing loss
	Tinnitus
	Cranial nerve deficits (rare)
	Basilar impression
	Increased cerebrospinal fluid pressure
	Spinal stenosis
	Paraplegia, quadriplegia, vascular steal syndrome
Cardiovascular	Congestive heart failure
	Increased cardiac output
	Aortic stenosis
	Generalized atherosclerosis
	Endocardial calcification
Metabolic	Immobilization hypercalciuria
	Hypercalcemia
	Hyperuricemia
	Nephrolithiasis
Neoplasia	Sarcoma (osteosarcoma, chondrosarcoma and fibrosarcoma)
	Giant cell tumor

Diagnosis (Recommendations)

1. Plain radiographs of suspicious regions
2. Radionuclide bone scan
3. ALP (specific markers of bone formation tend to correlate well with extent of skeletal involvement seen on radiograph)
4. **Serum P1NP** as a measure of bone formation is the best option. If cost or availability prevent use of this option, then resorption markers such as **serum CTx** or **urine NTx** provide accurate estimates of baseline bone metabolic activity and the response to treatment in such patients

Table 2. Recommended Bisphosphonate Dosing Regimens

Drug	Dosage
Zoledronate[a]	5 mg given as a single infusion over 15 min. Retreatment is seldom required within 5 y
Alendronate	40 mg/d for 6 mo. Retreatment may be required between 2 and 6 y
Risedronate	30 mg/d for 2 mo. Retreatment may be required between 1 and 5 y

[a] The authors recognize that the official generic name for this drug is "zoledronic acid." However, that is a misnomer. In fact, it is the sodium salt, not the acid, that is used in medical practice. Therefore, we have elected to use "zoledronate," which is consistent with the usual nomenclature for bisphosphonates.

*** The nitrogen-containing bisphosphonates, alendronate, risedronate, pamidronate, and zoledronic acid, offer the best results in management because of their greater potency.

Mechanism of action of bisphosphonates (summary)

Chemical structure

- Bisphosphonate nucleus consists of two phosphate groups joined through a central carbon atom
- Not metabolised in humans
- Chemical potency determined by *affinity for hydroxyapatite* and *extent of inhibition of farnesyl pyrophosphate synthase.*

1. During bone resorption, BIPs are taken up by osteoclasts
2. Inhibits the enzyme farnesyl pyrophosphate synthase (critical step in the mevalonate pathway for cholesterol, as well as to the production of geranylgeraniol -- critical to prenylation of intracellular proteins)
3. Disruption of above pathway leads to disruption of osteoclast cytoskeleton and eventual osteoclast apoptosis.

Some patients have contraindications to the use of **iv zoledronate**, such as **marked renal impairment**. In such individuals, **oral bisphosphonates represent a much safer option** because the peak serum drug concentration is substantially lower, with an accompanying reduction in the risk of renal tubular toxicity

Monitoring response to treatment

- ALP -- least expensive, ALP response is slower, reaches a nadir in 2-3 months.**
- Bone resorption markers such as BCTx fall rapidly, nadir in 10days
- The likely duration of treatment response can be predicted from the short-term (10-d) reduction in bone turnover markers such as urinary NTx, which correlates well with the final post-treatment ALP
- repeat x-ray approximately 1 year after radiological diagnosis *
- Biochemical assessment q1-2years after normal bone turnover is demonstrated.

***For most patients, measurement of total ALP or other baseline disease activity markers at 6 to12 weeks, when bone turnover will have shown a substantial decline, is an acceptable and cost-effective option*

* *Subsequent x-rays may be considered in the event of persistent elevations of biochemical markers of bone turnover or the presence of bone pain and to determine when there is resolution of the lesion.*

Indications for treatment

- **Symptoms that are caused by metabolically active Paget's disease** (i.e., there is evidence of increased bone turnover and the symptom is referable to the proven site of Paget's disease). Examples

are bone pain at a pagetic site including headache, limb or back pain, radicular or arthritic pain caused by bone involvement that affects nerve roots or joints, or other neurological symptoms arising in the setting of active pagetic bone impacting on neural tissue
- **Planned surgery at a metabolically active pagetic site** to reduce the increased vascularity that is found in the highturnover state, in an effort to avoid excessive bleeding during the operation
- **Hypercalcemia** -- an event that may rarely occur when a patient with polyostotic Paget's disease and very high bone turnover is immobilized for a period of time;
- **Prevention of disease progression and reduction in future complications** in patients with **active Paget's disease at skeletal sites such as the skull, spine, weight-bearing long bones, and bones adjacent to major joints** such as hip or knee, even in the absence of current symptoms

Indications for Drug Treatment of Paget's Disease

1. Bone pain
2. Hypercalcemia due to immobilization
3. Neurologic deficit associated with vertebral disease
4. High-output congestive heart failure
5. Preparation for orthopaedic surgery
6. Prevention of complications including hearing loss, deformity

Treat or not to treat asymptomatic Paget's disease

- Controversial recommendation because it has not been proven conclusively that restoring normal turnover reduces the risk of later complications.
- However, it has been shown that, in the untreated state, progression of disease can occur with extension of osteolytic changes and progression of bone deformity.

First, **calcium and vitamin D repletion must be assured to avoid hypocalcemia**. Before treatment, it is reasonable to measure **serum PTH and 25-hydroxyvitamin D levels** to assist in determining calcium and vitamin D requirements. Second, **iritis*** is a rare complication that has been seen with nitrogen-containing bisphosphonates.**

*** If it occurs, the agent must be discontinued, and the patient should be seen by an **ophthalmologist**. Further treatment with any **nitrogen-containing**

bisphosphonate is contraindicated, but the patient can be offered one of the non–nitrogen-containing agents, either **etidronate** or **tiludronate**, which do not seem to be associated with **iritis**

LIPID METABOLISM --- LIPIDOLOGY

10

Lipids, Obesity, and Nutrition	**12%** of Exam
Hypercholesterolemia	<2%
Primary disorders	
Familial hypercholesterolemia	
Familial defective apolipoprotein B-100	
Lipoprotein (a)	
Elevated high-density lipoprotein cholesterol	
Secondary disorders	
Hypertriglyceridemia	<2%
Primary disorders	
Familial hypertriglyceridemia	
Apoprotein and lipase disorders	
Secondary disorders	
Chylomicronemia	

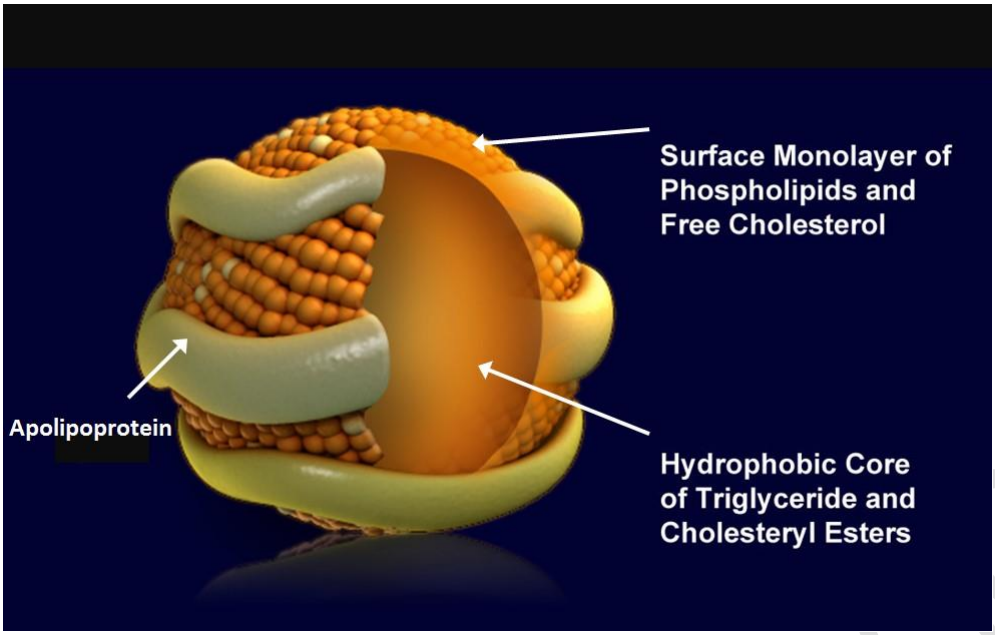
[10] ...none but he knows what that is which he can do, nor does he know until he has tried. Waldo Emerson

Mixed hyperlipidemia	2.5%
Primary disorders	
Familial combined hyperlipidemia	
Familial dysbetalipoproteinemia (type III)	
Secondary disorders	
Hypolipidemia	<2%
Primary disorders	
Secondary disorders	
Treatment of lipid disorders	2.5%
Diet	
Drugs	
Lifestyle	
Indications for treatment	
Obesity and nutrition	3%
Primary disorders	
Secondary disorders	
Comorbidities	
Treatment of obesity	
Diet	
Drugs	
Lifestyle	
Indications for treatment	

Lipoproteins

- Complex particles with a *central core* containing **cholesterol esters and triglycerides** *surrounded by* **free cholesterol, phospholipids, and apolipoproteins**, which facilitate lipoprotein formation and function
- Classification is based on size, lipid composition, and apolipoproteins
- **chylomicrons, chylomicron remnants, VLDL, IDL, LDL, HDL, and Lp (a)**

⊕→*Chylomicron remnants, VLDL, IDL, LDL, and Lp (a) are all pro-atherogenic while HDL is anti-atherogenic*



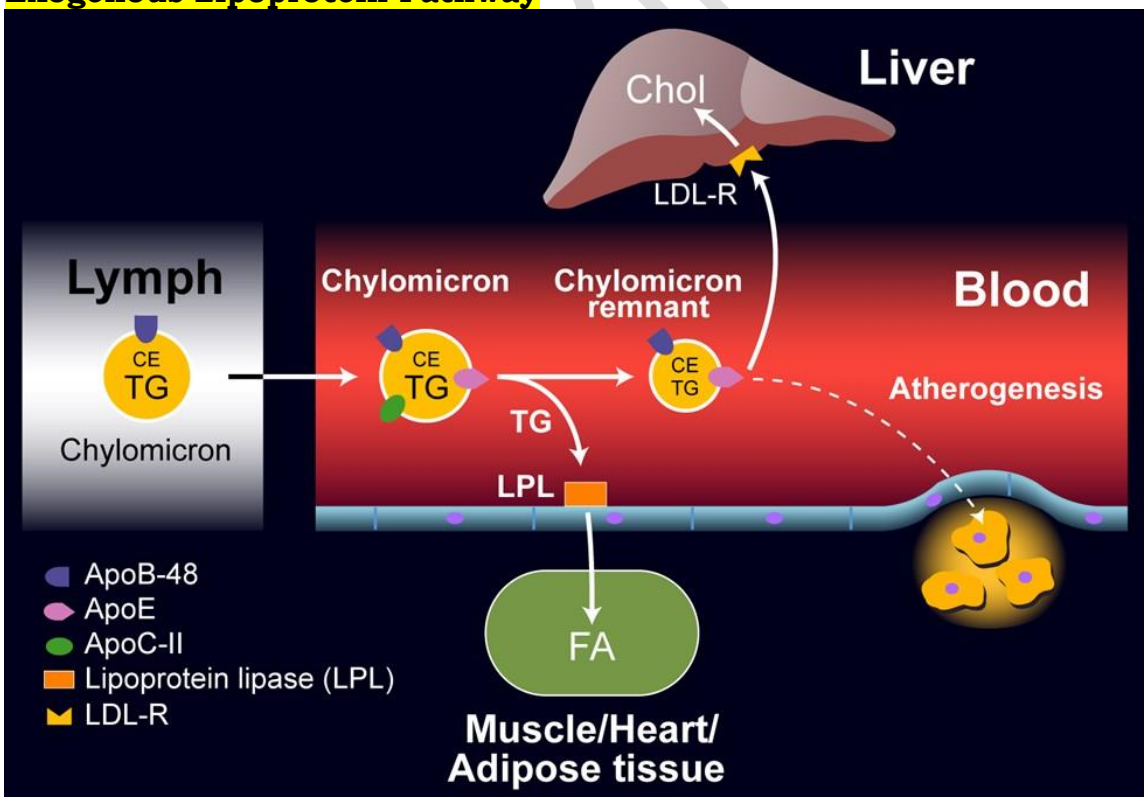
Function of apoproteins
1) serving a structural role 2) acting as ligands for lipoprotein receptors 3) guiding the formation of lipoproteins 4) serving as activators or inhibitors of enzymes involved in the metabolism of lipoproteins.

Exogenous lipoprotein pathway	Endogenous lipoprotein pathway
• Incorporation of dietary lipids into chylomicrons in the intestine. • In the circulation, the triglycerides carried in chylomicrons are metabolized in muscle and adipose tissue by lipoprotein lipase releasing free fatty acids • FFAs are subsequently metabolized by muscle and adipose tissue, and chylomicron remnants are formed. • Chylomicron remnants are then taken up by the liver.	• Begins in the liver with the formation of VLDL • The triglycerides carried in VLDL are metabolized in muscle and adipose tissue by lipoprotein lipase releasing free fatty acids and IDL are formed. • The IDL are further metabolized to LDL, which are taken up by via the LDL receptor in numerous tissues including the liver, the predominant site of uptake • Reverse cholesterol transport begins with the formation of nascent HDL by the liver and intestine. • *HDL then transports the*

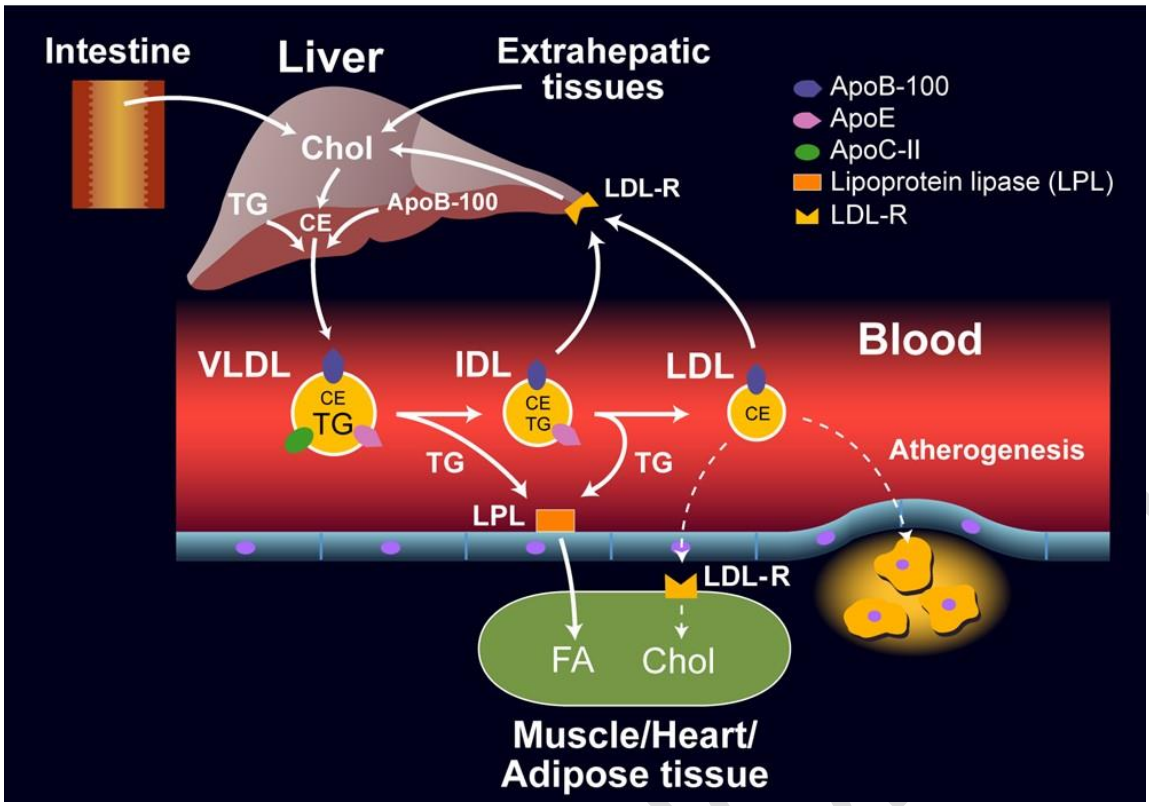
	cholesterol to the liver either directly by interacting with hepatic SR-B1 or indirectly by transferring the cholesterol to VLDL or LDL, a process facilitated by CETP**

**** CETP -- Cholesterol ester transfer protein**

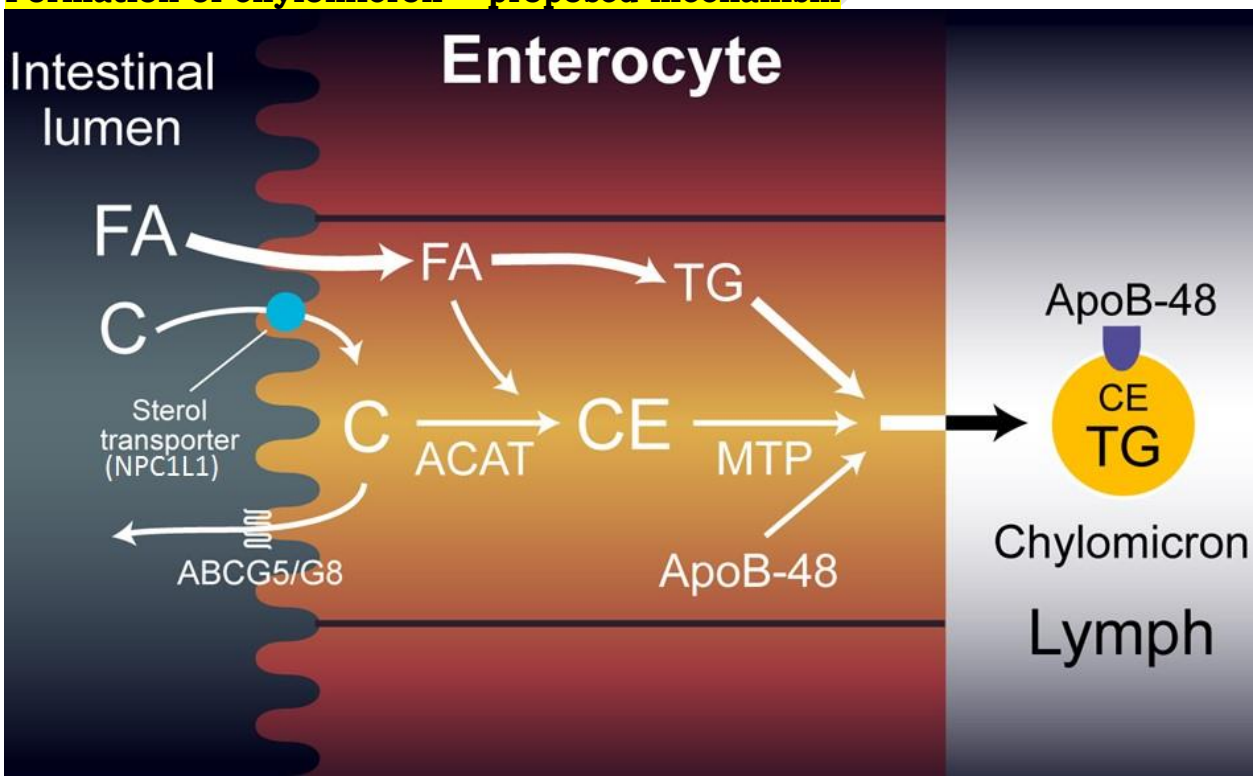
Exogenous Lipoprotein Pathway



Endogenous lipoprotein pathway



Formation of chylomicron -- proposed mechanism



FREDERICKSON CLASSIFICATION OF HYPERLIPOPROTEINEMIAS

PHENOTYPE	I	IIa	IIb	III	IV	V
Lipoprotein, elevated	Chylomicrons	LDL	LDL and VLDL	Chylomicron and VLDL remnants	VLDL	Chylomicrons and VLDL
Triglycerides	++++	–	++	++ to +++	++	++++
Cholesterol	+ to ++	+++	++ to +++	++ to +++	– to +	++ to +++
LDL-cholesterol	↓	↑	↑	↓	↓	↓
HDL-cholesterol	+++	+	++	++	++	+++
Plasma appearance	Lactescent	Clear	Clear	Turbid	Turbid	Lactescent
Xanthomas	Eruptive	Tendon, tuberous	None	Palmar, tuberoeruptive	None	Eruptive
Pancreatitis	+++	0	0	0	0	+++
Coronary atherosclerosis	0	+++	+++	+++	+/–	+/–
Peripheral atherosclerosis	0	+	+	++	+/–	+/–
Molecular defects	LPL and apoC-II	LDL receptor, apoB100, PCSK9, ARH, ABCG5 and ABCG8	Unknown	ApoE	ApoA-V and unknown	ApoA-V and unknown
Genetic nomenclature	FCS	FH, FDB, ADH, ARH, sitosterolemia	FCHL	FDBL	FHTG	FHTG

Note: LPL, lipoprotein lipase; apo, apolipoprotein; FCS, familial chylomicronemia syndrome; FH, familial hypercholesterolemia; FDB, familial defective apoB; ARH, autosomal recessive hypercholesterolemia; ADH, autosomal dominant hypercholesterolemia; FCHL, familial combined hyperlipidemia; FDBL, familial dysbetalipoproteinemia; FHTG, familial hypertriglyceridemia.

AACE LIPID GUIDELINES : SUMMARY

Table 5
Major Atherosclerotic Cardiovascular Disease Risk Factors

Major risk factors	Additional risk factors	Nontraditional risk factors
Advancing age[a-d] ⇧ Total serum cholesterol level[a,b,d] ⇧ Non–HDL-C[d] ⇧ LDL-C[a,d] Low HDL-C[a,d,e] Diabetes mellitus[a-d] Hypertension[a-d] Chronic kidney disease 3,4[h] Cigarette smoking[a-d] Family history of ASCVD[a,d,g]	Obesity, abdominal obesity[c,d] Family history of hyperlipidemia[d] ⇧ Small, dense LDL-C[d] ⇧ Apo B[d] ⇧LDL particle concentration Fasting/post-prandial hypertriglyceridemia[d] PCOS[d] Dyslipidemic triad[f]	⇧Lipoprotein (a) ⇧ Clotting factors ⇧ Inflammation markers (hsCRP; Lp-PLA$_2$) ⇧Homocysteine levels Apo E4 isoform ⇧ Uric acid ⇧ TG-rich remnants

Table 6
Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors[a]/10-year risk[b]	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – Diabetes or CKD 3/4 with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10-20% – Diabetes or CKD 3/4 with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Screening Recommendations by AACE

Familial hypercholesterolemia

Individuals should be screened for familial hypercholesterolemia (FH) when there is a family history of:

• Premature ASCVD (definite MI or sudden death before age 55 years in father or other male firstdegree relative, or before age 65 years in mother or other female first-degree relative)

or

• Elevated cholesterol levels (total, non-HDL and/or LDL) consistent with FH

Diabetes

Annually screen all adult individuals with T1DM or T2DM for dyslipidemia

Young Adults (Men Aged 20-45 Years, Women Aged 20-55 Years)

Evaluate all adults 20 years of age or older for dyslipidemia every 5 years as part of a global risk Assessment

Middle-Aged Adults (Men Aged 45-65 Years, Women Aged 55-65 Years)

In the absence of ASCVD risk factors, screen middle-aged individuals for dyslipidemia at least once every 1 to 2 years. More frequent lipid testing is recommended when multiple global ASCVD risk factors are present.

Older Adults (Older Than 65 Years)

Annually screen older adults with 0 to 1 ASCVD risk factor for dyslipidemia.

TABLE 21-5

SECONDARY FORMS OF HYPERLIPIDEMIA

LDL		HDL		VLDL	IDL	CHYLOMICRONS	Lp(a)
ELEVATED	REDUCED	ELEVATED	REDUCED	ELEVATED	ELEVATED	ELEVATED	ELEVATED
Hypothyroidism	Severe liver disease	Alcohol	Smoking	Obesity	Multiple myeloma	Autoimmune disease	Renal insufficiency
Nephrotic syndrome	Malabsorption	Exercise	DM type 2	DM type 2	Monoclonal gammopathy	DM type 2	Inflammation
Cholestasis	Malnutrition	Exposure to chlorinated hydrocarbons	Obesity	Glycogen storage disease	Autoimmune disease		Menopause
Acute intermittent porphyria	Gaucher's disease	Drugs: estrogen	Malnutrition	Hepatitis	Hypothyroidism		Orchidectomy
Anorexia nervosa	Chronic infectious disease		Gaucher's disease	Alcohol			Hyperthyroidism
Hepatoma	Hypothyroidism		Drugs: anabolic steroids, beta blockers	Renal failure			Acromegaly
Drugs: thiazides, cyclosporin, tegretol	Drugs: niacin toxicity			Sepsis			Nephrosis
				Stress			Drugs: growth hormone, isotretinoin
				Cushing's syndrome			
				Pregnancy			
				Acromegaly			
				Lipodystrophy			
				Drugs: estrogen, beta blockers, glucocorticoids, bile acid–binding resins, retinoic acid			

Note: LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low density lipoprotein; IDL, intermediate-density lipoprotein; Lp(a), lipoprotein A; DM, diabetes mellitus.

WHICH SCREENING TESTS ARE RECOMMENDED FOR THE DETECTION OF CARDIOVASCULAR RISK?

1. Use a **fasting lipid profile** to ensure the most precise lipid assessment; this should include total cholesterol,LDL-C, TG, and non-HDL-C.

2. LDL-C may be estimated using the **Friedewald equation: LDL-C = (total cholesterol – HDL-C) –TG/5**; however, this method is valid only for values obtained during the fasting state and becomes increasingly inaccurate and invalid when TG levels are greater than 200 mg/dL and 400 mg/dL, respectively

*TG levels should be part of routine lipid screening: moderate elevations (**≥150 mg/dL) may identify individuals at risk for the insulin resistance syndrome** and levels ≥200 mg/dL may identify individuals at substantially increased ASCVD risk*

Apo B measurements (reflecting the particle concentration of LDL and all other atherogenic lipoproteins) may be useful to assess the success of LDL-C– lowering therapy.

Apo B and/or an apo B/apo A1 ratio calculation and evaluation may be useful in at-risk individuals **(TG ≥150, HDL-C <40, prior ASCVD event, T2DM, and/or the insulin resistance syndrome** [even at target LDL-C levels]) to assess residual risk and guide decision-making

Use **hsCRP to stratify ASCVD risk in individuals with a standard risk assessment that is borderline**, or in those with an intermediate or higher risk with an LDL-C concentration <130 mg/dL

Measure **lipoprotein-associated phospholipase A2 (Lp-PLA2)**, which in some studies has demonstrated more specificity than hsCRP, when it is necessary to further stratify an individual's ASCVD risk, especially in the presence of hsCRP elevations.

The routine measurement of homocysteine, uric acid, plasminogen activator inhibitor-1, or other inflammatory markers is not recommended because the benefit of doing so is not sufficiently proven

Coronary artery calcification (CAC) measurement has been shown to be of high predictive value and is useful in refining risk stratification.

Carotid intima media thickness (CIMT) may be considered to refine risk stratification to determine the need for more aggressive ASCVD preventive strategies

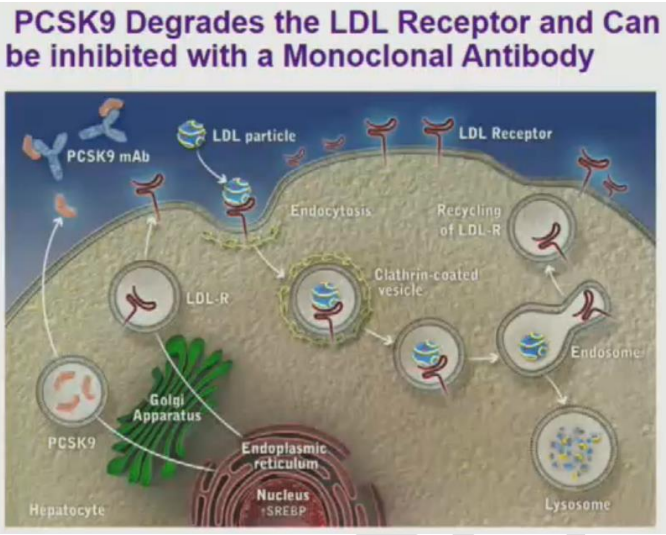
Lipoprotein(a)	- Elevated in aortic stenosis
Hypothyroidism and dyslipidemia	- Always rule out hypothyroidism
Role of fibrates in Diabetes	- Reduces risk of retinopathy

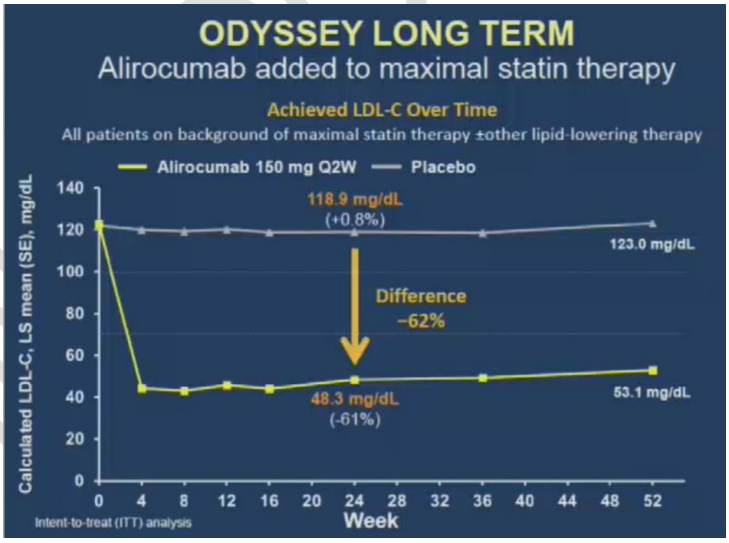
Table 11 Common Secondary Causes of Dyslipidemia	
Affected lipids	**Conditions**
↑ Total cholesterol and LDL-C	• Hypothyroidism
	• Nephrosis
	• Dysgammaglobulinemia (systemic lupus erythematosus, multiple myeloma)
	• Progestin[a] or anabolic steroid treatment
	• Cholostatic diseases of the liver due to abnormal lipoproteins, as in primary biliary cirrhosis
	• Protease inhibitors for treatment of HIV infection[b]
↑ TG and VLDL-C	• Chronic renal failure
	• T2DM[c]
	• Obesity
	• Excessive alcohol intake
	• Hypothyroidism
	• Antihypertensive medications (thiazide diuretics and β-adrenergic blocking agents)
	• Corticosteroid therapy (or severe stress that increases endogenous corticosteroids)
	• Orally administered estrogens[d], oral contraceptives, pregnancy
	• Protease inhibitors for treatment of HIV infection[b]

PROFILES FOR THERAPEUTIC OPTIONS.

Table 13 Primary Lipid-Lowering Drug Classes		
Drug class	**Metabolic effect[a]**	**Main considerations[b]**
HMG-CoA reductase inhibitors (statins: lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, rosuvastatin, pitavastatin)	Primarily ↓ LDL-C 21-55% by competitively inhibiting rate-limiting step of cholesterol synthesis in the liver, leading to upregulation of hepatic LDL receptors Effects on TG and HDL-C are less pronounced (↓ TG 6-30% and ↑ HDL-C 2-10%)	Liver function test prior to therapy and as clinically indicated thereafter. Myalgias and muscle weakness in some patients Potential for drug-drug interaction between some statins and CYP450 3A4 inhibitors, cyclosporine, warfarin, and protease inhibitors. Myopathy/rhabdomyolysis in rare cases; increased risk with co-administration of some drugs (see product labeling). Simvastatin dosages of 80 mg are no longer recommended. Do not exceed 20 mg simvastatin daily with amlodipine or ranolazine. Plasma elevations of rosuvastatin may be higher among Asian persons than other ethnic groups. New-onset diabetes is increased in patients treated with statins; however, it is dose-related, occurs primarily in patients with MetS, appears to be less common with pravastatin and possibly pitavastatin, and occurs overall to a lesser extent than the associated decrease in ASCVD.
Cholesterol absorption inhibitors (ezetimibe)	Primarily ↓ LDL-C 10-18% by inhibiting intestinal absorption of cholesterol and decreasing delivery to the liver, leading to upregulation of hepatic LDL receptors ↓ Apo B 11-16% In combination with statins, additional ↓ LDL-C 25%, total ↓ LDL-C 34-61% In combination with fenofibrate, ↓ LDL-C 20-22% and ↓ apo B 25-26% without reducing ↑ HDL-C	Myopathy/rhabdomyolysis (rare) Myopathy/ rhabdomyolysis (rare) When co-administered with statins or fenofibrate, risks associated with those drugs remain (e.g., myopathy/ rhabdomyolysis, cholelithiasis)

PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors (alirocumab, evolocumab)	↓LDL-C 48-71%, ↓ non-HDL-C 49-58%, ↓Total-C 36-42%, ↓Apo B 42-55% by inhibiting PCSK9 binding with LDLRs, increasing the number of LDLRs available to clear LDL, and lowering LDL-C levels	Requires subQ self-injection, and refrigeration is generally needed. Adverse reactions resulted in discontinuation in 2.2% overall, 1.2% more than placebo for evolocumab, and 5.3% overall, 0.2% more than placebo for alirocumab. Overall levels of adverse reactions and discontinuation very low. Adverse reactions with significantly different rates between drug and placebo were local injection site reactions (1.9% greater for alirocumab vs. placebo, 0.7% greater for evolocumab vs. placebo) and influenza (1.2% greater for alirocumab vs. placebo, 0.2% for evolocumab vs. placebo). The most common adverse reactions with similar rates for drug vs. placebo were for the following: Alirocumab (4-12%; most common to least common): nasopharyngitis, influenza, urinary tract infections, diarrhea, bronchitis, and myalgia; Evolocumab (2-4%; most common to least common): Nasopharyngitis, back pain, and upper respiratory tract infection.





Fibric acid derivatives (gemfibrozil, fenofibrate, fenofibric acid)	Primarily ↓ TG 20-35%, ↑ HDL-C 6-18% by stimulating lipoprotein lipase activity Fenofibrate may ↓ TC and LDL-C 20-25% Lower VLDL-C and LDL-C; reciprocal rise in LDL-C transforms the profile into a less atherogenic form by shifting fewer LDL particles to larger size Fenofibrate ↓ fibrinogen level	Gemfibrozil may ↑ LDL-C 10-15%. GI symptoms, possible cholelithiasis. May potentiate effects of orally administered anticoagulants. Gemfibrozil may ↑ fibrinogen level[c]. Gemfibrozil and fenofibrate can ↑ homocysteine independent of vitamin concentrations[d]. Myopathy/rhabdomyolysis when used with statin (uncommon with gemfibrozil, but increased risk with all statins except fluvastatin); interaction less likely with fenofibrate or fenofibric acid (no apparent difference by statin). Fibrates are associated with increased serum creatinine levels, which may not reflect renal dysfunction. Fenofibrate dose should be cut by two-thirds and gemofibrozil by one-half when eGFR is 15-60, and fibrates should be avoided when eGFR is <15. May cause muscle disorders. Can improve diabetic retinopathy.

Niacin (nicotinic acid)	↓ LDL-C 10-25%, ↓ TG 20-30%, ↑ HDL-C 10-35% by decreasing hepatic synthesis of LDL-C and VLDL-C ↓ Lipoprotein (a) Transforms LDL-C to less atherogenic form by increasing average particle size and also decreases LDL particle concentration	Potential for frequent skin flushing, pruritus, abdominal discomfort, hepatotoxicity (rare but may be severe), nausea, peptic ulcer, atrial fibrillation. Deleterious effect on serum glucose at higher dosages. Increases uric acid levels; may lead to gout.
Bile acid sequestrants (cholestyramine, colestipol, colesevelam hydrochloride)	Primarily ↓ LDL-C 15-25% by binding bile acids and preventing their reabsorption in the ileum (causing hepatic cholesterol depletion and LDLR upregulation) Colesevelam ↓ glucose and hemoglobin A1C (~0.5%); is FDA approved to treat T2DM	May ↑ serum TG Frequent constipation and/or bloating, which can reduce adherence Many potential drug interactions (decreased drug absorption), less so with colesevelam (see product labeling) May reduce absorption of folic acid and fat-soluble vitamins such as vitamins A, D, and K

MTP inhibitor (lomitapide)	↓ Up to LDL-C 40%, TC 36%, apo B 39%, TG 45%, and non-HDL-C 40% (depending on dose) in patients with HoFH by binding and inhibiting MTP, which inhibits synthesis of chylomicrons and VLDL	Can cause increases in transaminases (ALT, AST). Monitoring of ALT, AST, alkaline phosphatase, and total bilirubin prior to initiation, and of ALT and AST during treatment, is required per FDA REMS. Causes increases in hepatic fat (steatosis) with or without concomitant elevated transaminases, which may be a risk for progressive liver diseases. Also causes steatosis of the small intestine with resulting abdominal pain and steatorrhea unless a very-low-fat diet is followed. May also cause fat-soluble vitamin deficiency unless vitamin supplements are taken. Caution should be exercised when used with other drugs with potential hepatotoxicity. Because of hepatotoxicity risk, only available through REMS program.

Omega-3 fatty acids (icosapent ethyl, omega-3-acid ethyl esters)	↓ TG 27-45%, TC 7-10%, VLDL-C 20-42%, apo B 4%, and non-HDL-C 8-14% in individuals with severe hypertriglyceridemia, most likely by reducing hepatic VLDL-TG synthesis and/or secretion and enhancing TG clearance from circulating VLDL particles. Other potential mechanisms of action include: increased ß-oxidation; inhibition of acyl-CoA; 1,2-diacylglyceral acyltransferase; decreased hepatic lipogenesis; and increased plasma lipoprotein activity Icosapent ethyl ↓ LDL-C 5%, whereas omega-3-acid ethyl esters ↑ LDL-C 45%	TG levels should be carefully assessed prior to initiating therapy and periodically during therapy. Omega-3-acid ethyl esters can increase LDL-C levels. Monitoring of LDL-C levels during treatment is recommended. May prolong bleeding time. Periodic monitoring of coagulation status should be undertaken in patients receiving treatment with omega-3 fatty acids and other drugs affecting coagulation. Periodic monitoring of ALT and AST levels during treatment is recommended for patients with hepatic impairment. Some patients may experience increases in ALT levels only. Caution should be exercised when treating patients with a known hypersensitivity to fish and/or shellfish. The effect of omega-3 fatty acids on cardiovascular morbidity and mortality and the risk of pancreatitis has not been determined in patients with severe hypertriglyceridemia. In patients with paroxysmal or persistent AF, therapy with omega-3-acid ethyl esters may be associated with increased frequency of symptomatic AF or flutter, especially within the first 2 to 3 months after initiation. The most common adverse events in patients receiving omega-3 fatty acids included arthralgia (2.3%), eructation (4%), dyspepsia (3%), and taste perversion (4%). Patients may also experience constipation, gastrointestinal disorders, vomiting, rash, or pruritus. Omega-3 fatty acids should be used with caution in nursing mothers and should only be used in pregnant women if the benefits of treatment outweigh the potential risk of fetal harm.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) Inhibitors

PCSK9 inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH.

- PCSK9 inhibitors should be considered in individuals with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy.
- They should not be used as monotherapy except in statin-intolerant individuals

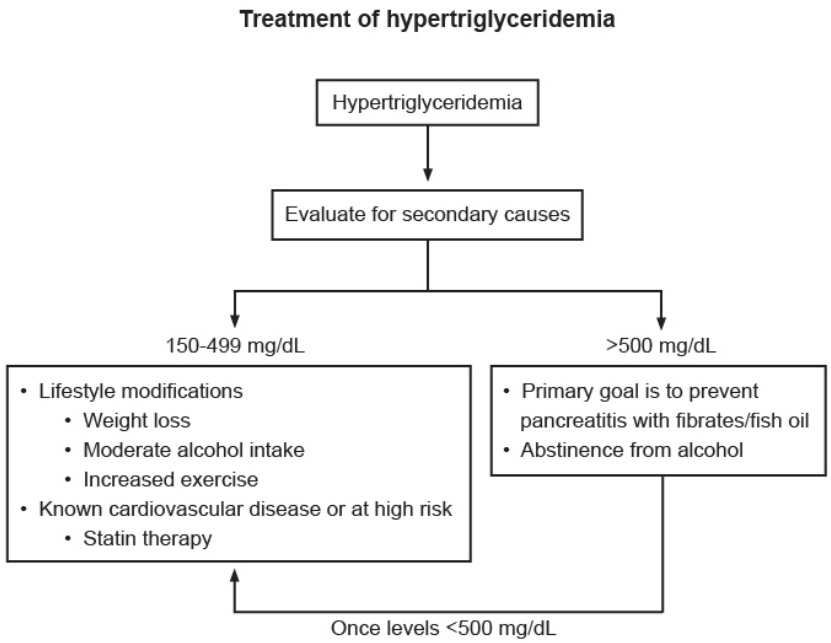
Follow-up and Monitoring

Re-assess individuals' lipid status 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved.

While on stable lipid therapy, individuals should be tested at 6- to 12-month intervals.

Liver transaminase levels should be measured before and 3 months after niacin or fibric acid treatment initiation because most liver abnormalities occur within 3 months of treatment initiation. Liver transaminase levels should be measured periodically thereafter (e.g., semiannually or annually)

Creatine kinase levels should be assessed and the statin discontinued, at least temporarily, when an individual reports clinically significant myalgias or muscle weakness on statin therapy.



Conditions resembling statin myopathy
• Alcohol-induced myopathy • Connective tissue disease (eg, SLE, RA) • Electrolyte disturbances (eg, hypokalemia) • Endocrine (eg, hypo/hyperthyroidism, hypo/hyperparathyroidism, Cushing's disease, Addison's disease, acromegaly) • Fibromyalgia • Peripheral neuropathy • Peripheral vascular disease • Polymyositis/dermatomyositis • Vitamin D deficiency

RA = rheumatoid arthritis; **SLE** = systemic lupus erythematosus.

AHA/ACC Guidelines 2013

4 major statin benefit groups were identified for whom the ASCVD risk reduction clearly outweighs the risk of adverse events based on a strong body of evidence.

1) secondary prevention in individuals with **clinical ASCVD**
2) **primary prevention** in individuals with **primary elevations of LDL-C 190 mg/dl**
3) primary prevention in individuals with diabetes **40 to 75 years of age** who have **LDL-C 70 to 189 mg/dL**
4) primary prevention in individuals without diabetes and with estimated 10-year ASCVD risk 7.5%, 40 to 75 years of age who have LDL-C 70 to 189 mg/dL.

Moderate evidence supports the use of statins for primary prevention in individuals with 5% to <7.5% 10-year ASCVD risk, 40 to75 years of age with LDL-C 70 to 189 mg/dL.

Selected individuals with <5% 10-year ASCVD risk, or <40 or >75 years of age may also benefit from statin therapy.

➤ **Endocrine board pearl**

Guidelines for lipid-lowering therapy	
Indication	**Recommended therapy**
Clinically significant atherosclerotic disease • ACS, MI • Stable or unstable angina • Coronary or other arterial revascularization • Stroke, TIA, PAD	• **Age ≤75:** High-intensity statin • **Age >75:** Moderate-intensity statin
LDL ≥190 mg/dL	**High-intensity statin**
Age 40-75 with diabetes	• **10-year ASCVD risk ≥7.5%:** High-intensity statin • **10-year ASCVD risk <7.5%:** Moderate-intensity statin
Estimated 10-year ASCVD risk ≥7.5% (Pooled Cohort Equations)	Moderate- to high-intensity statin*

ACS = Acute coronary syndrome; **ASCVD** = atherosclerotic cardiovascular disease; **MI** = myocardial infarction; **PAD** = peripheral arterial disease; **TIA** = transient ischemic attack.

* High-intensity statins include atorvastatin 40-80 mg, rosuvastatin 20-40 mg; moderate-intensity statins include atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40-80 mg, lovastatin 40 mg.

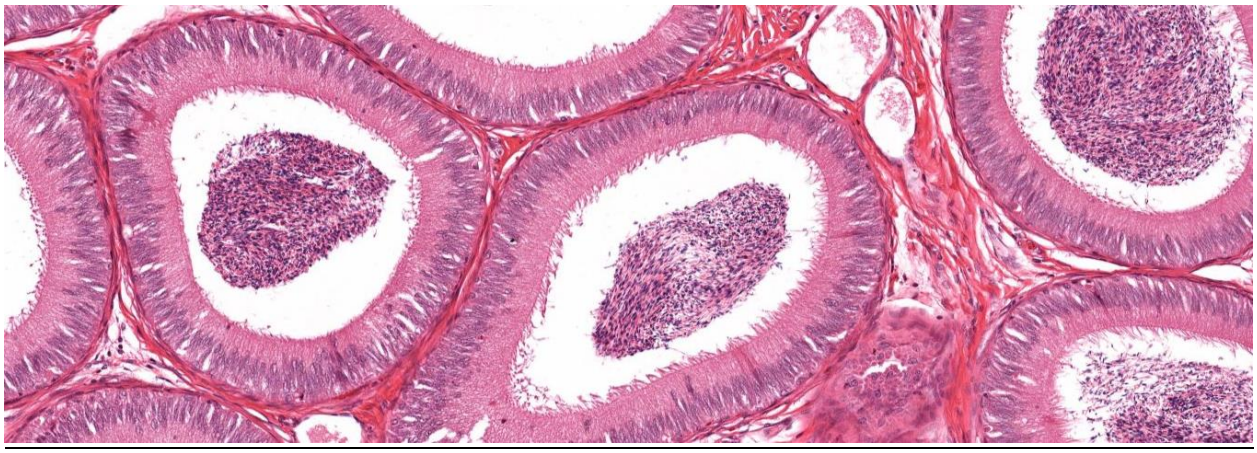
Clinical pearls (statin induced myopathy)

- **A**miodarone decreases statin metabolism (especially lovastatin, simvastatin and **a**torvastatin - these are lipid soluble statins) through **CYP3A4 inhibition in the liver,** which can substantially increase risk of muscle injury. (MNEMONIC Amiodorane causes muscle weakness (ALS , Lou-Gherig) with these statins. A …. L …. S
- Alternative statins in the setting would be **Rosuvastatin, fluvastatin and pravastatin. (these are water soluble statins)**

Table 5. High-, Moderate-, and Low-Intensity Statin Therapy (Used in the RCTs Reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by <30%
Atorvastatin (40†)–80 mg	**Atorvastatin 10 (*20*) mg**	*Simvastatin 10 mg*
Rosuvastatin 20 (*40*) mg	**Rosuvastatin (*5*) 10 mg**	**Pravastatin 10–20 mg**
	Simvastatin 20–40 mg‡	**Lovastatin 20 mg**
	Pravastatin 40 (*80*) mg	*Fluvastatin 20–40 mg*
	Lovastatin 40 mg	*Pitavastatin 1 mg*
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2–4 mg	

REPRODUCTIVE ENDOCRINOLOGY



Male Reproduction	**7%** of Exam
Hypogonadism	2%
Testosterone in hypogonadism	
Sex hormone binding globulin (SHBG)-dependent changes in testosterone	
Primary hypogonadism	
Secondary hypogonadism	
Genetic disorders of androgen production and action	
Testosterone therapy	
Gonadotropins	
Infertility	<2%
Causes	
Varicocele	
Cryptorchidism	
Klinefelter syndrome	
Cystic fibrosis and cystic fibrosis gene mutations	
Sertoli-cell-only syndrome	
Drug-induced infertility	
Obstructive azoospermia	
Idiopathic oligozoospermia	
Y-chromosome microdeletions	
Treatment	
Gonadotropins	
Testicular sperm extraction	
Intracytoplasmic sperm injection	

Gynecomastia <2%

- Causes
  - Drug-induced gynecomastia
  - Testicular tumors (Sertoli and Leydig cell tumors)
  - Extratesticular tumors
  - Androgen deprivation therapy for prostate cancer
  - Hyperthyroidism
  - Refeeding syndrome
  - Pubertal gynecomastia
  - Idiopathic gynecomastia
  - Congenital and familial aromatase excess syndromes
- Treatment
  - Tamoxifen
  - Aromatase inhibitors
  - Mammoplasty and mastectomy

Erectile dysfunction <2%

- Causes
  - Smoking
  - Diabetes mellitus
  - Hypertension
  - Hyperlipidemia
  - Peyronie's disease
  - Pelvic and prostate surgery
  - Obesity
- Diagnostic tests
  - Penile duplex Doppler ultrasound
  - Corpus cavernosography
- Treatment
  - Phosphodiesterase-5 and nonspecific phosphodiesterase inhibitors
  - Prostaglandin E1, intraurethral and intracavernosal
  - Alpha-adrenergic blockers
  - Penis pump (penile vacuum device)
  - Penile implant

Testosterone in aging men <2%

Abuse of androgens and anabolic steroids <2%

Sexual differentiation <2%

- Gender dysphoria
- Male-to-female transgender management

Ejaculatory dysfunctions <2%

- Premature ejaculation
- Delayed ejaculation

Disorders of sexual development/function
Testosterone Deficiency

- Total testosterone levels <300ng/dL in a blood sample b/n 7 and 10am in patients with clinical features is suggestive of testosterone deficiency.
- Circadian rhythm with highest levels at 8am and lowest levels at 8pm
- Free testosterone levels are measured in obese or elderly patients.
- Treatment: TD or IM testosterone preparations

Features suggestive of testosterone deficiency
• Incomplete sexual development • Decreased libido and potency • Decreased early-morning erections • Gynecomastia • Decreased secondary sexual characters (eg, decreased shaving frequency) • Small testicles (normal adult testes: length, 4-7 cm; volume, 20-25 mL) • Hot flashes (severe hypogonadism) • Low sperm count • Osteoporosis

Indications for pituitary MRI in patients with central hypogonadism
• Testosterone levels < 150 ng/dL (age > 65), < 200 ng/dL (age < 65) • Mass effects (e.g., headache and visual field defect) • Multiple pituitary hormone deficiencies (e.g., growth hormone, thyroid) • Hyperprolactinemia

Common causes of hypogonadotropic hypogonadism in men
• Gonadotroph cell damage (eg, tumor, trauma, suprasellar surgery or radiation, infiltrative diseases, apoplexy) • Prolactinoma • Cushing syndrome (endogenous & iatrogenic) • Narcotic use • Severe systemic illness • Diabetes mellitus • Hemochromatosis • Anabolic steroid & testosterone use • Morbid obesity

Hirsutism

- This is **excess terminal hair growth** (dark, coarse hair) in MALE PATTERN NOT **androgen dependent areas** (chin, upper lip, upper abdomen, chest and back)
- **Hypertrichosis** is however **non-androgen dependent hair growth**. Light unpigmented hair in non-sexual areas and can be due to systemic disorders (eg. hypothyroidism) or medications (phenytoin, minoxidil)

- Excess hair growth can be a normal variant
- All women wth hirsutism should have serum testosterone levels assessed to evaluate for an underlying androgen disorder. **Testosterone levels >150ng/dL** suggest possible androgen secreting tumor and will require pelvic USG.

axillary and pubic hair common to **both men and women** are also present in an androgen dependent
area but are not included in the "male pattern."

Hair are of two types: **terminal and vellus. The terminal hair are thick, coarse, and pigmented and are present in androgen-dependent areas as opposed to vellus hair which are fine, thin, and unpigmented and are distributed all over the body.

**Hair present in almost all areas of the body is androgen dependent except eyebrows, eyelashes, nostrils, and lateral and occipital scalp hair (asexual hair). The axillary and pubic hair are common to both gender and are sensitive to low levels of androgen (ambosexual hair).

hair on the upper lip, chin, chest, upper arms, abdomen, back, and thighs require a higher level of androgens and characterize the "male pattern" (sexual hair). On the contrary, **scalp hair are the
only exception where **androgen excess results in regression**. **This is due to shortened
anagen phase and possibly androgen receptor downregulation**.

Modified Ferriman–Gallaway score is an objective score to define hirsutism, and a score >8 is considered as significant. A score of 8–15 is classified as mild hirsutism and >15–36 as moderate to severe hirsutism

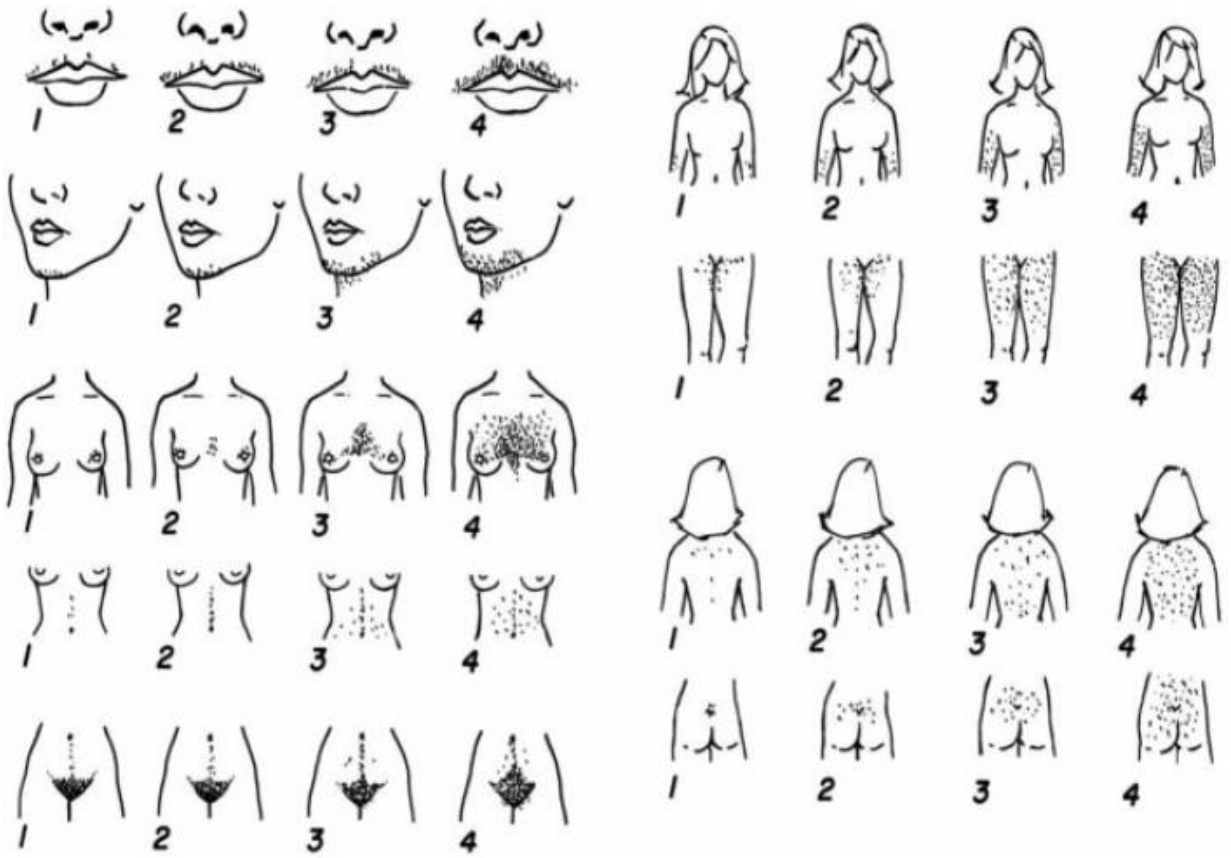


FIG. 1. Ferriman-Gallwey hirsutism scoring system. Each of the nine body areas most sensitive to androgen is assigned a score from 0 (no hair) to 4 (frankly virile), and these separate scores are summed to provide a hormonal hirsutism score. [Reproduced with permission from R. Hatch *et al.*: *Am J Obstet Gynecol* 140:815–830, 1981 (5). ©Elsevier.]

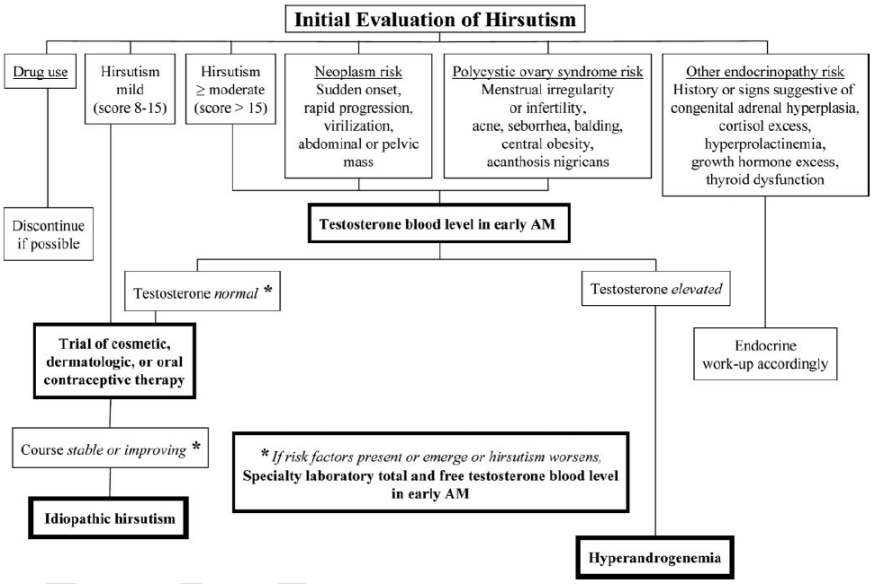
Diagnosis of hirsutism

- Do NOT measure androgen levels for mild hirsutism
- Testing elevated androgens is recommended ….

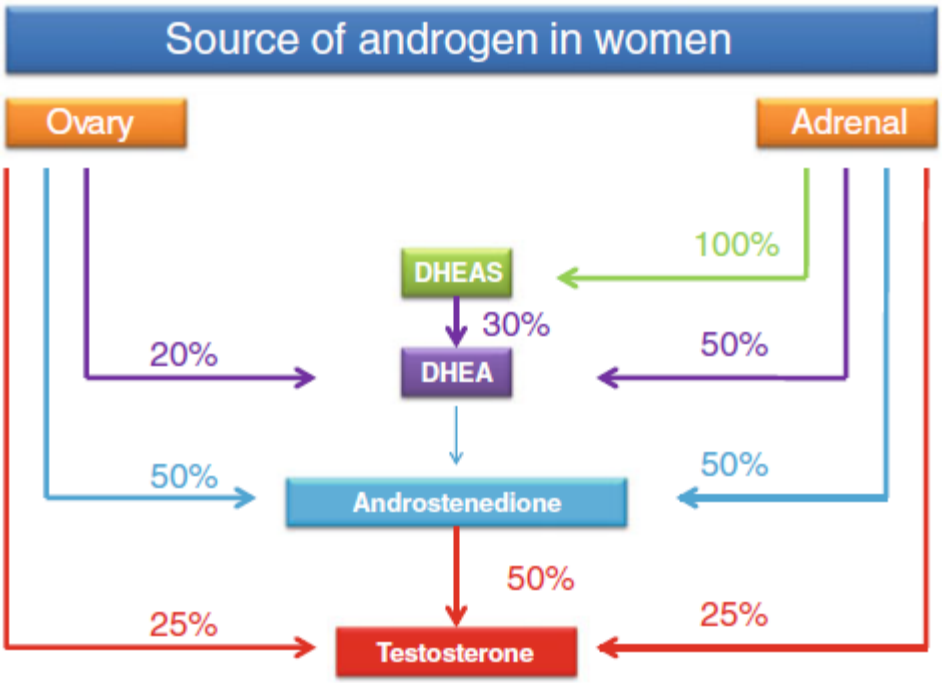
- Moderate or severe hirsutism
- Central obesity
- Acanthosis nigricans
- Rapid progession of hair gain
- clitoromegaly

Causes of hirsutism in women	
Etiology	**Clinical features**
PCOS	• Oligomenorrhea, hyperandrogenism, obesity • Associated with type 2 diabetes, dyslipidemia, hypertension
Idiopathic hirsutism	• Normal menstruation • Normal serum androgens
Nonclassic 21-hydroxylase deficiency	• Similar to PCOS • Elevated serum 17-hydroxyprogesterone
Androgen-secreting ovarian tumors, ovarian hyperthecosis	• More common in postmenopausal women • Rapidly progressive hirsutism with virilization • Very high serum androgens
Cushing syndrome	• Obesity (usually face, neck, trunk, abdomen) • Increased libido, virilization, irregular menses

PCOS = polycystic ovary syndrome.



source of androgens in a woman includes ovary and adrenal. Fifty percent of the circulating testosterone is directly produced by the adrenal and ovary, almost in equal proportions, and the rest is derived from the peripheral conversion of *weaker androgens like androstenedione, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS) secreted by the adrenal gland.*



Androgens are normally produced by the ovary and adrenals in women, but when it is associated with clinical features and/or biochemical evidence of androgen excess, they constitute "disorders of androgen excess."

- polycystic ovarian disease
- Lateonset congenital adrenal hyperplasia
- idiopathic hirsutism
- ACTH-dependent Cushing's syndrome
- glucocorticoid resistance syndrome
- Hyperprolactinemia
- virilizing ovarian and adrenal neoplasm.

clinical manifestations of androgen excess

- Hirsutism
- Acne
- Androgenic alopecia
- low-pitch voice
- clitoromegaly.
- oligo- or amenorrhea and anovulation.

The features of **virilization** in a woman include androgenic alopecia, acne, lowpitch voice, male torso, and clitoromegaly. These are the **manifestations of severe androgen excess** and are due to *ovarian/adrenocortical malignancy* or *ovarian hyperthecosis*. ***Hirsutism alone is usually not considered as a feature of virilization.***

Clinical manifestations of defeminization

- breast atrophy
- oligomenorrhea/amenorrhea
- loss of gluteofemoral adiposity

These are the features of estrogen deficiency; however, they may be present with severe virilization, as androgen excess interferes with the binding of estrogen to its nuclear receptor. In a rapidly growing androgen-secreting tumor, features of defeminization precede virilization

Drug Type	Active Ingredient	Example	Major Mechanism	Indication	Contraindications	Dose	Major Side Effects
Cell-cycle inhibitor	Eflornithine hydrochloride, 13.9%	Vaniqa	Irreversible inhibitor of ornithine decarboxylase	Focal hirsutism	Pregnancy, breastfeeding	Topical, twice daily	Rash, potential systemic toxicity with widespread application
Oral contraceptives*	Ethinyl estradiol 30 μg + drospirenone 35 μg + norgestimate 50 μg + ethynodiol diacetate	Yasmin Ortho-Cyclen Demulen 1–50	Suppresses ovarian function	Generalized hirsutism	Breast cancer, smoking (absolutely if age >35 yr), cardiovascular disease, uncontrolled hypertension	1 tablet by mouth at bedtime (the larger estrogen doses may be necessary in heavier women for menstrual regularity)	Irregular vaginal bleeding, venous thrombosis
Antiandrogens	Spironolactone		Competitive inhibitor of androgen-receptor binding	Moderate or severe hirsutism	Lack of contraception, kidney or liver failure	50–100 mg by mouth, twice daily	Male pseudohermaphroditism in fetus, irregular menstrual bleeding unless oral contraceptive administered, decreased libido, nausea, hyperkalemia, hypotension, liver dysfunction
	Cyproterone acetate		Competitive inhibitor of androgen-receptor binding	Moderate or severe hirsutism	Lack of contraception	Induction: 50–100 mg by mouth at bedtime, days 5–15 Maintenance: 5 mg by mouth at bedtime, days 5–15	Male pseudohermaphroditism in fetus, irregular menstrual bleeding unless estrogen administered cyclically, decreased libido, nausea
	Flutamide		Nonsteroidal competitive inhibitor of androgen-receptor binding	Severe hirsutism	Lack of contraception, liver disease	125–250 mg, twice daily	Male pseudohermaphroditism in fetus, hepatotoxicity
Glucocorticoids	Glucocorticoid	Prednisone	Suppresses adrenal function	Congenital adrenal hyperplasia	Uncontrolled diabetes, obesity	5–7.5 mg by mouth at bedtime	Changes typical of Cushing's syndrome, adrenal atrophy
Gonadotropin-releasing agonists	Leuprolide acetate, depot suspension	Lupron Depot	Suppresses gonadotropins	Alternative to oral contraceptive	Osteoporosis	7.5 mg monthly intramuscularly, with 25–50 μg transdermal estradiol	Osteoporosis without estrogen–progestin replacement

* The oral contraceptives included here are examples of preparations with low androgenic activity.

TABLE 1. Antiandrogens used for the treatment of hirsutism

	Dose
CPA[a]	50–100 mg/d on menstrual cycle d 5–15, with ethinyl estradiol 20–35 μg on d 5–25
Spironolactone	100–200 mg/d [given in divided doses (twice daily)]
Finasteride	2.5–5 mg/d
Flutamide	250–500 mg/d (high dose), 62.5 to <250 mg (low dose)

[a] Not available in the United States; also prescribed as an OCP (2 mg CPA plus 35 μg ethinyl estradiol).

TABLE 2. Glucocorticoid preparations used in monotherapy and combined with antiandrogens (spironolactone or CPA)

Glucocorticoid	Dosage	Frequency
Hydrocortisone	10–20 mg	Twice daily
Prednisone[a]	2.5–5 mg	Nightly or alternate days
Dexamethasone	0.25–0.50 mg	Nightly

[a] Prednisone is preferable to dexamethasone because the dose can be more finely titrated to avoid side effects (94).

POLYCYSTIC OVARY SYNDROME

POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS) is a dysmetabolic and reproductive disorder associated with androgen excess in women.

- four separate phenotypes (A to D)
- clinical or biochemical hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (PCOm)
- Women affected by it are often overweight and have oligoanovulation and cutaneous manifestations of androgen excess (hirsutism, hyperseborrhea, acne, androgenetic alopecia).
- *disabling condition from both a clinical and psychosocial point of view*

Parameter	Phenotype A	Phenotype B	Phenotype C	Phenotype D
PCOS features	HA/OD/PCOM	HA/OD	HA/PCOM	OD/PCOM
HA	+	+	+	–
OD	+	+	–	+
PCOM	+	–	+	+
NIH 1990 criteria	X	X		
Rotterdam 2003 criteria	X	X	X	X
AE-PCOS 2006 criteria	X	X	X	

View Table in HTML

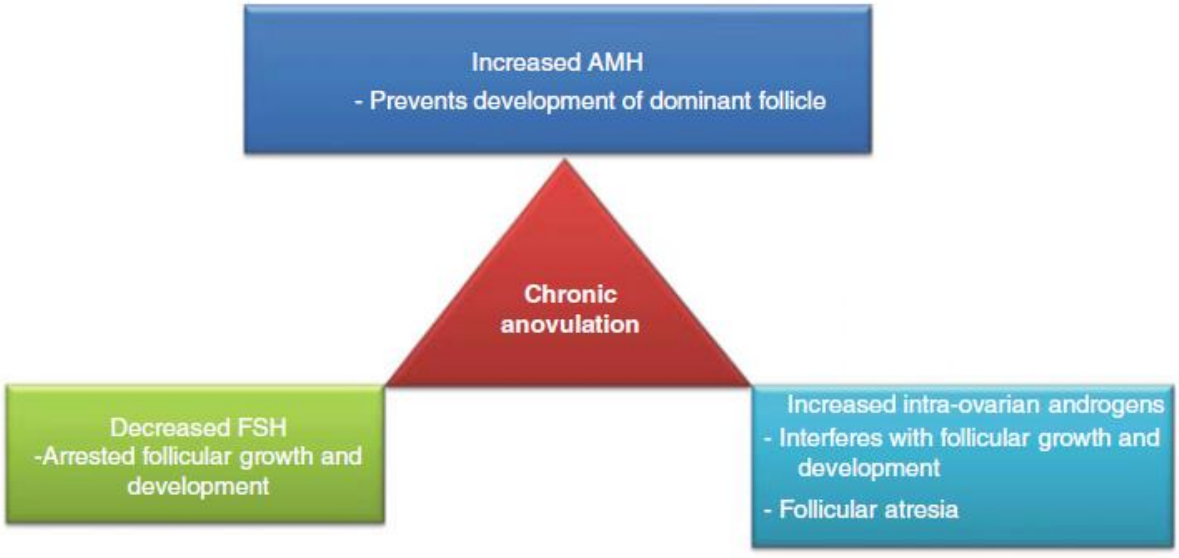
Note: AE-PCOS = Androgen Excess & PCOS Society; HA = hyperandrogenism; NIH = National Institutes of Health; OD = ovulatory dysfunction; PCOM = polycystic ovarian morphology.

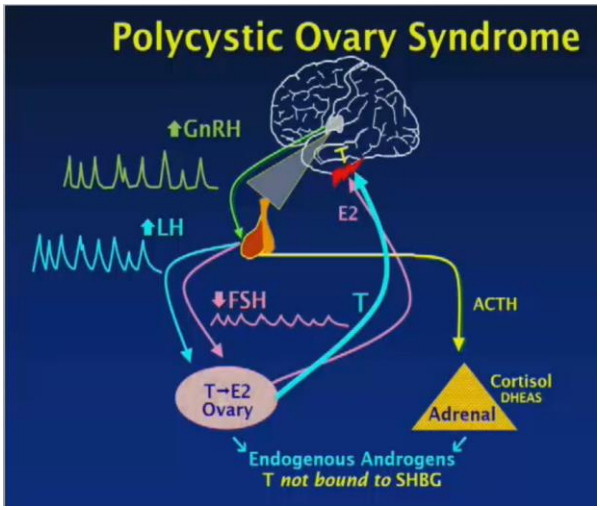
"Classic" PCOS (Phenotypes A and B)	• more pronounced menstrual dysfunction • increased insulin levels • higher rates of insulin resistance • risk for metabolic syndrome

	• prevalence of obesity • severe forms of atherogenic dyslipidemia • **increased risk of hepatic steatosis** • **highest antimüllerian hormone levels**
"Ovulatory PCOS" (Phenotype C)	• *intermediate levels of serum androgens, insulin, atherogenic lipids, hirsutism scores, and prevalence of metabolic syndrome*
"Nonhyperandrogenic PCOS" (Phenotype D)	• mildest degree of endocrine and metabolic dysfunction and the lowest prevalence of metabolic syndrome • lower LH to FSH ratios, lower total and free T levels, and higher sex hormone-binding globulin levels, as compared with subjects with classic PCOS

Polycystic ovarian syndrome (PCOS) is characterized by clinical and/or biochemical hyperandrogenism, menstrual irregularities, and polycystic ovaries. The classic syndrome originally described by **Stein–Leventhal** was based on the histomorphological description of the ovary.

- PCOS may not necessarily have polycystic ovaries.
- Insulin resistance is the prime abnormality in the pathogenesis of PCOS;





A treatise on pathophysiology of PCOS

1) Increased GnRH released from hypothalamus, increased pulse generation increases LH release and simultaneously decreases FSH release [differential release of gonadotrophs is based on pulse frequency] NB theca cells of ovaries make testosterone under direct stimulation by LH. Testosterone moves to the granulosa cells where it is aromatized to estradiol. Ability of the granulosa cells to aromatize T-E2 is based on their maturity, which is under direct control by FSH

2) These theca cells have increased steroidogenic pathway activity resulting in increased production of androgens

3) Increase testosterone circulation leads to hyperandrogenemia. Sensitivity of hair follicle to androgens (role of 5 alpha reductase, genetics etc determines the presence of hirsutism. As such not all patients will be hirsute!)

4) Increased testosterone interferes with estradiol's ability to slow down the GnRH pulse generator in the hypothalamus. This leads to the vicious cycle of PCOS.

5) There is also increased androgen production from the adrenals of 30% of women with PCOS. What is increased is actually endogenous androgens not bound to SHBG.

Polycystic ovary syndrome	
Diagnostic criteria	≥2 of 3 of the following: • Androgen excess: Biochemical or clinical (hirsutism, acne, androgenic alopecia) • Oligo- or anovulation • Polycystic ovaries on ultrasound: ≥12 follicles 2-9 mm in diameter or ovarian volume >10 mL **AND** Exclusion of other hyperandrogenic conditions (eg, hypothyroidism, hyperprolactinemia, nonclassic CAH, Cushing syndrome, androgen-secreting tumors)
Comorbidities	• Glucose intolerance/diabetes • Dyslipidemia • Obstructive sleep apnea • Hypertension • Nonalcoholic steatohepatitis
Treatment goals	• Management of hyperandrogenism • Improvement of reproductive function (eg, regular menses) • Ovulation induction for women who desire pregnancy • Prevention/management of comorbidities

CAH = congenital adrenal hyperplasia

Recommendations	Clinical or biochemical hyperandrogenism	Menstrual irregularity	Ultrasound criteria	Remarks
NIH	Must	Must	–	Only based on clinical and biochemical criteria
Rotterdam	May be	May be	May be	2 out of 3, more practical
Androgen Excess Society	Must	May be	May be	Focus only on hyperandrogenism
Endocrine Society Guideline	May be	May be	May be	2 out of 3, more practical

- Rotterdam/Endocrine society criteria are most useful in clinical practice.
- All guidelines essentially include clinical and/or biochemical hyperandrogenism and menstrual irregularities with or without polycystic ovaries on imaging.
- Ethnic variability in quantification of hirsute score, lack of assessmentof tissue sensitivity to androgens, alterations in androgen levels with age, and non-standardization of androgen assays across the laboratories are the deficits associated with criteria based on clinical and/or biochemical hyperandrogenism.

Table 2. Diagnostic Strengths and Weaknesses of the Main Features of PCOS as Adapted from the NIH Evidence-Based Methodology Workshop on PCOS

Diagnostic Criteria	Strength	Limitation
Hyperandrogenism	Included as a component in all major classifications	Measurement is performed only in blood
	A major clinical concern for patients	Concentrations differ during time of day
	Animal models employing androgen excess resembling but not fully mimicking human disease	Concentrations differ with age Normative data are not clearly defined Assays are not standardized across laboratories Clinical hyperandrogenism is difficult to quantify and may vary by ethnic group, eg, low rates of hirsutism in women with PCOS from east Asia Tissue sensitivity is not assessed
Ovulatory dysfunction	Included as a component in all major classifications	Normal ovulation is poorly defined
	A major clinical concern for patients	Normal ovulation varies over a woman's lifetime
	Infertility a common clinical complaint	Ovulatory dysfunction is difficult to measure objectively Anovulatory cycles may have bleeding patterns that are interpreted as normal
PCO morphology	Historically associated with syndrome	Technique dependent
	May be associated with hypersensitivity to ovarian stimulation	Difficult to obtain standardized measurement Lack of normative standards across the menstrual cycle and lifespan (notably in adolescence) May be present in other disorders that mimic PCOS Technology required to accurately image not universally available Transvaginal imaging possibly inappropriate in certain circumstances (eg, adolescence) or certain cultures

Common causes of **secondary PCOS are hypothyroidism, Cushing's syndrome, acromegaly, hyperprolactinemia, thyrotoxicosis, and late-onset CAH**. These disorders are associated with androgen excess, variability in LH pulses, alterations in sex hormone-binding globulin (SHBG), and/or insulin resistance. Therefore, all patients with PCOS should have a baseline TSH, prolactin, and 17 α-hydroxyprogesterone to exclude secondary PCOS.

Table 3. Other Diagnoses to Exclude in All Women Before Making a Diagnosis of PCOS

Disorder	Test	Abnormal Values	Reference for Further Evaluation and Treatment of Abnormal Findings; First Author, Year (Ref.)
Thyroid disease	Serum TSH	TSH > the upper limit of normal suggests hypothyroidism; TSH < the lower limit, usually < 0.1 mIU/L, suggests hyperthyroidism	Ladenson, 2000 (10)
Prolactin excess	Serum prolactin	> Upper limit of normal for the assay	Melmed, 2011 (11)
Nonclassical congenital adrenal hyperplasia	Early morning (before 8 AM) serum 17-OHP	200–400 ng/dL depending on the assay (applicable to the early follicular phase of a normal menstrual cycle as levels rise with ovulation), but a cosyntropin stimulation test (250 μg) is needed if levels fall near the lower limit and should stimulate 17-OHP > 1000 ng/dL	Speiser, 2010 (12)

Table 4. Diagnoses to Consider Excluding in Select Women, Depending on Presentation

Other Diagnoses[a]	Suggestive Features in the Presentation	Tests to Assist in the Diagnosis	Reference for Further Evaluation and Treatment of Abnormal Findings; First Author, Year (Ref.)
Pregnancy	Amenorrhea (as opposed to oligomenorrhea), other signs and symptoms of pregnancy including breast fullness, uterine cramping, etc	Serum or urine hCG (positive)	Morse, 2011 (17)
HA including functional HA	Amenorrhea, clinical history of low body weight/BMI, excessive exercise, and a physical exam in which signs of androgen excess are lacking; multifollicular ovaries are sometimes present	Serum LH and FSH (both low to low normal), serum estradiol (low)	Wang, 2008 (18)
Primary ovarian insufficiency	Amenorrhea combined with symptoms of estrogen deficiency including hot flashes and urogenital symptoms	Serum FSH (elevated), serum estradiol (low)	Nelson, 2009 (296)
Androgen-secreting tumor	Virilization including change in voice, male pattern androgenic alopecia, and clitoromegaly; rapid onset of symptoms	Serum T and DHEAS levels (markedly elevated), ultrasound imaging of ovaries, MRI of adrenal glands (mass or tumor present)	Carmina, 2006 (16)
Cushing's syndrome	Many of the signs and symptoms of PCOS can overlap with Cushing's (ie, striae, obesity, dorsocervical fat (ie, buffalo hump, glucose intolerance); however, Cushing's is more likely to be present when a large number of signs and symptoms, especially those with high discriminatory index (eg, myopathy, plethora, violaceous striae, easy bruising) are present, and this presentation should lead to screening	24-h urinary collection for urinary free cortisol (elevated), late night salivary cortisol (elevated), overnight dexamethasone suppression test (failure to suppress morning serum cortisol level)	Nieman, 2008 (19)
Acromegaly	Oligomenorrhea and skin changes (thickening, tags, hirsutism, hyperhidrosis) may overlap with PCOS. However, headaches, peripheral vision loss, enlarged jaw (macrognathia), frontal bossing, macroglossia, increased shoe and glove size, etc, are indications for screening	Serum free IGF-1 level (elevated), MRI of pituitary (mass or tumor present)	Melmed, 2009 (20)

Abbreviations: DHEAS, dehydroepiandrosterone sulfate; HA, hypothalamic amenorrhea; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging.

[a] Additionally there are very rare causes of hyperandrogenic chronic anovulation that are not included in this table because they are so rare, but they must be considered in patients with an appropriate history. These include other forms of congenital adrenal hyperplasia (eg, 11β-hydroxylase deficiency, 3β-hydroxysteroid dehydrogenase), related congenital disorders of adrenal steroid metabolism or action (eg, apparent/cortisone reductase deficiency, apparent DHEA sulfotransferase deficiency, glucocorticoid resistance), virilizing congenital adrenal hyperplasia (adrenal rests, poor control, fetal programming), syndromes of extreme IR, drugs, portohepatic shunting, and disorders of sex development.

Table 5. Cardiovascular Risk Stratification in Women with PCOS

At risk—PCOS women with any of the following risk factors:
Obesity (especially increased abdominal adiposity)
Cigarette smoking
Hypertension
Dyslipidemia (increased LDL-cholesterol and/or non-HDL-cholesterol)
Subclinical vascular disease
Impaired glucose tolerance
Family history of premature cardiovascular disease (<55 y of age in male relative; <65 y of age in female relative)
At high risk–PCOS women with:
Metabolic syndrome
T2DM
Overt vascular or renal disease, cardiovascular diseases
OSA

The Androgen Excess and Polycystic Ovary Syndrome Society relied upon evidence-based studies and concluded that women with PCOS be stratified as being either at risk or at high risk for cardiovascular disease using the criteria shown (167).

Primary concern	Must	First-line	Additive/ second line
Hirsutism	Lifestyle modification	Oral contraceptive pills	Antiandrogens
Menstrual irregularities	Lifestyle modification	Oral contraceptive pills	Metformin
Metabolic abnormalities (prediabetes/diabetes)	Lifestyle modification	Metformin	–
Ovulation induction	Lifestyle modification	Clomiphene citrate	Metformin

Oral contraceptive pills (OCPs) consisting of optimal amount of ethinyl estradiol (30–35 µg) and non-androgenic/antiandrogenic progesterone like cyproterone acetate, drospirenone, desogestrel, norgestimate, or gestodene are preferred in the management of PCOS with hirsutism and/or menstrual irregularity

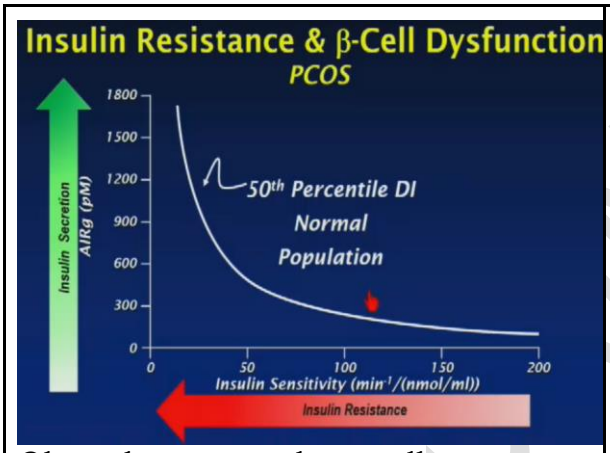
Role of contraceptives

- OCPs help in regularizing menstrual cycles and decrease hyperandrogenemia. Ethinyl estradiol increases SHBG and results in decreased free testosterone levels
- Further in conjunction with progesterone, ethinyl estradiol also decreases LH drive thereby resulting in reduced ovarian androgen production
- progestins have inhibitory effect on 5α-reductase activity and interfere with androgen action.

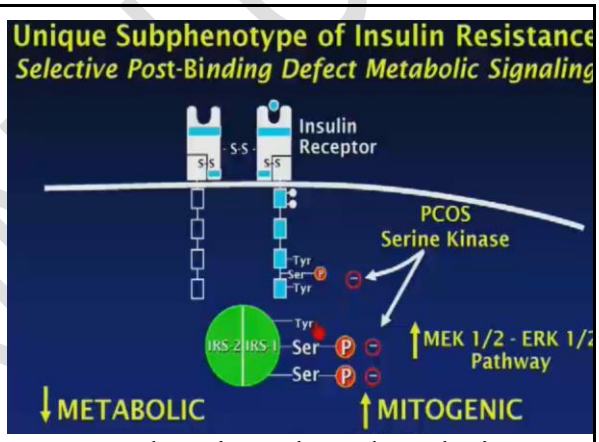
Why antiandrogens should not be used alone for treatment of PCOS ?

Antiandrogens are usually required as OCPs alone do not produce a rewarding outcome, especially in treating hirsutism. Lone use of antiandrogens is contraindicated

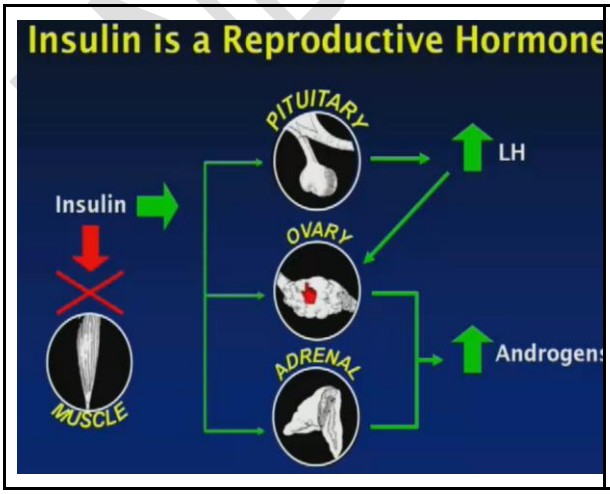
as it may lead to menstrual irregularities (mid-cycle bleed due to deficient progesterone production/action) and can cause under-virilization in the male fetus, if conceived.

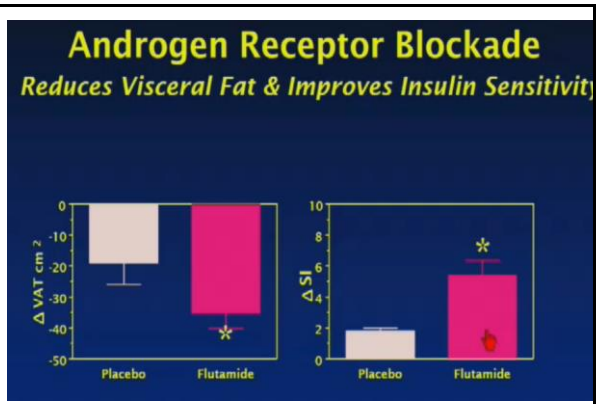


Obese have more beta cell dysfunction than non obese PCOS px.



Increased serine phosphorylation inhibits downstream/post receptor action of insulin.



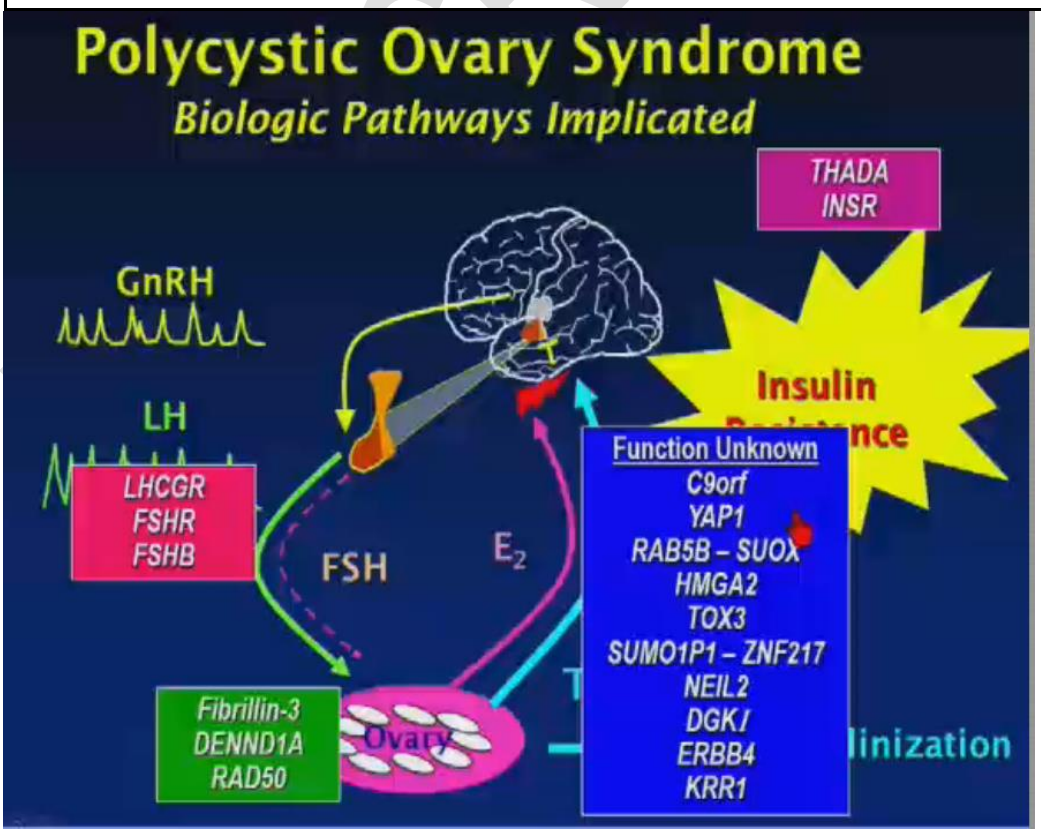


Role of Metformin in PCOS

- improves insulin sensitivity and reduces hyperinsulinemia by acting through AMP kinase pathway
- This results in a decrease in ovarian hyperandrogenism, thereby provides a conducive milieu for follicular growth and development and regularizes menstrual cycles
- current indications of metformin in patients with PCOS are *dysglycemia*, *contraindications to OCPs, clomiphene-resistant ovulatory dysfunction*, and *during in vitro fertilization to prevent ovarian hyperstimulation syndrome*.
- current guideline based on recent meta-analysis does not favor the continuation of metformin after the confi rmation of pregnancy as its use is not associated with the improved outcome in terms of fetal loss, dysglycemia,and preeclampsia.
-

PCOS contributes to about 20% of all causes of female infertility. Clomiphene alone or in combination with metformin is the preferred drug to treat infertility in PCOS. **Clomiphene is a selective estrogen receptor modulator (SERM)**, which acts at the level of hypothalamus and resets the GnRH–gonadotropin
Axis.

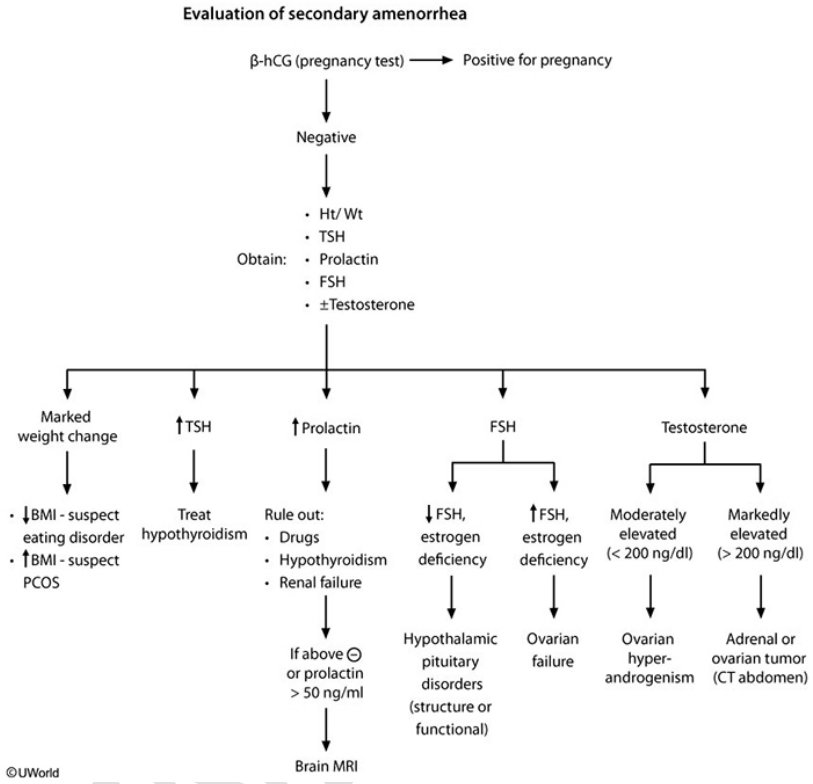
Non mendelian familial aggregation of PCOS
• 40% of sisters vs 7% population prevalence • 70% heritability in monozygotic twins



Non-classical CAH

- Deficiency of 21 hydroxylase
- Present in childhood or early adulthood with signs of androgen excess (premature pubarche, acne, accelerated bone growth , hirsutism, menstrual irregularities.
- No cortisol deficiency
- Common in ashkenazi jews, slavs, hispanic, italians
- Elevated 17 hydroxyprogesterone levels in early follicular phase >200ng/dl
- Confirm with increase in 17 OHP >1000ng/dl after high dose ACTH 250micgram

Evaluation of Amenorrhea



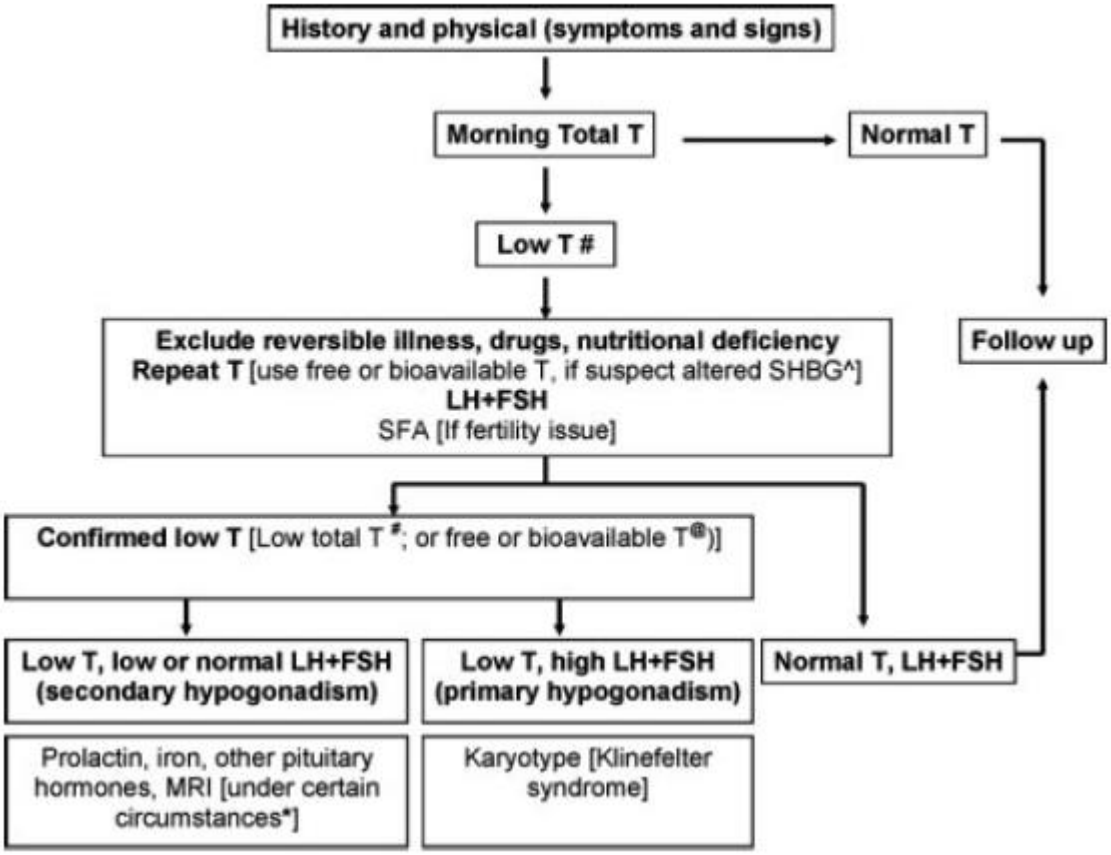
MALE HYPOGONADISM

Hypogonadism in a male refers to a decrease in one or both of the two major functions of the testes: **sperm production** or **testosterone production**. These abnormalities can result from disease of the testes (primary hypogonadism) or disease of the hypothalamus or pituitary (secondary hypogonadism).

Primary hypogonadism	**serum testosterone concentration** and/or the sperm count are **below normal** and the serum LH and/or FSH concentrations are above normal.
secondary hypogonadism	**serum testosterone concentration** and/or the sperm count are **below normal** and the serum LH and/or FSH concentrations are normal or low.

Definition of hypogonadism

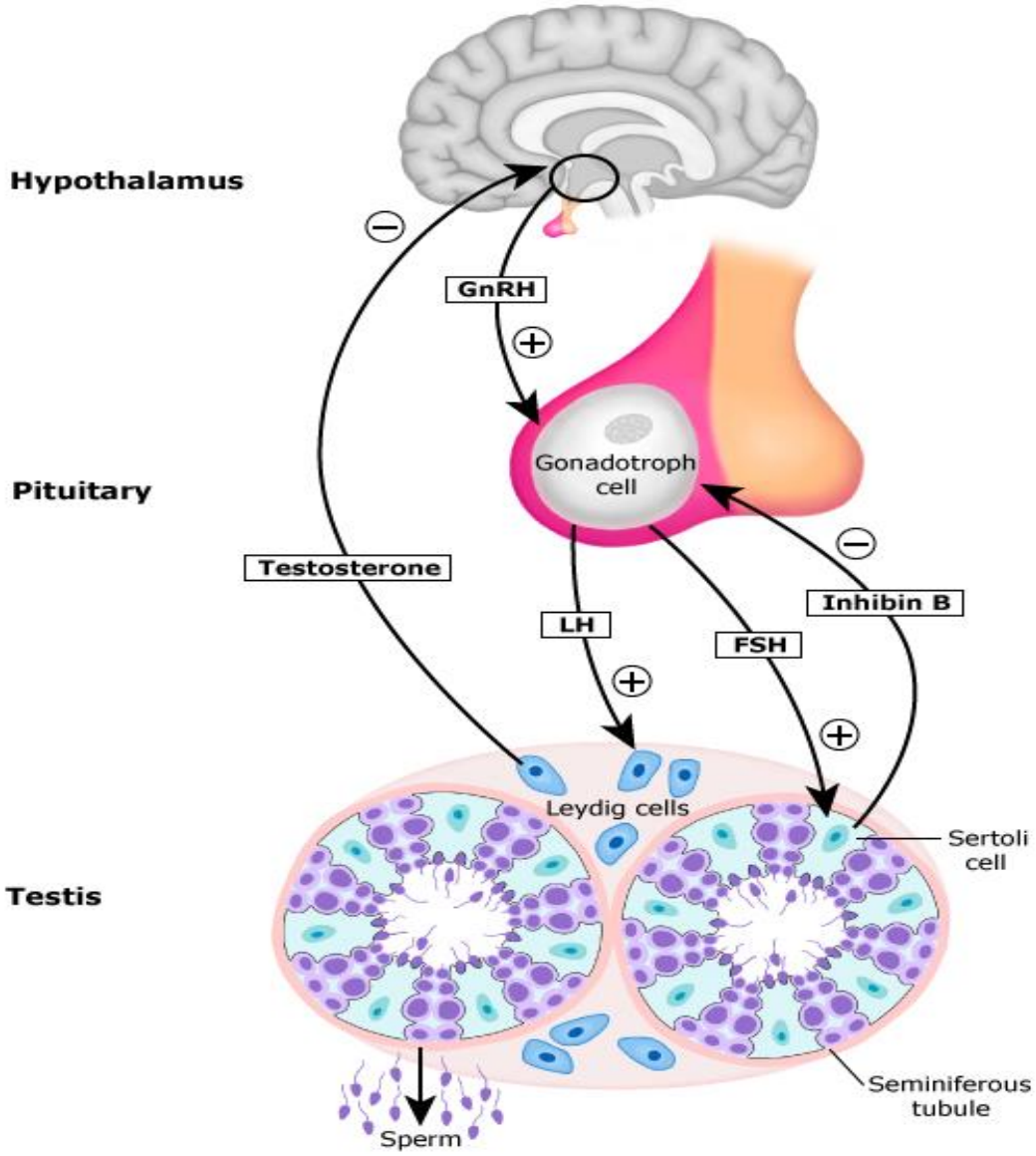
Hypogonadism in men is a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more



Congenital abnormalities
Klinefelter syndrome
Other chromosomal abnormalities
Mutation in the FSH and LH receptor genes
Cryptorchidism
Varicocele
Disorders of androgen synthesis
Myotonic dystrophy
Acquired diseases
Infections, especially mumps
Radiation
Alkylating agents
Suramin
Ketoconazole
Glucocorticoids
Environmental toxins
Trauma
Testicular torsion
Autoimmune damage
Chronic systemic illnesses
Hepatic cirrhosis
Chronic renal failure
AIDS
Idiopathic

Acquired
Tumors
Benign tumors and cysts
Craniopharyngiomas
Germinomas, meningiomas, gliomas, astrocytomas
Metastatic tumors (breast, lung, prostate)
"Functional" gonadotropin deficiency
Chronic systemic disease
Acute illness
Malnutrition
Hypothyroidism, hyperprolactinemia, diabetes mellitus, Cushing's dis
Anorexia nervosa, bulimia
Post-androgen abuse
Infiltrative diseases
Hemochromatosis
Granulomatous diseases
Histiocytosis
Head trauma
Pituitary apoplexy
Drugs - marijuana, opioids, anabolic steroids
Congenital
Isolated GnRH deficiency
Without anosmia
Kallmann syndrome
Associated with adrenal hypoplasia congenita
GnRH deficiency associated with mental retardation/obesity
Laurence-Moon-Biedl syndrome
Prader-Willi syndrome
Idiopathic forms of multiple anterior pituitary hormone deficienci
Congenital malformations often associated with craniofacial anon

History of exposure to an alkylating agent (oxaplatin) increases risk of primary testicular injury. Testosterone producing leydig cells are, however, less sensitive to alkylating agents compared to the germinal epithelium of the testis.



Testosterone is produced by the **Leydig cells of the testes** under **stimulation of LH**.

Sperm are produced in the **seminiferous tubules** under stimulation principally by the high concentration of testosterone in the testes but also by FSH.

Testosterone, in turn, inhibits both LH and FSH secretion, the latter via conversion to estradiol.

FSH is also inhibited by **inhibin, a product of the Sertoli cells of the seminiferous tubules**.

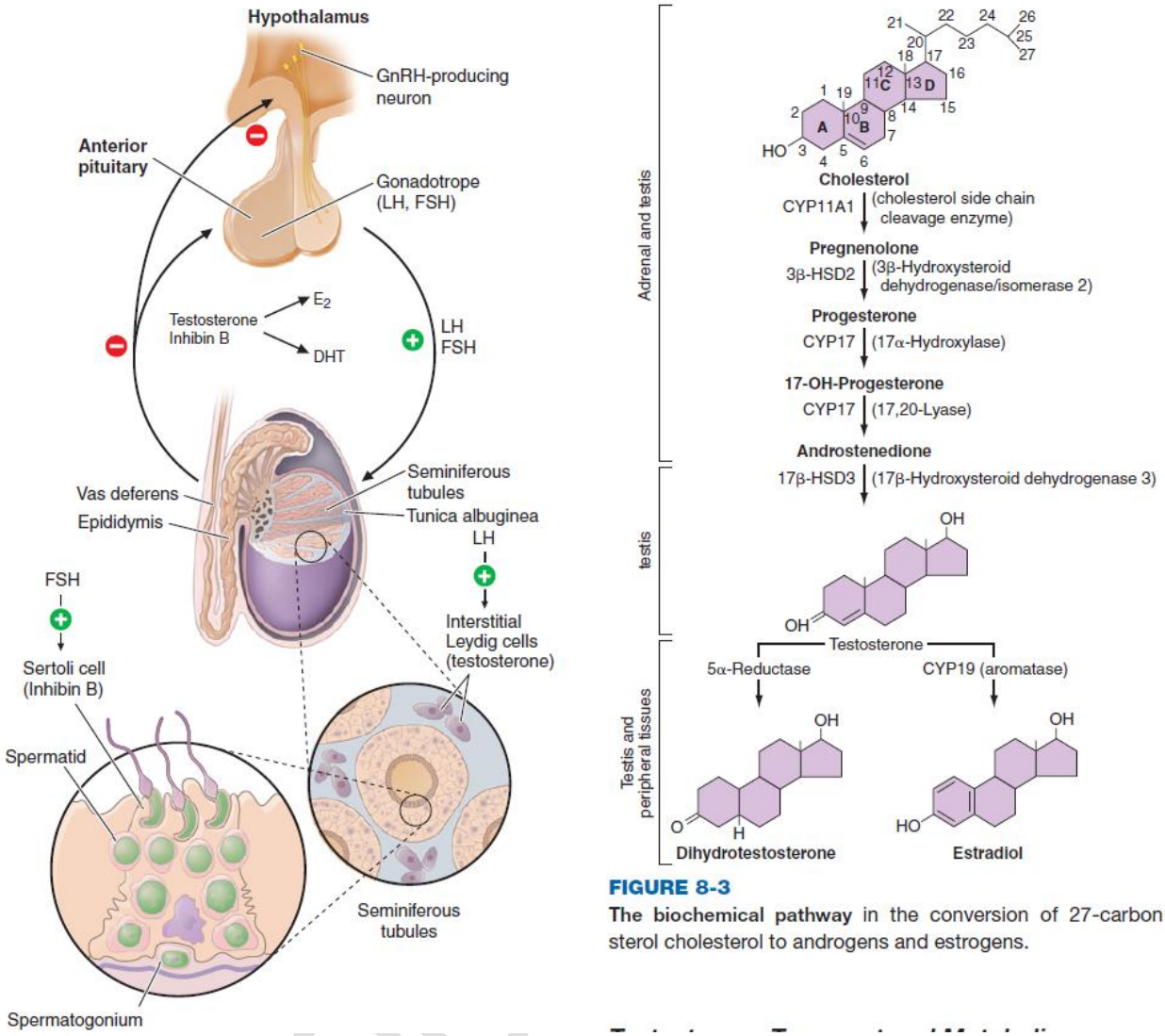


FIGURE 8-3
The biochemical pathway in the conversion of 27-carbon sterol cholesterol to androgens and estrogens.

Symptoms of hypogonadism

- young adults who have not yet completed puberty appear younger than their chronologic age
- small genitalia
- difficulty gaining muscle mass in spite of vigorous exercise
- lack of a beard,

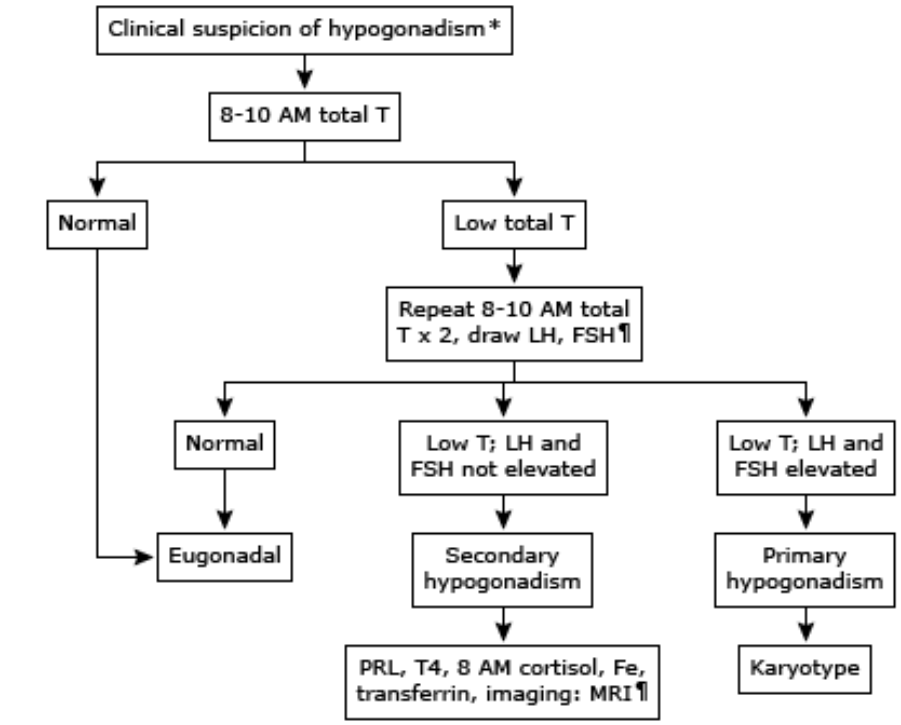
Physical Examination (male hypogonadism)

Prepubertal	**Adults**
• Do not develop body hair and a beard, temporal hair recession, full male musculature, or deep voice. • small testes (<20 mL) and a small phallus (<8 cm)	• may lose these characteristics if the hypogonadism is severe enough and/or of sufficient duration, usually years • the testes usually decrease in size if the hypogonadism is primary.but they usually do

• **eunuchoid proportions** in an adult male at any age indicates that the hypogonadism developed prepubertally. •	not decrease to a recognizable degree if it is secondary. **The phallus does not decrease in size**. • **Gynecomastia**, the presence of glandular breast tissue in a male, is more likely to occur in primary than secondary hypogonadism

Eunuchoid proportions include a lower body segment (floor to pubis) that is more than 2 cm longer than upper body segment (pubis to crown), and an arm span that is more than 5 cm longer than height.

Evaluation of the male with possible hypogonadism



Screening of hypogonadism (Endocrine society guidelines)

Population screening for male hypogonadism has not been shown to be cost-effective and is not recommended
• Diseases of the sellar region • Medications that affect testosterone production, such as high-dose glucocorticoids for a prolonged period and sustained-release opioids • Human immunodeficiency virus (HIV)-associated weight loss • End-stage renal disease and maintenance hemodialysis

- Moderate-to-severe chronic obstructive lung disease
- Infertility
- Osteoporosis or low-trauma fracture, especially in a young man
- Type 2 diabetes mellitus

Men with acute or subacute illness should not be assessed for hypogonadism, as they will have a transient functional secondary hypogonadism.

Testing of serum testosterone levels (important clinical considerations)

- Measurement of the serum total (free plus protein-bound) testosterone concentration is usually an accurate reflection of testosterone secretion.
- The normal range in adult men in most laboratories is about **300 to 800 ng/dL.**

TABLE 3. Conditions in which there is a high prevalence of low testosterone levels and for which we suggest measurement of serum testosterone levels

Sellar mass, radiation to the sellar region, or other diseases of the sellar region
Treatment with medications that affect testosterone production or metabolism, such as glucocorticoids and opioids
HIV-associated weight loss
End-stage renal disease and maintenance hemodialysis
Moderate to severe chronic obstructive lung disease
Infertility
Osteoporosis or low trauma fracture, especially in a young mar
Type 2 diabetes mellitus

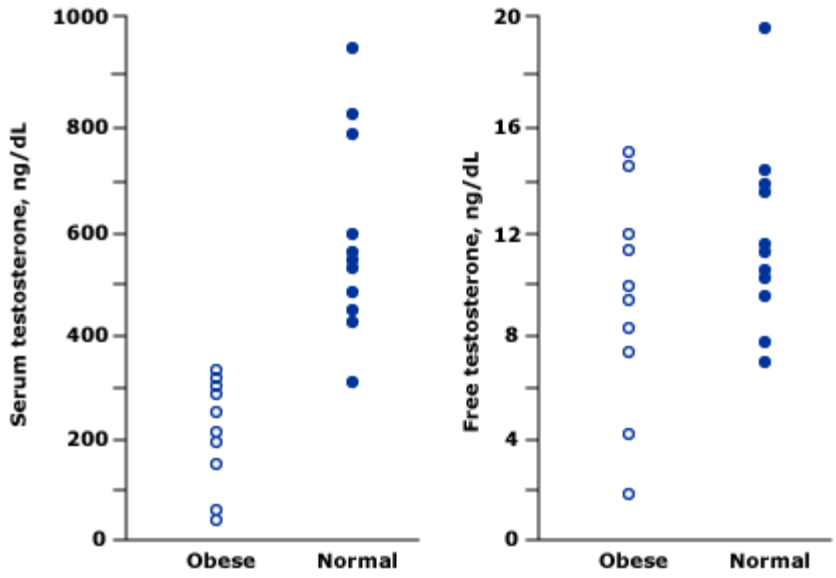
In men with chronic diseases such as diabetes mellitus, end-stage renal disease, and chronic obstructive lung disease, measurement of testosterone may be indicated by symptoms such as sexual dysfunction, unexplained weight loss, weakness, or mobility limitation. In men with some other conditions, such as a pituitary mass, HIV-associated weight loss, low trauma fracture, or treatment with medications that affect testosterone production, measurement of testosterone may be indicated regardless of symptoms.

TABLE 2. Conditions associated with alterations in SHBG concentrations

Conditions associated with decreased SHBG concentrations
Moderate obesity[a]
Nephrotic syndrome[a]
Hypothyroidism
Use of glucocorticoids, progestins, and androgenic steroids[a]
Acromegaly
Diabetes mellitus[a]
Conditions associated with increased SHBG concentrations
Aging[a]
Hepatic cirrhosis and hepatitis[a]
Hyperthyroidism
Use of anticonvulsants[a]
Use of estrogens
HIV disease

[a] Particularly common conditions associated with alterations in SHBG concentrations.

Serum testosterone concentrations in obesity



Obesity is characterized by a reduction in serum total testosterone concentration (left panel) but a normal serum free testosterone concentration (right panel) due to decreased SHBG.

SHBG: sex hormone-binding globulin.

Data from Glass AR, Swerdloff RS, Bray GA, et al. Low serum testosterone and sex-hormone-binding-globulin in massively obese men. J Clin Endocrinol Metab 1977; 45:1211.

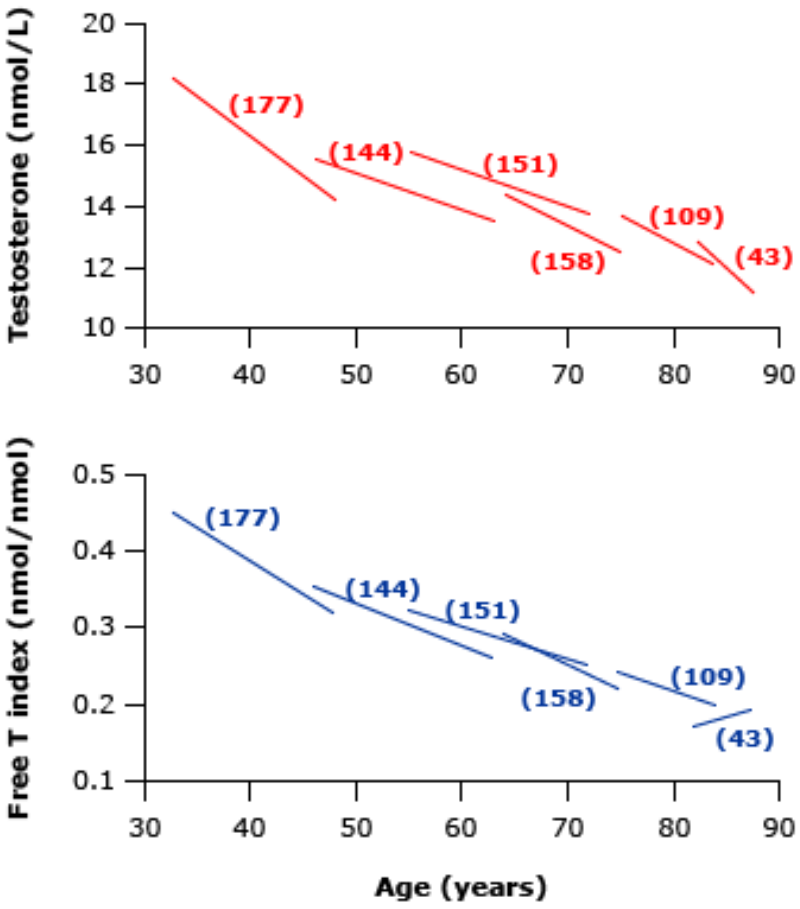
Common situations of abnormal testosterone binding

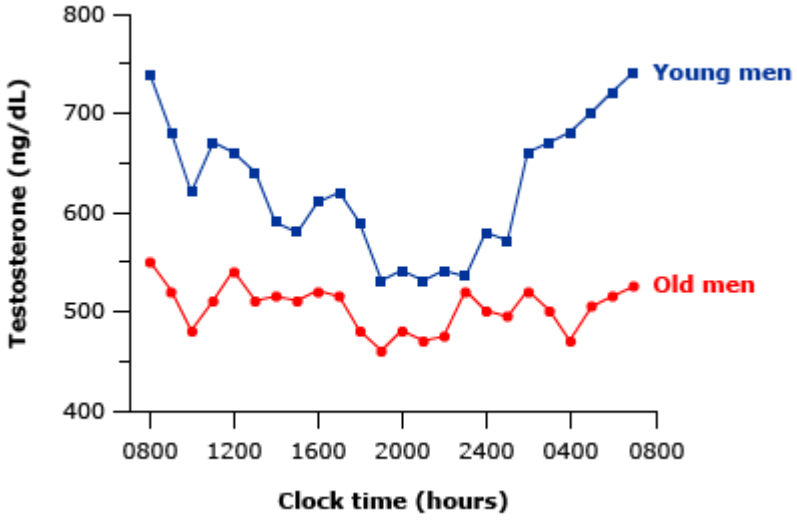
Obesity which decreases SHBG concentrations in proportion to the degree of obesity.	Male aging, which increases SHBG slightly

Obesity **decreases the serum concentration of SHBG**, thereby decreasing the serum total testosterone concentration usually **without lowering the free testosterone concentration** ● The binding abnormality is proportional to the degree of obesity and is corrected by weight loss. ● **severe obesity (body mass index [BMI] >40 kg/m2)** may cause hypothalamic hypogonadism as well as the binding abnormality. ● **equilibrium dialysis assay** accurately will distinguish between a binding abnormality and hypogonadism in an obese male.	● serum total testosterone concentration falls slightly with increasing age, the serum free testosterone falls to a greater degree ● What is unknown now is if this fall represents a physiologic or a pathologic phenomenon. If it were pathologic, treatment with testosterone would be considered.

Increased SHBG concentration	**Decreased SHBG concentrations**
● Aging ● Hyperthyroidism ● high estrogen concentrations ● liver disease ● HIV ● antiseizure drugs	● moderate obesity ● insulin resistance ● type 2 diabetes ● Hypothyroidism ● growth hormone excess ● exogenous androgens/anabolic steroids ● Glucocorticoids ● Progestins ● nephrotic syndrome ● acromegaly

Longitudinal effects of aging





Testing considerations for hypogonadism
• **diurnal fluctuation**, which **reaches a maximum at about 8 AM**

and a minimum, approximately 70 percent of the maximum, at about 8 PM • measurements should always be made in the morning, ideally between 8 to 10 AM • Food , especially glucose ingestion , also decreases the serum testosterone concentration, so the blood should also be drawn fasting.

primary hypogonadism	• serum testosterone concentration is subnormal, supranormal serum LH and FSH concentrations *(normal range for both approximately 1 to 8 mIU/mL in most laboratories)* • values that are not supranormal indicate secondary hypogonadism • Clearly elevated gonadotropin values , even if the serum testosterone concentration is in the low-normal range
primary hypogonadism with seminiferous tubule damage	subnormal sperm count, high serum FSH, but normal serum testosterone and LH concentrations. normal testosterone production by the Leydig cells

INDICATIONS FOR MRI IN PRIMARY HYPOGONADISM
• Other pituitary hormonal abnormalities • A visual field abnormality • Neurologic abnormalities • Man <40 years old, testosterone value of <250 ng/dL • Man >60 years old, testosterone value of <150 ng/dL

Primary gonadal failure (possible etiologies)

Klinefelter syndrome	• Most common cause of primary gonadal failure • Gynecomastia, small testes, elevated LH

	and FSH • Low or low normal testosterone
Inactivating FSH receptor mutation	• Rare • Small testes, elevated FSH but no gynecomastia • LH and testosterone levels are normal
CAH due to 17 OH deficiency	• **Range from female to ambiguous to mildly underdeveloped male genitalia** • **Most are hypertensive**
Mumps orchitis	• Rare since introduction of childhood vaccination program

Pubertal Gynecomastia (indications for surgery)

- Present for more than 1 year or after age of 17years
- Greater than 4cm in diameter
- Fails to respond to medical therapy
- Interferes with normal daily activities

Hereditary hemochromatosis

- Secondary hypogonadism, arthralgia and chondrocalcinosis are the earliest manifestations of hereditary iron overload syndromes.
- Diagnosis is suggested by transferrin saturation >45%
- Confirmed by mutations in HFE gene.

TESTOSTERONE REPLACEMENT THERAPY

- It can act directly by binding to the androgen receptor.
- It can also act in tissues that express the enzyme 5-alpha-reductase
- Conversion to dihydrotestosterone, which binds more avidly to the androgen receptor than testosterone itself.
- It can act as an estrogen following conversion by aromatase to estradiol, which binds to the estrogen receptor.

This mechanism provides the basis for the use of the 5-alpha-reductase inhibitor, finasteride, to treat benign enlargement of the prostate and male pattern baldness.	**Testosterone requires conversion to dihydrotestosterone** for its action on the external genitalia (which include the prostate gland) and sexual hair.
rare condition of aromatase deficiency in men, which results in failure of epiphyseal closure and severe osteoporosis. Treatment with estradiol corrects both.	**Testosterone requires conversion to estradiol** for much of its action on bone

Benefits of testosterone therapy	**Side effects of testosterone**

	therapy
• development or maintenance of secondary sexual characteristics • increases in libido • muscle strength, fat-free mass • bone density	• Acne • prostate disorders (such as benign prostatic hyperplasia [BPH] symptoms) • sleep apnea • erythrocytosis

Indications for urology referral before initiating testosterone therapy

1. Palpable prostate nodule or induration
2. Baseline PSA >4ng/ml in patients at average risk of prostate cancer
3. Baseline PSA >3ng/ml in patients considered to be at increased risk of prostate cancer, including those with a first degree relative with prostate cancer and african american men

Endocrine society guidelines (testosterone and hematocrit)

- If HCT >50% be cautious when supplementing T
- If HCT >54% with high testosterone hold T

Indication for urology referral in patients on testosterone

1. Increase in PSA level of >1.4ng/mL over 1 year
2. Absolute PSA level >4ng/mL

When to consider urine testosterone: epitestosterone ratio

Suspected anabolic steroid abuse.

Which gonadotrophs to use?

In secondary hypogonadism if testicular volume >4cm use only HCG, if less use HCG and FSH

For testosterone injections, use lower doses at shorter interval reduces peaks and troughs.

Testosterone therapy in adult men with classical androgen deficiency
• Recommend against testosterone therapy in patients with breast or prostate cancer. • Recommend against testosterone therapy without further urological evaluation in patients with **palpable prostate nodule or induration** or **PSA greater than 4 ng/ml or PSA greater than 3 ng/ml** in men at high risk of prostate cancer, such as African-Americans or men with first-degree relatives with prostate cancer. • Recommend against testosterone therapy in patients with **hematocrit above 50%**, **untreated severe obstructive sleep**

apnea, **severe lower urinary tract symptoms (AUA/IPSS 19)**, or uncontrolled or poorly controlled heart failure, or in those **desiring fertility**

Testosterone therapy ; treatment targets

- We suggest that when clinicians prescribe testosterone therapy, the therapeutic target should be to raise serum testosterone levels into **a range that is mid-normal for healthy, young men.**
- In men receiving **testosterone enanthate or cypionate**, serum testosterone levels vary during the dosing interval; we suggest aiming for testosterone levels **between 400 and 700 ng/dl midway between injections**

In men 40 yr of age or older who have a baseline PSA greater than 0.6 ng/ml, we recommend digital examination of the prostate and PSA measurement before initiating treatment.

TABLE 5. Potential adverse effects of testosterone replacement

Adverse events for which there is evidence of association with testosterone administration
Erythrocytosis
Acne and oily skin
Detection of subclinical prostate cancer
Growth of metastatic prostate cancer
Reduced sperm production and fertility
Uncommon adverse events for which there is weak evidence of association with testosterone administration
Gynecomastia
Male pattern balding (familial)
Growth of breast cancer
Induction or worsening of obstructive sleep apnea
Formulation-specific adverse effects
Intramuscular injections of testosterone enanthate, cypionate, or undecanoate
Fluctuation in mood or libido
Pain at injection site
Excessive erythrocytosis (especially in older patients)
Coughing episodes immediately after the im injection[a]
Transdermal patches
Frequent skin reactions at application site
Transdermal gel
Potential risk for testosterone transfer to partner or another person who is in close contact (need to remind patient to cover application sites with clothing and to wash skin and hands with soap before having skin-to-skin contact with another person)
Skin irritation
Buccal testosterone tablets
Alterations in taste
Irritation of gums
Pellet implants
Infection, expulsion of pellet
Oral tablets
Effects on liver and cholesterol (methyltestosterone)[b]

[a] The mechanism of cough, which has been reported rarely after im injections of testosterone undecanoate and even more rarely after testosterone enanthate and cypionate, is unknown, but it has been attributed to oil embolization.

[b] Liver toxicity has been reported mostly with oral 17-α alkylated androgens. The frequency of skin reactions is higher with the testosterone patch than with the transdermal gels.

TABLE 4. Conditions in which testosterone administration is associated with a high risk of adverse outcome and for which we recommend against using testosterone

Very high risk of serious adverse outcomes
Metastatic prostate cancer
Breast cancer
Moderate to high risk of adverse outcomes
Unevaluated prostate nodule or induration
PSA >4 ng/ml (>3 ng/ml in individuals at high risk for prostate cancer, such as African-Americans or men with first-degree relatives who have prostate cancer)
Hematocrit >50%
Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by AUA/IPSS >19
Uncontrolled or poorly controlled congestive heart failure

TABLE 7. Some recommended regimens[a] for testosterone replacement therapy

150 to 200 mg administered every 2 wk, or 75–100 mg of testosterone enanthate or cypionate administered im weekly
One or two 5-mg testosterone patches applied nightly over the skin of the back, thigh, or upper arm, away from pressure areas
5 to 10 g of testosterone gel applied daily over a covered area of skin
30 mg of a bioadhesive, buccal testosterone tablet applied to buccal mucosa twice daily
Testosterone pellets (dose and regimen vary with the formulation used)

[a] Formulations available in other countries but not in the United States include: 1) oral testosterone undecanoate (typically used at a dose of 40 to 80 mg orally two or three times daily with meals); 2) two testosterone matrix patches 30, 45, or 60 cm^2 applied every 2 d; 3); injectable testosterone undecanoate 1000 mg followed by a second 1000-mg injection 6 wk later, and then 1000 mg every 10 to 14 wk. Physicians in countries where these formulations are available should follow the approved drug regimens. See Tables 6 and 8 for additional safety and pharmacokinetics information.

TABLE 8. Monitoring men receiving testosterone therapy

1. Evaluate the patient 3 to 6 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects.
2. Monitor testosterone level 3 to 6 months after initiation of testosterone therapy:
   Therapy should aim to raise serum testosterone level into the mid-normal range.
   - Injectable testosterone enanthate or cypionate: measure serum testosterone level midway between injections. If testosterone is >700 ng/dl (24.5 nmol/liter) or <400 ng/dl (14.1 nmol/liter), adjust dose or frequency.
   - Transdermal patches: assess testosterone level 3–12 h after application of the patch; adjust dose to achieve testosterone level in the mid-normal range.
   - Buccal testosterone bioadhesive tablet: assess level immediately before or after application of fresh system.
   - Transdermal gels: assess testosterone level any time after patient has been on treatment for at least 1 wk; adjust dose to achieve serum testosterone level in the mid-normal range.
   - Testosterone pellets: measure testosterone levels at the end of the dosing interval. Adjust the number of pellets and/or the dosing interval to achieve serum testosterone levels in the normal range.
   - Oral testosterone undecanoate[a]: monitor serum testosterone level 3 to 5 h after ingestion.
   - Injectable testosterone undecanoate: measure serum testosterone level just prior to each subsequent injection and adjust the dosing interval to maintain serum testosterone in mid-normal range.
3. Check hematocrit at baseline, at 3 to 6 months, and then annually. If hematocrit is >54%, stop therapy until hematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea; reinitiate therapy with a reduced dose.
4. Measure bone mineral density of lumbar spine and/or femoral neck after 1–2 yr of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture, consistent with regional standard of care.
5. In men 40 yr of age or older with baseline PSA greater than 0.6 ng/ml, perform digital rectal examination and check PSA level before initiating treatment, at 3 to 6 months, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient.
6. Obtain urological consultation if there is:
   - An increase in serum PSA concentration >1.4 ng/ml within any 12-month period of testosterone treatment.
   - A PSA velocity of >0.4 ng/ml · yr using the PSA level after 6 months of testosterone administration as the reference (only applicable if PSA data are available for a period exceeding 2 yr).
   - Detection of a prostatic abnormality on digital rectal examination.
   - An AUA/IPSS of >19.
7. Evaluate formulation-specific adverse effects at each visit:
   - Buccal testosterone tablets: inquire about alterations in taste and examine the gums and oral mucosa for irritation.
   - Injectable testosterone esters (enanthate, cypionate, and undecanoate): ask about fluctuations in mood or libido, and rarely cough after injections.
   - Testosterone patches: look for skin reaction at the application site.
   - Testosterone gels: advise patients to cover the application sites with a shirt and to wash the skin with soap and water before having skin-to-skin contact, because testosterone gels leave a testosterone residue on the skin that can be transferred to a woman or child who might come in close contact. Serum testosterone levels are maintained when the application site is washed 4–6 h after application of the testosterone gel.
   - Testosterone pellets: look for signs of infection, fibrosis, or pellet extrusion.

[a] Not approved for clinical use in the United States.

TABLE 6. Clinical pharmacology of some testosterone formulations

Formulation	Regimen	Pharmacokinetic profile	DHT and E2	Advantages	Disadvantages
T enanthate or cypionate	150–200 mg im every 2 wk or 75–100 mg/wk	After a single im injection, serum T levels rise into the supraphysiological range, then decline gradually into the hypogonadal range by the end of the dosing interval	DHT and E2 levels rise in proportion to the increase in T levels; T:DHT and T:E2 ratios do not change	Corrects symptoms of androgen deficiency; relatively inexpensive, if self-administered; flexibility of dosing	Requires im injection; peaks and valleys in serum T levels
1% testosterone gel	Available in sachets, tubes and pumps 5–10 g T gel containing 50–100 mg T every d	Restores serum T and E2 levels to the physiological male range	Serum DHT levels are higher and T:DHT ratios are lower in hypogonadal men treated with the T gel than in healthy eugonadal men	Corrects symptoms of androgen deficiency, provides flexibility of dosing, ease of application, good skin tolerability	Potential of transfer to a female partner or child by direct skin-to-skin contact; skin irritation in a small proportion of treated men; moderately high DHT levels
Transdermal testosterone patch	1 or 2 patches, designed to nominally deliver 5–10 mg T over 24 h applied every d on nonpressure areas	Restores serum T, DHT, and E2 levels to the physiological male range	T:DHT and T:E2 levels are in the physiological male range	Ease of application, corrects symptoms of androgen deficiency	Serum T levels in some androgen-deficient men may be in the low-normal range; these men may need application of 2 patches daily; skin irritation at the application site occurs frequently in many patients
Buccal, bioadhesive, T tablets	30 mg controlled release, bioadhesive tablets twice daily	Absorbed from the buccal mucosa	Normalizes serum T and DHT levels in hypogonadal men	Corrects symptoms of androgen deficiency in healthy, hypogonadal men	Gum-related adverse events in 16% of treated men
T pellets	3–6 pellets implanted sc; dose and regimen vary with formulation	Serum T peaks at 1 month and then is sustained in normal range for 3–6 months, depending on formulation	T:DHT and T:E2 ratios do not change	Corrects symptoms of androgen deficiency	Requires surgical incision for insertions; pellets may extrude spontaneously

(*Continued*)

TABLE 6. Continued

Formulation	Regimen	Pharmacokinetic profile	DHT and E2	Advantages	Disadvantages
17-α -methyl T	This 17-α -alkylated compound should **not** be used because of potential for liver toxicity	Orally active			Clinical responses are variable; potential for liver toxicity; should **not** be used for treatment of androgen deficiency
Oral T undecanoate[a]	40 to 80 mg orally, twice daily or three times daily with meals	When administered in oleic acid, T undecanoate is absorbed through the lymphatics, bypassing the portal system; considerable variability in the same individual on different days and among individuals	High DHT:T ratio	Convenience of oral administration	Not approved in the United States; variable clinical responses, variable serum T levels, high DHT:T ratio
Injectable long-acting T undecanoate in oil	European regimen 1000 mg im, followed by 1000 mg at 6 wk, and 1000 mg every 10–14 wk	When administered at a dose of 750 to 1000 mg im, serum T levels are maintained in the normal range in a majority of treated men	DHT and E2 levels rise in proportion to the increase in T levels; T:DHT and T:E2 ratios do not change	Corrects symptoms of androgen deficiency; requires infrequent administration.	Requires im injection of a large volume (4 ml); cough reported immediately after injection in a very small number of men
Testosterone-in-adhesive matrix patch	2 × 60 cm^2 patches delivering approximately 4.8 mg T/d	Restores serum T, DHT and E_2 to the physiological range	T:DHT and T:E_2 are in the physiological range	Lasts 2 d	Some skin irritation

DHT, Dihydrotestosterone; E2, estradiol; T, testosterone.

[a] These formulations are not approved for clinical use in the United States, but are available outside the United States in many countries. Physicians in countries where these formulations are available should follow the approved drug regimens.

Approach to the patient with Gynecomastia

Gynecomastia is defined as the presence of palpable breast tissue in males and is common in normal individuals, particularly in the newborn period, at puberty, and in the Elderly.

Histopathology and pathophysiology

- Histologically, the primary feature of gynecomastia is ductular proliferation in a background stroma of fibrous connective tissue
- Receptors for androgens, estrogens, progesterone, and prolactin are found in the male breast.
- estrogens stimulate breast tissue proliferation, whereas androgens inhibit this process

1. Increase in circulating or tissue levels of estrogen
2. Decrease in circulating or tissue levels of androgen
3. Increased responsiveness of the breast to estrogen (e.g. increased numbers of estrogen receptors)
4. Decreased breast responsiveness to androgens (e.g. androgen insensitivity due to receptor mutations or drugs).

Reasons for gynecomastia in older men

1. Increased adiposity with age **[adipose tissue is a major site of aromatization of androgens to estrogens]**
2. Decreased serum free testosterone due to aging **[with decreased testosterone production as well as increased binding of testosterone to SHBG]**
3. greater use of medications that may alter androgen or estrogen concentrations or action

Several questions need to be answered in evaluating every male patient with breast enlargement:

1. Is the breast enlargement of recent onset or associated with pain or tenderness?
2. Is the breast enlargement due to increased glandular tissue or is it only adipose tissue (pseudogynecomastia)?
3. Are there findings suggestive of breast cancer?
4. Is there evidence of a testicular tumor, which might lead to gynecomastia by producing estrogen or stimulating its production?
5. Can a cause for the breast enlargement be identified?
6. Is the patient troubled by the breast enlargement?

TABLE 1. Causes of gynecomastia

I. Estrogen excess
   A. Exogenous estrogens: therapeutic or unintentional exposure, including exposure to aromatizable androgens (*e.g.* athletes)
   B. Endogenous estrogens
      1. Increased secretion from testis (Leydig cell or Sertoli cell tumors, stimulation of normal Leydig cells by LH or hCG)
      2. Increased secretion from adrenals (feminizing adrenocortical tumors)
      3. Increased aromatization of androgens to estrogens (aging, obesity, alcoholic cirrhosis, hyperthyroidism, drugs, hCG-secreting tumors, aromatase excess syndrome)

II. Androgen deficiency: primary or secondary hypogonadism due to disease, trauma, radiation, or drugs

III. Altered serum androgen/estrogen ratio (puberty, aging, refeeding gynecomastia, hepatic cirrhosis, renal failure and dialysis, hyperthyroidism, drugs)

IV. Decreased androgen action
   A. Androgen receptor antagonists (spironolactone, cimetidine, bicalutamide, flutamide)
   B. Absent or defective androgen receptors
   C. Expansion of CAG repeats in the androgen receptor gene (Kennedy disease)

Detailed evaluation of gynecomastia in the office setting

History	• Nonprescription pills, anabolic steroids, dietary

	supplements. • Family history of gynecomastia (androgen resistance syndrome, familial aromatase excess, estrogen producing sertoli cell cell tumors eg. Peutz-Jeghers syndrome or carney complex) • Family history of BRCA-2 positive breast cancer 8-10% lifetime risk.
Physical Examination	• features of virilization (voice, facial and body hair, skeletal muscle bulk) • testicular size and/or masses • penile size and development • signs of chronic liver or kidney disease, and evidence of hyperthyroidism • Differentiate true gynecomastia from pseudogynecomastia
Routine biochemical testing.	• thyroid,liver, and kidney function • measurements of serum testosterone (total and/or bioavailable), estradiol,LH, FSH, prolactin, and B-hCG.

If the breast enlargement has been present for more than 1 yr, complete regression is less likely, due to the predominance of dense fibrous tissue.

TABLE 2. Drugs commonly implicated in gynecomastia

Drugs that increase serum estrogens
- Estrogens, including topical preparations
- Aromatizable androgens
- hCG

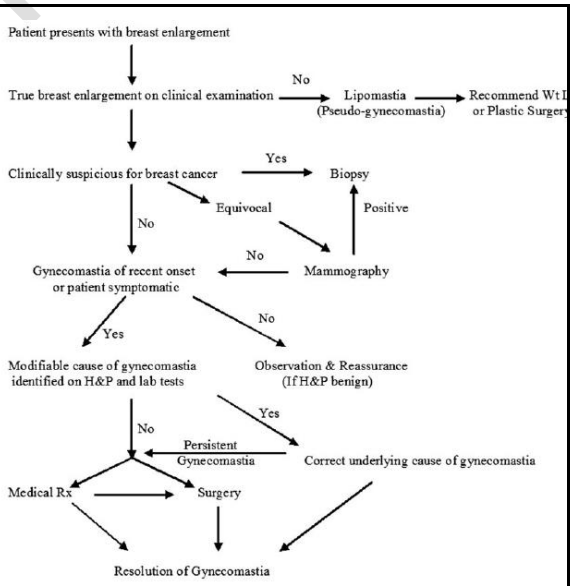
Drugs with estrogen-like activity
- Digitoxin

Drugs that decrease serum testosterone or dihydrotestosteron
- GnRH agonists/antagonists
- Leydig cell damage or inhibition
  - Ketoconazole, metronidazole
  - High-dose spironolactone
  - Cancer chemotherapy
- Finasteride or dutasteride

Androgen receptor blockers
- Flutamide, bicalutamide
- Spironolactone
- Cimetidine
- Marijuana

Increased serum prolactin
- Antipsychotic agents
- Metoclopramide
- Verapamil

Other—mechanism uncertain
- Isoniazid
- Amiodarone
- Antidepressants
- Human GH
- Highly active antiretroviral therapy (HAART)
- Proton pump inhibitors



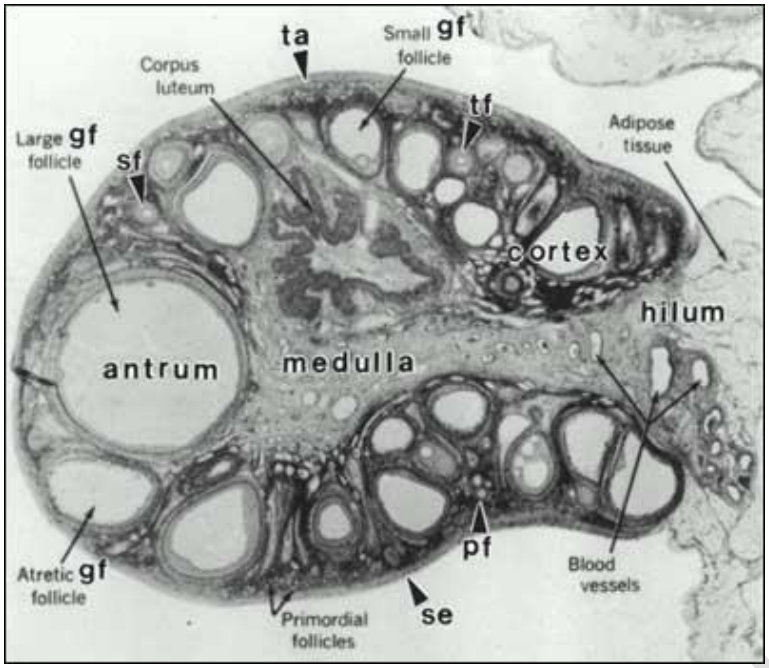
In the realm of therapy, medical treatment has its own controversies. **The overall response rate to tamoxifen has varied from 50–80%, although reported side effects have**

been few. It has not yet been clearly established whether tamoxifen and raloxifene are of equal benefit, although it seems reasonably clear that both are more effective
than aromatase inhibitors.

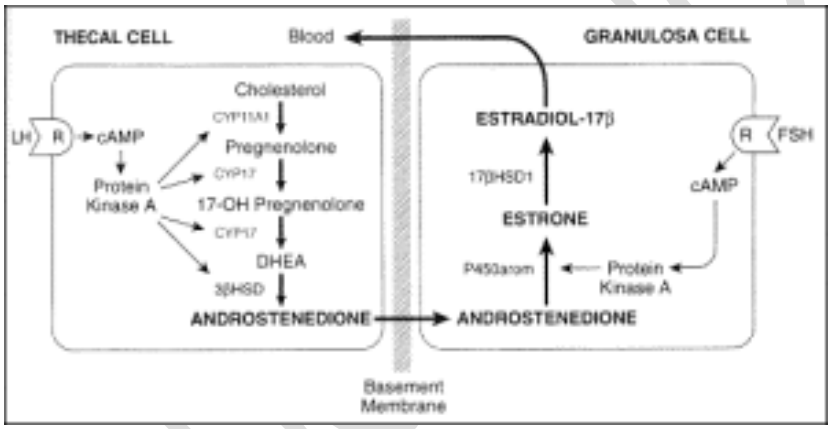
WOMENS HEALTH

Female Reproduction	7% of Exam
Amenorrhea	<2%
Primary	
Androgen insensitivity syndrome	
Turner syndrome	
Műllerian dysgenesis	
Congenital gonadotropin-releasing hormone (GnRH) deficiency	
Secondary	
Hyperandrogenism	<2%
Polycystic ovary syndrome	
Non-polycystic ovary syndromes	
Hyperthecosis	
Ovarian tumors	
Adrenal tumors	
Nonclassic congenital adrenal hyperplasia	
Pregnancy-associated	
Anabolic steroids	
Premenstrual syndrome and premenstrual dysphoric disorder	<2%
Endocrine causes of infertility	<2%
Anovulation	
Age-associated infertility (diminished ovarian reserve)	
Hormonal contraception	<2%
Combined estrogen-progestin contraceptives	
Progestin-only contraception	
Perimenopause and menopause	<2%
Perimenopause	
Menopause	
Estrogen–progestin therapy	
Sexual differentiation	<2%
Gender dysphoria	
Female-to-male transgender management	

Folliculogenesis begins with the recruitment of a primordial follicle into the pool of growing follicles and ends with either ovulation or death by atresia. In women, folliculogenesis is a very long process, requiring almost one year for a primordial follicle to grow and develop to the ovulatory stage.



The adult ovary can be subdivided into three regions: the **cortex**, **medulla**, and **hilum** regions. The cortex consists of the surface epithelium (se), tunica albuginea (ta), ovarian follicles (primordial, primary (pf), secondary (sf), small, medium, large Graafian follicle (gf)) and corpora lutea (cl). The medulla consists of large blood vessels and nerves. The hilum contains large spiral arteries and the hilum or ovary Leydig cells.

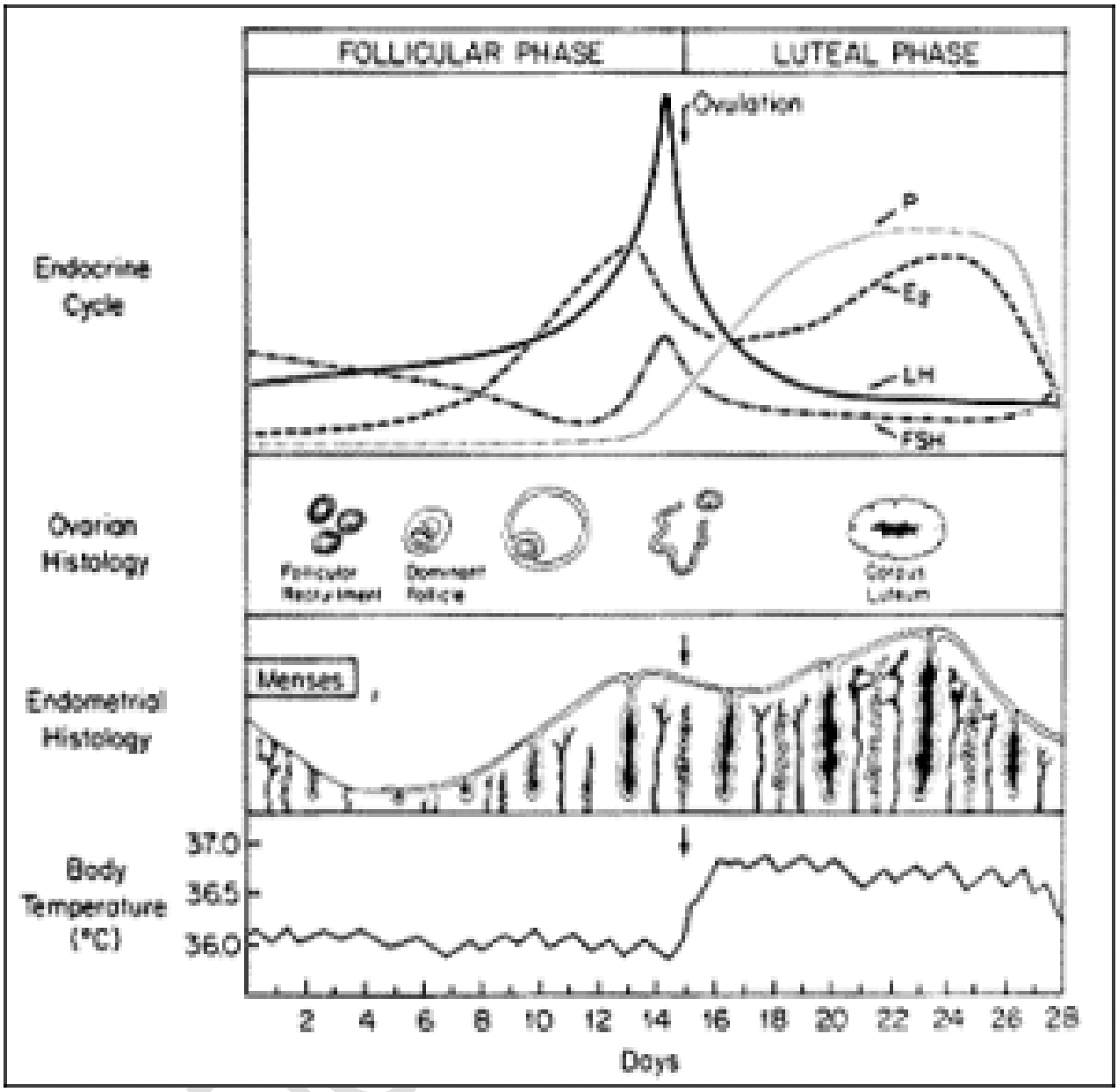


Two-cell, two-gonadotropin hypothesis *of regulation of estrogen synthesis in the human ovary*

The menstrual cycle

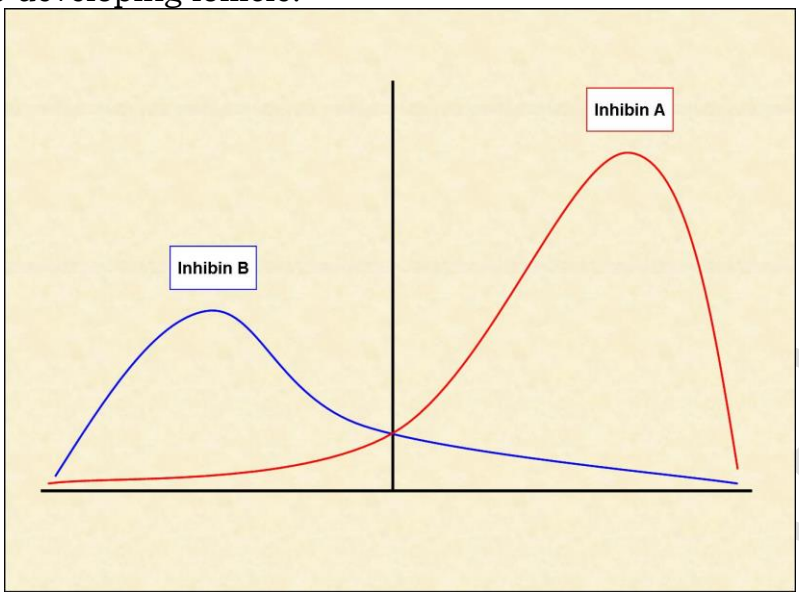
The length of a menstrual cycle is the number of days between the first day of menstrual bleeding of one cycle to the onset of menses of the next cycle. The median duration of a menstrual cycle is 28 days with most cycle lengths between 25 to 30 days.

Menstrual cycle may be divided into two phases: (1) follicular or proliferative phase, and (2) the luteal or secretory phase.



Follicular phase
• Folliculogenesis begins during the last few days of the preceding menstrual cycle until the release of the mature follicle at ovulation. • **Declining steroid production by the corpus luteum** and the dramatic fall of inhibin A allows for **follicle stimulating hormone (FSH) to rise** during the last few days of the menstrual cycle • Another influential factor on the FSH level in the late luteal phase is related to an increase in GnRH pulsatile secretion secondary to a decline in both estradiol and progesterone levels • This elevation in FSH allows for the recruitment of a cohort of ovarian follicles in each ovary, one of which is destined to ovulate during the next menstrual cycle • Once menses ensues, FSH levels begin to decline due to the negative

feedback of estrogen and the negative effects of inhibin B produced by the developing follicle.



- FSH activates the aromatase enzyme in granulosa cells, which converts androgens to estrogen. A decline in FSH levels leads to the production of a more **androgenic microenvironment within adjacent follicles to the growing dominant follicle**
- *Also, the granulosa cells of the growing follicle secrete a variety of peptides that may play an autocrine/paracrine role in the inhibition of development of the adjacent follicles.*

Development of a dominant follicle

Development of the dominant follicle has been described in three stages: (1) Recruitment, (2) Selection, and (3) Dominance

1. The recruitment stage takes place **during days 1 through 4 of the menstrual cycle**. During this stage, FSH leads to recruitment of a cohort of follicles from the pool of non-proliferating follicles.
2. Between cycle **days 5 and 7, selection of a follicle takes place whereby only one follicle is selected** from the cohort of recruited follicles to ovulate, and the remaining follicles will undergo atresia.**Anti-Müllerian hormone (AMH)**, a product of granulosa cells, is believed to play a role in the selection of the dominant follicle.
3. By cycle day 8, one follicle exerts its dominance by promoting its own growth and suppressing the maturation of the other ovarian follicles thus becoming the dominant follicle.

During the follicular phase, serum estradiol levels rise in parallel to the growth of follicle size as well as to the increasing number of granulosa cells

The rise in estradiol secretion appears to increase the total number of estradiol receptors on the granulosa cells

In the presence of estradiol, FSH stimulates the formation of LH receptors on granulosa cells allowing for the secretion of small quantities of progesterone and 17-hydroxyprogesterone (17-OHP) which may exert a positive feedback on the estrogen- primed pituitary to augment luteinizing hormone (LH) release

In contrast to granulosa cells, ***LH receptors are located on theca cells during all stages of the menstrual cycle.*** *LH principally stimulates androstenedione production, and to a lesser degree testosterone production in theca cells. In the human, androstenedione is then transported to the granulosa cells where it is aromatized to estrone and finally converted to estradiol by 17-β-hydroxysteroid dehydrogenase type I. This is known as the two-cell, two-gonadotropin hypothesis of regulation of estrogen synthesis in the human ovary*

ovulation

Ovulation occurs approximately 10-12 hours after the LH peak

- The LH surge is initiated by a dramatic rise of estradiol produced by the preovulatory follicle
- To produce the critical concentration of estradiol needed to initiate the positive feedback, the **dominant follicle is almost always >15mm in diameter on ultrasound**
- *ovulation occurs more commonly from the right ovary and right sided ovulation carries a higher potential for pregnancy*
- Though the precise mechanism is not known, proteolytic enzymes and prostaglandins are activated and digest collagen in the follicular wall, leading to an explosive release of the oocyte-cumulus complex
- Prostaglandins may also stimulate ovum release by stimulation of smooth muscle within the ovary
- The point of the dominant follicle closest to the ovarian surface where this digestion occurs is called the stigma

Luteal phase

- After ovulation, the remaining granulosa cells that are not released with the oocyte continue to enlarge, become vacuolated in appearance, and begin to accumulate a yellow pigment called lutein.
- The luteinized granulosa cells combine with the newly formed theca-lutein cells and surrounding stroma in the ovary to become what is known as the corpus luteum
- **corpus luteum is a transient endocrine organ that**

predominantly secretes progesterone, and its primary function is to prepare the estrogen primed endometrium for implantation of the fertilized ovum

- If pregnancy does not occur, the **corpus luteum undergoes luteolysis** under the influence of estradiol and prostaglandins, and forms a scar tissue called the **corpus albicans.**

Functional Hypothalamic amenorrhea

FHA is a form of chronic anovulation that is not due to identifiable organic causes

Table 1. Potential Etiologies of Amenorrhea

Congenital malformation
- Septo-optic dysplasia
- Holoprosencephaly
- Encephalocele

Constitutional delay

Genetic conditions
- Congenital deficiency of hypothalamic or pituitary transcription factors (gonadotropin deficiency)
- Single-gene mutations (hypogonadotropic hypogonadism)

Hyperprolactinemia

Pituitary gland or stalk damage
- Tumors and cysts [hypothalamic or pituitary tumor (hormone-secreting), craniopharyngioma, Rathke cleft cyst, other cysts, and tumors]
- Infiltrative disorders (germinoma, autoimmune hypophysitis, sarcoidosis, hemochromatosis, tuberculosis, Langerhans cell histiocytosis, IgG4-related hypophysitis)
- Irradiation
- Infarction [apoplexy in pre-existing pituitary tumors, or following postpartum hemorrhage (Sheehan syndrome)]
- Surgery
- Trauma

Others
- Eating disorders
- Competitive athletics
- Chronic disease
- Mood disorders
- Stress or psychiatric illness
- Drugs

Thyroid
- Hypothyroidism or hyperthyroidism

Adrenals
- Congenital adrenal hyperplasia (select types)
- Cushing syndrome
- Addison disease (adrenal insufficiency)
- Tumor (androgen-secreting)

Ovaries
- Associated with high levels of gonadotropins
  - Gonadal agenesis or dysgenesis (in the setting of Turner syndrome/other)
  - Ovarian insufficiency
  - Autoimmune oophoritis
  - Irradiation or surgery
- Not associated with high levels of gonadotropins
  - Polycystic ovary syndrome
  - Tumor (estrogen- or androgen-secreting)

Uterus (eugonadism)
- Müllerian anomalies (obstructive outflow anomalies)
- Asherman syndrome
- Synechiae (integral to Asherman syndrome)
- Pregnancy
- Infectious (*e.g.,* tuberculous endometritis)
- Agenesis (uterine or cervical)

Vagina (eugonadism)
- Agenesis
- Transverse septum

Hymen (eugonadism)
- Imperforate

Functional Hypothalamic Amenorrhea : Evaluation

History

- eating disorders; exercise and athletic training; attitudes,such as perfectionism and high need for social approval
- Weight fluctuations; sleep patterns; stressors; mood; menstrual pattern; fractures; and substance abuse

- history of galactorrhea, severe or persistent headache, nausea, vomiting, or changes in vision, thirst, or urination (both volume and frequency), suggesting the possibility of a prolactinoma or other pituitary or intracranial tumor.
- Symptoms of thyroid dysfuncttion
- Symptoms of PCOS or androgen excess
- Medications, including antipsychotics, antidepressants, contraceptive agents, and opioids, can alter menses,

Physical Exam

- external gynecologic and bimanual examination. consider a transabdominal or transvaginal pelvic sonogram on initial presentation instead of the bimanual examination.
- galactorrhea, thyromegaly, hirsutism, acne, or clitoromegaly
- Signs of androgen excess (e.g.,acne, hirsutism, male pattern alopecia, clitoromegaly) and hyperinsulinism (e.g., acanthosis nigricans and skin tags) should raise concerns of PCOS or other causes of androgen excess (e.g., nonclassic CAH and virilizing ovarian and adrenal tumors)

Labs

- B-human chorionic gonadotropin to rule out pregnancy
- serum TSH, free T4, prolactin,LH, FSH, E2, and AMH.
- Total testosterone and DHEA-S levels in patients with clinical hyperandrogenism and 8 AM 17-hydroxyprogesterone levels if clinicians suspect late-onset CAH

• The pattern of hormone levels is more critical than absolute values. • Patients with FHA have characteristically low or low normal LH, normal FSH concentrations (which are usually higher than LH concentrations)
• E2 < 50 pg/mL, and progesterone < 1 ng/mL; the acute gonadotropin response to GnRH stimulation is preserved (defined as a twofold to threefold rise in LH and FSH compared with baseline levels). • E2 measurements are typically limited by the fact that a measurement reflects a single time point, and no single E2 value can confirm a diagnosis of FHA. However, in patients whose E2 is persistently,20 pg/mL, the response to GnRH is the only feature that may differentiate FHA from hypogonadotropic hypogonadism
• With the latter diagnosis, the acute LHresponse would be low, but normalizes with prolonged pulsatile GnRH therapy •

ovarian insufficiency

Elevated FSH and LH levels with low E2 (< 20 pg/mL) and progesterone (<1 ng/mL) indicate low or absent ovarian reserve consistent with complete or impending ovarian insufficiency

Table 2. Common Causes of Anovulation and Accompanying Laboratory Patterns

	LH (IU/L)	FSH (IU/L)	LH/FSH	E2 (pg/mL)	P4 (ng/mL)	AMH (ng/mL)	PRL (ng/mL)	TSH (μU/mL)	T4 (μg/dL)	DHEA-S (μg/dL)	17OHP (ng/dL)	T (ng/dL)
Functional hypothalamic anovulation	<10	<10	~1	<50	<1	>1	Low nl	Low nl	Low nl	nl	nl	Low nl
Ovarian insufficiency menopause	>15	>15	FSH > LH	<50	<1	<0.5	nl	nl or ↑	nl or ↓	nl	nl	Low nl
PCOS	<15	<10	LH > FSH	<50	<1	nl or ↑	High nl	nl	nl	High nl	nl	High nl or slight↑
Nonclassical CAH	<15	<10	LH > FSH	<50	≤1	nl	nl	nl	nl	High nl	↑	↑
Hyperprolactinemia	<10	<10	LH < FSH	<50	<1	nl	↑	nl or ↑	nl	nl or slight ↑	nl	nl

Abbreviations: 17OHP, 17-hydroxyprogesterone; nl, normal; P4, progesterone; PRL, prolactin; T, testosterone.

A serum AMH concentration is an indicator of ovarian reserve

Non classical CAH

- If the patient has signs of virilization and/or substantial elevations in DHEA-S and/or testosterone (free or total), an 8 AM 17-hydroxyprogesterone level can serve as an initial screen for nonclassic CAH
- high-dose ACTH stimulation test may be necessary to confirm the diagnosis.

Adrenal Tumor

- High DHEA-S levels in concentrations that far exceed the normal range (e.g., DHEAS >600 mg/dL)
- Some patients with poorly differentiated adrenal tumors may have higher circulating levels of DHEA than DHEA-S

After excluding pregnancy, we suggest **administering a progestin challenge in patients with FHA to induce withdrawal bleeding** (as an indication of chronic estrogen exposure) and ensure the integrity of the outflow tract)

Progestin Challenge testing

- Absence of withdrawal bleeding after a course of progestin may indicate outflow tract obstruction or low endometrial estrogen exposure

- The response to a progestin challenge can provide additional information about a patient's estrogen status, especially in those cases in which there is overlay between FHA and PCOS.
- **medroxyprogesterone acetate** (5 to 10 mg/d for 5 to 10 days), **norethindrone acetate** (5 mg/d for 5 to 10 days), or **micronized progesterone** (200 to 300 mg/d for 10 days).
- Follow-up with a pelvic ultrasound may be necessary if the patient does not have a withdrawal bleed and is useful in determining endometrial thickness and Mullerian tract integrity. The latter may require confirmation with MRI.

When do we recommend Brain MRI

- We recommend a brain MRI (with pituitary cuts and contrast) in adolescents or women with presumed FHA and a history of severe or persistent headaches; persistent vomiting that is not self-induced; change in vision, thirst, or urination not attributable to other causes; lateralizing neurologic signs; and clinical signs and/or laboratory results that suggest pituitary hormone deficiency or excess.

When do we recommend DEXA

- obtain a baseline BMD measurement by DXA from any adolescent or woman with 6 or more months of amenorrhea
- history or suspicion of severe nutritional deficiency, other energy deficit states, and/or skeletal fragility

MENOPAUSE

In a woman with an intact uterus, menopause is a clinical diagnosis based upon cessation of menses for at least 12 months. Sex steroids, gonadotropins, inhibin B, or anti-Mullerian hormone measurements do not further inform the diagnosis.

In women having undergone a hysterectomy but not bilateral oophorectomy, elevated FSH levels and estradiol concentrations 20 pg/mL on several occasions support the diagnosis.

Table 1. Definitions of Spectrum of Menopause

Menopause
Clinical status after the final menstrual period, diagnosed retrospectively after cessation of menses for 12 mo in a previously cycling woman and reflecting complete or nearly complete permanent cessation of ovarian function and fertility.
Spontaneous menopause
Cessation of menses that occurs at an average age of 51 y in the absence of surgery or medication (316–318).
Menopausal transition (or perimenopause)
An interval preceding the menopause characterized by variations in menstrual cycle length and bleeding pattern, mood shifts, vasomotor, and vaginal symptoms and with rising FSH levels and falling anti-Mullerian hormone and inhibin B levels, which starts during the late reproductive stage and progresses during the menopause transition (15, 319).
Climacteric
The phase in the aging of women marking the transition from the reproductive phase to the nonreproductive state. This phase incorporates the perimenopause by extending for a longer variable period before and after the perimenopause.
Climacteric syndrome
When the climacteric is associated with symptomatology.
Menopause after hysterectomy without oophorectomy
Spontaneous cessation of ovarian function without the clinical signal of cessation of menses.
Induced menopause
Cessation of ovarian function induced by chemotherapy, radiotherapy, or bilateral oophorectomy.
Early menopause
Cessation of ovarian function occurring between ages 40 and 45 in the absence of other etiologies for secondary amenorrhea (pregnancy, hyperprolactinemia, and thyroid disorders).
POI
Loss of ovarian function before the age of 40 y with waxing and waning course and potential resumption of menses, conception, and pregnancy (320). The prevalence of POI is approximately 1% (321) and is differentiated into idiopathic, autoimmune (associated with polyglandular autoimmune syndromes), metabolic disorders, and genetic abnormalities (including fragile X premutation).

Medications for menopausal symptoms	
Estrogen	• Most effective therapy • Can be given orally, transdermally, or vaginally depending on symptoms • **Transdermal preparations** have a lower risk of venous thromboembolism & stroke • Raises risk of endometrial cancer in patients with intact uterus
Estrogen-progesterone	• Should be given to patients with intact uterus (rather than unopposed estrogen) to avoid risk of endometrial cancer
SSRIs/SNRIs	• Relieve hot flashes & affective symptoms • Not beneficial for other menopausal symptoms (eg, vaginal atrophy) • Should **NOT** be given to patients on **tamoxifen** for **breast cancer**
Gabapentin	• Given at bedtime for predominantly nocturnal symptoms or through the day • Associated with significant dizziness & sedation

Table 2. Conditions That May Cause or Mimic Vasomotor Events and That Can Be Distinguished From Menopausal Symptoms by History, Examination, and Investigations, as Indicated

Hormone excess
Thyroid hormone excess
Carcinoid syndrome (flushing without sweating)
Pheochromocytoma (hypertension, flushing, and profuse sweating)
Dietary factors
Alcohol
Spicy food
Food additives (eg, monosodium glutamate, sulfites)
Pharmaceuticals
Chronic opioid use
Opiate withdrawal
SSRIs (may cause sweats)
Nicotinic acid (intense warmth, itching lasting up to 30 min)
Calcium channel blockers
Medications that block estrogen action or biosynthesis
Chronic infection (increased body temperature)
Other medical conditions
Postgastric surgery dumping syndrome
Mastocytosis and mast cell disorders (usually with gastrointestinal symptoms)
Some cancers: medullary carcinoma of the thyroid, pancreatic islet-cell tumors, renal cell carcinoma, lymphoma
Anxiety disorders

Table 3. Genitourinary Syndrome of Menopaus

Symptoms
Vulvar pain, burning, or itching
Vaginal dryness
Vaginal discharge
Dyspareunia
Spotting or bleeding after intercourse
Dysuria, urinary frequency, urgency
Recurrent urinary tract infections
Signs, external genitalia
Decreased labial size
Loss of vulvar fat pads
Vulvar fissures
Receded or phimotic clitoris
Prominent urethra with mucosal eversion or prolapse
Signs, vagina
Introital narrowing
Loss of elasticity with constriction
Thin vaginal epithelial lining
Loss of mature squamous epithelium
Pale or erythematous appearance
Petechiae, ulcerations, or tears
Alkaline pH (>5.5)
Infection (yellow or greenish discharge)

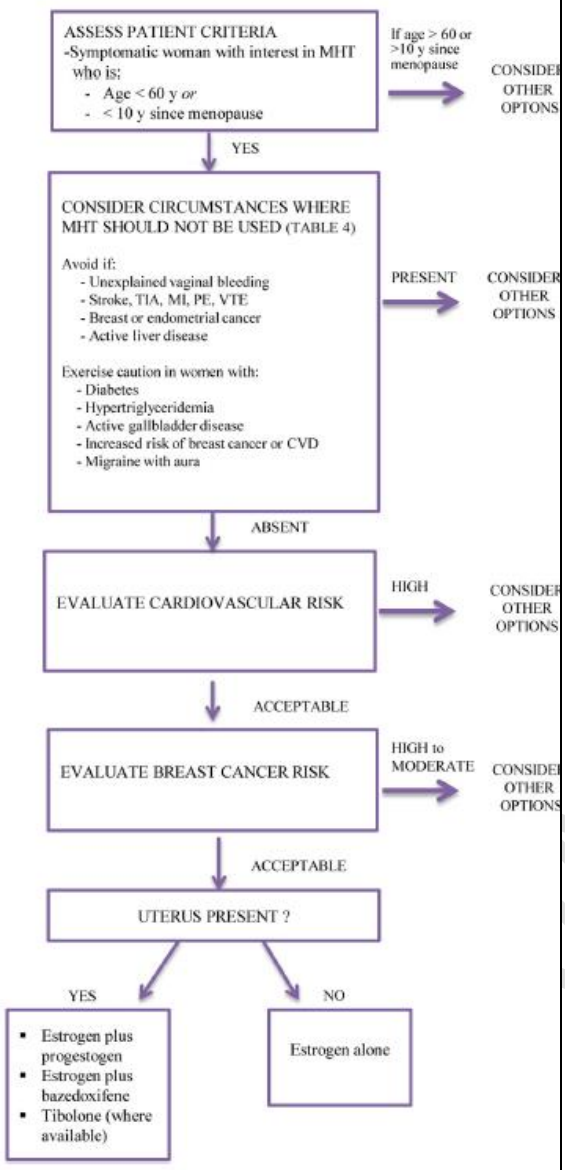


Figure 2. Approach to the patient with VMS contemplating MHT. TIA, transient ischemic attack.

Table 4. Specific Cautions to Use of Systemic MHT or SERMs[a,b] for Treatment of Menopausal Symptoms

In general, ET should not be used in women with any of the following conditions:
Undiagnosed abnormal genital bleeding
Known, suspected, or history of cancer of the breast
Known or suspected estrogen-dependent neoplasia including endometrial cancer
Active DVT, pulmonary embolism, or history of these conditions
Active arterial thromboembolic disease (for example, stroke, MI) or a history of these conditions
Known anaphylactic reaction or angioedema in response to any ingredient in the medication[c]
Known liver impairment or disease
Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders[c]
Known or suspected pregnancy
Caution should also be exercised in women with:
Gallbladder disease (oral ET)
Hypertriglyceridemia (>400 mg/d) (oral ET)
Diabetes
Hypoparathyroidism (risk of hypocalcemia)
Benign meningioma
Intermediate or high risk of breast cancer
High risk of heart disease
Migraine with aura (oral ET)
Other conditions[d]

[a] Also apply to conjugated estrogens/BZA, ospemifene, and tibolone therapies.

[b] Advice not to use estrogens in the specific conditions listed is based on FDA recommendations and package labeling in the United States. The advice to exercise caution is based on a review of the literature (including package labeling) and not dictums generally included in various Menopause Society guidelines. Because these guidelines are meant to be used internationally, it should be noted that these considerations may vary from country to country.

[c] Specific to CEE ± combination with BZA.

[d] Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

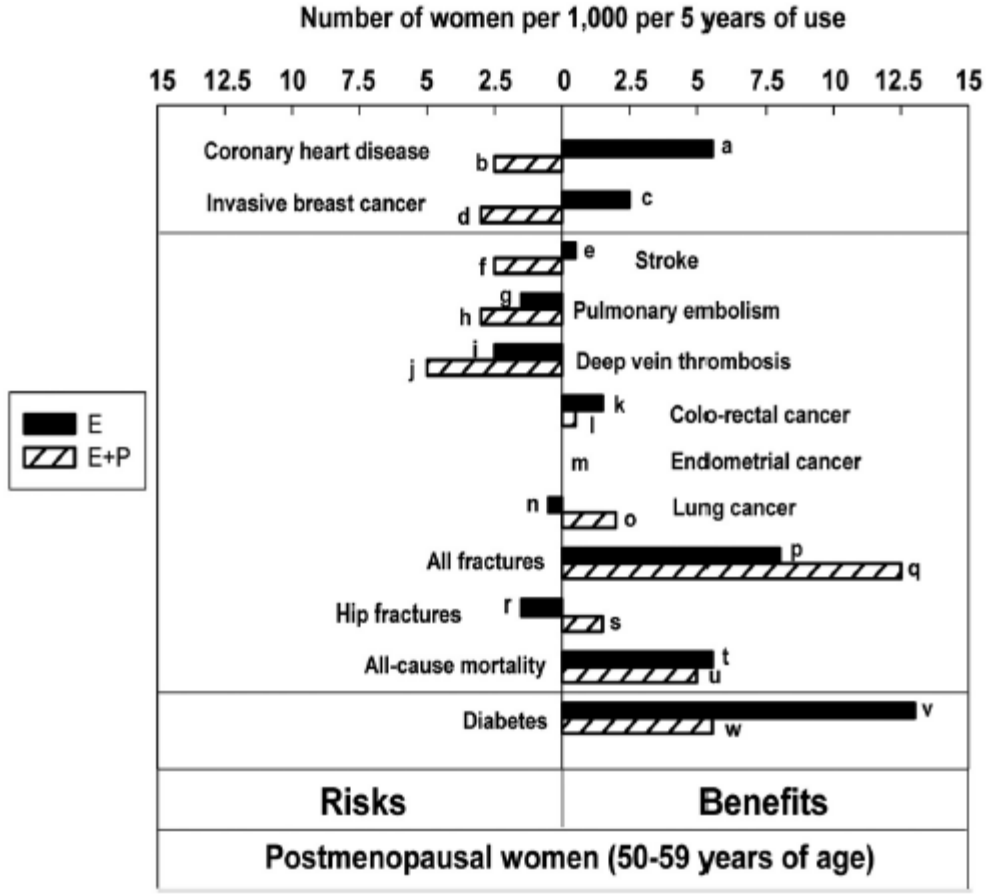


Figure 3. Updated summary of the effects of orally administered CEE alone or combined with MPA in women ages 50–59 years during intervention phase of WHI. One set of analyses examined the risks and benefits of these agents in women ages 50–59 years. This figure plots these data, which are expressed here as excess risks and benefits per 1000 women using MHT for 5 years. Because women deciding to use MHT are more likely to continue this for a period of years rather than 1 year, this figure is constructed according to that assumption. WHI studies were not powered for age-related subset analyses, and none of the data presented in the figure are statistically significant. Nonetheless, this figure represents the best estimates that are available at the present time and are likely more reliable than similar estimates based on observational studies as reported previously in The Endocrine Society Scientific Statement (38).

Table 5. Commonly Prescribed Hormone Therapies

Preparation	Doses	Comments
Systemic estrogen therapies[a]		
Oral estrogen tablets		
Micronized E2	0.5, 1.0, 2.0 mg/d	
Estradiol valerate[b]	1.5 mg/d	
CEE	0.3, 0.45, 0.625 mg/d	Higher doses available Preparation used in WHI
Transdermal estrogens		
Estradiol patch	0.025 to 0.1 mg once or twice weekly depending on preparation 0.014 mg/wk	Corresponds to 0.5 to 2.0 mg estradiol tablets Diffusion can be different from one patch to another Preserved bone in women >60 y old
Estradiol percutaneous gel	0.25–1.5 mg qd	Corresponds to 0.5 to 2.0 mg estradiol tablets Can be transferred to persons and pets by skin contact
Estradiol transdermal spray	1.5 mg qd	Estradiol via spray Can be transferred to persons and pets by skin contact
Vaginal ring		
Estradiol acetate	0.05–0.10 mg/d	Systemic levels of estradiol provide relief of VMS; 90-d duration/ring
Progestogen therapies		
Oral progestin tablets		
Medroxyprogesterone acetate	2.5, 5, 10 mg/d	Utilized in WHI
Norethindrone	0.35 mg/d	
Neta	5.0 mg/d	
Megestrol acetate	20, 40 mg/d	
Dydrogesterone[b]	10 mg/d	
Chlormadinone acetate[b]	5, 10 mg/d	
Medrogestone[b]	5 mg/d	
Nomegestrol acetate[b]	3.75, 5 mg/d	
Promegestone[b]	0.125, 0.25, 0.5 mg/d	
Oral progesterone capsule		
Micronized progesterone	100, 200 mg/d	In peanut oil; avoid if peanut allergy. May cause drowsiness and should be taken at bedtime
Intrauterine system progestin[c]		
LNorg	20 μg released/d 6 μg/d	IUD for 5-y use IUD for 3-y use
Vaginal gel progesterone[c]	4%, 8%	45- or 90-mg applicator
Combination hormone therapies		
Oral		
CEE + MPA	0.3–0.625 mg/1.5–5 mg/d	Cyclic or continuous
E2 + Neta	0.5–1 mg/0.1–0.5 mg/d	Continuous
E2 + drospirenone	0.5–1 mg/0.25–1 mg/d	Continuous
E2 + norgestimate	1 mg/0.09 mg/d	Cycle 3 d E alone, 3 d E + progesterone
E2 + dydrogesterone[b]	1–2 mg/5–10 mg/d	Cyclic and continuous
E2 + cyproterone acetate[b]	2 mg/1 mg/d	Continuous
E2 + MPA[b]	1–2 mg/2–10 mg/d	Continuous
CEE + BZA[d]	0.45 mg/20 mg/d	Continuous
Transdermal		
E2 + Neta	50 μg/0.14–0.25 mg/patch	Twice weekly
E2 + LNorg	45 μg/0.015 mg/patch	Once weekly

Table 8. Clinical Caveats During Treatment With MHT

Symptom/Condition When MHT Started	Approach to Resolution
Persistent, intolerable VMS	Switch mode of administration or adjust dose of estrogen and/or progestogen.
Hot flashes that persist after treatment adjustment	Consider another etiology of flashes (Table 2). Ensure absorption: if transdermal, consider serum estradiol determination.
Bleeding: approach depends on time since menopause, MHT regimen, duration of therapy, duration and character of bleeding	Sequential regimen may be more appropriate for recently menopausal (<2 y), because unscheduled bleeding with continuous combined MHT can be problematic. Persistent irregular bleeding (>6 mo) should be evaluated for endometrial pathology; if obese, diabetic, or having family history for endometrial cancer, evaluate sooner. Atrophic endometrium in women more remote from menopause may respond to increased estrogen dose if otherwise appropriate.
Breast tenderness	Usually responds to a reduction in estrogen dose or change in progestogen preparation. CEE/BZA may improve symptoms. Changing to tibolone may be helpful in women who develop mastalgia on conventional MHT.
Baseline TG level >200 mg/dL	Review family history and seek contributing factors. Transdermal ET is preferred. If oral estrogen is selected, monitor serum TG levels 2 wk after starting therapy.
Hypothyroid on thyroid replacement	Monitor TSH 6 to 12 wk after starting oral MHT; T_4 dose may need to be increased (209).

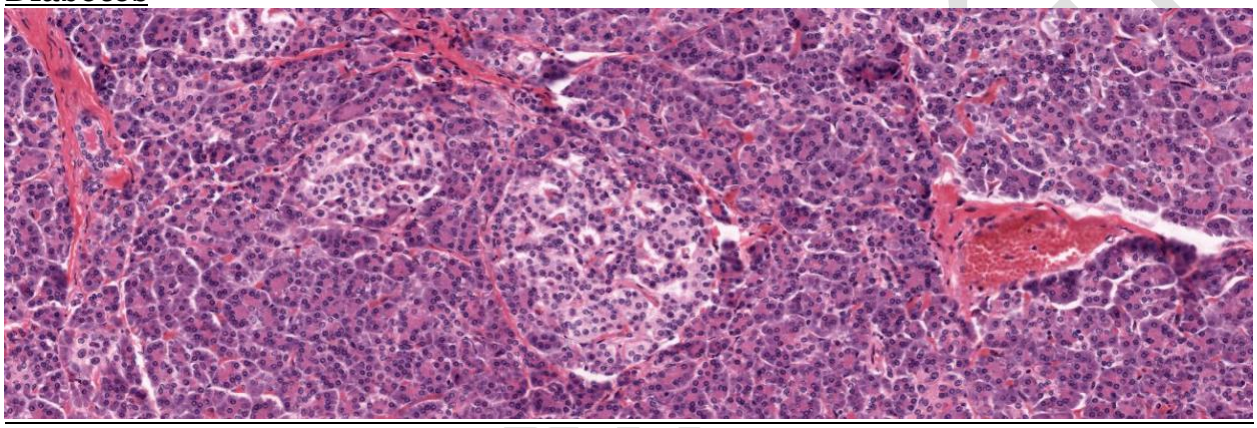
Abbreviation: TG, triglycerides.

Table 9. Alternative Therapies for Treatment of VMS

Agents	Comments	Refs.
Agents with inconsistent reports of benefit		
Genistein	Purified isoflavone ±Estrogenically active Breast safety not established	324–336
Daidzein	Purified isoflavone ±Estrogenically active Breast safety not established	324–336
S-equol	Metabolite of daidzein	337
Nonpurified isoflavones	Breast safety not established	338
Flaxseed		225, 236, 328, 339–341
Red clover	Breast safety not established	225, 236, 328, 339–341
High-dose extracted or synthesized phytoestrogen		225, 236, 328, 339–341
Dietary soy	Agreement about breast safety	248
Vitamin E	10% benefit in some studies	217, 342, 343
Reports with predominantly no benefit		
Black cohosh	Some short-term trials report benefit, most report no benefit Breast safety not established Reports of liver toxicity	225, 344–352
Omega-3 fatty acids	No benefit in MSFLASH trial	246
Acupuncture	Not effective when compared to "sham acupuncture" controls	353–356
Exercise	Exercise with sweating may increase hot flashes	357
Other complementary approaches	Ginseng, dong quai, wild yam, progesterone creams, traditional Chinese herbs, reflexology, magnetic devices	225, 332
Agents requiring further study		
Stellate ganglion block	Need further RCTs to establish lack of complications	358
Guided relaxation	Stress management, deep breathing, paced respiration, guided imagery, mindfulness training	217, 225, 247, 359–365
Hypnosis	Recent studies suggest efficacy	247
Cognitive behavior modification	Recent studies suggest efficacy with trained practitioners	366, 367

DIABETES PATHOPHYSIOLOGY AND MANAGEMENT

Diabetes



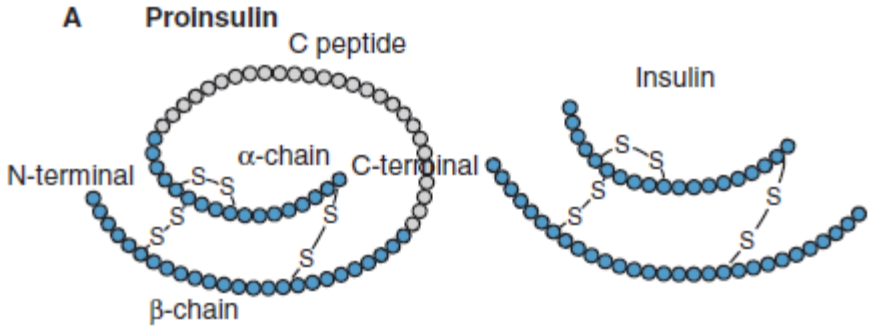
Diabetes Mellitus and Hypoglycemia	**24%** of Exam
Prediabetes	2%
Impaired fasting glucose	
Impaired glucose tolerance	
Screening	
Monitoring glycemic control	2%
Hemoglobin A_{1C}	
Fructosamine and 1,5-anhydroglucitol	
Conventional glucose monitoring	
Ketone testing	
Continuous glucose monitoring (CGM)	
Type 1 diabetes mellitus	3.5%
Ketoacidosis	
Recent-onset type 1 diabetes	
Latent autoimmune diabetes of the adult (LADA)	
Hyperglycemia in type 1 diabetes	
Hypoglycemia due to insulin management	
Pathogenesis of type 1 diabetes	
Type 2 diabetes mellitus	4.5%
Hyperosmolar nonketotic state	
Hyperglycemia in type 2 diabetes	
Hypoglycemia due to oral agents and insulin management	
Pathogenesis of type 2 diabetes	
Additional types of diabetes mellitus	<2%
Monogenic diabetes	
Ketosis-prone diabetes (KPD)	
New-onset diabetes after transplant (NODAT) [post-transplant diabetes mellitus (PTDM)]	
Pancreatic diabetes	
Cystic fibrosis-related diabetes	
Drug-induced diabetes	
Recognition and management of associated conditions	<2%
Hypertension	
Dyslipidemia	
Obesity	
Sleep apnea	
Fatty liver	
Thyroid disease	
Celiac disease	
Polycystic ovary syndrome	

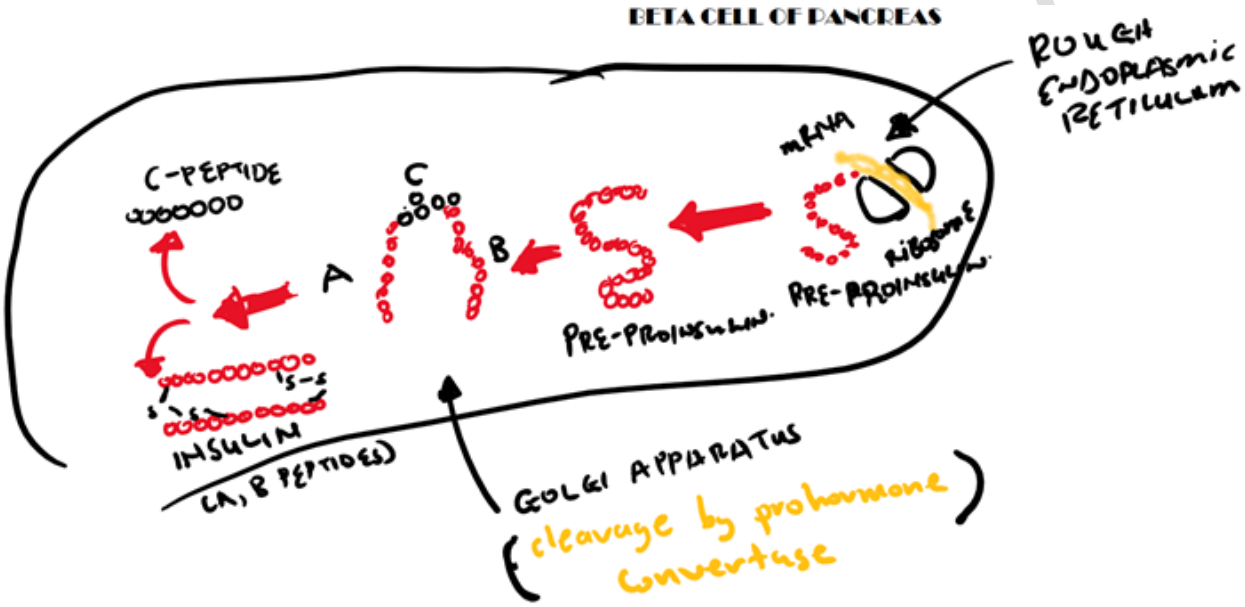
Eating disorders	
Dead-in-bed syndrome	
Pregnancy	<2%
Gestational diabetes	
Pre-gestational diabetes	
Diabetes mellitus complications	4.5%
Microvascular	
Retinopathy	
Nephropathy	
Neuropathy	
Macular edema	
Mononeuropathies	
Macrovascular	
Coronary artery disease	
Heart failure	
Peripheral vascular disease	
Diabetic foot	
Skin disorders	
Lipohypertrophy	
Lipoatrophy	
Necrobiosis lipoidica	
Acanthosis nigricans	
Neuropsychiatric	
Islet cell and pancreas transplantation	<2%
Hypoglycemia independent of diabetes mellitus	2%
Insulinoma	
Non-insulinoma causes	
Hypoglycemia unawareness	
Inpatient diabetes mellitus management	<2%
Intensive care unit	
Non–intensive care unit	

Pancreas

5 identified cell types in the islet of langerhans

1. Alpha cells (25%) produce glucagon
2. Beta cells (60%) produce insulin and amylin
3. Delta cells (10%) produce somatostatin
4. F or PP cells (small percentage) -- Pancreatic polypeptide
5. Epsilon cells (small percentage) -- Ghrelin (paracrine effects)



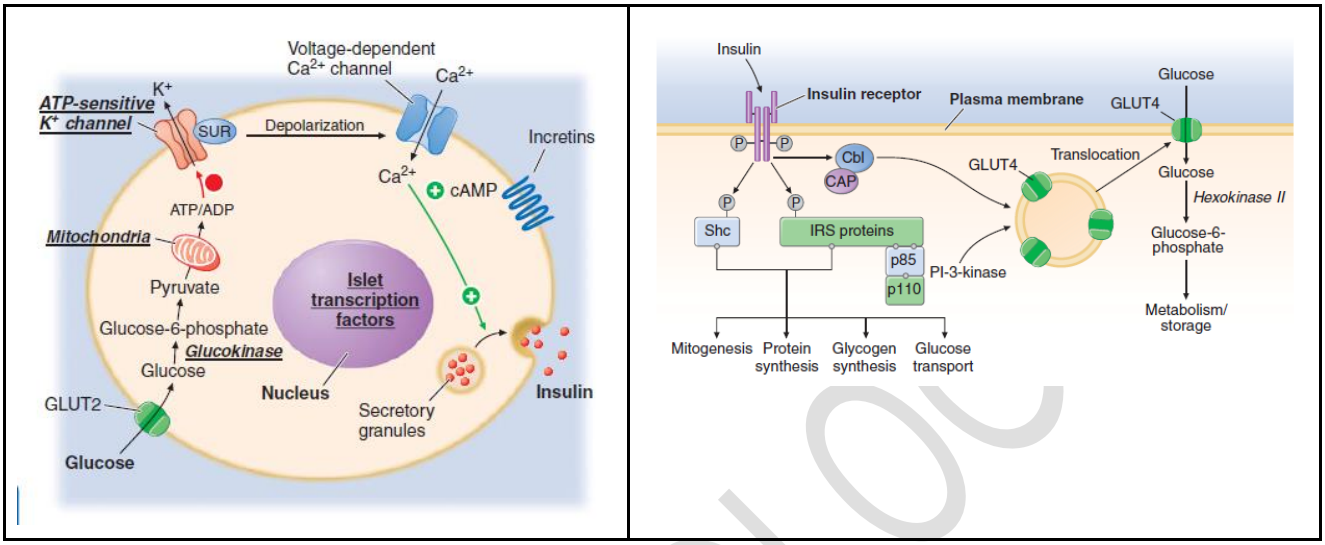


- Insulin and c-peptide are stored in secretory granules until they are released into circulation
- Insulin binds to the tyrosine kinase insulin receptor on target cells, resulting in translocation of glucose transport proteins (GLUTs) from the golgi apparatus to the plasma membrane.
- Each cell has a different type of GLUT transporter to hand glucose uptake.

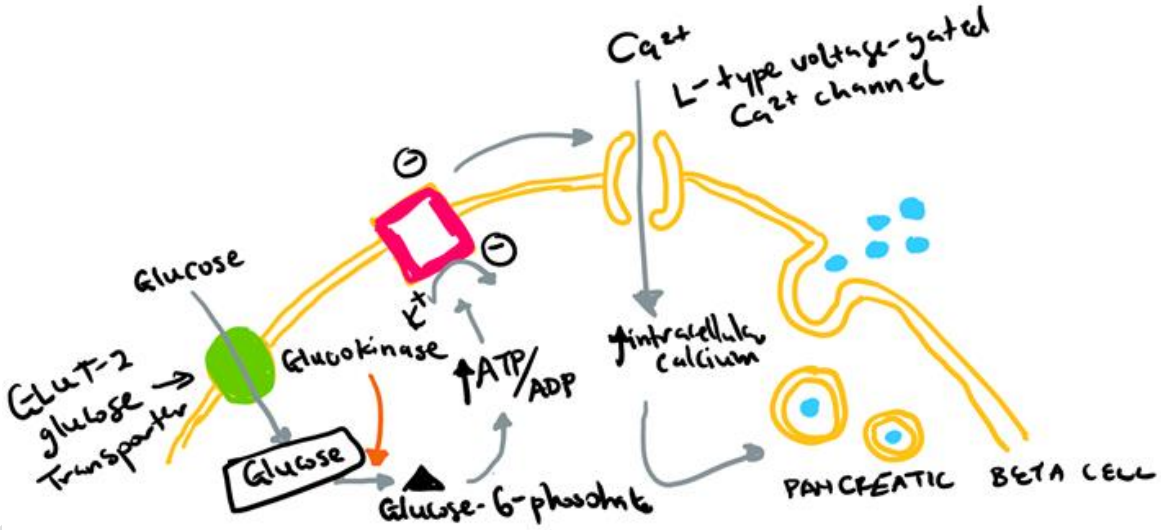
NB : GLUT-2 transporters in the pancreatic beta cells and hepatocytes are insulin independent and respond to the presence of glucose in circulation. GLUT-4 in striated muscle and adipose tissue, are insulin dependent and are expressed in response to insulin.

GLUT-1	Erythrocytes, blood-brain barrier	Low level of basal glucose uptake required to sustain respiration in cells.
GLUT-2	B-cells, renal tubular cells, liver, intestinal epithelial cells	
GLUT-3	Neurons and placenta	

GLUT-4	Striated muscle and adipose tissue	ONLY insulin-regulated GLUT : responsible for insulin regulated glucose uptake

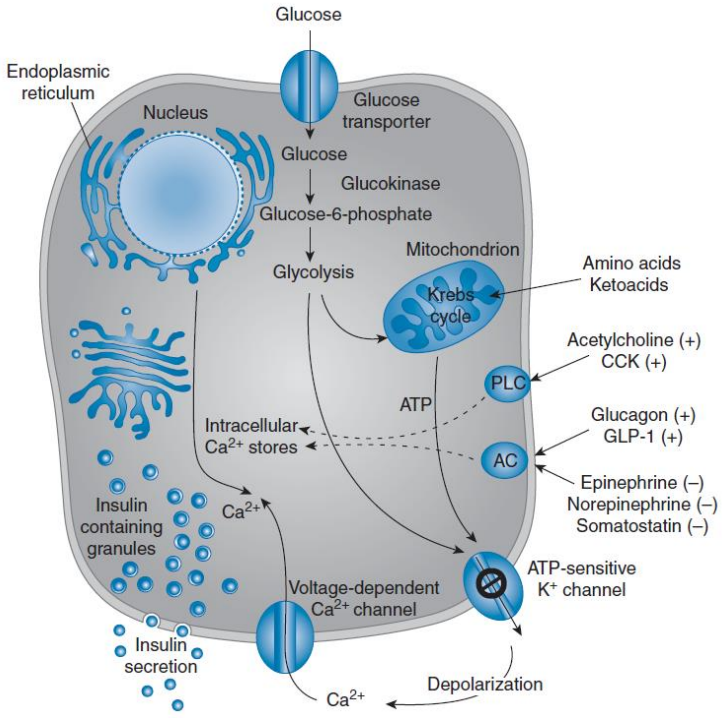


Mechanism of insulin secretion in the post prandial period



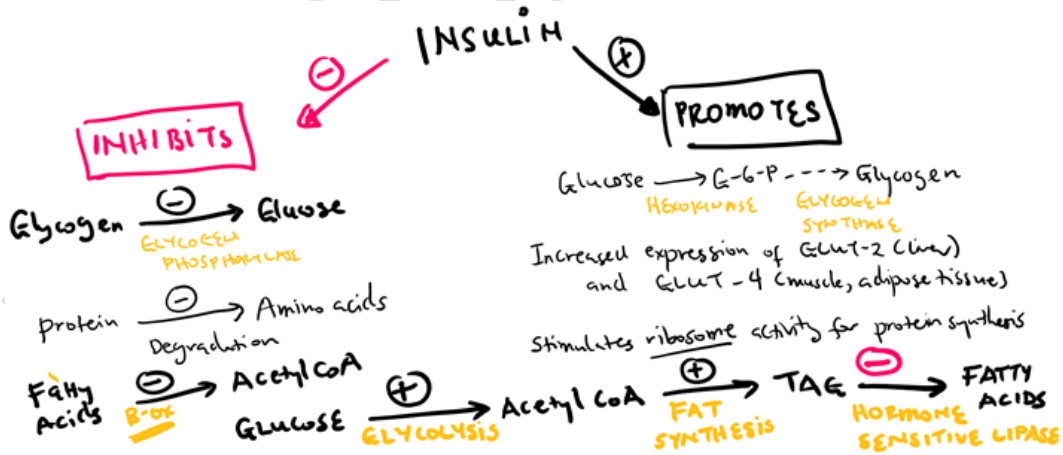
- In the **basal state,** the plasma membrane is hyperpolarized and the rate of insulin secretion from the cell is low.
- When glucose is available (post prandial), it **enters the cell via GLUT-2 transporters** in the plasma membrane and is metabolized to generate intracellular ATP.
- ATP bind to and inhibits the plasma membrane potassium channels
- Inhibition of the **K/ATP channel decreases plasma membrane K+ conductance**
- This causes depolarization of the membranes, thus activating voltage gated Calcium channels.

- There is an influx of Calcium into the cell. High intracellular calcium then mediates the fusion of insulin containing secretory vesicles with the plasma membrane leading to insulin secretion.



EFFECTS of Insulin

The **first phase of insulin secretion** is responsible for suppression of hepatic glucose output, while the **second phase regulates the entry of glucose** into insulin- dependent target sites including muscle and adipocytes.



Diabetes Mellitus – Diagnostic Criteria (Non-Pregnant Adults)

- Random plasma glucose ≥ 200 mg/dl and symptoms of diabetes (polyuria, polydipsia, ketoacidosis, or unexplained weight loss) ***OR***
- Glycated Hemoglobin (A1C) ≥ 6.5%** **OR**
- Fasting plasma glucose (FPG)* ≥126 mg/dl **OR**
- Results of a 2-hour 75-g Oral Glucose Tolerance Test (OGTT)* ≥ 200 mg/dl at 2 hours

** These tests should be confirmed by a repeat test, on a different day, unless unequivocally high*
*** Only an A1C test that has been referenced to an accepted laboratory method (standardized) should be utilized for diagnostic purposes*

Goals of Glycemic Control for People with Diabetes

Biochemical Index	Normal	Goal[1]
fasting plasma glucose or preprandial glucose (mg/dl)	**< 100**	**80 – 130**
2 hours post-prandial (mg/dl)	**< 140**	**< 180**
bedtime glucose (mg/dl)	**< 120**	**90 – 150**
A1C (%) sustained	**< 6%**	**< 7%** A1C target goal should be individualized for each patient. A goal of < 7% is chosen as a practical level for most patients to reduce the risk of complications. Achieving normal blood glucose and A1C is recommended if it can be done practically and safely. Less stringent goals may be considered for older adults or those with advanced comorbidities (see Joslin's Guideline for Older Adults with Diabetes).

Table 2.1—Staging of type 1 diabetes (4,5)

	Stage 1	Stage 2	Stage 3
Stage	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New-onset hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple autoantibodies • No IGT or IFG	• Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Clinical symptoms • Diabetes by standard criteria

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

- To test for prediabetes, fasting plasma glucose, 2-h plasma glucose after 75-g oral glucose tolerance test, and A1C are equally appropriate. B
- In patients with prediabetes, identify and, if appropriate, treat other cardiovascular disease risk factors. B
- Testing for prediabetes should be considered in children and adolescents who are overweight or obese and who have two or more additional risk factors for diabetes. E

Recommendations

- Screening for prediabetes and risk for future diabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults. B
- Testing for prediabetes and risk for future diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and who have one or more additional risk factors for diabetes. B
- For all people, testing should begin at age 45 years. B
- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. C

Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
   - A1C ≥5.7% (39 mmol/mol), IGT, or IFG on previous testing
   - first-degree relative with diabetes
   - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - women who were diagnosed with GDM
   - history of CVD
   - hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - women with polycystic ovary syndrome
   - physical inactivity
   - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans).
2. For all patients, testing should begin at age 45 years.
3. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

Table 2.6—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

If the plasma glucose level measured 1 h after the load is ≥130 mg/dL, 135 mg/dL, or 140 mg/dL* (7.2 mmol/L, 7.5 mmol/L, or 7.8 mmol/L), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

	Carpenter/Coustan (59)	or	NDDG (60)
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

NDDG, National Diabetes Data Group. *The ACOG recommends either 135 mg/dL (7.5 mmol/L) or 140 mg/dL (7.8 mmol/L). A systematic review determined that a cutoff of 130 mg/dL (7.2 mmol/L) was more sensitive but less specific than 140 mg/dL (7.8 mmol/L) (55).

POSTTRANSPLANTATION DIABETES MELLITUS

Recommendations

- Patients should be screened after organ transplantation for hyperglycemia, with a formal diagnosis of posttransplantation diabetes mellitus being best made once a patient is stable on an immunosuppressive regimen and in the absence of an acute infection. E
- The oral glucose tolerance test is the preferred test to make a diagnosis of posttransplantation diabetes mellitus. B
- Immunosuppressive regimens shown to provide the best outcomes for patient and graft survival should be used, irrespective of posttransplantation diabetes mellitus risk. E

CYSTIC FIBROSIS–RELATED DIABETES

Recommendations

- Annual screening for cystic fibrosis–related diabetes with oral glucose tolerance test should begin by age 10 years in all patients with cystic fibrosis not previously diagnosed with cystic fibrosis–related diabetes. B
- A1C as a screening test for cystic fibrosis–related diabetes is not recommended. B
- Patients with cystic fibrosis–related diabetes should be treated with insulin to attain individualized glycemic goals. A
- Beginning 5 years after the diagnosis of cystic fibrosis–related diabetes, annual monitoring for complications of diabetes is recommended. E

Immunization

Recommendations

- Provide routine vaccinations for children and adults with diabetes according to age-related recommendations. C
- Annual vaccination against influenza is recommended for all persons with diabetes ≥6 months of age. C
- Vaccination against pneumonia is recommended for all people with diabetes 2 through 64 years of age with pneumococcal polysaccharide vaccine (PPSV23). At age ≥65 years, administer the pneumococcal conjugate vaccine (PCV13) at least 1 year after vaccination with PPSV23, followed by another dose of vaccine PPSV23 at least 1 year after PCV13 and at least 5 years after the last dose of PPSV23. C
- Administer 3-dose series of hepatitis B vaccine to unvaccinated adults with diabetes who are age 19–59 years. C
- Consider administering 3-dose series of hepatitis B vaccine to unvaccinated adults with diabetes who are age ≥60 years. C

Table 7.1—Treatment for overweight and obesity in type 2 diabetes

	BMI category (kg/m^2)				
Treatment	23.0* or 25.0–26.9	27.0–29.9	27.5* or 30.0–34.9	35.0–39.9	≥40
Diet, physical activity, and behavioral therapy	†	†	†	†	†
Pharmacotherapy		†	†	†	†
Metabolic surgery			†	†	†

*Cutoff points for Asian American individuals.
†Treatment may be indicated for selected motivated patients.

CONSIDERATIONS FOR SELECTING NON-INSULIN GLUCOSE LOWERING MEDICATIONS

START WITH METFORMIN UNLESS CONTRAINDICATED

Action: Decreases hepatic glucose production, increases GLP-1 secretion. Use as initial therapy unless contraindicated.
Side effects: Gas, diarrhea, lactic acidosis; B-12 deficiency (long-term). Initiate at low dose, increase dose slowly and take with food to decrease gas, diarrhea. Extended release formulation may decrease GI symptoms.
Dosing:

- Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m^2.
- Starting metformin in patients with an eGFR <45 mL/min is not recommended.
- Obtain eGFR at least annually in all patients taking metformin. In patients at increased risk for renal impairment such as the elderly, assess renal function more frequently.
- If eGFR later falls below 45 mL/min, assess benefits and risks of continuing treatment. Discontinue metformin if eGFR later falls below 30 mL/min.
- Discontinue metformin at time of or before an iodinated contrast imaging procedure if eGFR is between 30-60 mL/min; in patients with a history of liver disease, alcoholism, or heart failure; or who will undergo intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

FIRST LINE ADD ON TO METFORMIN OR USE AS MONOTHERAPY IF METFORMIN IS CONTRAINDICATED

Insulin Secretagogue (sulfonylurea, meglitinide or D-phenylalanine derivative)	Dipeptidyl Peptidase IV Inhibitors (DPP-4 Inhibitors)	Glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists)	Sodium-glucose co-transporter 2 (SGLT-2 Inhibitors)[11]	α-Glucosidase Inhibitors (AGIs)	Thiazolidinediones[7,8,9] (TZDs)
Action: Stimulates beta cell insulin secretion. **Side effects**: Potential for hypoglycemia **Contraindications:** Sulfonylureas use is contraindicated in severe liver or renal disease. **Notes**: Metabolites of glipizide are less active than other sulfonylureas. Consider the use of short acting sulfonylureas, such as glipizide or glimepiride, in setting of renal disease. Glyburide is not preferred due to the increased risk of hypoglycemia. Repaglinide or nateglinide may be useful for those with postprandial hyperglycemia or with hypoglycemia on a sulfonylurea	**Action:** In a glucose dependent manner, slow inactivation of incretin hormones, resulting in increased insulin secretion and decreased glucagon levels . **Side effects:** URI symptoms. **Notes**: Reduce dose in renal disease with all members of the class except linagliptin. -Post marketing reports of hepatic failure with alogliptin -Clinical trials reported no adverse CV outcomes, except increased secondary outcome of heart failure with saxagliptin -It is unknown if DPP-4 inhibitors increase the risk for pancreatitis[10]	**Action:** In a glucose dependent manner increase insulin secretion, decrease glucagon secretion, slow gastric emptying, and increase satiety. **Side effects:** nausea, diarrhea, renal impairment **Contraindications:** Gastroparesis requiring treatment with metoclopramide. Personal or family history of medullary thyroid cancer or patients with MEN2. **Notes**: Use may be associated with weight loss. To avoid hypoglycemia when using a GLP-1 RA with a sulfonylurea or basal insulin, consider initially decreasing sulfonylurea or insulin dose. - increased risk of biliary disease and gallstones -liraglutide reduced the major CV outcomes in a large clinical trial in patients with CVD or high risk of CVD. -It is unknown if GLP-1 agonists increase the risk for pancreatitis[10]	**Action**: Block reabsorption of glucose by the kidney thereby increasing excretion of glucose in the urine. **Side effects:** Hypotension, genital mycotic infections, UTI, dehydration, hyperkalemia, increased LDL cholesterol, ketoacidosis in the absence of severe hyperglycemia[11] **Contraindications**: Do not use in moderate to severe renal disease as it may worsen renal function. **Notes**: Use may be associated with modest decrease in BP and in weight. Adjust dose in mild renal disease. Mechanism of action results in positive test for urine glucose. -Dapagliflozin is contraindicated in setting of bladder cancer, use with caution if there's history of bladder cancer. -A small increase in fracture rate has been reported with canagliflozin and dapagliflozin. -Cases of acute kidney injury have been reported with canagliflozin and dapagliflozin. Promptly discontinue these drugs if this occurs and treat the renal impairment. -Empagliflozin reduced CV mortality, CHF, and heart failure in one trial, in those with pre-existing CVD as well as risk of renal disease progression	**Action:** Delay absorption and breakdown of carbohydrates **Side effects:** Gas, diarrhea. **Contraindications:** Chronic intestinal disorders, acarbose in cirrhosis Acarbose and miglitol in renal impairment (creatinine >2.0) **Notes**: Use if postprandial hyperglycemia predominates. Ideally use pure glucose to treat hypoglycemia when used in combination therapy as the drug decreases absorption of other forms of carbohydrate. Initiate at low dose and increase slowly to decrease flatulence	**Action**: Improves glucose transport, and decreases hepatic glucose production. **Side effects**: Weight gain, fluid retention **Contraindications:** Liver disease, severe LV dysfunction at risk for CHF. Do not use pioglitazone in setting of bladder cancer, see footnote **Notes**: Full effect of initiation or titration of therapy may take 2-4 weeks. May increase risk for macular edema. Increases bone loss and risk for bone fracture. Can be used in renal impairment but may increase fluid retention.

OTHER THERAPY

Bile Acid Sequestrant (colesevelam)	Centrally Acting Agent (bromocriptine mesylate)
• Mechanism of action re glucose lowering is unclear • Modest effect on A1C. Also lowers LDL-C Note: *Reduces gastric absorption of some drugs. If known interaction or unknown*	• Mechanism of action re glucose lowering is unclear • Most effective when used in combination with other antidiabetes medications • Modest effect on A1C

ORAL GLUCOSE LOWERING MEDICATIONS

Biguanides	Insulin Secretagogues	Dipeptidyl Peptidase IV Inhibitors (DPP-4 Inhibitors)	Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors)	α-Glucosidase Inhibitors	TZDs[9] (Thiazolidinediones)
• liquid metformin* (*Riomet*) • metformin (*Glucophage*) • metformin extended release (*Glucophage XR, Fortamet, Glumetza*) *Glucophage, Glucophage XR and Fortamet* are available as generic medications * Liquid metformin formulation can be used for patients unable to swallow large tablets and who are post gastric bypass	**Sulfonylureas** • glimepiride (*Amaryl*) • glipizide (*Glucotrol*) • glipizide extended release (*Glucotrol XL*) • glyburide(*Micronase, Diabeta*) • micronized glyburide (*Glynase*) (glimepiride, glipizide and glyburide are available as generic medications) **Meglitinides** •repaglinide (*Prandin*) **D-phenylalanine Derivatives** •nateglinide (*Starlix*) (repaglinide and nataglinide are available as generic medications)	• sitagliptin (*Januvia*) • saxagliptin (*Onglyza*) • linagliptin (*Tradjenta*) • alogliptin (*Nesina*) • vildagliptin(Galvus) –(not available in the United States)	•canagliflozin (*Invokana*) •dapagliflozin (*Farxiga*) •empagliflozin (*Jardiance*)	•acarbose (*Precose*) •miglitol (*Glyset*) (acarbose is available as a generic medication)	• pioglitazone (*Actos*) • rosiglitazone (*Avandia*) (pioglitazone and rosiglitazone are available as generic medications)

FIXED DOSE COMBINATION MEDICATIONS

• metformin and glipizide (*Metaglip*)	• linagliptin and metformin (Jentadueto)	• rosiglitazone and glimepiride (*Avandaryl*)[9]
• metformin and glyburide (*Glucovance*)	• linagliptin and metformin ER (Jentadueto XR)	• rosiglitazone and metformin (*Avandamet*)
• sitagliptin and metformin (*Janumet*)	• alogliptin and pioglitazone (*Oseni*)	• dapagliflozin and metformin (*Xigduo*)
• sitagliptin and metformin ER (*Janumet XR*)	• repaglinide and metformin (PrandiMet)	• empagliflozin and metformin (*Synjardy*)
• saxagliptin and metformin ER (Kombiglyze XR)	• pioglitazone and metformin (*Actoplus MET*)[9]	• empagliflozin and linagliptin (*Glyxambi*))
• alogliptin and metformin (Kozano)	• pioglitazone and glimepiride (Duetact)[9]	• canagliflozin and metformin (*Invokamet*)

Others

Bile Acid Sequestrant
• colesevelam (*Welchol*)

Centrally Acting
•bromocriptine (*Cycloset*)

INJECTABLE DIABETES MEDICATIONS AVAILABLE IN THE USA

INCRETIN MIMETICS AND NON-INSULIN SYNTHETIC ANALOGS

Product	Mechanism of Action	Diabetes Type	Injection Frequency
exenatide (*Byetta*)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins.	2	2/day
liraglutide (*Victoza*)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins	2	1/day
extended release exenatide (*Bydureon*)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins. **Not approved for use with insulin**	2	1/week
albiglitude (*Tanzeum*)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins. Has not been studied in use with prandial insulins	2	1/week
dulaglutide (*Trulicity*)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins. Has not been studied in use with basal insulins	2	1/week
pramlintide (*Symlin*)	Synthetic analog of human amylin, a naturally occurring hormone made in the beta cells, which slows gastric emptying, suppresses glucagon secretion, and regulates food intake. A significant reduction in insulin dose may be required when insulin is used in conjunction with pramlintide.	1 and 2	1-4 /day (with meals)

INSULINS (U-100 except where noted)

Insulin Type	Product	Onset	Peak	Duration
Rapid-Acting				
Insulin aspart analog Insulin glulisine analog Insulin lispro analog	Novolog Apidra Humalog U-100 and U-200	10 – 30 minutes	30 minutes – 3 hours	3 – 5 hours
Short-Acting				
Human Regular	Humulin R Novolin R	30 – 60 minutes	2 – 5 hours	up to 12 hours*
Intermediate-Acting				
Human NPH insulin	Humulin N Novolin N	90 minutes – 4 hours	4 – 12 hours	up to 24 hours**
Long-Acting				
Insulin detemir	Levemir	45 minutes – 4 hours	Minimal peak	up to 24 hours ***
Insulin glargine	Lantus U-100,	45 minutes – 4 hours	Minimal peak	up to 24 hours ***
Insulin glargine concentrated	Toujeo U-300	6 hours	Minimal peak	up to 36 hours
Insulin degludec	Tresiba U-100	1 hour	Minimal peak	up to 42 hours
Insulin degludec concentrated	Tresiba U-200	1 hour	Minimal peak	up to 42 hours
U-500 insulin				
Human regular insulin concentrated 500 units per mL	U-500 concentrated Humulin R	<15 minutes	4 -8 hours	13 - 24 hours
Inhaled insulin				
Insulin human inhalation	Afrezza	12 – 30 minutes	30 – 90 minutes	3 hours

Premixed Insulin Combinations

Insulin Type	Product
70% NPH; 30% Regular	Humulin 70/30
70% NPH; 30% Regular	Novolin 70/30
50% lispro protamine suspension, 50% lispro	Humalog Mix 50/50
75% lispro protamine suspension, 25% lispro	Humalog Mix 75/25
70% aspart protamine suspension, 30% aspart	Novolog Mix 70/30
70% degludec, 30% insulin aspart	Ryzodeg 70/30

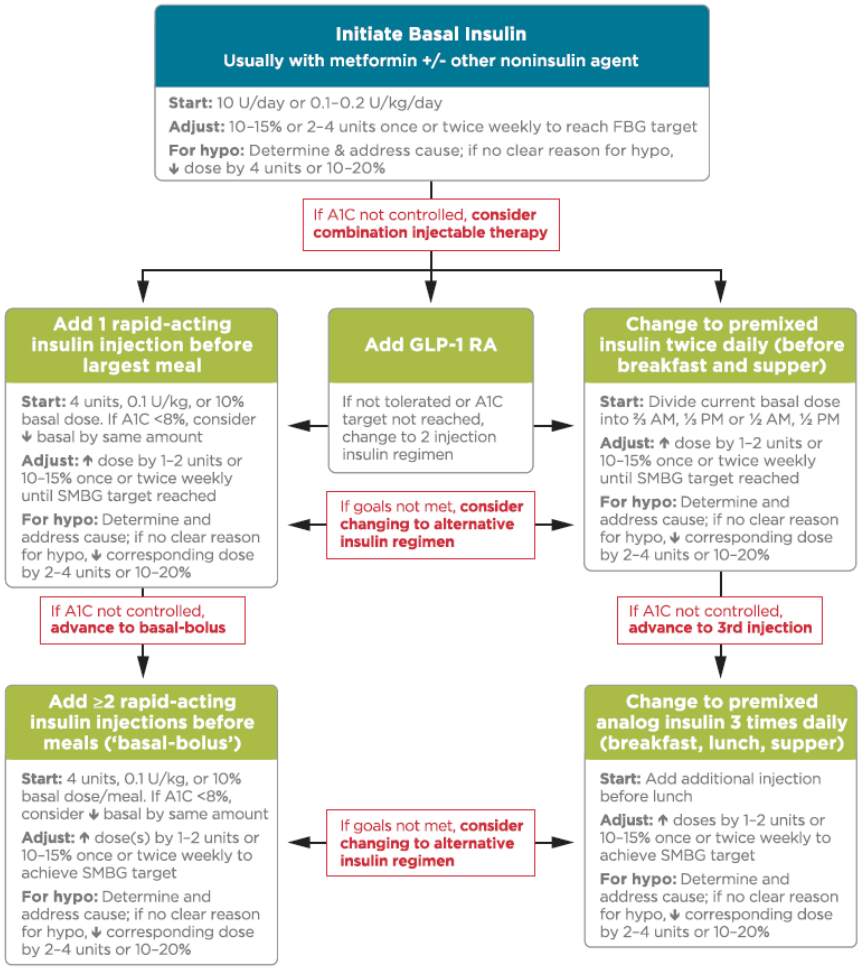


Figure 8.2—Combination injectable therapy for type 2 diabetes. FBG, fasting blood glucose; GLP-1 RA, GLP-1 receptor agonist; hypo, hypoglycemia. Adapted with permission from Inzucchi et al. (21).

Table 8.1—Properties of available glucose-lowering agents in the U.S. that may guide individualized treatment choices in patients with type 2 diabetes (21)

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Biguanides	• Metformin	Activates AMP-kinase (? other)	• ↓ Hepatic glucose production	• Extensive experience • Rare hypoglycemia • ↓ CVD events (UKPDS) • Relatively higher A1C efficacy	• Gastrointestinal side effects (diarrhea, abdominal cramping, nausea) • Vitamin B12 deficiency • Contraindications: eGFR <30 mL/min/1.73 m^2, acidosis, hypoxia, dehydration, etc. • Lactic acidosis risk (rare)	Low
Sulfonylureas	2nd generation • Glyburide • Glipizide • Glimepiride	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS) • Relatively higher A1C efficacy	• Hypoglycemia • ↑ Weight	Low
Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • ↑ Weight • Frequent dosing schedule	Moderate
TZDs	• Pioglitazone‡ • Rosiglitazone§	Activates the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity	• Rare hypoglycemia • Relatively higher A1C efficacy • Durability • ↓ Triglycerides (pioglitazone) • ? ↓ CVD events (PROactive, pioglitazone) • ↓ Risk of stroke and MI in patients without diabetes and with *insulin resistance* and history of recent stroke or TIA (IRIS study [42], pioglitazone)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosiglitazone)	Low
α-Glucosidase inhibitors	• Acarbose • Miglitol	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• Rare hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events in prediabetes (STOP-NIDDM) • Nonsystemic	• Generally modest A1C efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Low to moderate
DPP-4 inhibitors	• Sitagliptin • Saxagliptin • Linagliptin • Alogliptin	Inhibits DPP-4 activity, increasing postprandial incretin (GLP-1, GIP) concentrations	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent)	• Rare hypoglycemia • Well tolerated	• Angioedema/urticaria and other immune-mediated dermatological effects • ? Acute pancreatitis • ↑ Heart failure hospitalizations (saxagliptin; ? alogliptin)	High
Bile acid sequestrants	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production	• ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• Rare hypoglycemia • ↓ LDL-C	• Modest A1C efficacy • Constipation • ↑ Triglycerides • May ↓ absorption of other medications	High

Continued on p. S69

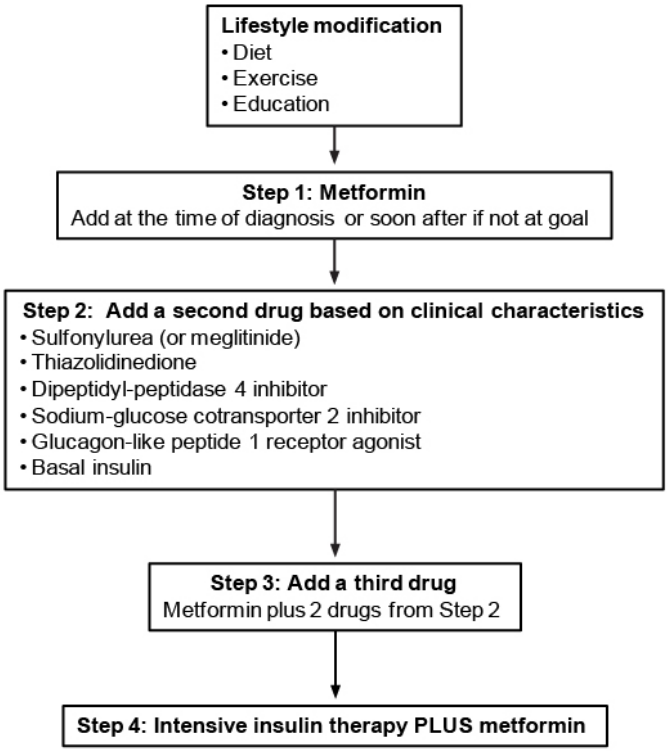
Table 8.1—Continued

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Dopamine-2 agonists	• Bromocriptine (quick release)§	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• Rare hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial)	• Modest A1C efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin‡ • Empagliflozin	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption by the kidney, increasing glucosuria	• Rare hypoglycemia • ↓ Weight • ↓ Blood pressure • Associated with lower CVD event rate and mortality in patients with CVD (empagliflozin EMPA-REG OUTCOME)	• Genitourinary infections • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis	High
GLP-1 receptor agonists	• Exenatide • Exenatide extended release • Liraglutide • Albiglutide • Lixisenatide • Dulaglutide	Activates GLP-1 receptors	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent) • Slows gastric emptying • ↑ Satiety	• Rare hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some cardiovascular risk factors • Associated with lower CVD event rate and mortality in patients with CVD (liraglutide LEADER) (30)	• Gastrointestinal side effects (nausea/vomiting/diarrhea) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements	High
Amylin mimetics	• Pramlintide§	Activates amylin receptors	• ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• ↓ Postprandial glucose excursions • ↓ Weight	• Modest A1C efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule • Training requirements	High
Insulins	• Rapid-acting analogs - Lispro - Aspart - Glulisine - Inhaled insulin • Short-acting - Human Regular • Intermediate-acting - Human NPH	Activates insulin receptors	• ↑ Glucose disposal • ↓ Hepatic glucose production • Suppresses ketogenesis	• Nearly universal response • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • Training requirements • Patient and provider reluctance • Injectable (except inhaled insulin) • Pulmonary toxicity (inhaled insulin)	High#

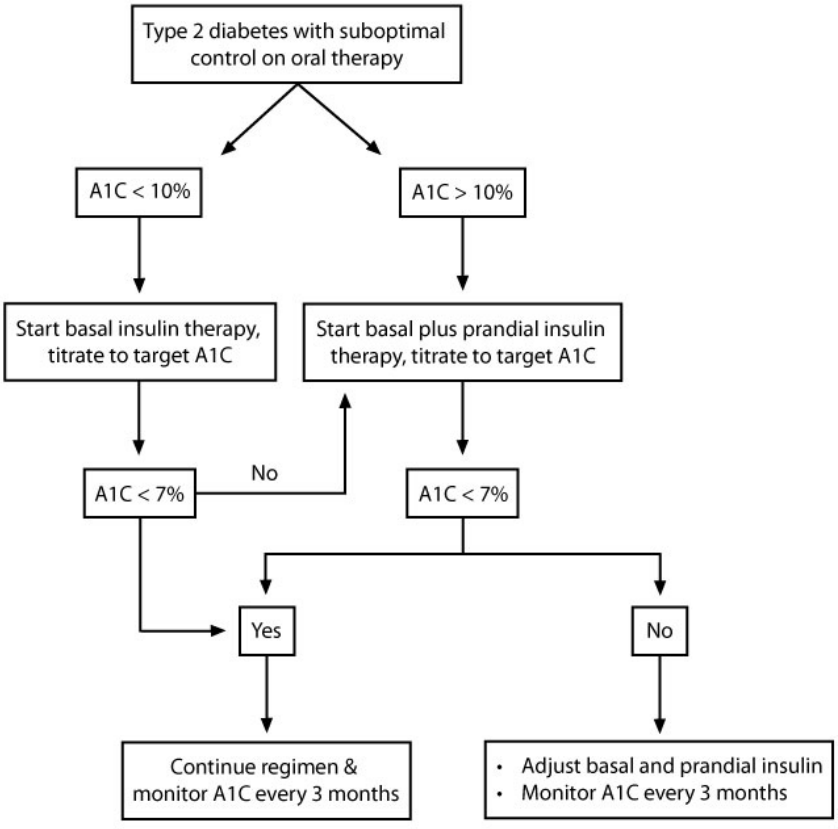
Continued on p. 570

Overview of diabetic amyotrophy	
Background	• Usually occurs in reasonably well-controlled or new-onset diabetics • Patients may not have other diabetic end-organ damage (e.g., retinopathy) • May be presenting feature of diabetes in 21% of patients
Pathophysiology	• Ischemic injury from nonsystemic microvasculitis
Clinical features	• Acute, asymmetric, focal onset of pain followed by weakness in the proximal leg • Associated autonomic failure • Weight loss > 10%
Prognosis	• Condition usually progresses to involve contralateral limb and distal legs • Majority of patients require ambulatory assistance at some point • This progress is followed by partial to full recovery in most patients • Some patients may have foot drop and lingering neuropathic pain for years

Antihyperglycemic therapy in type 2 diabetes



- Metformin is contraindicated in patients with renal insufficiency.
- Consider **2-drug therapy** for patients with **A1c ≥9%** .
- Consider **insulin** for patients with severe hyperglycemia (**A1c >10%**, fasting blood glucose >250 mg/dL, random blood glucose >300 mg/dL), particularly those with polyuria, polydipsia, and weight loss.



Evidence : **treat to target trial.** To compare the abilities and associated hypoglycemia risks of insulin glargine and human NPH insulin added to oral therapy of type 2 diabetes to achieve 7% HbA1c.

Treat-to-Target Trial offers the basis for a simple, standardized way to initiate basal insulin in routine practice for an important group of patients, those overweight patients with type 2 diabetes who have HbA1c between 7.5 and 10% despite using one or two oral agents. The regimen requires just one daily injection added to oral therapy and one daily fasting glucose test to guide adjustment of dosage. In this trial, it achieved the 7% HbA1c target for a majority of patients. Furthermore, the lower risk of nocturnal hypoglycemia with glargine relative to NPH reduces the leading barrier to starting insulin therapy: the fear of hypoglycemia.

Insulin	Peak effect (hr)	Duration of effect (hr)	Characteristics
Short-acting • Regular	2-5	5-8	• Slow onset & offset • Peak does not coincide with food peak
Analogs • Lispro • Aspart • Glulisine	0.5-3.0	3-5	• Fast onset & offset • Peak coincides with food peak
Long-acting • NPH	4-12	12-18	• Peak effect more likely to cause hypoglycemia
• Detemir	4-9	16-20	• Sometimes requires twice-daily administration
• Glargine	None	20-24	• Peakless effect less likely to cause hypoglycemia

NPH = neutral protamine Hagedorn.

Oral hypoglycemic agents

Sulphonylureas can accumulate in elderly patients with CKD and cause hypoglycemia.

Effect can be potentiated by TMP-SMZ

Oral antidiabetic agents		
Class	**Primary drugs**	**Side effects**
Insulin secretagogues	• Sulfonylureas (eg, glimepiride) • Meglitinides (eg, repaglinide)	• **Hypoglycemia** • Weight gain
Biguanides	• Metformin	• **Gastrointestinal upset** • Lactic acidosis • **Weight loss**
Thiazolidinediones	• Pioglitazone	• Weight gain • **Edema**, heart failure
DPP-4 inhibitors	• Sitagliptin • Saxagliptin	• Headache • Nasopharyngitis
GLP-1 receptor agonists	• Exenatide • Liraglutide	• Nausea/vomiting • Abdominal pain • **Weight loss**
α-glucosidase inhibitors	• Acarbose • Miglitol	• Diarrhea • Flatulence
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin	• Polyuria • **Urinary tract infections** • Hypotension

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium-glucose cotransporter-2.

Side effects of SGLT2 inhibitors	
Genital candidiasis	• Higher risk in females & uncircumcised males
Urinary tract infections	• Higher risk in females
Fluid loss, hypotension & dizziness	• Higher risk in elderly patients & patients on diuretics or agents that work on RAS • Decreased renal perfusion & GFR, increased creatinine
Hyperkalemia	• Higher risk in patients with renal impairment & patients on potassium-sparing diuretics or agents that work on RAS

SGLT2= sodium-glucose co-transporter 2; **RAS**= renin-angiotensin-aldosterone system; GFR=glomerular filtration rate.

Latent Autoimmune Diabetes of Adulthood

Screening criteria for latent autoimmune diabetes of adulthood (LADA)
• Age of onset > 35 but < 50 • Acute onset of symptoms • BMI < 25 kg/m2 • Personal or family history of autoimmune disease Two or more of the above criteria is associated with 90% sensitivity and 70% specificity for LADA

- **10% of T2DM** patients actually have **T1DM**

- Positive circulating anti-islet cell antibodies and anti-glutamic acid decarboxylase antibodies
- Lower BMI
- **Increased risk for DKA**
- Poor response to dietary therapy and oral diabetic agents
- Require insulin soon after diagnosis, unlike most T2DM patients

11

Treatment options for diabetic peripheral neuropathy

- Antidepressants (e.g., amitriptyline, duloxetine)
- Anticonvulsants (e.g., pregabalin, valproic acid)
- Topical capsaicin cream
- Alpha-lipoic acid
- Transcutaneous electrical nerve stimulation (TENS)
- Lidocaine patch

Table 9.1—Recommendations for statin and combination treatment in people with diabetes

Age	Risk factors	Recommended statin intensity*
<40 years	None	None
	ASCVD risk factor(s)**	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ASCVD	High
	ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or in patients with a history of ASCVD who cannot tolerate high-dose statins	Moderate plus ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or in patients with a history of ASCVD who cannot tolerate high-dose statins	Moderate plus ezetimibe

*In addition to lifestyle therapy. **ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD.

[11] Undoubtedly the student tries to learn too much, and we teachers try to teach him too much - neither, perhaps, with great success

Table 11.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes

Patient characteristics/health status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5% (58 mmol/mol)	90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%† (69 mmol/mol)	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<150/90 mmHg	Consider likelihood of benefit with statin (secondary prevention more so than primary)

This represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The patient characteristic categories are general concepts. Not every patient will clearly fall into a particular category. Consideration of patient and caregiver preferences is an important aspect of treatment individualization. Additionally, a patient's health status and preferences may change over time. ADL, activities of daily living. ‡A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden. *Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. By "multiple," we mean at least three, but many patients may have five or more (40). **The presence of a single end-stage chronic illness, such as stage 3–4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy. †A1C of 8.5% (69 mmol/mol) equates to an estimated average glucose of ~200 mg/dL (11.1 mmol/L). Looser A1C targets above 8.5% (69 mmol/mol) are not recommended as they may expose patients to more frequent higher glucose values and the acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing.

Table 14.1—Insulin dosing for enteral/parenteral feedings

Situation	Basal/nutritional	Correctional
Continuous enteral feedings	Continue prior basal or, if none, calculate from TDD or consider 5 units NPH/detemir every 12 h or 10 units glargine daily Nutritional: regular insulin every 6 h or rapid-acting insulin every 4 h, starting with 1 unit per 10–15 g of carbohydrate; adjust daily	SQ regular insulin every 6 h or rapid-acting insulin every 4 h for hyperglycemia
Bolus enteral feedings	Continue prior basal or, if none, calculate from TDD or consider 5 units NPH/detemir every 12 h or 10 units glargine daily Nutritional: give regular insulin or rapid-acting insulin SQ before each feeding, starting with 1 unit per 10–15 g of carbohydrate; adjust daily	SQ regular insulin every 6 h or rapid-acting insulin every 4 h for hyperglycemia
Parenteral feedings	Add regular insulin to TPN IV solution, starting with 1 unit per 10 g of carbohydrate; adjust daily	SQ regular insulin every 6 h or rapid-acting insulin every 4 h for hyperglycemia

IV, intravenous; SQ, subcutaneous; TDD, total daily dose; TPN, total parenteral nutrition.

Table 10.2—Management of CKD in diabetes

eGFR (mL/min/1.73 m^2)	Recommended management
All patients	Yearly measurement of UACR, serum Cr, potassium
45–60	Referral to a nephrologist if possibility for nondiabetic kidney disease exists (duration of type 1 diabetes <10 years, persistent albuminuria, abnormal findings on renal ultrasound, resistant hypertension, rapid fall in eGFR, or active urinary sediment on urine microscopic examination) Consider the need for dose adjustment of medications Monitor eGFR every 6 months Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus, and parathyroid hormone at least yearly Assure vitamin D sufficiency Vaccinate against Hep B virus Consider bone density testing Referral for dietary counseling
30–44	Monitor eGFR every 3 months Monitor electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin, and weight every 3–6 months Consider the need for dose adjustment of medications
<30	Referral to a nephrologist

HYPOGLYCEMIA

Symptomatic hypoglycemia which fulfills Whipple's Triad with glucose level <55mg/dL

TABLE 7. ADA Workgroup on Hypoglycemia classification of hypoglycemia in persons with diabetes (136)

Severe hypoglycemia. An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Documented symptomatic hypoglycemia. An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤70 mg/dl (3.9 mmol/liter).

Asymptomatic hypoglycemia. An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dl (3.9 mmol/liter).

Probable symptomatic hypoglycemia. An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤70 mg/dl [3.9 mmol/liter]).

Relative hypoglycemia. An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, with a measured plasma glucose concentration >70 mg/dl (3.9 mmol/liter) but approaching that level.

TABLE 8. Risk factors for hypoglycemia in diabetes

Conventional risk factors–relative or absolute insulin excess

1. Insulin or insulin secretagogue doses are excessive, ill-timed, or of the wrong type.
2. Exogenous glucose delivery is decreased (*e.g.* after missed meals and during the overnight fast).
3. Glucose utilization is increased (*e.g.* during exercise).
4. Endogenous glucose production is decreased (*e.g.* after alcohol ingestion).
5. Sensitivity to insulin is increased (*e.g.* after weight loss, an increase in regular exercise or improved glycemic control, and in the middle of the night).
6. Insulin clearance is decreased (*e.g.* with renal failure).

Risk factors for hypoglycemia-associated autonomic failure

1. Absolute endogenous insulin deficiency.
2. A history of severe hypoglycemia, hypoglycemia unawareness, or both as well as recent antecedent hypoglycemia, prior exercise, and sleep.
3. Aggressive glycemic therapy *per se* (lower HbA_{1c} levels, lower glycemic goals, or both).

Table 53.1 Factors increasing risk of hypoglycemia in insulin-treated diabetes

Non-remedial patient characteristics	
	Age (under 5 or elderly)
	Diabetes duration
	Female gender
	C-peptide negativity
	Comorbidities and polypharmacy
	Enhanced insulin sensitivity of early pregnancy
Precipitants of individual events	
	Insulin dose error
	Lower than anticipated carbohydrate intake
	Exercise[a]
	Alcohol excess[a]
	Massage or heating of injection site
	Co-incident use of recreational drugs
Prolongation of insulin action/reduced insulin clearance	
	Exogenous insulin therapy
	Insulin secretagogue therapy
	Abnormal liver function
	Renal failure
	Hypothyroidism
	High insulin-binding antibodies
Impaired endogenous glucose production	
	Liver failure
	Alcohol toxicity
	Glycogen storage disease
	Malnutrition
Loss of counterregulatory function	
	Impaired awareness of hypoglycemia
	Hypopituitarism
	Addison's disease
	Growth hormone deficiency
Failure of glucose absorption	
	Celiac disease
	Eating disorder
	Exocrine pancreatic failure
	Other malabsorptive disease

[a]Hypoglycemia may be delayed, commonly occurring in the early hours of the next morning or after breakfast next day.

Physiology of hypoglycemia

1) a decrease in insulin secretion as glucose levels decline within the physiological range;
2) an increase in glucagon secretion; or, in its absence
3) an increase in epinephrine secretion, both occurring as glucose levels decline just below the physiological range.
*** Increased cortisol and GH secretion are involved in defense against prolonged hypoglycemia. If these defenses fail to abort the episode, plasma glucose levels will continue to fall.

Hypoglycemia develops when the sum of **glucose utilization from the circulation (largely by the brain but also by obligatory glycolytic tissues, such as the renal medullae and erythrocytes, and insulinsensitive tissues, such as muscle)** exceeds the sum of glucose delivery into the circulation (from ingested carbohydrates and hepatic and renal glucose production)

Symptoms, which prompt the behavioral defense of food ingestion, normally develop at a mean plasma glucose concentration of approximately 55 mg/dl (3.0 mmol/liter).

At that and lower glucose levels, insulin secretion is suppressed virtually completely
; **plasma insulin levels are below 3 U/ml** (18 pmol/liter), **C-peptide levels are below 0.6 ng/ml** (0.2 nmol/liter), and **proinsulin levels are below 5.0 pmol/liter**

<u>patients with hypoglycemia without diabetes mellitus</u>

- episode of spontaneous hypoglycemia, and observe the plasma glucose response to iv injection of 1.0 mg glucagon
- fast of up to 72 h or after a mixed meal.
- In a patient with documented fasting or postprandial endogenous hyperinsulinemic hypoglycemia, negative screening for oral hypoglycemic agents, and no circulating insulin antibodies, conduct procedures for localizing an insulinoma
- Hypoglycemia caused by nonislet cell tumors or endogenous hyperinsulinism is rare

TABLE 1. Causes of hypoglycemia in adults

Ill or medicated individual
1. Drugs
   - Insulin or insulin secretagogue
   - Alcohol
   - Others (Table 2)
2. Critical illnesses
   - Hepatic, renal, or cardiac failure
   - Sepsis (including malaria)
   - Inanition
3. Hormone deficiency
   - Cortisol
   - Glucagon and epinephrine (in insulin-deficient diabetes mellitus
4. Nonislet cell tumor

Seemingly well individual
5. Endogenous hyperinsulinism
   - Insulinoma
   - Functional β-cell disorders (nesidioblastosis)
     - Noninsulinoma pancreatogenous hypoglycemia
     - Post gastric bypass hypoglycemia
   - Insulin autoimmune hypoglycemia
     - Antibody to insulin
     - Antibody to insulin receptor
   - Insulin secretagogue
   - Other
6. Accidental, surreptitious, or malicious hypoglycemia

TABLE 2. Drugs other than antihyperglycemic agents and alcohol reported to cause hypoglycemia (24)

Moderate quality of evidence (⊕⊕⊕◯)
- Cibenzoline
- Gatifloxacin
- Pentamidine
- Quinine
- Indomethacin
- Glucagon (during endoscopy)

Low quality of evidence (⊕⊕◯◯)
- Chloroquineoxaline sulfonamide
- Artesunate/artemisin/artemether
- IGF-I
- Lithium
- Propoxyphene/dextropropoxyphene

Very low quality of evidence (⊕◯◯◯)
Drugs with >25 cases of hypoglycemia identified
- Angiotensin converting enzyme inhibitors
- Angiotensin receptor antagonists
- β-Adrenergic receptor antagonists
- Levofloxacin
- Mifepristone
- Disopyramide
- Trimethoprim-sulfamethoxazole
- Heparin
- 6-Mercaptopurine

Drugs with <25 cases of hypoglycemia identified (see Ref. 24)

Hypoglycemia after Gastric Bypass surgery

- Hyperinsulinemic hypoglycemia has been recognized relatively recently as a complication of gastric bypass surgery.
- 6 months to 8 years after bypass surgery.

⊕Diagnosis of a true hypoglycemic disorder requires a low plasma glucose (< 50–55 mg/dl) in
the presence of symptoms compatible with neuroglycopenia that are ameliorated by correction of the low glucose
(Whipple's triad).

DUMPING SYNDROME	• **Dumping can occur postoperatively in up to half of gastric bypass patients with ingestion of simple sugars.** • **Noted soon after the surgery and improves with time** **Early dumping** -- a result of rapid emptying of food into the jejunum because of the surgically altered anatomy, is characterized by vasomotor symptoms (flushing, tachycardia), abdominal pain, and diarrhea **Late dumping** -- a form of "reactive hypoglycemia," occurs 1–3 hours after meal ingestion and is a consequence of the brisk insulin response to hyperglycemia resulting from rapid absorption of simple sugars from the proximal small intestine. Treatment -- Most patients with dumping respond to nutrition modification, comprising frequent, small, low-carbohydrate meals **Acarbose and somatostatin**
Post-RYGB hypoglycemia (hyperinsulinemic hypoglycemia)	• Presents several months to years (usually > 1 year) after gastric bypass surgery. • **Pancreatic nesidioblastosis** (islet cell enlargement, β-cells budding from ductal epithelium, and islets in apposition to ducts) has been proposed as the underlying

	mechanism for this disorder Treatment -- responds suboptimally to carbohydrate restriction alone. **α-glucosidase inhibitor acarbose, octreotide, verapamil, and diazoxid**e • Some patients with severe symptoms and a positive selective arterial calcium-stimulated test have responded well to partial pancreatectomy • reversal of the gastric bypass may be required for severe cases
noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS)	• Endogenous hyperinsulinemic hypoglycemia (another form) • Postprandial hypoglycemia and is characterized by nesidioblastosis, • Patients who have not had a gastric bypass procedure
Insulinoma	• Although this typically causes fasting hypoglycemia, **postprandial hypoglycemia may be reported in ~ 10%**

Diagnosis of Hyperinsulinemic Hypoglycemia

1. Fulfillment of the Whipple's triad
2. Concomitantly elevated insulin (> 3 µU/ml) and C-peptide (> 0.6 ng/ml) ***
3. Negative oral hypoglycemic agent screen.

*** *applying fasting criteria for the diagnosis of hyperinsulinemic hypoglycemia19 in the postprandial period is problematic given the biological half-life of C-peptide of ~ 30 minutes. C-peptide and insulin may still be detectable after meal ingestion even if insulin secretion is appropriately suppressed at the time of postprandial hypoglycemia.*

A liquid mixed-meal test is likely fraught with the same pitfalls as the OGTT in gastric bypass patients given the rapid rate of absorption of the liquid formulation.

Interpretation of biochemical testing for hypoglycemia				
Test	**Normal**	**Insulinoma**	**Factitious: Insulin injections**	**Factitious: Oral hypoglycemic agent**
Insulin (mU/L)	<3	Normal to high	Very high	Normal to high
C-peptide (nmol/L)	<0.2	Normal to high	Low	Normal to high
Oral hypoglycemic screen	Negative	Negative	Negative	Positive
Proinsulin (pmol/L)*	<5	High	Low	High

*Proinsulin levels may be relatively higher in insulinoma compared to oral hypoglycemic agent-induced hypoglycemia due to release of insulin precursors by the tumor.

Hypoglycemia is typically the result of the interplay of relative or absolute therapeutic insulin excess and compromised physiological and behavioral defenses against falling plasma glucose concentrations in T1DM and long-standing T2DM

Relative, or even absolute, insulin excess must occur from time to time during treatment with an insulin secretagogue or insulin because of the pharmacokinetic imperfections of these therapies.

the incidence of hypoglycemia is relatively low (at least with current glycemic goals), even during treatment with insulin, early in the course of T2DM when glycemic defenses are intact. However, the risk increases progressively over time and approaches that in
T1DM as glycemic defenses become compromised.

******hypoglycemic defenses are compromised in T1DM and in long-standing T2DM**

T1DM ; mechanistic explanation of hypoglycemia

- In fully developed T1DM, circulating insulin levels do not decrease as plasma glucose levels decline. Furthermore, in the absence of a -cell signal, including a decrease in intraislet insulin.
- The α-cell glucagon response to hypoglycemia is also lost
- response to hypoglycemia is often attenuated

Hypoglycemia unawareness: attenuated sympathetic neural response causes the clinical syndrome of hypoglycemia unawareness—impairment or even loss of the warning symptoms that previously prompted the behavioral defense, i.e. the ingestion of carbohydrates. Hypoglycemia unawareness is associated with a 6-fold increased risk for severe hypoglycemia

HAAF : Hypoglycemia associated autonomic failure

The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes is based on pivotal findings in nondiabetic individuals and patients with T1DM and was first documented in T1DM.
It posits that recent antecedent hypoglycemia or prior exercise or sleep causes both defective glucose counterregulation (by reducing the epinephrine response in the setting of absent insulin and glucagon responses) and hypoglycemia unawareness (largely by reducing the sympathetic neural response and the resulting neurogenic symptoms) and, thus, a vicious cycle of recurrent hypoglycemia.
• clinical impact of HAAF in T1DM is the finding that as little as 2–3 wk of scrupulous avoidance of treatment-induced hypoglycemia reverses hypoglycemia unawareness, and improves the reduced epinephrine component of defective glucose counterregulation in most affected patients • long-standing T2DM and absolute insulin deficiency

A prolonged corrected QT interval has been found to be associated with episodes of nocturnal hypoglycemia in patients with T1DM

Action to Control Cardiovascular Risk in Diabetes (ACCORD) study
• 10,251 patients with T2DM at high cardiovascular risk (but with no history of frequent or recent serious hypoglycemic events) were randomized to either intensive glycemic therapy with an HbA1C goal of less than 6.0% or to standard glycemic therapy. • After a median follow-up of 3.4 yr,with stable median HbA1C levels of 6.4 and 7.5%, respectively, intensive glycemic therapy was discontinued because 5.0% of the patients in the intensive therapy group, compared with 4.0% of those in the standard therapy group, had died (hazard ratio, 1.22; 95% confidence interval, 1.01–1.46; P=0.04
Nonetheless, the most plausible cause of excess mortality during intensive therapy in **ACCORD is iatrogenic hypoglycemia.**

<u>Exercise induced hypoglycemia</u>

Guidelines

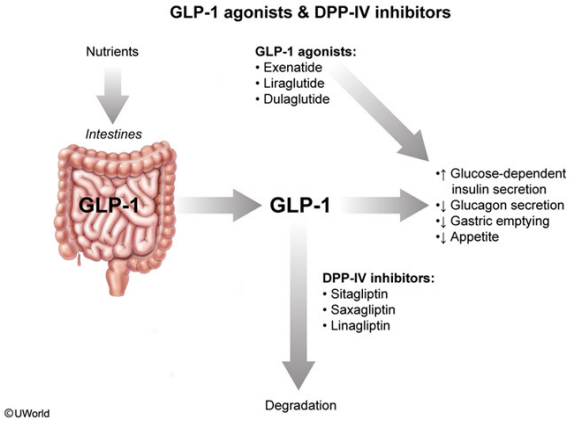
- Adequate fluids
- decrease insulin dose prior to exercise by 30%
- Consume 15-30g of rapidly absorbed carbohydrates (hard candies, juice) if glucose is <100mg/dl before or during exercise

<u>EVALUATION OF INSULINOMA</u>

Diazoxide	Diminishes insulin secretion Causes marked edema and hirsutism
Octreotide	• analog of somatostatin (growth hormone-inhibitory hormone), inhibits growth hormone secretion but, in large doses, also inhibits the secretion of thyroid-stimulating hormone (TSH), insulin, and glucagon • highly effective in controlling the symptoms associated with glucagonomas, VIPomas, and carcinoid tumors, **efficacy is less predictable for symptomatic patients with insulinoma**
Everolimus	• an inhibitor of the mammalian (mechanistic) target of rapamycin (mTOR)
Verapamil or phenytoin	• Second line

Medication	↓ A1c	Points to remember
Metformin (biguanide)	1.0%-2.0%	• Initial therapeutic agent for most type 2 diabetics • Weight neutral, low risk of hypoglycemia • Lactic acidosis is a life-threatening complication
Sulfonylureas	1.0%-2.0%	• Generally added in patients with metformin failure • Weight gain & hypoglycemia are main side effects
Pioglitazone (TZDs)	1.0%-1.5%	• Used if unable to tolerate metformin or sulfonylureas • Side effects: weight gain, edema, CHF, bone fracture, bladder cancer • Low risk of hypoglycemia when used alone or with metformin • Can be used in renal insufficiency
DPP-IV inhibitors (eg, sitagliptin)	0.5%-0.8%	• Low risk of hypoglycemia • Weight neutral • Can be used in renal insufficiency
GLP-1 receptor agonist (eg, exenatide)	0.5%-1.0%	• Possible second agent for metformin failure, especially if weight loss is desired • Low hypoglycemia risk when used alone or with metformin

CHF = congestive heart failure; **DPP** = dipeptidyl peptidase-4; **GLP-1** = glucagonlike peptide-1; **IV** = intravenous; **TZDs** = thiazolidinediones.



Antihypertensives in diabetic & prediabetic patients	
ACE inhibitors/ **A**ngiotensin receptor blockers	• Minimal to no effect on glucose • Prevent progression of nephropathy • First-line therapy in patients with heart failure, diabetics & post MI
Beta **b**lockers	• Increased risk of developing diabetes or glucose intolerance (**not** carvedilol) • Benefit for patients with recent MI or stable CHF
Calcium **c**hannel blockers	• Little effect on glucose metabolism • Useful in combination therapy with ACE inhibitors (dihydropyridine CCBs)
Thiazide **d**iuretics	• Greatest effect on glucose & lipid metabolism of all antihypertensive drugs • Favorable effects on cardiovascular outcomes (especially CHF & stroke), favorable cost profile • Especially effective in African Americans & older women

Thiazide diuretics affect serum glucose the most compared to other antihypertensive medications. Additional adverse effects include hypokalemia, hyponatremia, hyperuricemia, and elevated triglycerides. The ALLHAT trial and subsequent meta-analysis showed that chlorthalidone was associated with an increased risk of developing diabetes compared to the other drugs (amlodipine, lisinopril, and doxazosin). The risk of hyperglycemia parallels hypokalemia and is likely related.

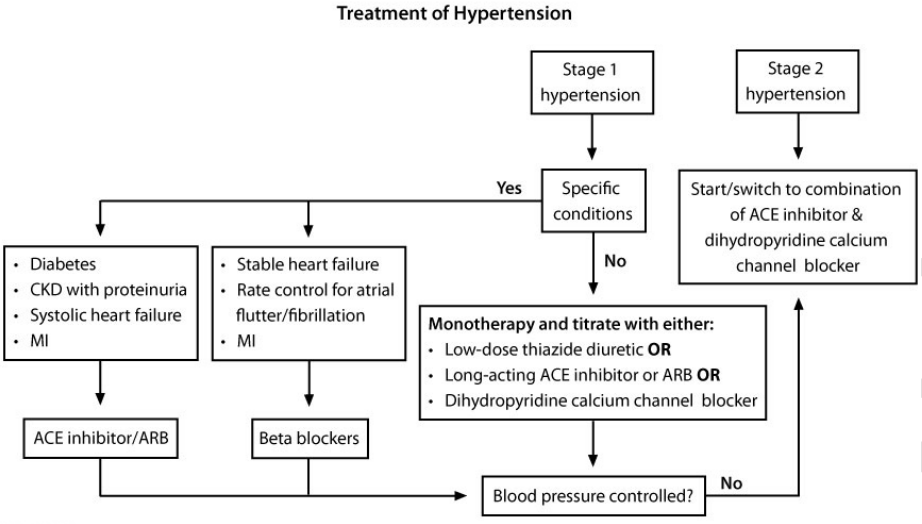
However, thiazide diuretics do have favorable effects on cardiovascular outcomes (eg, congestive heart failure, stroke) in hypertensive patients with diabetes or at risk for diabetes. They also can be combined at low doses with other antihypertensives for additional blood pressure lowering while maintaining a favorable side effect and cost profile. The hyperglycemia risk is dose dependent and clinically less significant at lower doses. Thiazides are especially useful in African Americans and older women *(HYVET Trial)*. Chlorthalidone is likely the most beneficial thiazide diuretic for preventing cardiovascular events but may also induce greater hyperglycemia.

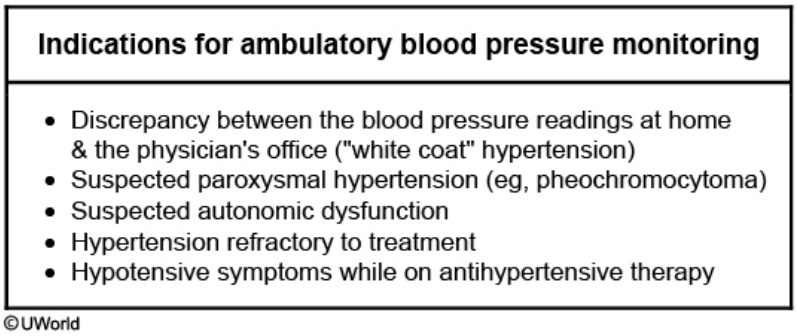
Dihydropyridine calcium channel blockers

- Cause peripheral edema which does not respond to diuretics

- Mechanism : preferential arterial dilation, *which increases pressure gradient between capillaries and interstitium*, leading to extravasation of intravascular fluid
- *RAS blockers* added to CCBs, reduced the risk of peripheral edema by *promoting venule dilation and therefore decreasing the pressure gradient between capillaries and the interstitium*

Evidence : **ACCOMPLISH trial** ACEi + CCB is superior to ACEi + thiazide diuretic





Gestational Diabetes

According to ADA guidelines, individuals with a high risk of having type 2 diabetes require screening at the first trimester of pregnancy.

- prepregnant BMI >25 kg/m 2 with one additional
- hypertension or polycystic ovarian disease, ethnic group with high diabetes prevalence
- the presence of family history of diabetes in the fi rst-degree relatives
- personal history of abnormal glucose intolerance or
- bad obstetric outcome

All pregnant women require screening for hyperglycemia with oral glucose challenge test at 24–28 weeks of gestation except those who were diagnosed with overt diabetes (FPG ≥126 mg/dl, RPG ≥200 mg/dl, or HbA1c ≥6.5%) in the fi rst trimester.

How to screen for hyperglycemia at first trimester?

At first antenatal visit, a pregnant woman can be screened with fasting plasma glucose (FPG) or random plasma glucose (RPG) or HbA1c. FPG ≥126 mg/dl or RPG ≥200 mg/dl or HbA1c ≥6.5% confirms the diagnosis of preexisting diabetes; however, it requires confirmation on a subsequent day in case of equivocal hyperglycemia.

A FPG value of 92–125 mg/dl establishes the diagnosis of GDM at the first trimester of pregnancy.

How to screen for hyperglycemia at 24–28 weeks of gestation?

There are two approaches to screen for hyperglycemia at 24–28 weeks of gestation: a one-step approach or two-step approach. A one-step approach involves screening with a 75-g 2-h oral glucose tolerance test (OGTT).

The two-step approach includes a 50-g oral glucose challenge test (GCT) irrespective of time of the day and meal intake, and if 1-h plasma glucose value ≥140 mg/dl, then a 100-g 3-h OGTT should be performed.

Parameters	One-step approach	Two-step approach
Recommendations	IADPSG	NIH
Time	24–28 weeks	24–28 weeks
Fasting	Required	*Step 1:* GCT—not required *Step 2:* GTT—required
Samples	Fasting, 1, 2 h	*Step 1:* GCT—1 h *Step 2:* GTT—fasting, 1, 2, 3 h
Dose of glucose load	75 g	*Step 1:* GCT—50 g *Step 2:* GTT—100 g
Diagnostic cutoffs (mg/dl)	Fasting ≥92[a] 1 h ≥180 2 h ≥153	*Step 1:* GCT—if 1 h ≥140, proceed to step 2 *Step 2:* GTT[b] Fasting ≥95 1 h ≥180 2 h ≥155 3 h ≥140
Remarks	Higher number of women diagnosed with GDM Benefits of intervention based on a single abnormal value are to be explored	*Step 1* Does not require fasting May underdiagnose GDM *Step 2* 4 samples required Requirement of two abnormal values improves diagnostic specificity

[a]Any one value should be abnormal
[b]Two values should be abnormal

Plasma glucose (mg/dl)	O'Sullivan and Mahan[a] 100-g OGTT (1964)	Carpenter and Coustan[a] 100-g OGTT (1973)	DIPSI 75-g OGTT (2006)	IADPSG[b] 75-g OGTT (2010)	WHO[b] 75-g OGTT (2013)
Fasting (h)	≥105	≥95	–	92–125	92–125
1	≥190	≥180	–	≥180	≥180
2	≥165	≥155	140–199	153–199	153–199
3	≥145	≥140	–		

[a]Two values should be abnormal
[b]Any one value should be abnormal

Conventionally, the diagnosis of GDM was considered on the basis of OGTT performed between 24 and 28 weeks of gestation. However, the current guidelines (IADPSG) recommend estimation of FPG, RPG, or HbA1c during the fi rst trimester, and if FPG is 92–125 mg/dl, then a diagnosis of GDM can be made, even during fi rst trimester

International Association of Diabetes and Pregnancy Study Groups (IADPSG) defined the criteria for the diagnosis of GDM from the data available from the **HAPO study**. This was done by individual estimation of the mean FPG, 1- and 2-h glucose level for the entire HAPO cohort, and these were taken as a reference value with odds ratio of 1 for the occurrence of perinatal complications like birth weight >90th percentile, cord serum C-peptide >90th percentile, or percent infant body fat >90th percentile.

The glucose levels at which the odds ratio for these complications reached a threshold of 1.75 were estimated, and these values were FPG ≥92, 1 h ≥180, and 2 h ≥153 mg/dl. Henceforth, the diagnostic criteria for GDM were derived.

HAPO trial : Hyperglycemia and adverse pregnancy outcomes trial :
A multicenter and international RCT. over 25000 pregnant women underwent 75g oral glucose testing at 24 to 32 weeks gestation.
Primary outcomes : birthweight above 90th centile for GA, primary CS, cord blood c-peptide above 90th centile.
There were no obvious thresholds at which risks increased. Significant associations were observed for secondary outcomes.

The glycemic targets in patients with hyperglycemia during pregnancy, either GDM or overt diabetes, are similar. These include FPG <95 mg/dl (ideally <90 mg/dl), 1-h PPG ≤140 mg/dl, and 2-h PPG ≤120 mg/dl, provided these targets can be achieved without an undue risk of hypoglycemia. In addition, in women with overt diabetes, HbA1C should be maintained ≤6.5%.

Self-monitoring of blood glucose (SMBG) is recommended in all women with hyperglycemia during pregnancy, and this includes fasting, premeal and postmeal (1 h or 2 h) and at 4 am. However, a practical approach is to reduce the frequency of monitoring to 4-point profi le (fasting and post-meal) once the glycemic targets are achieved and sustained.

Targeting fasting plasma glucose is important as FPG >90 mg/dl is associated with increased risk of macrosomia. Although 1-h or 2-h post-meal value is recommended for monitoring, targeting 1-h post-meal glucose value may be more rewarding. This is extrapolated from the HAPO study which showed that 1-h post-OGTT blood glucose level at diagnosis had higher odds ratio for adverse maternal and fetal outcomes as compared to 2-h glucose value.

However, in women with overt diabetes, HbA1C should be monitored and maintained ≤6.5%. HbA1c is not recommended for monitoring of GDM because the data is scarce.

Medical nutrition therapy (MNT) is recommended for all women with GDM or overt diabetes with the aim to provide adequate nutrition for appropriate trimester specific weight gain. One of the key components of MNT is to restrict the carbohydrate intake to 35–45% of total calories ingested. This should be complemented with moderate physical activity for 30 min a day comprising of aerobic and non-weight- bearing exercises

An initial trial of MNT and lifestyle modifications for 2 weeks is recommended in all patients with GDM, and if it fails to achieve FPG ≤95 mg/dl and 2-h PPG ≤120 mg/dl, then insulin therapy should be initiated. However, in patients with overt diabetes insulin therapy should be initiated along with MNT.

How to initiate insulin therapy in GDM?

Insulin is a category B drug (no risk of teratogenicity based on animal data), and at physiological levels, it does not cross the placenta.

1) fasting hyperglycemia > NPH insulin/detemir should be initiated at a dose of 0.1–0.2 units/kg/day.
2) postprandial hyperglycemia > regular/lispro/aspart should be initiated at a dose of 0.1 units/kg preprandially to target the corresponding postprandial blood glucose level.
3) fasting and postprandial hyperglycemia > basal–bolus regimen

The dose of insulin should be titrated based on SMBG profile. Patients with overt diabetes may require higher doses of insulin, even at initiation. **However, with advancing pregnancy, insulin requirement progressively increases both in women with GDM and overt diabetes.**

- Insulin analogues lispro and aspart and the long-acting analogue detemir have been approved for use in pregnancy.
- The safety data for glargine appears to be reassuring but is not yet FDA approved for the use in pregnancy. However, glargine may be continued in women who were receiving it preconceptionally
- Short-acting analogues have the advantage of flexibility in administration (no lag time required between insulin administration and meal intake), better control of early postprandial hyperglycemia, and avoidance of late prandial hypoglycemia, as compared to regular insulin

- However, the efficacy of short-acting analogues is similar to regular insulin, and there is no difference in maternal or fetal outcomes in women treated with short-acting analogues versus regular insulin.
- Glargine and detemir less risk of nocturnal hypoglycemia, but cost more than NPH.

Metformin is a category B drug and 10–16% of drug crosses the placental barrier. **Metformin in Gestational diabetes study (MIG)**, and metformin wasVshown to be safe during pregnancy, although there was an increased incidenceVof preterm birth. In addition, almost 50% of women in the same study required supplemental insulin along with metformin for glycemic control. (MIG study disproved the theoretical risk of fetal hypoglycemia)

Why is monitoring with HbA1c not useful during pregnancy?

- does not accurately reflect the true glycemic status during pregnancy due to hemodilution (falsely low)
- increased RBC turnover (falsely low)
- concurrent iron deficiency (falsely high).
- HbA1c takes long time (3 months) to reflect alterations in glycemic status

DIabetic ketoacidosis and HHS

Management of DKA & HHS	
IV fluids	• High-flow 0.9% normal saline is initially recommended • Add dextrose 5% when serum glucose is ≤200 mg/dL
Insulin	• Initial continuous **IV** insulin infusion • Switch to **SQ** (basal bolus) insulin for the following: Able to eat, glucose <200 mg/dL, anion gap <12 mEq/L, serum HCO_3 ≥15 mEq/L • Overlap SQ & IV insulin by 1-2 hours
Potassium	• Add IV potassium if serum K^+ ≤5.2 mEq/L • Hold insulin for serum K^+ <3.3 mEq/L • Nearly all patients K^+ depleted, even with hyperkalemia
Bicarbonate	• Consider for patients with pH <6.9
Phosphate	• Consider for serum phosphate <1.0 mg/dL, cardiac dysfunction, or respiratory depression • Monitor serum calcium frequently

DKA = diabetic ketoacidosis; **HHS** = hyperglycemic hyperosmolar nonketotic state; **IV** = intravenous; **SQ** = subcutaneous.

Insulin titration is based on the following

1) Glucose targets
2) Pattern recognition
3) Outlier glucose clarification (increased physical activity,rebound hyperglycemia, dietary factors). Do not adjust insulin for outlier events.

DIABETES PART II (Advanced level concepts)

Classification of Diabetes

Evolution of classification based on pharmacotherapy to an aetiopathogenesis nomenclature.

Year	1979	1997
Proposed by	NDDG	ADA
Subtypes of diabetes	IDDM NIDDM GDM MRDM Other types	Type 1 diabetes (T1DM) Type 2 diabetes (T2DM) Other specific types GDM
Prediabetes	IGT	IFG, IGT

Type 1.5 diabetes

- **Latent autoimmune diabetes in adults (LADA)**
- Smouldering T1DM or slowly progressive type 1 diabetes
- **clinical phenotype of T1DM** but **lack ketosis/ketoacidosis at presentation**, despite **evidence of islet autoimmunity**

Clinicopathologic presentation

- Slow progression of immuno-inflammatory destruction of β-cells
- <35 years of age, insulin independent for at least initial 6 months after the diagnosis
- Have at least one of the autoantibodies (islet-cell autoantibody and autoantibodies to GAD-65, IA-2, insulin, and zinc transporter 8).
- Predisposed to other autoimmune conditions
- Familial clustering of diabetes.
- **Insulin is the treatment of choice**
- **Sulfonylureas should be avoided**

Parameters	T1DM	LADA
Age of onset	Childhood	Young adults
Presentation with DKA	Common	Unusual
Islet autoimmunity	Multiple autoantibodies	Single autoantibody Most common GAD65
Treatment	Insulin dependence since diagnosis	Insulin independence for at least initial 6 months

Type 1b diabetes

- **fulminant type 1 diabetes**, is commonly seen in Japanese population
- acute onset severe hyperglycemia, ketosis/ketoacidosis, near-normal glycated hemoglobin (suggest short duration of disease)
- predisposition in those with **HLA-DR-DQ4,** and **negative islet autoimmunity (non-autoimmune disorder).**
- Pancreatic histopathology demonstrates **subclinical pancreatitis but**

not insulitis

Clinicopathology

- Ketosis or ketoacidosis within a week after onset of hyperglycemic symptoms
- HbA1c<8.5% at first visit
- Fasting plasma C-peptide <0.3 ng/ml and glucagon-stimulated C-peptide <0.5 ng/ml at onset
- >20years, flu like symptoms common

Flatbush Diabetes or Ketosis Prone Diabetes

- African-American obese adults who presented with osmotic symptoms and diabetic ketosis/ketoacidosis similar to T1DM, but the subsequent course was akin to T2DM.
- Described in other ethnic groups and is now referred to as ketosis-prone diabetes (KPD).
- glucotoxicity has been proposed as a possible mechanism for rapid decline in β-cell function, which improves after treatment with insulin.

Clinicopathology

- obese, have strong family history of T2DM
- **(A+ β−) should be continued on insulin**
- **preserved β-cell function(A−β+) ; best responders to OHAs**
- **majority (50%) of patients with KPD are A−β+, which suggests preserved β-cell function and subsequent insulin independence.**

Category of KPD	Prevalence (%)
A−β+	50
A−β−	22
A+β−	17
A+β+	11

Type 1a diabetes mellitus

- most important loci determining the risk of T1DM are within the major histocompatibility complex on chromosome 6p21, in particular **HLA class II molecules** (**DR3**-DQ2 or **DR4**-DQ8)
- **Non-HLA genes** associated with **type 1a diabetes** are autoimmune regulator gene (AIRE) on chromosome 21, gene encoding fork head box P3 (FOXP3) leading to IPEX syndrome

Clinicopathology

- young age of onset, absolute insulin deficiency, and presence of islet autoimmunity.
- T1DM has tri-modal presentation with the first peak at 3–6 years, second at peripubertal age, and fi nally at 35–40 years of age.
- Destruction of 90% of β-cells is required to manifest as diabetic ketoacidosis (DKA).
- absence of DKA at presentation in (17–30%)
- screening with **TSH, anti-TPO, and anti-tissue transglutaminase (IgA-tTG)** should be done at diagnosis in all patients with T1DM
- **Retesting should be done periodically at intervals of 1–2 years**

	Age at diagnosis		Duration of disease	
Antibody	<15 years (%)	>15 years (%)	At diagnosis (%)	At 10 years (%)
ICA	80–85	60–80	85	10
Anti-GAD65	60	70–80	80	50
IA-2	70–80	40–60	80	50
IAA	30–65	20–35	–	–
ZnT8	–	–	60–80	–

Connecting peptide

- C-peptide is a 31 amino-acid peptide that connects A and B chains of insulin in the proinsulin molecule.
- C-peptide is cosecreted with insulin and is a marker of β-cell function
- Important in categorizing patients into T1DM or T2DM, especially in those with young onset of disease
- Advantages of estimation of C-peptide over insulin include its **longer half-life (30 min vs. 4 min)**, **negligible hepatic extraction**, and usefulness even in **patients on exogenous insulin therapy**.
- C-peptide should be measured only after optimizing blood glucose profile to avoid the effect of glucotoxicity on β-cells.

Clinical application
Fasting C-peptide level ≥0.6 ng/ml and glucagon-stimulated C-peptide ≥0.96 ng/ml suggest optimal endogenous β-cell reserve.

A couple with T1DM (both parents with DM) plans to have a child and is worried about the risk of T1DM in the progeny. How to counsel?

- **Majority (>85%) of patients with T1DM lack family history of T1DM**
- The risk of developing T1DM in the offspring is 10%, if both parents have T1DM.
- **In case of a single parent having T1DM, the risk to offspring is higher if father (4.6%) has T1DM as compared to mother (2%).**
- In the present case scenario, parents can be counseled that the probability of not having T1DM in the offspring is 90%.

Risk for T1DM (twins)

- The risk of developing T1DM in a sibling with a dizygotic twin is 6%, while the risk becomes 8-fold higher (50%) in monozygotic twins

Diabetes Control and Complication Trial (DCCT)

- landmark study involving 1,441 patients with T1DM
- intensive or conventional insulin therapy -- followed up for 6.5 years
- Intensive with MDI/CSII with average A1C of 7.2% vs conventional with average A1C of 9%
- **prevention as well as delayed the progression of microvascular complications**

Epidemiology of Diabetes Interventions and Complications (EDIC) study
- Follow up of the DCCT cohort
- beneficial effect of initial good glycemic control on *future development of cardiovascular complications*

Metabolic memory or legacy effect

A period of early intensive glycemic control in patients with diabetes prevents
the development of micro- and macrovascular complications in the long run

despite discontinuation of intensive therapy later on.

- first demonstrated in the EDIC study and later in the follow-up cohort of UKPDS

What is the pathophysiology?

- Decreased oxidative stress
- Reduction in advanced glycated end products
- Epigenetic changes (DNA methylation/histone acetylation) associated with reduction in gluco-lipotoxicity

Treatment modalities for T1DM

Modality	Remarks
Basal-bolus insulin therapy	Most commonly practiced High glycemic variability as compared to CSII
Insulin pumps (CSII)	Expensive Risk of DKA in the event of mechanical failure

Modality	Remarks
DPP4 inhibitors, GLP-1 agonists (in addition to insulin)	Experimental Reduces glycemic variability and/or improves hypoglycemic unawareness
SGLT2 inhibitors (in addition to insulin)	Experimental No risk of hypoglycemia Action is insulin-independent Increased risk of urogenital infections
Pancreatic islet transplantation	Potentially curative therapy Insulin-independence progressively declines Risks associated with immunosuppressive therapy Limited availability of pancreatic islets Expensive
Immunomodulatory therapy	Serious adverse events Poor efficacy

Parameter	Detemir	Glargine	Degludec
No of amino acid	50	53	50
Fatty acid chain	Present (myristic acid)	No	Present (hexadecanedioic acid)
pH	Neutral	Acidic	Neutral
Mechanism of prolonged duration of action	Binding to albumin in circulation	Precipitation at neutral pH in subcutaneous tissue	Multihexamer chain formation in subcutaneous tissue
Onset of action	1 h	1 h	1–1.5 h
Peak effect	3–9 h	No peak	No peak
Duration	6–23 h	11–24 h	40 h
Intra-/interindividual variation	Low	High	Lowest
Nocturnal hypoglycemia	Low	Low	Lowest
Binding affinity to IGF-1 receptor (as compared to regular insulin)	18-fold	641-fold	2-fold
Miscibility with short-acting analogue	No	No	Yes
Miscibility with GLP-1 receptor agonists	No	Yes	Yes

What is insulin lipodystrophy?
-- localized hypertrophy or atrophy of adipose tissue at the injection site.

Lipoatrophy	**Lipohypertrophy**
Common with use of insulin derived from animal sources and is rare with the use of human insulin.	Common with all insulin preparations, including analogues.
• localized production of cytokines (TNFα) in response to immunological reaction against insulin (acting as hapten) • It may respond to local steroids	• insulin-mediated lipogenesis through activation of lipoprotein lipase • managed by changing the site of insulin administration and, rarely, surgical excision

What is insulin-induced amyloidosis?
--occurs at sites of insulin injections

-- mimics lipohypertrophy
-- has a firm to hard nodular consistency as opposed to the soft consistency of lipoatrophy.

Comparing risk of hypoglycemia in T1DM and T2DM

In normal physiology

- First line defense against hypoglycemia is decrease in insulin secretion
- Second line defense -- release of glucagon from α-cells in response to decrease in intra-islet insulin (Δ change in intra-islet insulin)
- Normally, rising glucose levels result in suppression of glucagon secretion, whereas declining glucose levels stimulate glucagon secretion

T1DM	T2DM
Because of absolute insulin deficiency, patients with T1DM have impaired fi rst- as well as second- line defense mechanism against hypoglycemia	Some endogenous β-cell reserve with intact first- and second-defense mechanisms against hypoglycemia

Additional pathophysiologic mechanisms contributing to hypoglycemia in T1DM

- failure of upregulation of glucose receptors on α-cells despite reduced glucose levels
- with advanced duration of disease, concurrent presence of autonomic neuropathy predisposes to hypoglycemia as appropriate glucagon secretory response during hypoglycemia requires the presence of catecholamines and intact intra-islet nerves

Insulin pump therapy?

1. T1DM who have wide swings in blood glucose
2. recurrent hypoglycemia
3. hypoglycemic unawareness
4. patients who fail to achieve target HbA1c <8.5% despite multiple insulin injections

INSULIN PUMP THERAPY

Advantages	Disadvantages
Decreased frequency and severity of hypoglycemia	Technical failure with risk of DKA
Reduced glycemic variability	Cost
Avoidance of multiple daily injections	Increased unhealthy eating

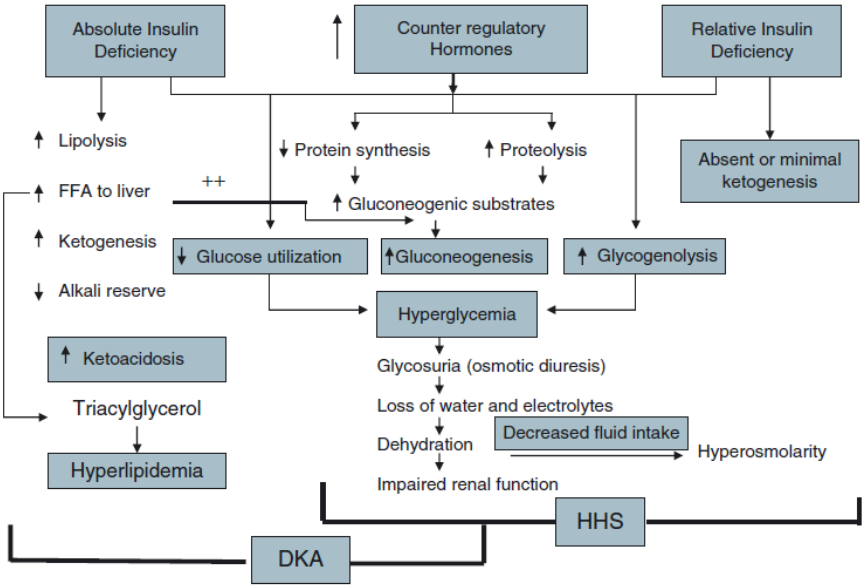
Advantages	Disadvantages
Precise insulin dosing	Requires frequent blood glucose testing
Administration of basal insulin at different rates over 24 h (circadian variation)	Requires intensive education and motivation
Reduction in insulin requirement by 10–20%	Equipment needs to be carried throughout
Better glycemic control	Change of needle twice a week
Flexibility of lifestyle	
Improved quality of life	

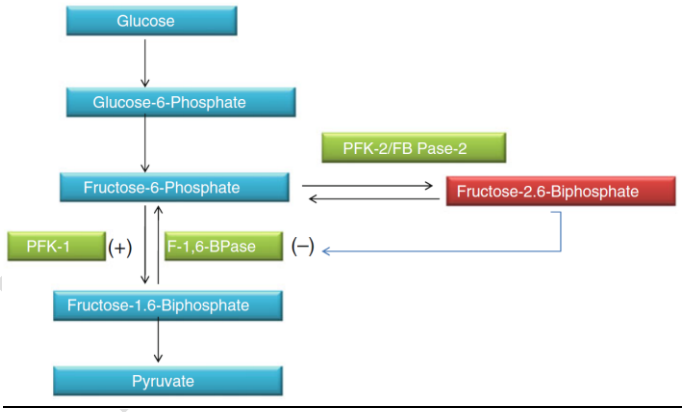
OPEN LOOP SYSTEM	CLOSED LOOP SYSTEM
• Delivers insulin at a preset rate and the insulin delivery rate has to be adjusted manually • Conventional insulin pumps, sensor augmented pumps, and sensor augmented pumps with threshold suspension represent “open-loop” insulin delivery systems	• automated adjustment in the rate of insulin delivery depending on the ambient blood glucose level • **Medtronic 670G**

Table 49.1 Insulin pump comparison chart

Manufacturer	Animas	Medtronic MiniMed	OmniPod®	Roche	Tandem® Diabetes Care	Valeritas
Model	One Touch™ Ping™[3]	MiniMed® 530G with Enlite®	Diabetes Insulin Pump	ACCU-CHEK Spirit Insulin Pump	t:slim® Insulin Pump	V-Go™ Insulin Delivery System (technically not a "pump")
Website	http://www.animas.com/animas-insulin-pumps/onetouch-ping	http://www.medtronicdiabetes.com/treatment-and-products/minimed-530g-diabetes-system-with-enlite	http://www.myomnipod.com/about-omnipod/system-overview/	https://www.accu-chekinsulinpumps.com/ipus/products/insulinpumps/spirit.html	www.tandemdiabetes.com/products/t-slim/	http://www.go-vgo.com/
Dimensions	3.25 × 2 × 0.86	3.6 × 2 × 0.8 inches	1.6 × 2.4 × 0.7 inches	3.2 × 2.2 × 0.8 inches	3.13 × 2 × 0.6 inches	2.4 × 1.3 × 0.5 inches
Weight		< 4 oz. full	1.2 oz. full		3.95 oz. full	0.7 to 1.8 oz.
Basal increments	0.025–25 U h^{-1}	0.025–35 U h^{-1}	0.05–30 U h^{-1}	0.1–25.0 U h^{-1}	0.1–15.0 U h^{-1}	2 units increments up to 36 total in 24 h
Reservoir capacity	200 units	300 units	200 units	315 units	300 units	3 sizes: 56, 66, and 76 unit capacity (basal plus 36 unit bolus)
Basal patterns	12	• 3 basal patterns—customizable • Temporary basal options changeable at a moment's notice	• 7 programs with up to 24 segments each • Programmable in 30-min increments • Temporary basal options and presets	• 5 basal rate profiles • 24 hourly basal rates • Temporary basal rate in 10% increments from 0% to 200%, and 15-min increments from 15 min to 24 h	• 4 basal profile programs • 16 basal rate segments per profile • Temporary basal rates from 15 min to 72 h • Range 0% to 250%	3 sizes or basal rates: 20(0.83 U h^{-1}), 30(1.25 U h^{-1}), 40(1.67 U h^{-1})
Insulin on board calculation		Yes	• Linear degradation. Tracks correction boluses • Insulin duration can be programmed in 30-min segments from 2–6 h		Yes	N/A
Special features	Meter remote Color screen is self-illuminating	• Built-in CGM, automatic pump suspend when threshold glucose reached, unless user cancels • Always tracks active insulin in bolus calculations • Contour Next Link Meter that transmits BG result to pump and downloads pump to Carelink • Lowest available insulin to carb ratio of 1:1 • Capture events feature • Missed meal bolus reminder • BG reminder	• Tubeless and wireless pump • Integrated BG meter • Integrated food library • Automatic cannula insertion • Continuous Insulin Delivery; no need to ever disconnect from your pump	Reversible screen Backup pump The pump can wirelessly download to a handheld device or computer for analysis	Color screen Flat cartridge design	• Uses one fast-acting insulin (Humalog® or NovoLog®) • No tubing or cannula • No need to plan your meals on an insulin schedule for mealtime bolus dosing • The V-Go buttons can be pressed through your clothes • Flexibility to choose a new V-Go application site every 24 h to work with your clothing

DIABETIC KETOACIDOSIS -- REVIEW OF UNDERLYING BIOCHEMISTRY





Key metabolite in the genesis of Hyperglycemia in DKA is **Fructose-2,6-biphosphate**

F-2,6-P2 allosterically stimulates the **enzyme phsophofructokinase-1 (PFK1)** and inhibits **fructose-1,6-bisphosphatase**, thereby resulting in **stimulation of glycolysis** and **inhibition of gluconeogenesis**, respectively

In the presence of **high glucagon/insulin ratio**, the levels of fructose-2,6-biphosphate are decreased which results in suppression of glycolysis and promotion of gluconeogenesis

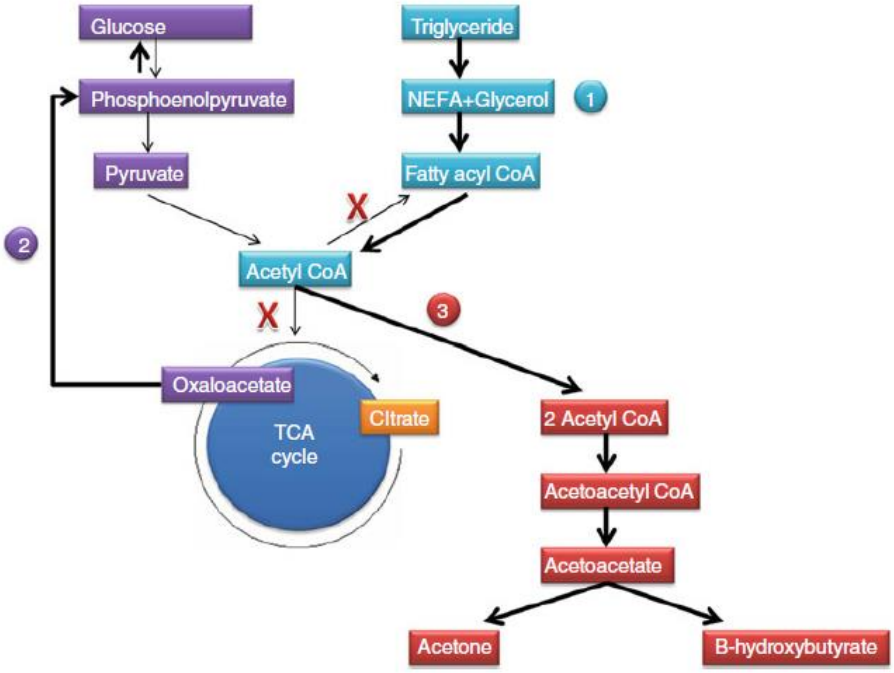
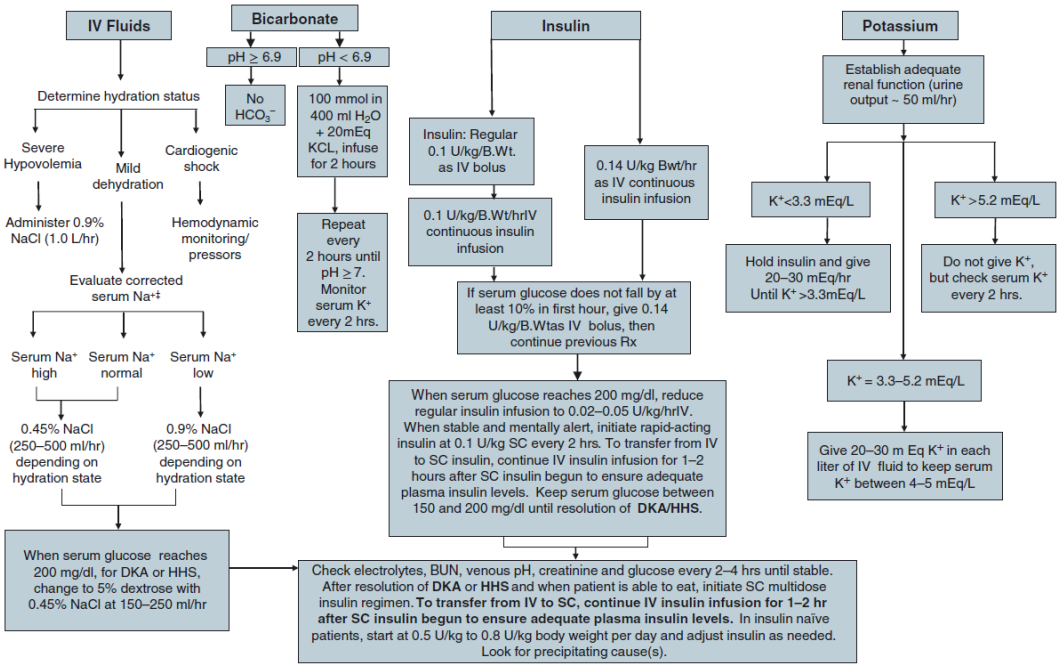


Fig. 16.3 Pathophysiology of ketogenesis in DKA. (*1*) Accelerated lipolysis due to severe insulin deficiency and excess glucagon, resulting in formation of acetyl-CoA. (*2*) Acetyl-CoA cannot enter into TCA cycle due to non-availability of oxaloacetate, which is diverted to gluconeogenic pathway as a consequence of insulin deficiency. (*3*) Acetyl-CoA is shunted to ketogenic pathway

Ketone bodies include **acetone**, **acetoacetate**, and **β-hydroxybutyrate**

1. **Oxidation of free fatty acids (FFAs) leads to synthesis of acetyl-CoA and two molecules of acetyl-CoA combine to form acetoacetate**
2. **This is further converted to either β-hydroxybutyrate or acetone**
3. **Acetoacetate is excreted through urine and acetone through lungs, while β-hydroxybutyrate is converted to acetoacetate**

In the physiological state, the ratio of acetoacetate to β-hydroxybutyrate in blood is 1:3, and it may increase up to 1:8 in severe DKA, hypotension, and fasting state.



*DKA diagnostic criteria: blood glucose 250 mg/dl, arterial pH 7.3, bicarbonate 15, mEq/l, and moderate ketonuria or ketonemia
† 15–20 ml/kg/h
‡ Serum Na should be corrected for hyperglycemia (for each 100 mg/dl glucose 100 mg/dl, add 1.6 mEq to sodium value for corrected serum value)

Rhino–orbito–cerebral mucormycosis

- Rhizopus fungi -- **Mucor** is characteristically **ferrophilic** and **angioinvasive**
- **Acidosis increases the availability of free iron in circulation due to decreased binding with transferrin**
- Patient with DKA who manifests ptosis, vision loss, epistaxis, blackish eschar (nasal concha or hard palate), or hemiplegia
- Isodense or hyperdense lesions in ethmoid and/or paranasal sinuses on CT
- Aseptate, right-angled hyphae on cytology confirms the diagnosis of Mucormyosis
- Amphotericin B along with aggressive surgical debridement is curative in majority of patients

TYPE II DIABETES RELATED CONCEPTS

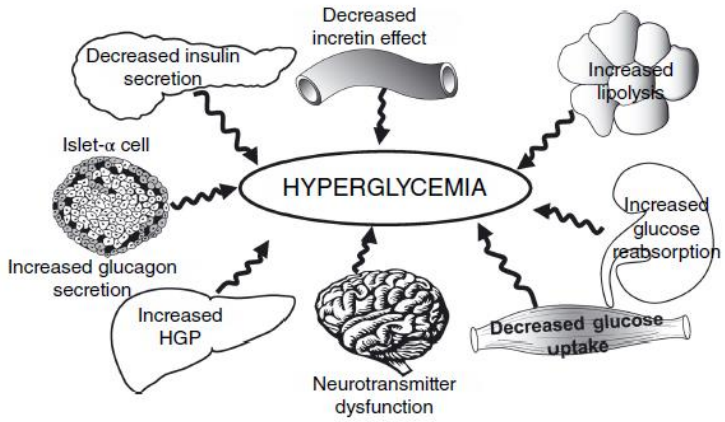
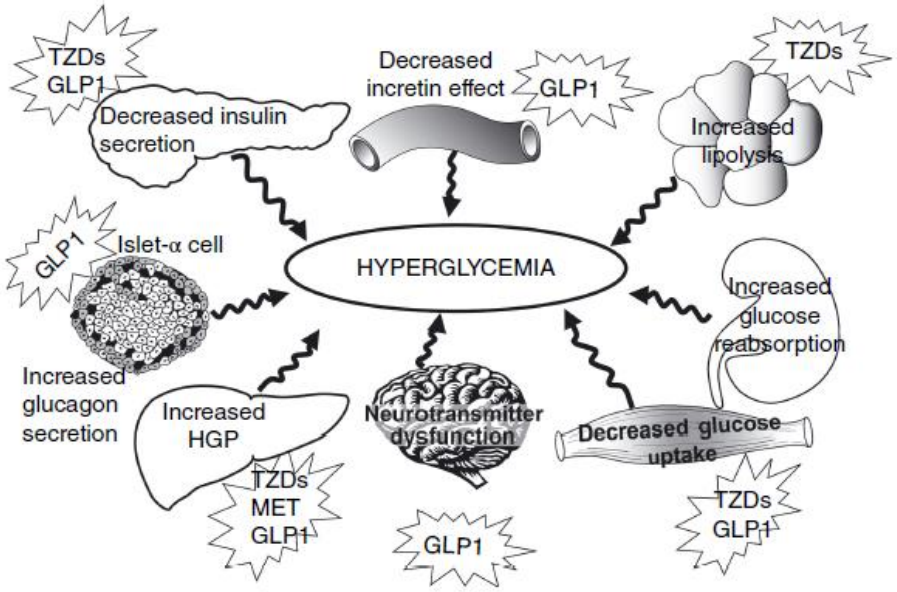
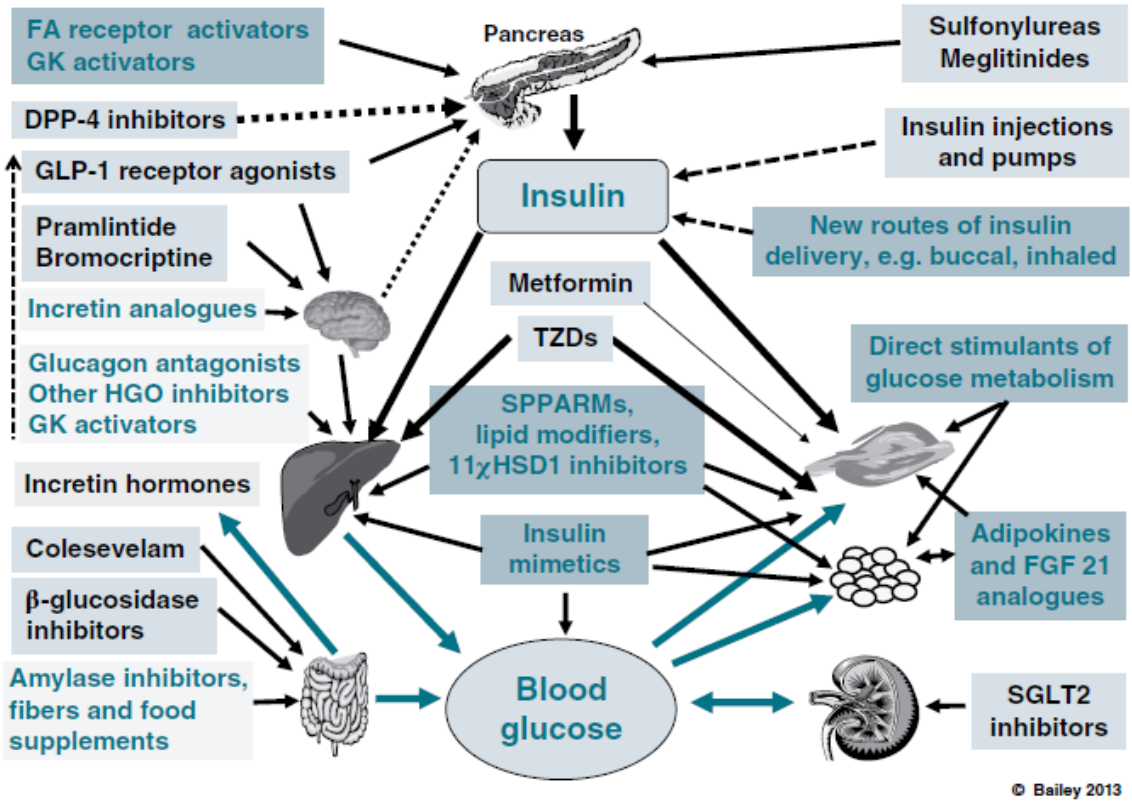


Figure 46.1 The Ominous Octet: eight distinct pathophysiologic defects contribute to the pathogenesis of type 2 diabetes mellitus. Source: DeFronzo 2009 [3].





Defects in Type 2 diabetes mellitus

- Insulin resistance alone cannot produce T2DM as long as β-cells are able to compensate for increasing insulin resistance. The failure of β-cells eventually leads to onset of hyperglycemia.

What is insulin resistance?

- **Insulin resistance is defined as subnormal biological response to optimal levels of insulin**
- Associated with **altered carbohydrate**, fat, and protein **metabolism**
- With advancing age, insulin resistance progressively increases as a result of increasing adiposity and adaptation to sedentary lifestyle
- prime sites of insulin resistance are the liver, skeletal muscle, and adipose tissue

**Some degree of insulin resistance is inbuilt in every healthy individual, as it protects from hypoglycemia

Clinical markers of insulin resistance

- obesity (central/generalized)
- acanthosis nigricans, skin tags, double chin, lipodystrophy

- Women -- features of androgen excess (alopecia, hirsutism, oligomenorrhea).
- The body mass index (>23 kg/m 2 , as per Asian criteria) and waist circumference (>80 cm in women and >90 cm in men, as per Asian criteria)
- high requirement of insulin (>2–3 IU/kg of body weight) for optimal glycemic control

Assessment of insulin resistance

- hyperinsulinemic-euglycemic clamp is the "gold standard" for detection of insulin resistance/sensitivity
- **Insulin suppression test**

These represent indirect measures of insulin resistance

- frequently sampled intravenous glucose tolerance test **(FSIVGTT)**
- **short insulin tolerance test**
- fasting plasma insulin
- glucose/insulin ratio
- homeostasis model assessment-insulin resistance (HOMA-IR)
- Quantitative insulin sensitivity check index (QUICKI)
- Matsuda insulin sensitivity index

β-cell defects in the evolution of T2DM

- **Ultradian rhythmicity** appears to be characteristic of several endocrine systems.
- **Insulin release is a multioscillatory process** with **rapid pulses of about 10 min** and **slower ultradian oscillations (50–120 min)**.
- Pancreas has a "pacemaker like function"

- The **meal-related first phase of insulin secretion** is due to the release of **preformed granules** and is responsible for knocking down hepatic glucose output in the immediate postprandial period

- The **second phase of insulin secretion** is responsible for postprandial glucose disposal to skeletal muscle and is due to insulin biosynthesis

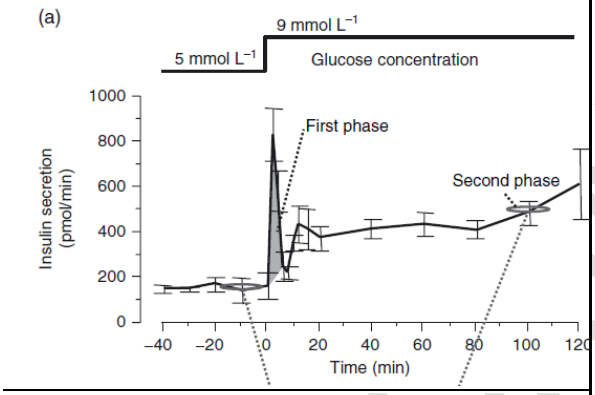
Earliest abnormality in T2DM is the loss of

pulsatile insulin secretion **(results in fasting hyperglycemia) ⇒** loss of glucose induced first phase insulin secretion ⇒ delayed and prolonged second phase of insulin secretion (**postprandial hyperglycemia**)

⊕ *The concurrent presence of incretin deficiency/ resistance contributes further to ß-cell dysfunction and impaired crosstalk between a and ß-cell, thereby resulting in worsening of hyperglycemia*

Hyperglycemic clamp (Intravenous glucose tolerance testing)

The **β-cell response to glucose stimulus is biphasic**, with an initial insulin secretion burst lasting about 5–8min **(first-phase secretion)**, followed by a **drop towards basal levels** and then by a relatively rapid increase that persists as far as hyperglycemia is maintained **(second-phase secretion)**.



The **β-cell dose-response** is a fundamental characteristic of insulin secretion; its slope, which represents the sensitivity of the β cell to glucose, is a key β-cell function parameter.

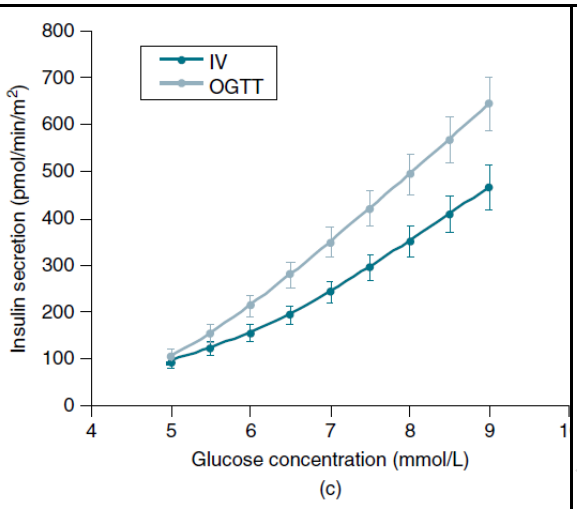
The incretin effect -- response to oral glucose

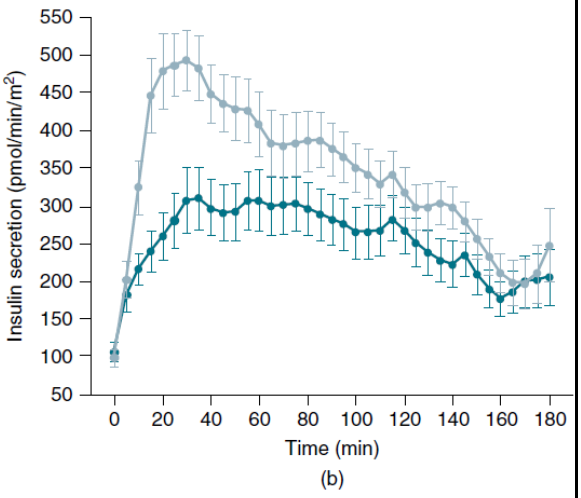
- An increase in insulin secretion of ~1.6–1.7-fold with oral (75 g OGTT) compared to intravenous glucose administration
- **Incretin effect** is mainly attributed to the action of two hormones: *glucose-dependent insulinotropic peptide (GIP)* and *glucagon-like peptide 1 (GLP-1)*
- K cells for GIP and the L cells for GLP-1 (sections of the small intestine)

Clinical application -- comparing SUR and meglitinides

- Unlike sulfonylureas, **meglitinides stimulate first-phase insulin release in a glucose-sensitive manner, theoretically reducing the risk of hypoglycemic events**.
- Rapid **suppression of hepatic glucose production**, and reducing

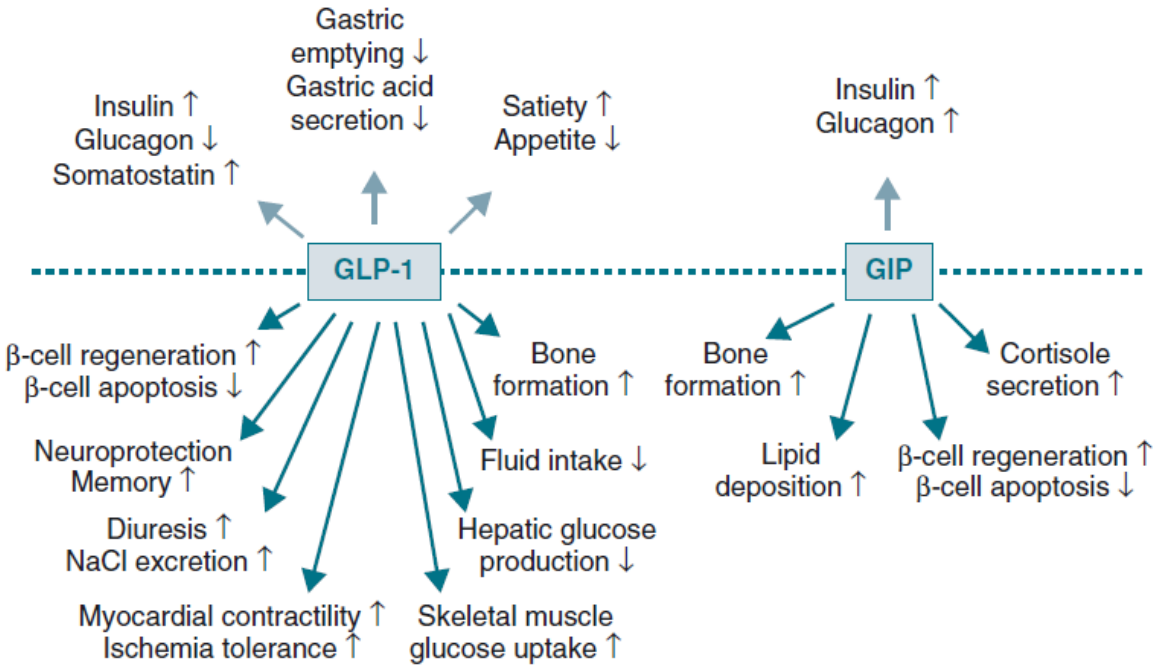
the stimulus for additional insulin that would be required subsequently to dispose of a larger glucose load. Thus, the rapid onset/short duration stimulation of insulin release by meglitinides enhances the control of prandial hyperglycemia, while reducing the risk for post-absorptive hypoglycemia and limiting exposure to hyperinsulinemia.





Incretin effect

$$= \frac{(AUC_{\text{oral glucose}} - AUC_{\text{intravenous glucose}})}{AUC_{\text{oral glucose}}} 100\ [\%],$$



MODY

MODY, the most common form of monogenic diabetes is due to mutations in the genes involved in pancreatic embryogenesis, β-cell function, or glucose sensing

- **onset of diabetes <25 years of age**
- strong family history of diabetes particularly in three successive generations with onset of disease <40 years of age.
- **absence of ketosis**
- **lack of features of insulin resistance**
- response to sulfonylureas for initial 2 years
- there are thirteen forms of MODY

Type	Genetic defect	Phenotype	Treatment
1	Hepatocyte nuclear factor-4α	Macrosomia Transient neonatal hypoglycemia, Hypotriglyceridemia, raised HDL-C	Sulfonylurea
2	Glucokinase gene	Mild hyperglycemia, Non-progressive	Life style modifications
3	Hepatocyte nuclear factor-1α	Most common	Sulfonylurea
4	Insulin promoter factor 1 (IPF/PDX1)	Pancreatic agenesis	Insulin
5	Hepatocyte nuclear factor-1β	Pancreatic atrophy, Urogenital anomalies	Insulin
6	Neurogenic differentiation factor-1	Very rare	Insulin

- Maturity-onset diabetes in the young occurs due to defect in insulin secretion rather than insulin resistance
- Respond well to therapy with sulfonylureas/insulin
- The risk of developing both microvascular and macrovascular complications is possibly simliar to patients with T2DM, except in MODY2 (glucokinase gene defect)

Properties	GLP1 agonist	DPP4 inhibitors
Mode of administration	Injectable	Oral
Increase in GLP1 level	10 fold	2–3 fold
Effect on satiety	Increased	None
Effect on weight	Weight loss (2–5 kg)	Weight neutral
HbA1c reduction	1–1.3%	0.6–0.8%
Gastric emptying	Delayed	No effect
Glycemic durability	Pronounced	Modest
Cardiovascular safety	Yes	Possibly safe

Parameters	DPP4 inhibitors	Sulfonylureas
Insulin secretion	Glucose-dependent	Glucose-independent
Insulin biosynthesis	Increases	No effect
Risk of hypoglycemia	Mild	Severe
Proinsulin–insulin ratio	Favors insulin	Favors proinsulin
Inhibition of gllucagon secretion	Moderate	Mild
α-cell sensitivity to glucose	Restores	No effect
Improvement in β-cell mass	Possible	No
Effect on body weight	Neutral	Usually weight gain

Characters	Basal insulin	GLP1 agonist
Targets	Insulin deficiency β-cell dysfunction	Incretin defect ? β-cell dysfunction/mass
FPG	Reduced ↓Hepatic glucose output	Reduced ↓Glucagon
PPG	Reduced ↑glucose uptake Skeletal muscle Adipocyte	Reduced ↑Glucose-dependent insulin secretion ↓Glucose-dependent glucagon secretion ↓Gastric emptying
Body weight	3–5 kg gain ↑Appetite ↑Adipogenesis	2–3 kg loss ↓Appetite ↑Satiety Delayed gastric emptying
Risk of hypoglycemia	Increased	Decreased Glucose-dependent insulin secretion Restoration of glucose–glucagon axis
Cardiovascular safety	Possibly neutral	Cardioprotective Decrease in SBP Favorable lipid profile

	ACC/AHA guidelines	ADA guidelines
High-intensity statin therapy	Established CAD LDL-C >190 mg/dl Age 40–75 years with LDL-C between 70 and 189 mg/dl and have an estimated 10-year cardiovascular risk ≥7.5%	Established CAD Age 40–75 years with ≥1 CVD risk factor (LDL-C >100 mg/dl, hypertension, smoking, and overweight/obesity)
Moderate-intensity statin therapy	Age 40–75 years with LDL-C between 70 and 189 mg/dl and have an estimated 10-year cardiovascular risk <7.5%	Age 40–75 years, even without cardiovascular risk factors

In individuals <40 or >75 years of age with CVD risk factors, ADA recommends moderate- to high-intensity statin therapy, whereas ACC/AHA guidelines recommend individualization of statin therapy depending upon the presence of risk factors, side effect profile, and patient preference

Pleiotropic effects of statins

- stabilization of coronary plaques
- Reduction in proteinuria
- resolution of retinal hard exudates
- increase in bone mineral density
- antioxidant/anti-inflammatory effects.
- reduced risk of dementia.

Oral Antihyperglycemic agents and chronic kidney disease

Metformin

- Do not initiate metformin below a GFR of 45
- Dose reduction and close monitoring for GFR 30-45
- Absolute contraindication below 30

REACH (REduction of Atherothrombosis for Continued Health) registry showedd decreased mortality associated with metformin use, even in patients with moderate kidney disease.

- *Possible renoprotective effects of metformin (animal and cell culture models)*

sulfonylureas

Glipizide undergoes *Hepatic Metabolism* into several inactive metabolites, as such its clearance and elimination half-life is not affected by a reduction in the estimated GFR. DOSE adjustments NOT required in CKD. SU of choice in CKD

Glibenclamide and **glyburide** both undergo *Hepatic Metabolism*, but are *eliminated equally in bile and urine*
Both drugs contraindicated in estimated GFR <60mL/min

Glimepiride undergoes *Hepatic Metabolism* into two main metabolites, one of which has hypoglycemic activity. In CKD, the metabolites may accumulate. Comparatively causes less hypoglycemia than glyburide. contraindicated in estimated GFR <60mL/min

Gliclazide has inactive metabolites that are eliminated mainly in the urine (80%) and presents a lower risk of hypoglycemia than glibenclamide and glimepiride. Pay particular attention to dose and avoid if GFR falls below 40

Meglitinides

Nateglinide (starlix) is hepatically metabolized with renal excretion of metabolites -- but not repaglinide (prandin)
Nateglinide should be used with caution in patients with advanced renal disease. (60mg ac)
Repaglinide is safe until GFR is <30mL/min/1.73m2 (0.5mg ac)

Alpha glucosidase inhibitors

- Acarbose is almost entirely metabolized in the GIT, less than 2% of drug is recovered as the active or its metabolites in the urine.
- Miglitol is absorbed systemically and excreted unchanged in the urine.
- Modest efficacy in glycemic control and lack of long term trials in patients with kidney disease. Avoid in CKD IV and V.
- *Avoid if GFR <30*

Thiazolidinediones

- Pharmacokinetic profile of pioglitazone is similar between healthy subjects and patients with moderately or severely impaired renal function who do not require dialysis.
- Cause significant fluid retention as such should be used with caution in patients with heart failure and CKD and a signficant reduction in GFR.
- No dose adjustment is required

DPP4 inhibitors

There is structural heterogeneity with varying PK-PD profiles for this class.

- Sitagliptin is mostly excreted unchanged in the in the urine.
- Vildagliptin is metabolized mainly in the kidneys into inactive metabolites. 25% excreted unchanged in the urine.
- Saxagliptin is metabolized mainly in the liver into an active metabolite that is eliminated in the urine.
- Linagliptin is the only DPP-4 inhibitor that is eliminated entirely via the biliary system. This is the agent of choice in patients in all stages of kidney failure, without any dose adjustments.

Dose adjustments
Sitagliptin (100mg daily if GFR <50, 50mg daily if 30-50, 25mg daiy if GFR <30)
Saxagliptin 5mg daily if GFR >50, 2.5mg daily if GFR <50
Linagliptin -- No dose adjustment

Incretin mimetics
Glucagon like peptide 1 is an incretin produced from the PROGLUCAGON gene in L cells of the small intestine and is secreted in response to nutrients. It is deficient in patients with T2DM DPP-4 inhibitors inhibit DPP-4 which is a ubiquitous enzyme expressed on the surface of most cell types that deactivates GLP-1; therefore, its inhibition could potentially affect glucose regulation through multiple effects

DPP-4 inbibitors	GLP-1 agonist therapy
• Increases endogenous GLP-1 • Stimulate glucose dependent insulin secretion from B cells • Lower glucagon secretion • Overall -- lower hepatic glucose output NO EFFECT ON INSULIN ACTION,GASTRIC EMPTYING OR SATIETY	Exert all the effects of DPP-4 agents • Slow gastric emptying • Decrease food intake

NON ALCOHOLIC FATTY LIVER DISEASE/NASH/NAFLD (Cusi et al lecture series)

NAFLD in patients with T2DM

- Single most important finding in determining a patients chance of developing cirrhosis

Answer : liver fibrosis

Elevated ALT may indicate fatty liver (NAFLD) or NASH but approximately ⅔ of patients with NAFLD have normal LFTs

- Most common cause of death

Cardiovascular disease (Give statins to patients with NASH)

- What treatment has proven to improve liver histology in patients with T2DM.

Pioglitazone

NAFLD

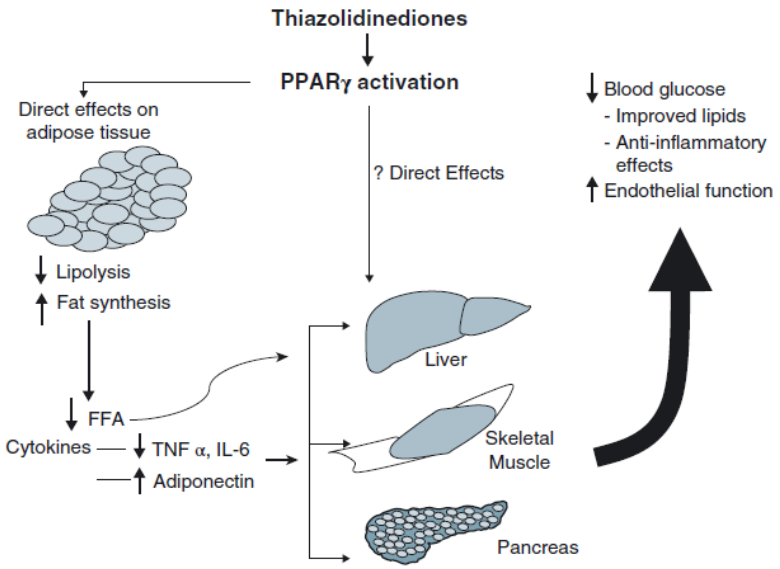
- Chronic liver condition characterized by hepatic fat accumulation in the absence of ethanol abuse and other identifiable causes, insulin resistance and frequently associated with impaired glucose tolerance or T2DM

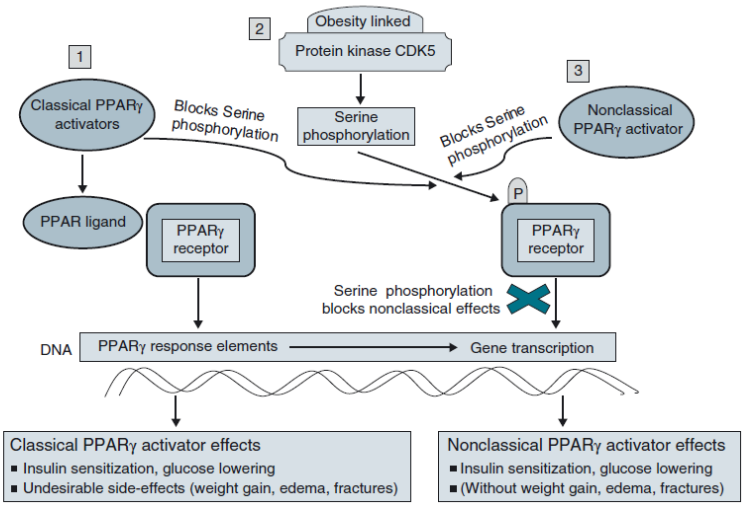
Steatosis may range from simple steatosis to NASH with progressive liver damage, necrosis, inflammation and cirrhosis.

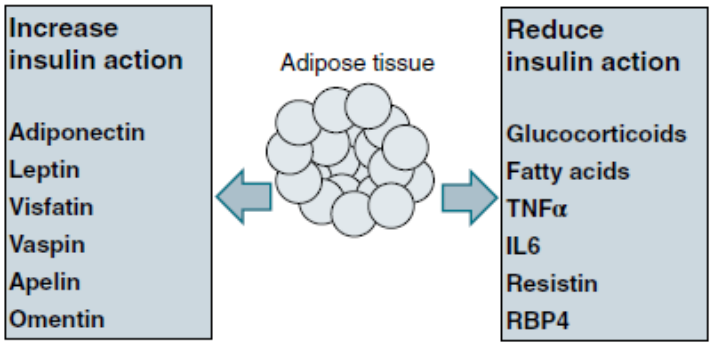
Fatty liver >5% liver fat. Common in about 70% of diabetic patients

Diagnosis of NASH/NAFLD

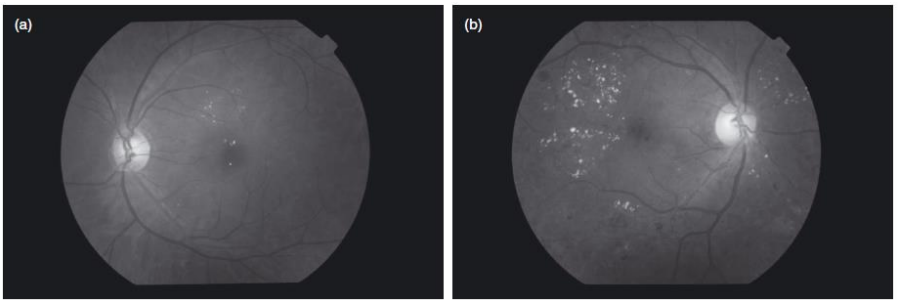
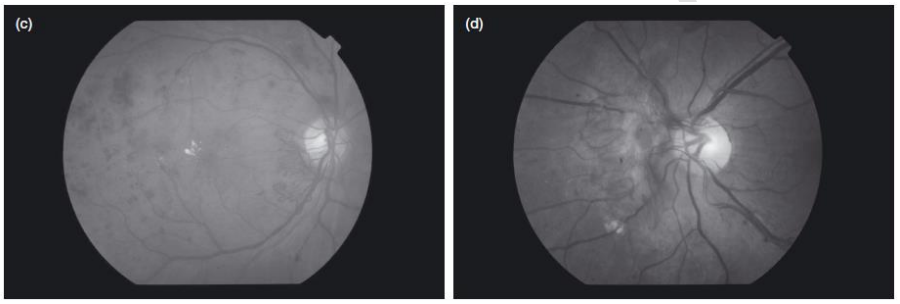
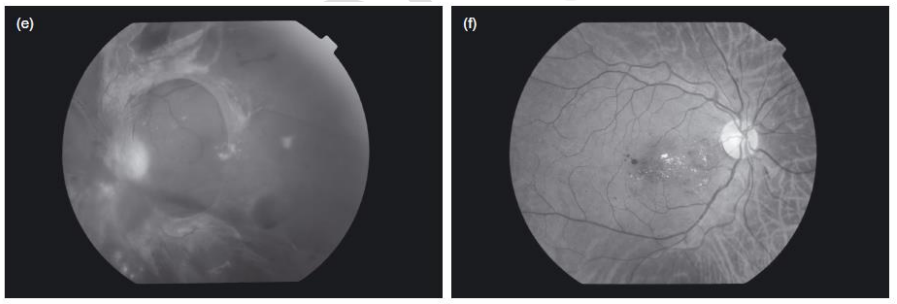
- Few clinical symptoms (i.e RUQ discomfort)
- High degree of clinical suspicion
- May be associated with elevated liver aminotransferases ALT>AST
- May not be associated with elevated liver enzymes
- Rule out these differentials (Hepatitis C genotype 3, autoimmune, PBC,A-1AT, Wilson dx, HIV, acute fatty liver of pregnancy, drugs like MTX, steroids,amiodarone,ARVs,tamoxifen,diltiazem)
- USG : increased echogenicity 65-80% sensitivity for NAFLD. USG is however limited because it misses many cases eg. High BMI, cannot quantify amount of steatosis and cannot differentiate b/n steatosis and fibrosis.
- Fibroscan (USG Elastography) is a better image of fibrosis. It rules out severe disease. A study of 15-20% of T2DM with steatosis have liver fibrosis.
- MRI and spectroscopy. Correlates well with biopsy
- Diabetics vs non-diabetics. Higher incidence in diabetics when matched for BMI







DIABETIC RETINOPATHY (BOARD PEARLS)

(a) Mild nonproliferative diabetic retinopathy (b) severe nonproliferative diabetic retinopathy	
(c) proliferative diabetic retinopathy (d) new vessels at disc	
(e) proliferative diabetic retinopathy with fibrovascular proliferation (f) clinically significant macular edema.	

International Clinical Diabetic Retinopathy Disease severity scale [130]	Defining features	ETDRS scale [18,224]	Defining features (based on 7 × 30° field stereo photographs)
No retinopathy	No retinal abnormalities	No retinopathy	No retinal abnormalities
Mild nonproliferative diabetic retinopathy (NPDR)	Microaneurysms only	Mild nonproliferative diabetic retinopathy (NPDR)	Microaneurysms only, *or* Venous loops in 1 field; retinal hemorrhages present; hard exudates or soft exudates in 1 field
Moderate NPDR	More than just microaneurysms but less than severe NPDR	Moderate NPDR	Microaneurysm and hemorrhages moderate in 4 fields or severe in 1 field or IRMA
		Moderately severe NPDR	Two out of three moderate characteristics and or one of the following: microaneurysms and hemorrhages severe in 2 or 3 fields, IRMA present in 4–5 fields or venous beading in 1 field
Severe NPDR	Any of the following: 1 More than 20 intraretinal hemorrhages in each of four quadrants 2 Definite venous beading in two or more quadrants 3 *Prominent* IRMA in one or more quadrants *and* no signs of proliferative retinopathy.	Severe NPDR	Microaneurysms and hemorrhages severe in 4–5 fields, *or* Venous beading definite in 2 fields, *or* IRMA moderate in 1 field.
Proliferative diabetic retinopathy (PDR)	Neovascularization of optic disc (NVD) or elsewhere (NVE), preretinal hemorrhage, or vitreous hemorrhage.	Mild PDR Moderate PDR	Fibrous proliferation on the optic disc or elsewhere or visible NVEs. NVE ≥1/2 disc area, *or* visible NVD, *or* Vitreous or preretinal hemorrhage and NVE < 1/2 disc area.
		High-risk PDR	NVD ≥1/4–1/3 disc area, *or* NVD < 1/4 disc area and vitreous or preretinal hemorrhage, *or* NVE ≥1/2 disc area and vitreous or preretinal hemorrhage, *or* Vitreous or preretinal hemorrhage. obscuring ≥1 disc area
Diabetic macular edema (DME)	Any apparent retinal thickening or hard exudates in posterior pole.	Macular edema	Any retinal thickening or hard exudates in posterior pole.
Mild DME	Some retinal thickening or hard exudates in the posterior pole but distant from the center of the macula.	Clinical significant macular edema	Retinal thickening at or within 500 μm of the center of the macula, *or* Hard exudate at or within 500 μm of the center of the macula *with* associated thickening of the adjacent retina, *or* A zone or zones of retinal thickening one disc diameter or larger, any part of which is within one disc diameter of the center of the macula.
Moderate DME	Retinal thickening or hard exudates approaching the center of the macula but not involving the center.		
Severe DME	Retinal thickening or hard exudates involving the center of the macula.		

Intervention	Recommendation	Evidence
Diabetic macular edema (DME)		
Focal laser	Focal laser therapy is recommended in eyes with CSME and has long-term visual acuity benefits. Treatment should be considered to DME threatening the center of the macula.	A, I
Intravitreal anti-VEGF agents	Intravitreal anti-VEGF therapy is effective as primary treatment for most cases of DME and is superior in the short term to laser treatment for visual acuity again. It is recommended for center involving DME with loss of vision secondary to DME.	A, I
Intravitreal steroids	Intravitreal steroids are not effective as primary treatment for most cases of DME, but may have a role in diffuse DME unresponsive to focal laser.	A, II
Vitrectomy	Vitrectomy may have a role in selected cases of diffuse severe DME unresponsive to focal laser, especially in the presence of vitreomacular traction.	B, III
Medical therapies	There is currently insufficient evidence to recommend the routine use of PKC inhibitors and other treatments.	C, III
Diabetic retinopathy (DR)		
Panretinal photocoagulation (PRP)	PRP is recommended in cases with proliferative DR. Treatment should be promptly institutes if high-risk features are present.	A, I
	PRP is recommended in severe nonproliferative DR if any difficulty or delay in follow-up is anticipated or there are associated risk factors or signs of progression, especially in patients with type 2 diabetes.	A, II
Vitrectomy	Early vitrectomy is recommended within 3 months in patients with type 1 diabetes with severe vitreous hemorrhage and significant DR. Type 2 diabetics benefit from vitrectomy for persistent vitreous hemorrhage, although the benefit of early vitrectomy is less. Vitrectomy should be considered in eyes with severe PDR not responsive to extensive PRP, associated with traction involving the macula, or both.	B, II

ROLE OF DIET IN DIABETES MELLITUS

What is carbohydrate counting?

- CHO counting is based on the concept that each serving of CHO equals approximately 15 gms of CHO.
- The average person needs about 3 to 4 choices (45-60 gms) of CHO at each meal. This number could vary more or less depending on calorie needs (i.e., pregnant/nursing, ill, etc.), medication, and activity.

Advantages	Disadvantages
• improved glucose control • flexibility in food choices • simplification of meal planning.	• weight gain • unhealthy eating • Hypoglycemia • high lipid levels.

There are no evidence-based studies showing superiority over other dietary management methods, and CHO counting requires motivation on the patient's part.

What is glycemic index?
A scale that ranks carbohydrate rich foods by how much they raise blood glucose levels

The basic technique for following low GI guidelines is simply a "**this for that" approach – i.e.: replacing high GI foods with low GI foods.** One need not count numbers or do any sort of mental arithmetic to make sure they are eating a healthy, low GI diet.

General tips for a low GI diet

- Increasing the consumption of whole grains, nuts, legumes, fruit, and non-starchy vegetables
- Decreasing the consumption of starchy high-glycemic index foods like potatoes, white rice, and white bread
- Decreasing the consumption of sugary foods like cookies, cakes, candy, and soft-drinks

What is glycemic load?
• It is defined as the GI multiplied by the amount of carbohydrate per serving of food in grams and dividing the total by 100 • It was introduced as a measure of the overall effect of a food on blood glucose and insulin levels. • The GL is a more accurate indicator of the relative response to carbohydrate.

$$\text{Glycemic load (GL)} = \frac{\text{Carbohydrate content (g)} \times \text{Glycemic index}}{100}$$

Hypoglycemia management ; 15-15 rule
1. 3 or 4 glucose tablets 2. 1/2 cup (4 ounces) of any fruit juice 3. 1/2 cup (4 ounces) of a regular (not diet) soft drink 4. 8-10 pieces of hard candy (such as Lifesavers) 5. 2 Tbsp raisins 6. 1 cup nonfat milk **15/15 rule:** take 15 gms of simple carbohydrate which should increase blood glucose by 30-45 mg/dL within 15 minutes After 15 minutes, blood glucose should be checked again to make sure that it is increasing. If it is still too low, another serving is advised. Repeat these steps until blood glucose is at least 70 mg/dL. Then, a snack should be consumed if it will be an hour or more before the next meal

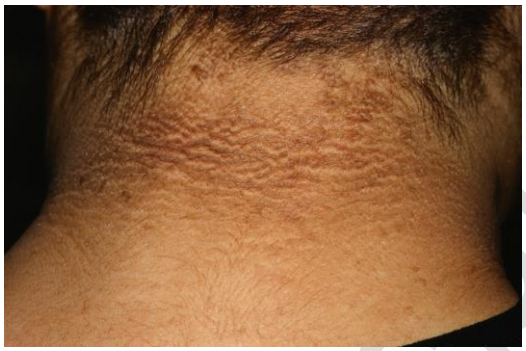
Dermatologic manifestations of Diabetes mellitus

Between **thirty and seventy percent of patients with diabetes mellitus**, both type 1 and type 2, will present with a cutaneous complication of diabetes mellitus at some point during their lifetime

Acanthosis nigricans
● Higher prevalence in T2DM ● Common in darker-skinned individuals ● Associated endocrinopathies -- resistance to insulin such as acromegaly, Cushing syndrome, obesity, polycystic ovarian syndrome, and thyroid dysfunction. ● Unrelated to insulin resistance, AN can also be associated with malignancies such as **gastric adenocarcinomas** and other carcinomas

- multiple poorly demarcated plaques with grey to dark-brown hyperpigmentation and a thickened velvety to verrucous texture. Classically, AN has a symmetrical distribution and is located in intertriginous or flexural surfaces such as the back of the neck, axilla, elbows, palmer hands (also known as “tripe palms”), inframammary creases, umbilicus, or groin
- hyperinsulin state activates insulin growth factor receptors (IGF), specifically IGF-1, on keratinocytes and fibroblasts, provoking cell proliferation, resulting in the aforementioned cutaneous manifestations of AN

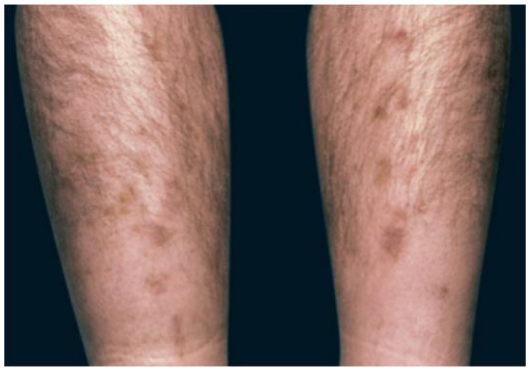
- AN is best managed with lifestyle changes such as dietary modifications, increased physical activity, and weight reduction. In patients with diabetes, pharmacologic adjuvants, such as metformin, that improve glycemic control and reduce insulin resistance are also beneficial



Diabetic Dermopathy

- DD initially presents with rounded, dull, red papules that progressively evolve over one-to-two weeks into well-circumscribed, atrophic, brown macules with a fine scale. Normally after about eighteen to twenty-four months, lesions dissipate and leave behind an area of concavity and hyperpigmentation. At any time, different lesions can present at different stages of evolution.

- Treatment is typically avoided given the asymptomatic and self-resolving nature of DD as well as the ineffectiveness of available treatments



Diabetic Foot Syndrome

- **Diabetic Foot Syndrome (DFS)** encompasses the neuropathic and vasculopathic complications that develop in the feet of patients with diabetes.
- DFS is slightly more prevalent in type 1 diabetes compared with type 2 diabetes
- DFS presents initially with callosities and dry skin related to diabetic neuropathy. In later stages, chronic ulcers and a variety of other malformations of the feet develop.
- Diabetic neuro-osteoarthropathy (also known as Charcot foot), is an irreversible debilitating and deforming condition involving progressive destruction of weight-bearing bones and joints

Diabetic Thick Skin

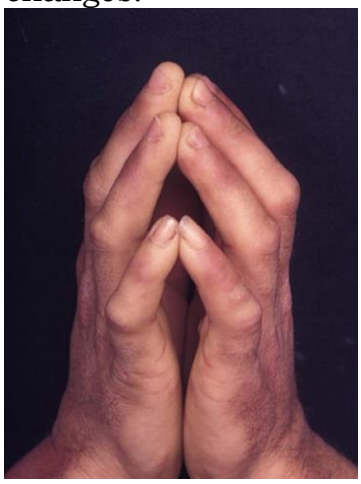
- Skin thickening is frequently observed in patients with diabetes. Affected areas of skin can appear thickened, waxy, or edematous. These patients are often asymptomatic
- **Diabetic thick skin** may represent another manifestation of **scleroderma-like skin changes** or **limited joint mobility**

Scleroderma-like skin changes

- painless, indurated, occasionally waxy appearing, thickened skin. These changes occur symmetrically and bilaterally in acral areas.
- diabetic hand syndrome which may present with limited joint mobility, palmar fibromatosis (Dupuytren's contracture), and stenosing tenosynovitis (“trigger finger”)

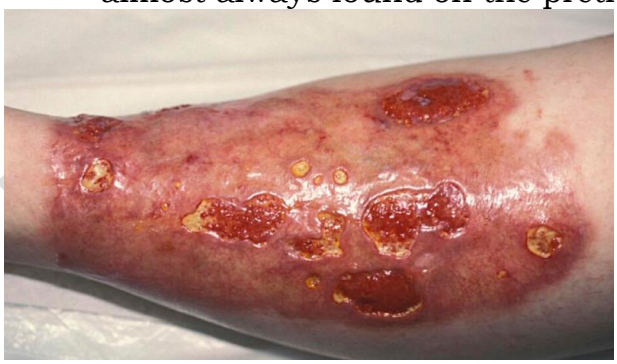
Limited Joint Mobility (LJM), also known as diabetic cheiroarthropathy, is a relatively common complication of long-standing diabetes mellitus.

The majority of patients with LJM also present with scleroderma-like skin changes.



Necrobiosis lipoidica diabeticorum

- Necrobiosis lipoidica (NL) is a rare chronic granulomatous dermatologic disease that is seen most frequently in patients with diabetes.
- NL generally occurs in type 1 diabetes during the third decade of life, as opposed to type 2 diabetes in which it commonly presents in the fourth or fifth decades of life
- NL begins as a single or group of firm **well-demarcated rounded erythematous papules.** The papules then expand and aggregate into plaques characterized by **circumferential red-brown borders and a firm yellow-brown waxen atrophic center containing telangiectasias.**
- NL occurs bilaterally and exhibits Koebnerization. Lesions are almost always found on the pretibial areas of the lower extremities



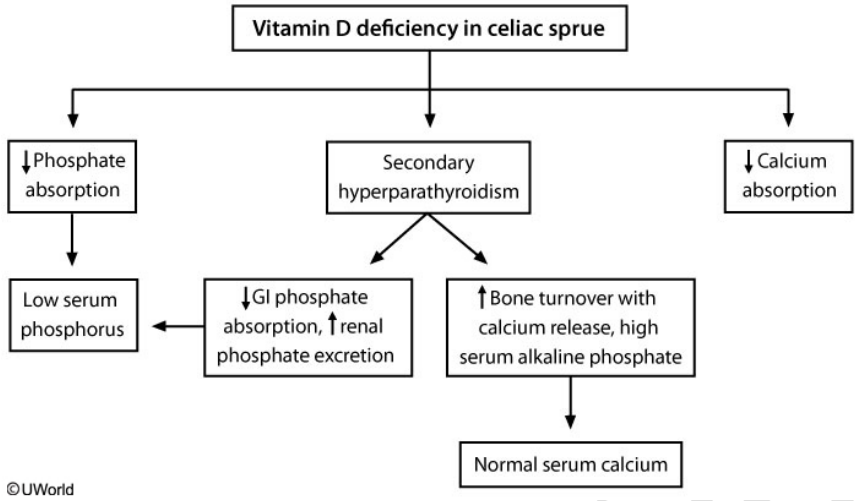
Bullosis diabeticorum

- Bullosis diabeticorum (BD) is an uncommon eruptive blistering condition that presents in those with diabetes mellitus
- BD presents at sites of previously healthy-appearing skin with the

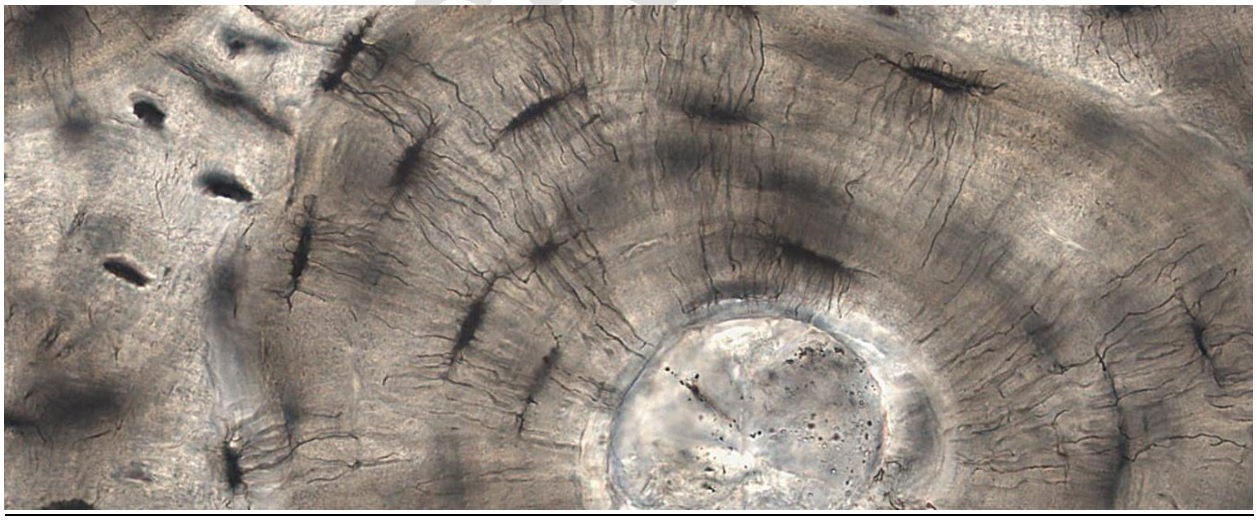
abrupt onset of one or more non-erythematous, firm, sterile bullae. Shortly after forming, bullae increase in size and become more flaccid, ranging in size from about 0.5 cm to 5 cm.

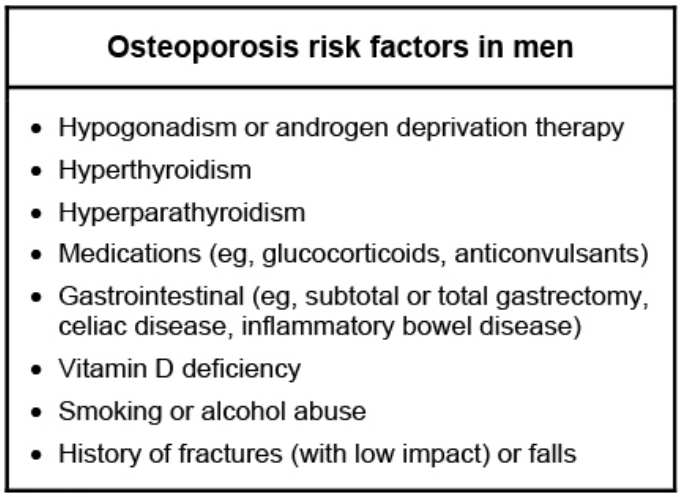
OSTEOPOROSIS

Celiac disease and vitamin D deficiency

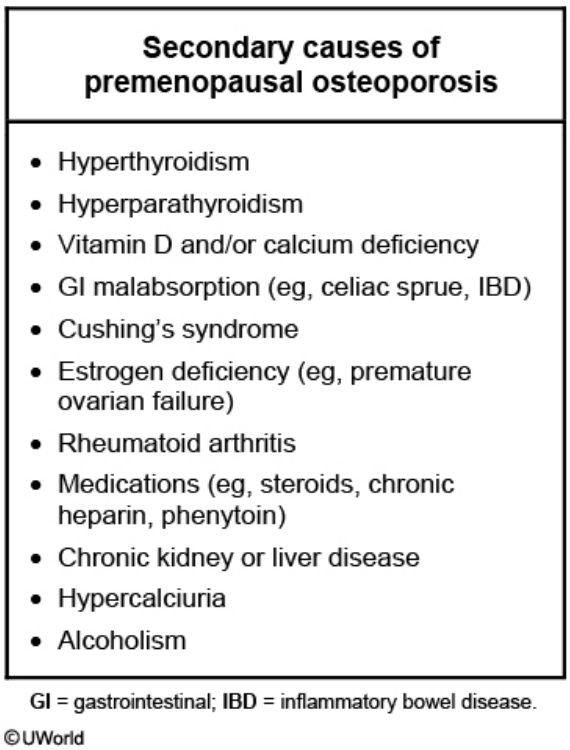


Osteoporosis





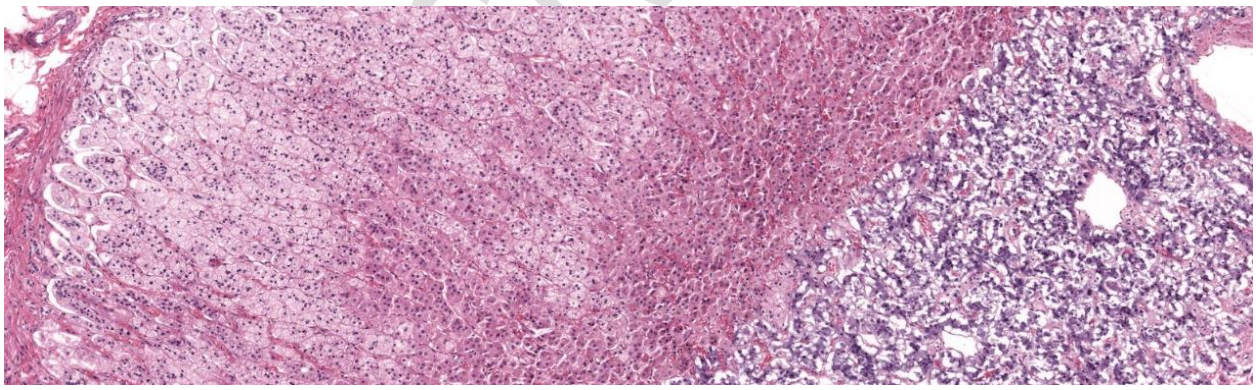
- Routine screening in men is controversial
- Screening and potential treatment should be pursued in men with risk factors (androgen deprivation therapy, chronic corticosteroid use, low trauma fractures)
- Osteoporosis fractures occur within 5 years of starting androgen deprivation therapy



Treatment options for osteoporosis	Indications/cautions
1200 mg of elemental calcium **plus** 800 IU of vitamin D daily	• Indicated for most postmenopausal women
Oral or IV bisphosphonates (eg, alendronate, risedronate, or zoledronic acid)	• Not recommended for patients with creatinine clearance < 35 mL/min
Denosumab	• Risk of infection and skin reactions • Hypocalcemia in patients with chronic kidney disease
Recombinant human parathyroid hormone (eg, teriparatide)	• For patients who cannot tolerate or fail (eg, fracture, reduced BMD) bisphosphonates • Should not be used in renal insufficiency • Monitor serum calcium, uric acid, & renal function
Nasal calcitonin	• Modestly reduces risk of fracture • Not first-line therapy
Selective estrogen receptor modulators (eg, raloxifene)	• Option for postmenopausal women intolerant to bisphosphonates & at increased risk of breast cancer • Increased risk of thromboembolic events & hot flashes

12

ADRENAL DISORDERS



Adrenal Incidentaloma

Adrenal "incidentaloma" is an adrenal mass >1 cm, detected incidentally on imaging during evaluation for a reason unrelated to adrenal disorder. It excludes those detected while staging for cancer.

- An adrenal incidentaloma is defined as a mass >1cm diameter discovered incidentally on radiology studies.
- Determine if the mass is functional or malignant

[12] Every medical student should remember that his end is not to be made a chemist or physiologist or anatomist, but to learn how to recognize and treat disease, how to become a practical physician.

- Malignancy vs benign is based on **size**, **attenuation** by measuring Hounsefield units HU, and t**ime of contrast washout.** HU are an estimate of the density of a lesion compared to fat (-20 to -150) and the kidney (20 to 150HU)
- All patients should have a hormonal assay
- Functional adrenal masses should be evaluated for surgical resection
- Non functioning adrenal masses which appear benign should be followed q6monthly

YOU CANNOT MEASURE Hounsefield Units WITH CONTRAST STUDIES!!

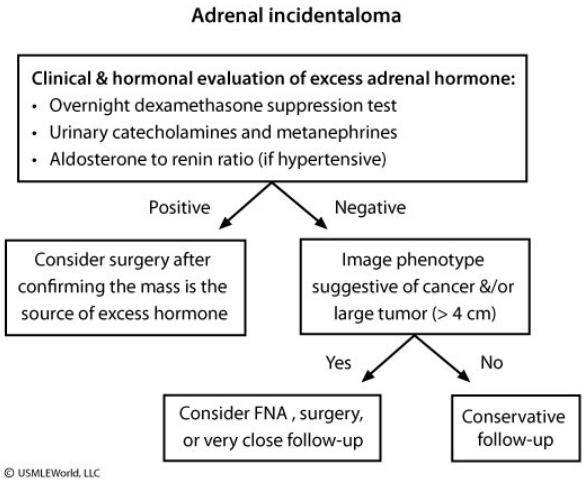
Benign CT scan features
- Low attenuation (<10HU) and <4cm
- Smooth border with sharp margins
- Homogenous
- Unilateral
- Rapid contrast washout, >50% after 10minutes of contrast
  very low CT attenuation value (–10 to –20HU) is characteristic of adrenal myelolipoma.

Malignant CT scan features
- High attenuation >20HU and >4cm diameter
- Increased mass vascularity
- Delayed contrast medium washout, <50% after 10 minutes of contrast
- May be unilateral or bilateral.
- necrosis,hemorrhage or calcification

Hormonal studies to be sent as part of workup
- Pheochromocytoma (**plasma** and 24hr urine metanephrines)
- Cushings syndrome, 24hr urine free cortisol (symptomatic), 1mg overnight dex supp test (asymptomatic)
- Primary aldosteronism, Plasma Aldosterone/renin ratio >20
- Adrenocortical carcinoma, serum DHEA is elevated
- Autonomous functioning adrenal mass or adrenal insufficiency, serum DHEA is low

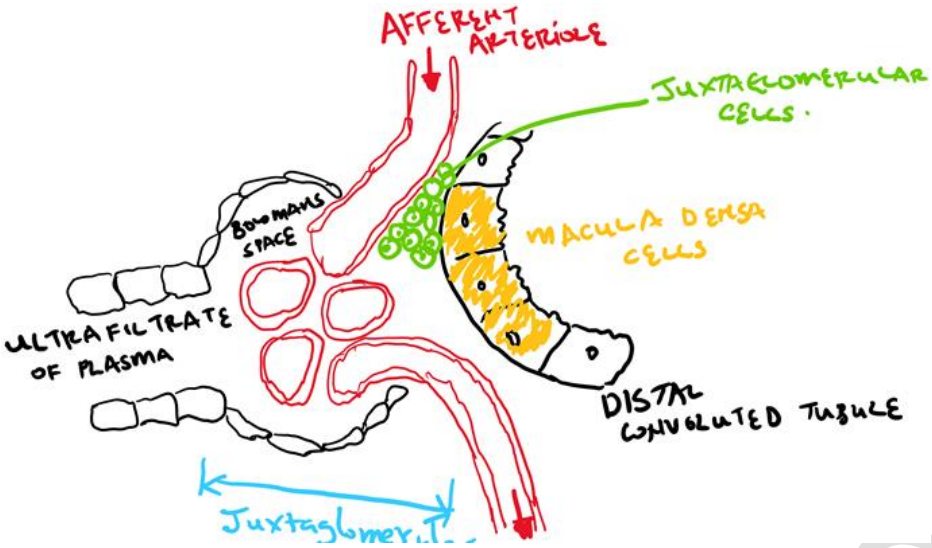
**** hyperandrogenemia and hypertension is adrenocortical carcinoma until proven otherwise.**

Characteristic	Adenoma	Carcinoma	Pheochromocytoma	Metastasis
Size	<4 cm	>4 cm	Variable	>4 cm
Shape	Round	Irregular	Round	Irregular
Border	Smooth	Irregular	Well delineated	Irregular
Laterality	Unilateral	Unilateral	May be bilateral or unilateral	May be bilateral
Appearance	Round, homogeneous	Inhomogeneous with central necrosis. May have calcifications	Cystic and hemorrhagic changes.	Inhomogeneous
Vascularity	Normal	Increased	Increased	Increased
Growth rate	Slow (1 cm/year)	Fast (>2 cm/year)	Slow (0.5-1 cm/year)	Variable/Fast
Lipid content	Lipid rich or poor	Lipid poor	Lipid poor	Lipid poor
CT attenuation	<10 HU unenhanced. >50% absolute washout.	>20 HU unenhanced. <50% absolute washout.	>20 HU unenhanced. <50% absolute washout.	>20 HU unenhanced. <50% absolute washout.
MRI	Isointense with liver in T1 and T2-w. Chemical shift	Hypointense compared to liver on T1-w High to intermediate signal on T2-w	High signal intensity on T2-w	Hypointense compared to liver on T1-w High to intermediate signal on T2-w
FDG-PET-CT	Low SUV	High SUV	Variable SUV	High SUV
Other		Evidence of invasion or metastasis		History of prior cancer



Workup for hyperaldosteronism

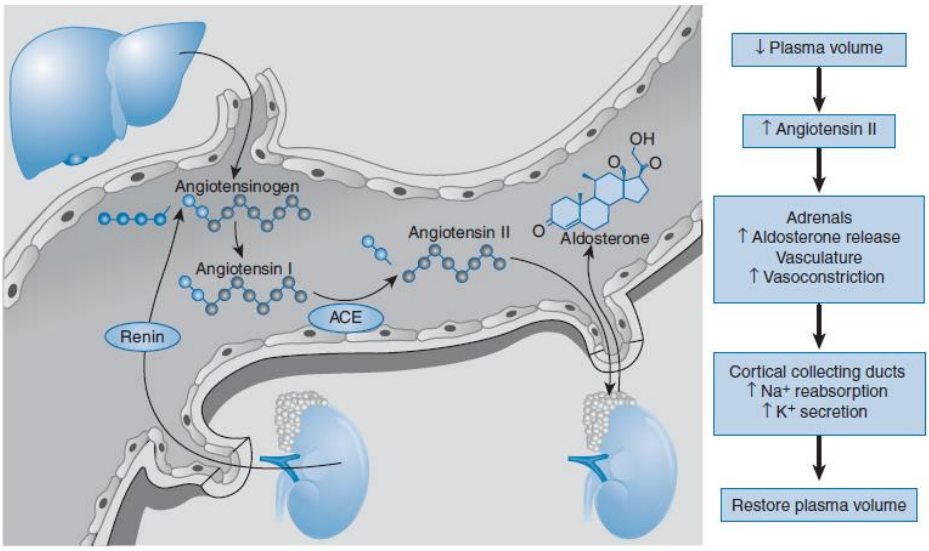
Renin angiotensin aldosterone axis (physiology)



Mechanisms of release of Renin from the juxtaglomerular cells

1) Baroreceptor mechanism : decreased pressure in the afferent arteriole promotes renin release.
2) Sympathetic nerve mechanism : B1 adrenergic nerve stimulates renin release
3) Macula densa mechanism : chemoreceptors in the DCT, which detects the level of NaCl. they directly stimulate the juxtaglomeular cells to produce renin when NaCl levels are low.

Renin (an enzyme) is released directly into the blood stream.
Renin converts angiotensinogen (produced by the liver) into angiotensin 1.
Angiotensin Converting enzyme in the lung subsequently changes Angiotensin 1 to Angiotensin 2.



Physiologic role of angiotensin II
• AngII acts as a **direct arterial vasopressor** and can induce

vasoconstriction to address the systemic hypotension;
- AngII **stimulates vasopressin (antidiuretic hormone)** release to induce distal nephron water reabsorption and expand intravascular volume;
- AngII acts at the proximal tubule of the nephron to **maximize proximal sodium (and therefore water) reabsorption** to expand intravascular volume;
- AngII maximizes renal sodium reabsorption by **stimulating adrenal aldosterone synthesis**; aldosterone then acts at the principal cell to increase sodium reabsorption as described earlier

Clinical features of primary hyperaldosteronism	
Clinical presentation	• Hypertension, metabolic alkalosis, hypokalemia, mild hypernatremia • No significant peripheral edema due to aldosterone escape
Diagnosis	• Elevated plasma aldosterone, low plasma renin • Plasma aldosterone to plasma renin activity ratio >20 suggests diagnosis • Adrenal suppression testing after oral saline load confirms diagnosis • Abdominal imaging (eg, CT) & adrenal venous sampling to distinguish between unilateral adrenal adenoma & bilateral adrenal hyperplasia
Treatment	**Unilateral adrenal adenoma** • Surgery (preferred) • Aldosterone antagonists (eg, spironolactone, eplerenone) for poor surgical candidates or patients refusing surgery **Bilateral adrenal hyperplasia**: Aldosterone antagonists

A "treatise" on Aldosterone Escape:

1. Escape from the sodium-retaining effects of excess aldosterone (or other mineralocorticoids) in primary hyperaldosteronism, manifested by volume and/or pressure natriuresis.
2. The inability of ACE inhibitor therapy to reliably suppress aldosterone release, for example, in patients with heart failure or diabetes, usually manifested by increased salt and water retention. This latter sense may rather be termed refractory hyperaldosteronism.

In patients with hyperaldosteronism, chronic exposure to excess aldosterone does not cause edema as might be expected.

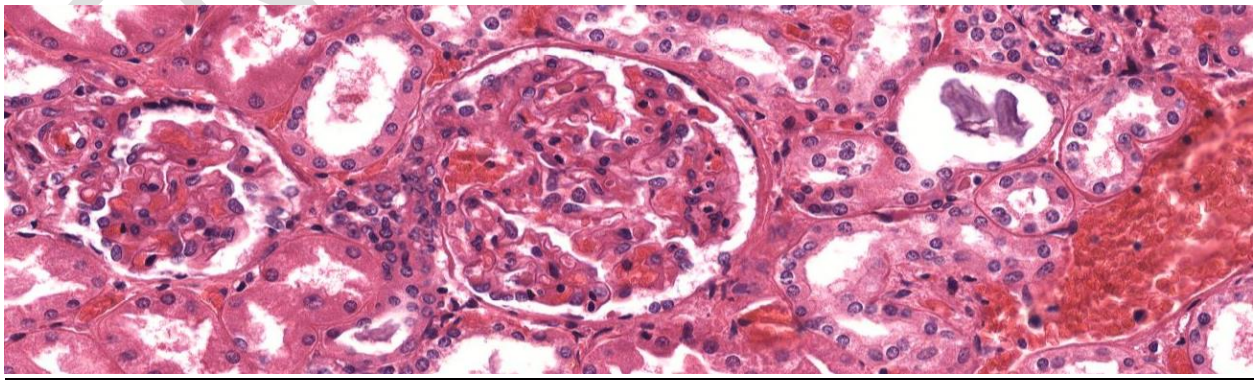
- **Aldosterone** initially results in an increase in **Na^+ reabsorption** in these patients through stimulation of **ENaC channels in principal cells of the renal collecting tubules**. Increased ENaC channels situated in the **apical membranes of the principal cells** allow for more Na^+reabsorption, which may cause a transient increase in fluid reabsorption as well.

- However, within a few days, Na^+ reabsorption returns to normal as evidenced by normal urinary Na^+ levels in these patients.
- The proposed mechanism for this phenomenon does not include a reduced sensitivity of mineralocorticoid receptors to aldosterone, because low serum potassium is often seen in these patients, which is the direct result of aldosterone-induced expression of ENaC channels.
- Furthermore, electrolyte homeostasis is maintained in these patients, which excludes the possibility that other Na^+transporters elsewhere in the kidney are being shut down. If, in fact, other transporters such as the **Na^+-H^+ antiporter in the proximal tubule** or the **$Na^+/K^+/2Cl^-$ symporter in the thick ascending loop of Henle** were being blocked, other electrolyte disturbances would be expected, such as seen during use of diuretics.

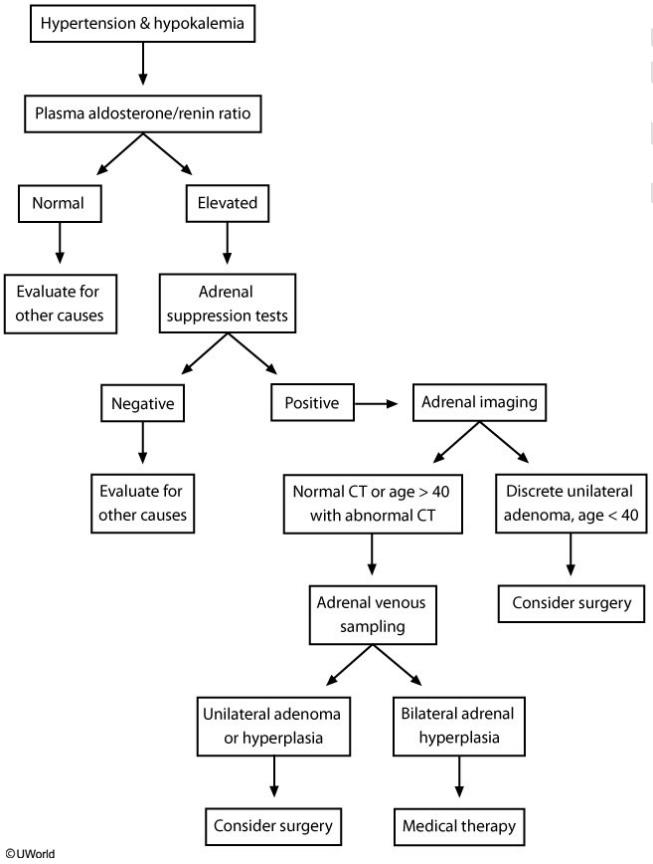
Instead, experiments isolating the perfusion pressures seen by glomerular capillaries from heightened systemic pressures due to hyperaldosteronism have shown that **Na^+ excretion remains minimal until the kidney is exposed to heightened perfusion pressures**. These experiments brought about the **proposition that initially high perfusion pressures due to increased Na^+ and water reabsorption in a hyperaldosterone state actually causes "backflow" of Na^+ and water into the tubules**.

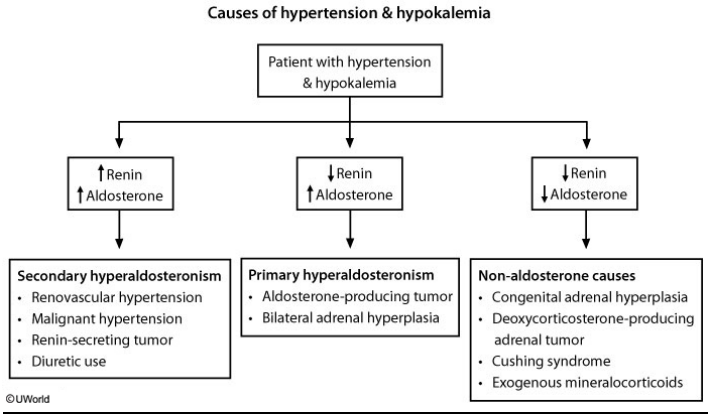
Normally Na^+ and water are reabsorbed from the tubules and **dumped into the interstitium.** From there, **Starling forces** dictate the gradient for movement of water and Na^+ into the peritubular capillaries. Because **hydrostatic pressures in the tubules, interstitium and peritubular capillaries** are **normally equivalent**, oncotic pressures govern flow.

Typically, oncotic pressures are higher in the peritubular capillaries, because protein composition in the interstitium is nominal; therefore, Na^+ and water leave the interstitial space and enter the capillaries. When hydrostatic pressures are raised in the peritubular capillaries such as seen in hyperaldosteronism, Starling forces begin to favor "backflow" of Na^+ and water from the interstitium into the tubules—thus, increasing Na^+ excretion. **This is the proposed mechanism of "mineralocorticoid escape" for how patients with increased levels of aldosterone are able to maintain Na^+ balance and avoid an edematous state**.



Adrenal Disorders	10% of Exam
Glucocorticoids	4%
Cushing's syndrome	
Management of glucocorticoid therapy	
Adrenal insufficiency	
Glucocorticoid resistance	
Mineralocorticoids	2%
Hyperaldosteronism	
Hypoaldosteronism	
Adrenal androgens	<2%
Congenital adrenal hyperplasia	
Adrenal incidentaloma	<2%
Adrenal medulla	<2%
Pheochromocytoma	
Neurofibromatosis type 1	
von Hippel-Lindau syndrome	
Multiple endocrine neoplasia (MEN) types 2A and 2B	
Familial paraganglioma syndromes	
Familial paraganglioma-pheochomocytoma syndromes	
Adrenal cancer	<2%





Condition	Cause	Renin	Aldosterone	Cortisol	ACTH
Adrenal insufficiency	High renin due to volume depletion and hypotension	↑	↓	↓	↑
Hyporeninemic hypoaldosteronism (type 2 renal tubular acidosis)	Mediated by effects of renal disease Impaired conversion of prorenin to renin and volume expansion-induced atrial NP -> suppresses renin and aldo. secretion	↓	↓	↔	↔
Pituitary insufficiency		↔	↔	↓	↓
Congenital 1ary hypoaldo	Uncommon condition due to defect in CYP11B2 gene (encodes 11/18beta-hydroxylase Dx in childhood	↑	↓	↔	↔
Pseudohypoaldosteronism type 1	Aldosterone resistance Rare; Dx in childhood	↑	↑	↔	↔

Hyperaldosteronism is defined as increased secretion of aldosterone which may result in hypertension and/or hypokalemia. Hyperaldosteronism may be primary or Secondary.

Primary hyperaldosteronism is due to autonomous production of aldosterone

Secondary hyperaldosteronism is due to activation of renin–angiotensin–aldosterone system because of intravascular volume depletion

Pathogenesis	Disorders
Primary aldosteronism	Aldosterone-producing adrenal adenoma (35%) Bilateral idiopathic adrenal hyperplasia (60%) Unilateral idiopathic adrenal hyperplasia (2%) Familial hyperaldosteronism (2%)
Secondary aldosteronism	Renovascular hypertension Renin secreting tumors
Deoxycorticosterone-related	Congenital adrenal hyperplasia (11β-hydroxylase and 17α-hydroxylase deficiency) Deoxycorticosterone producing tumors Glucocorticoid resistance syndrome
11β-hydroxysteroid dehydrogenase type 2 (loss of function)	Congenital apparent mineralocorticoid excess syndrome Licorice administration
Specificity spillover due to cortisol excess	Cushing's syndrome
Gain-of-function mutation of ENaC in collecting tubule	Liddle's syndrome

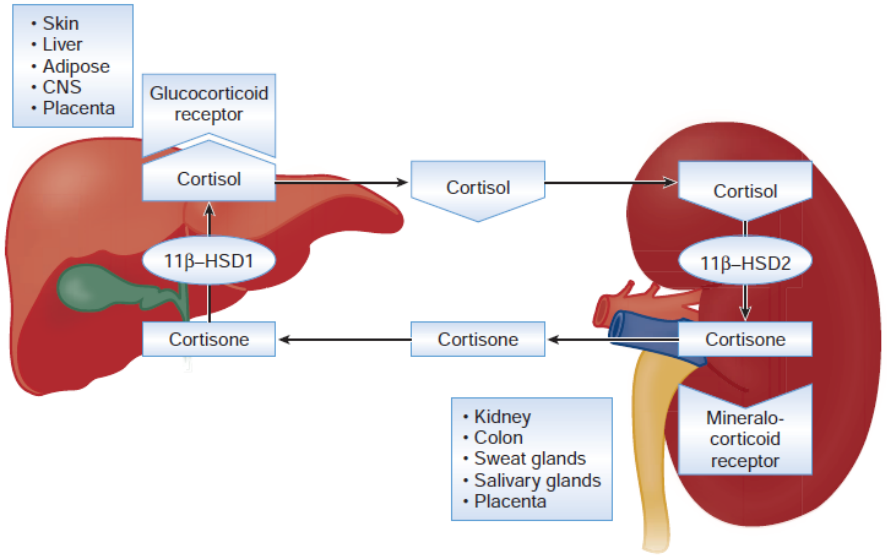
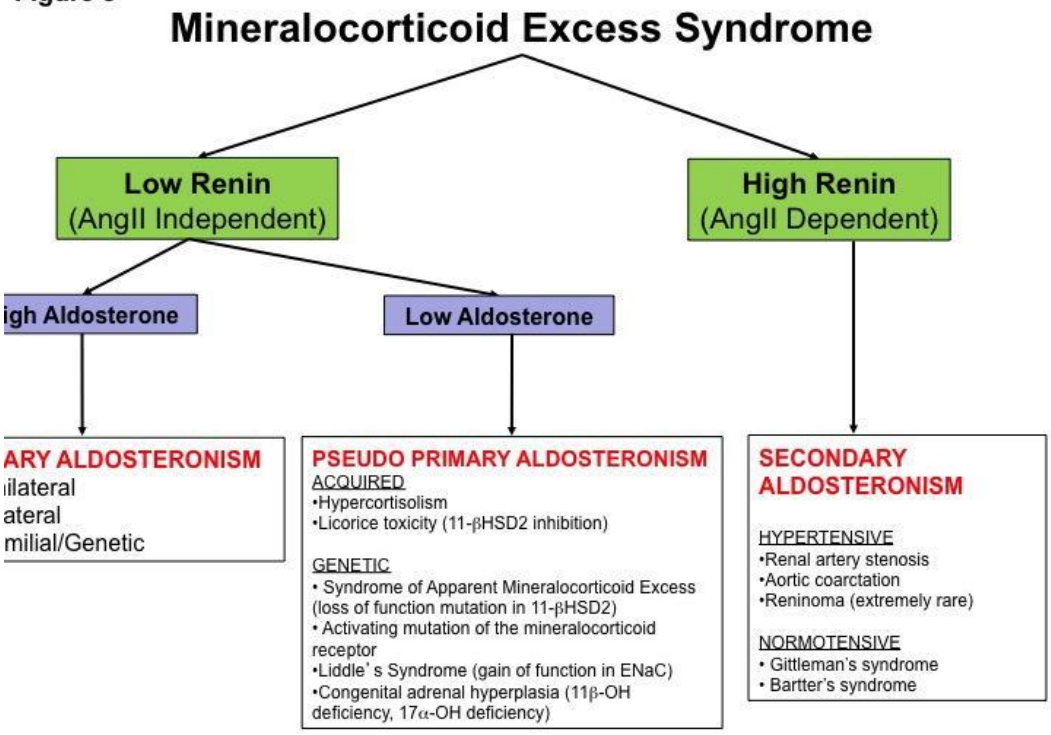


FIGURE 9–8 Cortisol-cortisone shunt. Contrasting functions of the isozymes of 11β-HSD. 11β-HSD2 is an exclusive 11β-dehydrogenase that acts in classical aldosterone target tissues to exclude cortisol from otherwise nonselective mineralocorticoid receptors. Inactivation of cortisol also occurs in placenta. 11β-HSD1 is a predominant 11β-reductase in vivo that acts in many tissues to increase local intracellular glucocorticoid concentrations and thereby maintain adequate exposure of relatively low affinity glucocorticoid receptors to their ligand.

Figure 3



Screening for hyperaldosteronism

- hypertension at a young age (<20 years)
- severe hypertension (BP >160/100 mmHg)
- drug-resistant hypertension (three antihypertensives in optimal doses including a diuretic)
- hypertension with spontaneous or diuretic induced hypokalemia, and hypertension with adrenal incidentaloma.
- patient with a family history of young hypertension or cerebrovascular accident (<40 years) or hypertensive first-degree relative of a patient with primary aldosteronism needs screening. **Universal screening is not recommended as the available data do not support its benefit.**

Clinical Manifestations of primary aldosteronism

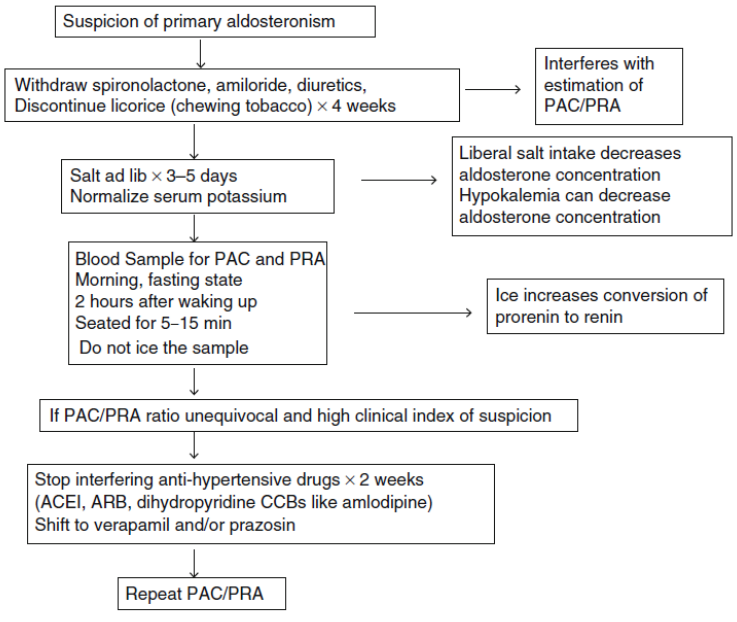
Aldosterone related	• **severe diastolic hypertension** with target organ • **Target organ damage** (left ventricular hypertrophy, hypertensive retinopathy, and proteinuria) disproportionate to the duration and degree of hypertension
Hypokalemia related	• fatigue, muscle weakness, polyuria, polydypsia, • periodic paralysis, and ventricular arrhythmias.

13

Dysglycemia in patients with primary aldosteronism occurs due to **impaired insulin secretion (hypokalemia)** and **reduced insulin sensitivity (aldosterone excess)**.

Clinical feature	Pathogenesis
Fatigue, muscle weakness, periodic paralysis	Decreased activity of Na^+/K^+-ATPase leading to impaired contractility of actin–myosin complex
Polyuria and polydypsia	Due to impaired concentrating ability of distal convoluted tubule
Metabolic alkalosis	Hypokalemia-induced
Impaired glucose tolerance	Impaired β-cell function

Parameters	Aldosterone-producing adenoma	Idiopathic bilateral adrenal hyperplasia
Prevalence	35%	60%
Age of onset	Young	Middle-aged
Hypertension	Severe	Mild–moderate
Hypokalemia	50%	17%
Plasma aldosterone concentration	Very high	High
Plasma aldosterone concentration/plasma renin activity ratio (PAC/PRA)	Very high	High
Saline suppression	Non-suppressible	Usually intermediate
Adrenal imaging	Adenoma	Usually normal
Adrenal venous sampling	Unilateral gradient	No gradient
Effective treatment	Surgery	Medical management

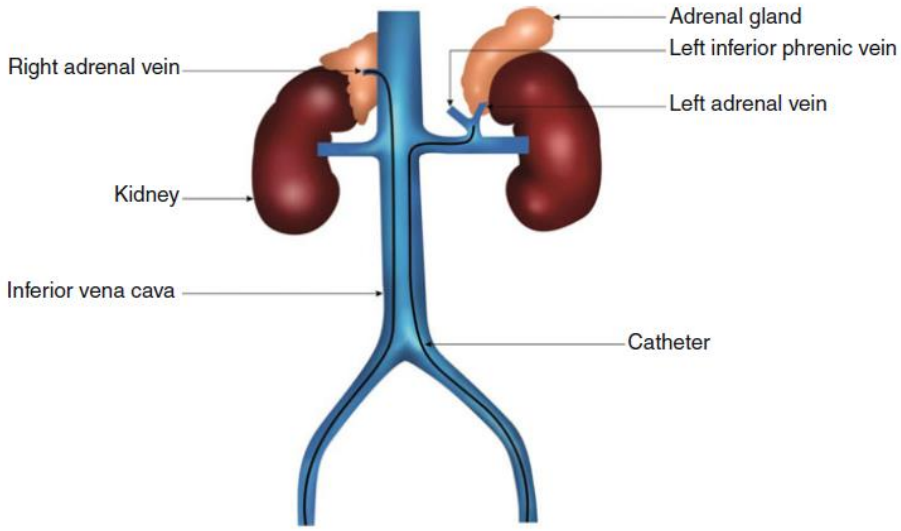


[13] Every patient you see is a lesson in much more than the malady from which he suffers

PAC (ng/dl)	PRA (ng/ml/h)	PAC/PRA ratio	Interpretation
↑	↑	<10	Renovascular hypertension Reninoma
↓	↓	–	Cushing's syndrome DOC-mediated hypertension Liddle's syndrome Apparent mineralocorticoid syndrome
↑ (>15)	↓(<1)	>20 favors >30 diagnostic	Primary aldosteronism

Tests	Procedure	Cutoffs	Remarks
Oral salt loading test	6 g/day for 3 days Ensure eukalemia Measurement of 24-h urinary aldosterone on day 4	Urinary aldosterone > 12 µg/24 h	Cumbersome Poses a risk in patients with CHF/renal insufficiency Poor sensitivity of urinary aldosterone assay
Saline infusion test	Recumbent position 1 h prior to test 2 liters of 0.9% saline i.v. over 4 h Sampling at 4 h	PAC > 10 ng/dl diagnostic PAC 5–10 ng/dl probable PAC < 5 ng/dl excludes	Poses a risk in patients with CHF/renal insufficiency
Fludrocortisone suppression test	100 µg 6 hourly for 4 days Measure PAC and PRA on day 4 at 10 am	PAC > 6 ng/dl and PRA < 1 ng/ml/h	Cumbersome Most sensitive

Adrenal Vein Sampling



Step 1. Before adrenal vein catheterization, cosyntropin should be administered for 30 min at the rate of 50 µg/h to minimize the stress-induced fluctuations in aldosterone secretion and to maximize the aldosterone secretion from APA.

14

[14] It always better to do a thing wrong the first time

Step 2. After 30 min of initiation of ACTH infusion, procedure for catheterization of adrenal vein is started. Preferably, both the adrenal veins should be cannulated simultaneously to avoid variation in the results. The catheter tip is placed in right adrenal vein on the right side and distal to the confluence
of left inferior phrenic vein and left adrenal vein on left side.

Step 3. Simultaneous sampling of cortisol from the respective adrenal vein and external iliac vein is performed to ensure the correct positioning of the catheter tip. An adrenal vein to peripheral vein cortisol ratio >10:1 is suggestive of successful catheterization.

Step 4. Aldosterone : cortisol corrected ratio is preferred over plasma aldosterone levels, to minimize the dilutional effect during sampling, as catheter tip is placed distal to the confl uence of the left inferior phrenic vein and left adrenal vein on the left side.

Step 5. Aldosterone : cortisol corrected ratio (A : C ratio) is calculated by dividing the plasma aldosterone value by the respective adrenal vein plasma cortisol value.

A : C ratio (high side/ low side)	Interpretation	Etiology
>4:1	Unilateral aldosterone hypersecretion	Aldosterone-producing adenoma Unilateral primary adrenal hyperplasia
<3:1	Bilateral aldosterone hypersecretion	Bilateral idiopathic adrenal hyperplasia Bilateral adrenal adenoma

*** AVS for detecting unilateral aldosterone hypersecretion (APA or UAH) has a sensitivity
of 95% and specificity of 100%*
APA -- Aldosterone producing adenoma
UAH -- unilateral adrenal hyperplasia.

PRACTICE PEARL

Patients with lateralization ratios between 3:1 and 4:1 may have either unilateral or bilateral disease, and the AVS results must be cautiously interpreted in conjunction with the clinical setting,
CT scan, ancillary tests, and if possible, repeat AVS!

cortisol-corrected aldosterone ratios

Dividing the right and left adrenal vein PACs by their **respective cortisol**

concentrations corrects for dilutional effects of the inferior phrenic vein flowing into the left adrenal vein and, if suboptimally sampled, of inferior vena cava flow into the right adrenal vein

Parameters	Pseudohypoaldosteronism I	Pseudohypoaldosteronism II (Gordon's syndrome)
Inheritance	Autosomal recessive (AR) Autosomal dominant (AD)	Autosomal dominant (AD)
Age of presentation	Infancy	Adolescence or early adulthood
Clinical and biochemical features	Normo- or hypotension Renal salt wasting Hyponatremia Hyperkalemia Metabolic acidosis Elevated PAC and PRA Elevated Na^+ and Cl^- in sweat and saliva	Hypertension Normal or elevated sodium Hyperkalemia Metabolic acidosis Suppressed/normal PAC and PRA
Genetics	AR-ENaC channel (loss-of-function) AD-mineralocorticoid receptor (loss of function)	WNK-1 and WNK-4 mutations (gain-of-function)
Treatment	Salt supplementation Mineralocorticoid therapy	Salt restriction Thiazides

Bartter's Syndrome

Pathophysiology	Defective epithelial transport of sodium and chloride in the thick ascending limb of loop of Henle (TALH) due to mutations in any one of the following transporter/channel/pump
Features	• Salt wasting • Hypokalemia, metabolic alkalosis, hypomagnesemia, hypercalciuria, • Elevated prostaglandin E • Normal to low blood pressure • Elevated PAC and PRA. • Polyuria, polydypsia, muscle weakness • Growth retardation, and nephrocalcinosis
Treatment	• liberal salt intake • supplementation of

	potassium and magnesium. • NSAIDS • Spironolactone or amiloride

Gitelman's syndrome

Pathophysiology	The disorder is due to inactivating mutations in thiazide-sensitive sodium chloride co-transporter in the distal convoluted tubule (DCT)
Clinical Features	• Salt wasting • hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria • elevated PAC and PRA levels. • polyuria, weakness and fatigue and are attributed to hypokalemia • Arthritis occurs due to chondrocalcinosis secondary to hypomagnesemia • Carpopedal spasms and muscle cramps can occur because of metabolic alkalosis and hypomagnesemia (even in the absence of hypocalcemia)
Treatment	• salt intake with potassium and magnesium supplementation. • Spironolactone and amiloride

Parameters	Bartter's syndrome	Gitelman's syndrome
Inheritance	Autosomal recessive/dominant	Autosomal recessive
Site of defect in kidney	TALH	DCT
Age of presentation	Intrauterine to early childhood	Adolescence to young adulthood
Specific manifestations	Polyhydramnios, premature birth, failure to thrive, growth retardation	Carpopedal spasm, arthritis
Urinary calcium excretion	Increased	Low
Nephrocalcinosis	Present	Absent
Hypomagnesemia	Mild to moderate	Severe
Prostaglandin E	Increased	Normal
Treatment with NSAIDs	Effective	Not effective

Disorders	Rationale for use of spironolactone
Cushing's syndrome	Recalcitrant hypokalemia, hypertension
Glucocorticoid resistance syndrome	Hypertension, hypokalemia, and hirsutism (complementary to dexamethasone)
Apparent mineralocorticoid excess syndrome	Hypertension, hypokalemia, and metabolic alkalosis
DOC-producing tumor	Hypertension, hypokalemia, and metabolic alkalosis
Bartter's syndrome	Hypokalemia and metabolic alkalosis
Gitelman's syndrome	Hypokalemia and metabolic alkalosis
CHF	Myocardial remodeling, edema
Cirrhosis, nephrotic syndrome	Edema
Reninoma, renovascular hypertension	Hypertension, hypokalemia
Polycystic ovarian disease, idiopathic hirsutism	Hirsutism, acne

The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline - 2016 updates

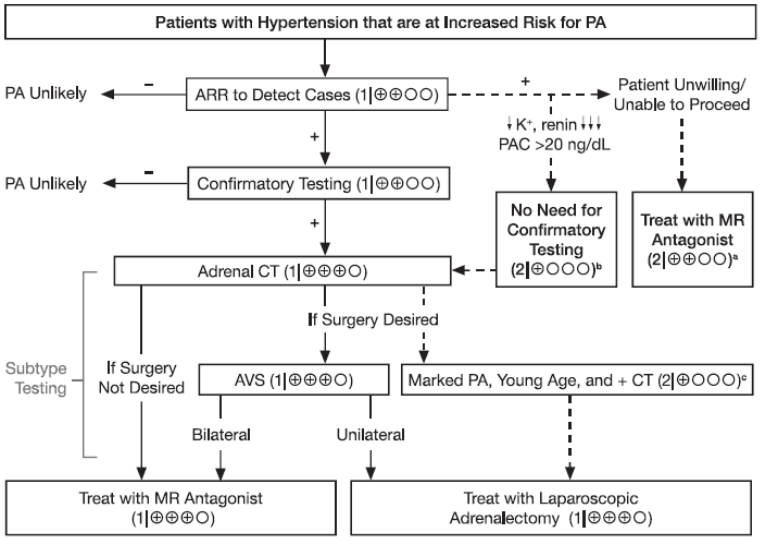
Who should be screened for primary hyperaldosteronism?

1. Patients with sustained blood pressure (BP) above 150/100 mm Hg on each of three measurements obtained on different days
2. hypertension (BP 140/90 mm Hg) resistant to three conventional antihypertensive drugs (including a diuretic)
3. controlled BP (140/90 mm Hg) on four or more antihypertensive drugs
4. hypertension and spontaneous or diuretic-induced hypokalemia
5. hypertension and adrenal incidentaloma;
6. hypertension and sleep apnea
7. hypertension and a family history of early onset hypertension or cerebrovascular acciden at a young age (40 years)
8. all hypertensive first-degree relatives of patients with PA.

Case Detection

Patients with a **positive ARR** should undergo one or more confirmatory tests to definitively confirm or exclude the diagnosis.

In the setting of **spontaneous hypokalemia**, plasma **renin below detection levels** plus plasma **aldosterone concentration (PAC) > 20 ng/dL** , we suggest that there may is no need for further confirmatory testing



*** “if renin is suppressed, the screen is valid” - John Archus MD

Subtype classification
When is adrenal venous sampling recommended?

All patients with PA undergo adrenal computed tomography (CT) as in the initial study in subtype testing to **exclude large masses** that may **represent adrenocortical carcinoma** and to assist the interventional radiologist and surgeon where anatomically appropriate
when **surgical treatment is feasible** and desired by the patient, an experienced radiologist should use **adrenal venous sampling (AVS)** to make the distinction between **unilateral and bilateral adrenal disease**

*** The sensitivity and specificity of AVS (95 and 100%, respectively) for detecting unilateral aldosterone excess are superior to that of adrenal CT (78 and 75%, respectively)

** AVS is the “gold standard” test to distinguish unilateral (APA or UAH) from bilateral (IHA) disease in patients with PA.

Who can proceed directly to surgery or unilateral adrenalectomy

Younger patients (age < 35 years) with **spontaneous hypokalemia**, **marked aldosterone excess**, and **unilateral adrenal lesions** with radiological features consistent with a cortical adenoma on adrenal CT scan may not need AVS before proceeding to unilateral adrenalectomy

When is genetic testing recommended?

- confirmed PA earlier than 20 years of age
- family history of PA
- stroke at a young age (< 40 years)

- genetic testing for **familial hyperaldosteronism type 1 (FH-I**) (glucocorticoid remediable aldosteronism [GRA]
- testing for **germline mutations in KCNJ5** causing **familial hyperaldosteronism type 3 (FH-III)**

Treatment recommendations

1) unilateral laparoscopic adrenalectomy

- patients with documented unilateral PA (ie, aldosterone-producing adenoma [APA]
- unilateral adrenal hyperplasia [UAH]

2) medical therapy, including a mineralocorticoid receptor (MR) antagonist

- Patient is unable or unwilling to undergo surgery,
- An ARR-positive patient is unwilling or unable to undergo further investigations
- PA due to bilateral adrenal disease

- **In patients with GRA, we recommend administering the lowest dose of glucocorticoid to lower ACTH andthus normali ze BP and potassium levels as the first-line treatment.**
- if BP fails to normalize with glucocorticoid alone, an MR antagonist may be added.

Interfering drugs — Most antihypertensive medications can be continued, and posture stimulation is not required. For example, although beta-adrenergic antagonists do lower PRA and PRC measurements and raise the PAC/PRA ratio , the increased PAC/PRA ratio is not clinically important in this setting, because of the low PAC (<10 ng/dL) in patients without primary aldosteronism . In addition, one should consider the risks of modifying antihypertensive medication programs (eg, hypertensive crisis, severe hypokalemia, atrial fibrillation, heart failure)

There are potentially clinically important issues with the following drugs:

- **Mineralocorticoid receptor antagonists** – It may be difficult to interpret data obtained from patients treated with a mineralocorticoid receptor antagonist (spironolactone and eplerenone). These drugs

prevent aldosterone from activating the receptor, resulting sequentially in sodium loss, a decrease in plasma volume, and an elevation in PRA, which will reduce the utility of the PAC/PRA ratio. For this reason, spironolactone and eplerenone should not be initiated until the evaluation is completed and the final decisions about treatment are made.

However, there are exceptions to this rule. For example, if the patient is hypokalemic despite treatment with spironolactone or eplerenone, then the mineralocorticoid receptors are not fully blocked and PRA or PRC should be suppressed in such a patient with primary aldosteronism.

In addition, most patients with primary aldosteronism who are treated with mineralocorticoid receptor antagonists are given subtherapeutic doses. Thus, PAC and PRA should be measured in patients treated with spironolactone or eplerenone, and if PRA is suppressed, these medications are not interfering. Thus, if PRA is suppressed, case-detection testing, confirmatory testing, and adrenal vein sampling (AVS) can be performed without discontinuing the mineralocorticoid receptor antagonists. However, if PRA is not suppressed, then the mineralocorticoid receptor antagonist should be discontinued for four to six weeks before retesting. Other potassium-sparing diuretics, such as amiloride and triamterene, usually do not interfere with testing unless the patient is on high doses.

● **ACE inhibitors, ARBs, direct renin inhibitors** – Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and direct renin inhibitors could potentially elevate PRC and have variable effects on PRA in patients with primary aldosteronism. Thus, in a patient treated with one of these drugs, a PRA >1 ng/mL/hour does not exclude the diagnosis of primary aldosteronism. On the other hand, a strong predictor for primary aldosteronism is a PRA <1 ng/mL/hour or low PRC in a patient taking one of these drugs.

Table 3. Factors That May Lead to False-Positive or False-Negative ARR Results

Factor	Effect on Aldosterone Plasma Levels	Effect on Renin Levels	Effect on ARR
Medications[a]			
β-Adrenergic blockers	D	D D	U (FP)
Central agonists (eg, clonidine, α-methyldopa)	D	D D	U (FP)
NSAIDs	D	D D	U (FP)
K^+-wasting diuretics	R U	U U	D (FN)
K^+-sparing diuretics	U	U U	D (FN)
ACE inhibitors	D	U U	D (FN)
ARBs	D	U U	D (FN)
Ca^{2+} blockers (DHPs)	R D	U	D (FN)
Renin inhibitors	D	D U	U (FP) D (FN)
Potassium status			
Hypokalemia	D	R U	D (FN)
Potassium loading	U	R D	U
Dietary sodium			
Sodium restriction	U	U U	U (FN)
Sodium loading	D	D D	U (FP)
Advancing age	D	D D	U (FP)
Premenopausal women (vs males)[b]	R U	D	U (FP)
Other conditions			
Renal impairment	R	D	U (FP)
PHA-2	R	D	U (FP)
Pregnancy	U	U U	D (FN)
Renovascular HT	U	U U	D (FN)
Malignant HT	U	U U	D (FN)

Abbreviations: D, down arrow; U, up arrow; R, right arrow; NSAIDs, nonsteroidal anti-inflammatory drugs; K^+, potassium; ACE, angiotensin-converting enzyme; ARBs, angiotensin II type 1 receptor blockers; DHPs, dihydropyridines; PHA-2, pseudohypoaldosteronism type 2 (familial hypertension and hyperkalemia with normal glomerular filtration rate); HT, hypertension; FP, false positive; FN, false negative.

[a] Renin inhibitors lower PRA, but raise DRC. This would be expected to result in false-positive ARR levels for renin measured as PRA and false negatives for renin measured as DRC.

[b] In premenopausal, ovulating women, plasma aldosterone levels measured during the menses or the proliferative phase of the menstrual cycle are similar to those of men but rise briskly in the luteal phase. Because renin levels are lower, the ARR is higher than in men for all phases of the cycle, but especially during the luteal phase during which aldosterone rises to a greater extent than renin. False positives can occur during the luteal phase, but only if renin is measured as DRC and not PRA. In preliminary studies, some investigations have found false positives on the current cutoffs for women in the luteal phase. Accordingly, it would seem sensible to screen women at risk in the follicular phase, if practicable.

Testing Conditions

ARR is most sensitive when collected in the morning, after patients have been ambulatory for 2 hours, and have been seated for 5-15 minutes prior to blood drawing.

- Hypokalemia should ideally be corrected prior to screening as it directly inhibits aldosterone secretion
- Drugs that alter aldosterone or renin secretion can result in false positive or false negative results
  - Beta-adrenergic blockers and central alpha agonists lower PRA secretion and often produce a false positive ARR in patients with essential hypertension

- Diuretics, ACE-inhibitors (ACEI) and angiotensin receptor blockers (ARB) can increase PRA and result in false negative screening results.
- mineralocorticoid receptor antagonists spironolactone and eplerenone, as well as renin inhibitors, can cause false negative ARR by virtue of raising the PRA
- If a PRA is suppressed while on a mineralocorticoid receptor antagonist, the ARR may still be interpretable; however, in the context of an unsuppressed PRA, mineralocorticoid receptor antagonists should be discontinued for weeks-to-months until the PRA is suppressed, before the ARR is informative.

However, if the ARR while on any medication is high, with frankly elevated PAC and suppressed PRA, the likelihood of primary aldosteronism remains very high

If renin is suppressed, the screen is valid -- Dr. Archus

Non-dihydropyridine calcium channel blockers, hydralazine, or alpha-blockers, can be used instead to control arterial pressure during the screening evaluation.

Table 4. Measurement of ARR: A Suggested Approach

A. Preparation: agenda
1. Attempt to correct hypokalemia. Measure plasma potassium in blood collected slowly with a syringe and needle [preferably not a Vacutainer to minimize the risk of spuriously raising potassium]. During collection, avoid fist clenching, wait at least 5 seconds after tourniquet release (if used) to achieve insertion of needle, and ensure separation of plasma from cells within 30 minutes of collection. A plasma [K^+] of 4.0 mmol/L is the aim of supplementation.
2. Encourage patient to liberalize (rather than restrict) sodium intake.
3. Withdraw agents that markedly affect the ARR (219) for at least 4 weeks:
   a. Spironolactone, eplerenone, amiloride, and triamterene
   b. Potassium-wasting diuretics
   c. Products derived from licorice root (eg, confectionary licorice, chewing tobacco)
4. If the results of ARR after discontinuation of the above agents are not diagnostic, and if hypertension can be controlled with relatively noninterfering medications (see Table 5), withdraw other medications that may affect the ARR (219) for at least 2 weeks, such as:
   a. β-Adrenergic blockers, central α-2 agonists (eg, clonidine, α-methyldopa), and nonsteroidal anti-inflammatory drugs
   b. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and dihydropyridine calcium channel antagonists
5. If necessary to maintain hypertension control, commence other antihypertensive medications that have lesser effects on the ARR (*e.g.* verapamil slow-release, hydralazine [with verapamil slow-release, to avoid reflex tachycardia], prazosin, doxazosin, terazosin; see Table 5).
6. Establish OC and HRT status because estrogen-containing medications may lower DRC and cause false-positive ARR when DRC (rather than PRA) is measured (220). Do not withdraw OC unless confident of alternative effective contraception.

B. Conditions for blood collection
1. Collect blood midmorning, after the patient has been up (sitting, standing, or walking) for at least 2 hours and seated for 5–15 minutes.
2. Collect blood carefully, avoiding stasis and hemolysis (see A.1 above).
3. Maintain sample at room temperature (and not on ice, as this will promote conversion of inactive to active renin) during delivery to laboratory and prior to centrifugation and rapid freezing of plasma component pending assay.

C. Factors to take into account when interpreting results (see Table 3)
1. Age: in patients aged >65 years, renin can be lowered more than aldosterone by age alone, leading to raised ARR.
2. Gender: premenstrual, ovulating females have higher ARR levels than age-matched men, especially during the luteal phase of the menstrual cycle, during which false positives can occur, but only if renin is measured as DRC and not as PRA (220).
3. Time of day, recent diet, posture, and length of time in that posture
4. Medications
5. Method of blood collection, including any difficulty doing so
6. Level of potassium
7. Level of creatinine (renal failure can lead to false-positive ARR)

Table 5. Medications With Minimal Effects on Plasma Aldosterone Levels That Can Control Hypertension During Case Finding and Confirmatory Testing for PA

Drug	Class	Usual Dose	Comments
Verapamil slow-release	Non-dihydropyridine slow-release antagonist calcium channel	90–120 mg twice daily	Use singly or in combination with the other agents listed in this table
Hydralazine	Vasodilator	10–12.5 mg twice daily, increasing as required	Commence verapamil slow-release first to prevent reflex tachycardia. Commencement at low doses reduces risk of side effects (including headaches, flushing, and palpitations)
Prazosin hydrochloride	α-Adrenergic blocker	0.5–1 mg two or three times daily, increasing as required	Monitor for postural hypotension
Doxazosin mesylate	α-Adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension
Terazosin hydrochloride	α-Adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension

[Adapted from J. W. Funder et al: Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93:3266–3281 (3), with permission. © Endocrine Society.]

Testing conditions with ARR

- The ARR test is most sensitive when samples are collected in the morning after patients have been out of bed for at least 2 hours, usually after they have been seated for 5–15 minutes
- **patients should have unrestricted dietary salt intake before testing and should be potassium-replete**
- MR antagonists should be withdrawn for at least 4 weeks before ARR testing
- A washout of all interfering antihypertensive medications is feasible in patients with mild hypertension
- patients with severe PA, treatment with an **MR antagonist cannot be safely discontinued**; in this setting, **PA-related testing can be pursued as long as renin is suppressed**.

The lack of uniformity in diagnostic protocols and assay methods for measuring the ARR has been associated with substantial variability in cutoff values

- A limitation of the ARR is that in the presence of very low renin levels (for example, at PRA values of 0.1 ng/mL/h), the ARR may be elevated even when plasma aldosterone is also low.

Test and Procedure	Interpretation	Concerns
Oral sodium loading test Patients should increase their sodium intake to >200 mmol (~6 g)/d for 3 d, verified by 24-h urine sodium content. Patients should receive adequate slow-release potassium chloride supplementation to maintain plasma potassium in the normal range. Urinary aldosterone is measured in the 24-h urine collection from the morning of day 3 to the morning of day 4.	PA is unlikely if urinary aldosterone is <10 μg/24 h (28 nmol/d) in the absence of renal disease where PA may coexist with lower measured urinary aldosterone levels. Elevated urinary aldosterone excretion (>12 μg/24 h [>33 nmol/d] at the Mayo Clinic; >14 μg/24 h [39 nmol/d] at the Cleveland Clinic) makes PA highly likely.	This test should not be performed in patients with severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, or severe hypokalemia. 24-h urine collection may be inconvenient. Laboratory-specific poor performance of the RIA for urinary aldosterone (aldosterone 18-oxo-glucuronide or acid labile metabolite) may blunt diagnostic accuracy—a problem obviated by the currently available HPLC-tandem mass spectrometry methodology (223). Aldosterone 18-oxo-glucuronide is a renal metabolite, and its excretion may not rise in patients with renal disease.

SIT Patients stay in the recumbent position for at least 1 h before and during the infusion of 2 L of 0.9% saline iv over 4 h, starting at 8–9.30 AM. Blood samples for renin, aldosterone, cortisol, and plasma potassium are drawn at time zero and after 4 h, with BP and heart rate monitored throughout the test. In a modified approach, which appears (in preliminary studies) to have much higher sensitivity for diagnosing PA, patients remain in a seated position for at least 30 min and during the infusion (73).	Postinfusion plasma aldosterone levels <5 ng/dL (140 pmol/L) make the diagnosis of PA unlikely, whereas levels >10 ng/dL (280 nmol/L) are a sign of very probable PA. Values between 5 and 10 ng/dL are indeterminate, although a cutoff of 6.8 ng/dL (190 pmol/L) has been found to offer the best trade-off between sensitivity and specificity (57, 58, 224, 225). For the seated SIT, a postinfusion plasma aldosterone of >6 ng/dL (170 pmol/L) confirms PA, provided plasma cortisol concentration is lower than the value obtained basally (to exclude a confounding ACTH effect) (73).	This test should not be performed in patients with severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, or severe hypokalemia.
FST Patients receive 0.1 mg oral fludrocortisone every 6 h for 4 d, together with slow-release KCl supplements (every 6 h at doses sufficient to keep plasma K^+, measured four times a day, close to 4.0 mmol/L), slow-release NaCl supplements (30 mmol three times daily with meals) and sufficient dietary salt to maintain a urinary sodium excretion rate of at least 3 mmol/kg body weight. On day 4, plasma aldosterone and PRA are measured at 10 AM with the patient in the seated posture, and plasma cortisol is measured at 7 and 10 AM.	Upright plasma aldosterone >6 ng/dL (170 nmol/L) on day 4 at 10 AM confirms PA, provided PRA is <1 ng/mL/h and plasma cortisol concentration is lower than the value obtained at 7 AM (to exclude a confounding ACTH effect) (39, 52, 53, 112, 226).	Although some centers (23, 27) conduct this test in the outpatient setting (provided that patients are able to attend frequently to monitor their potassium), in other centers several days of hospitalization are customary. Most of the data available come from the Brisbane group (39, 52, 53, 89, 112, 226) who have established, on the basis of a very large series of patients, a cutoff of a PAC of 6 ng/dL (170 nmol/L) at 10 AM in an ambulatory patient on day 4. Proponents of the FST argue that: a) it is the most sensitive for confirming PA; b) it is a less intrusive method of sodium loading than SIT and therefore less likely to provoke non-renin-dependent alterations of aldosterone levels; c) it allows for the potentially confounding effects of potassium to be controlled, and for ACTH (via cortisol) to be monitored and detected; and d) it is safe when performed by experienced hands.
Captopril challenge test Patients receive 25–50 mg of captopril orally after sitting or standing for at least 1 h. Blood samples are drawn for measurement of PRA, plasma aldosterone, and cortisol at time zero and at 1 or 2 h after challenge, with the patient remaining seated during this period.	Plasma aldosterone is normally suppressed by captopril (>30%). In patients with PA it remains elevated and PRA remains suppressed (58, 60, 163, 227). Differences may be seen between patients with APA and those with IAH, in that some decrease of aldosterone levels is occasionally seen in IAH (228).	There are reports of a substantial number of false-negative or equivocal results (59, 229).

plasma aldosterone concentration (PAC) and plasma renin activity (PRA) with validated, sensitive assays, for calculation of a plasma aldosterone to renin ratio (ARR)

- ARR > 20 is considered highly suspicious for PA.
- An ARR >30, especially in the setting of a PAC ≥ 15 ng/dL, has been shown to be 90% sensitive and 91% specific for the diagnosis of PA

Interpretation of the ARR should be made after confirming that renin is suppressed in the setting of inappropriately high endogenous aldosterone production.

The **absence of renin suppression** should raise suspicion for **secondary aldosteronism (not primary)** and/or the **use of medications that raise renin** (mineralocorticoid receptor antagonists, renin inhibitors, renin-angiotensin-aldosterone system inhibitors, ENaC inhibitors, other diuretics that induce volume contraction)

Cardiovascular complications of hyperaldosteronism

- **Aldosterone --** deleterious effects on the cardiovascular system, at least partly independent of its effects on BP
- Increased LV dimensions and myocardial fibrosis
- Increased carotid intima thickness

- Increased femoral pulse velocity
- Reduced endothelial function

Why is surgery better then medical management of this condition? BOARD PEARL

1. **Arterial stiffness** reduced by unilateral adrenalectomy after 1 year but not spironolactone.
2. Greater **reduction of LV size**
3. Improved **hypertension** and **hypokalemia** better than medical therapy (in unilateral and or bilateral aldosterone-producing adenoma)

Surgical management

Compared with open adrenalectomy, laparoscopic adrenalectomy is associated with shorter hospital stays and fewer complications.

- Persistent hyperaldo in 10% of subjects with unilateral APA
- 27% of surgically removed adrenals are found to have multiple nodules!!

Post Operative considerations

1. **Assessment of biochemical response**
   - measure plasma aldosterone and renin activity levels shortly after surgery (renin levels may not fall immediately)
2. **Recommendations**
   - Stop potassium supplementation on post operative day #1
   - Discontinue spironolactone
   - Reduce antihypertensives if clinically appropriate
   - **Generous sodium diet to avoid hyperkalemia that can develop from hypoaldosteronism due to chronic contralateral gland suppression.**
   - **Persistent hypoaldosteronism may occur in 5%** -- require mineralocorticoids (fludrocortisone)

When should I expect improvement in my blood pressure?

BP typically normalizes or shows **maximum improvement in 1–6 months after unilateral adrenalectomy** for unilateral APA but can continue to fall for up to 1 year in some patients

Primary aldosteronism due to bilateral dissease
medical treatment with an MR antagonist ; **spironolactone as the primary agent**, with eplerenone as an alternative.

Glucocorticoid remediable aldosteronism
• lowest dose of glucocorticoid to **lower ACTH thus normalize BP** and potassium levels as first-line treatment. • If BP fails to normalize with glucocorticoid alone, an MR antagonist maybe added • A synthetic glucocorticoid that is **longer acting than hydrocortisone**, such as dexamethasone or prednisone, to **suppress ACTH secretion**. Ideally, the glucocorticoid should be taken at bedtime to suppress the early morning ACTH surge.

NON CLASSICAL ADRENAL HYPERPLASIA

Steroidogenesis in the adrenal gland reflects the zone-specific expression of enzymes, which comprise pathways to efficiently complete the biosynthesis of aldosterone, cortisol, and dehydroepiandrosterone sulfate.

The most common form of congenital adrenal hyperplasia is 21-hydroxylase deficiency, in which a block in cortisol biosynthesis shifts precursors to pathways that make excess adrenal-derived androgens.

Non-classic 21-hydroxylase deficiency differs from the classic form in that cortisol deficiency and virilization of newborn girls are absent.

Treatment for classic 21-hydroxylase deficiency consists of glucocorticoid and mineralocorticoid replacement, and for both classic and non-classic disease, sufficient glucocorticoid is administered to correct the androgen excess.

Patients with 21-hydroxylase deficiency are prone to developing adrenal cortical adenomas and myelolipomas, as well as adrenal rest tumors in the testis or elsewhere.

Congenital adrenal hyperplasia (CAH) refers to a group of inherited enzymatic defects in cortisol biosynthesis. Impaired cortisol production relieves negative feedback to the hypothalamus and the pituitary gland, which in response amplify the secretion of corticotropin-releasing hormone (CRH) and ACTH, respectively, resulting in hyperplasia of the adrenal cortex.

Steroid 21-hydroxylase deficiency (21OHD) accounts for over 90% of CAH cases

Conventionally, 21OHD is dichotomized into classic and nonclassic forms, based on the presence or absence of cortisol insufficiency. The classic forms of 21OHD are further grouped into “salt wasting” and “simple virilizing” subtypes, depending on whether or not mineralocorticoid synthesis is sufficiently impaired to cause spontaneous hypotensive crises in the infant.

Nonclassic 21OHD is much more frequent, occurring in approximately 1 of 1,000 Caucasians and more commonly in certain ethnic groups, such as Ashkenazi Jews (1:27), Hispanics (1:53), Yugoslavs (1:62) and Italians (1:300)

As a result of 21-hydroxylase dysfunction, upstream steroid precursors accumulate and are diverted towards accessible pathways to form potent androgens

Elevations of 17OHP, the main substrate of CYP21A2, are a hallmark of 21OHD, and 17OHP has traditionally been used for both diagnosis and monitoring of the disease.

A high prevalence of benign adrenal masses has been reported in patients with 21OHD. Over 80% of homozygous and 45% of heterozygous patients had adrenal tumors in one study, although no correlation between tumor size and serum 17OHP concentrations was found. Most tumors had a diameter of less than 2 cm, but several giant myelolipomas have also been reported

Management

- Glucocorticoids and mineralocorticoids are the mainstays of treatment for 21OHD. Glucocorticoids exert two principal actions: replacement of the deficient cortisol and suppression of the adrenal androgen overproduction, by exerting negative feedback on the hypothalamus and the pituitary, which subsequently decreases CRH production and ACTH stimulation.
- *Hydrocortisone is preferred in children and adolescents, until growth is completed, due to its short action, which limits the potential to suppress growth*
- *Hydrocortisone also serves as replacement therapy for* ***adults, but long-acting synthetic glucocorticoids are often preferred****, owing to less frequent dosing. The longer duration of action and higher potency of drugs like* ***prednisolone and dexamethasone, however, might increase the risk of detrimental effects, including weight gain, dermal atrophy, poor sleep, and bone loss***
- ***Stress doses of steroids should be given in patients with classic 21OHD during surgery, physical illness, labor and delivery***
- women attempting to conceive and during pregnancy, a glucocorticoid that is inactivated by **placental 11β-hydroxysteroid dehydrogenase type 2** (e.g., hydrocortisone, prednisone, and prednisolone) should be used, to avoid fetal exposure
- **Asymptomatic patients with nonclassic 21OHD do not require treatment, and stress doses of steroids are rarely needed.**

TABLE 2. Characteristics of different forms of congenital adrenal hyperplasia

Disease	21-Hydroxylase deficiency	11β-Hydroxylase deficiency	Aldosterone synthase deficiency	17α-Hydroxylase deficiency	3β-Hydroxysteroid dehydrogenase deficiency	Lipoid hyperplasia
Defective gene	*CYP21*	*CYP11B1*	*CYP11B2*	*CYP17*	*HSD3B2*	*STAR*
Alias	P450c21	P450c11	P450aldo	P450c17	3β-HSD	
Chromosomal location	6p21.3	8q24.3	8q24.3	10q24.3	1p13.1	8p11.2
Ambiguous genitalia	+ in ♀	+ in ♀	No	+ in ♂ No puberty in ♀	+ in ♂ Mild in ♀	+ in ♂ No puberty in ♀
Addisonian crisis	+	Rare	Salt wasting only	No	+	++
Incidence (gen. pop.)	1:10–18,000	1:100,000	Rare	Rare	Rare	Rare
Hormones						
Glucocorticoids	↓	↓	Normal	Corticosterone normal	↓	↓
Mineralocorticoids	↓	↑	↓	↑	↓	↓
Androgens	↑	↑	Normal	↓	↓ in ♂ ↑ in ♀	↓
Estrogens	Relatively ↓ in ♀	Relatively ↓ in ♀	Normal	↓	↓	↓
Physiology						
Blood pressure	↓	↑	↓	↑	↓	↓
Na balance	↓	↑	↓	↑	↓	↓
K balance	↑	↓	↑	↓	↑	↑
Acidosis	+	± Alkalosis	+	± Alkalosis	+	+
Elevated metabolites	17-OHP	DOC, 11-deoxycortisol	Corticosterone, ±18-hydroxy-corticosterone	DOC corticosterone,	DHEA, 17Δ⁵Preg	None
Reference		(13)	(13)	(14)	(15)	(6)

17-OHP, 17-Hydroxyprogesterone; DOC, deoxycorticosterone; DHEA, dehydroepiandrosterone; 17Δ⁵Preg, 17-Δ⁵-hydroxypregnenolone.

Treatment considerations for CAH

1. **Glucocorticoid treatment is primarily given to children with sexual precocity and advanced bone age or to women with infertility due to this condition**
2. **women with infertility due to this condition**

3. For other consequences of androgen excess, including acne, hirsutism, or body odor, alternatives therapies include anti-androgens (spironolactone), oral contraceptives, and mechanical depilation.

Goals of Therapy in CAH

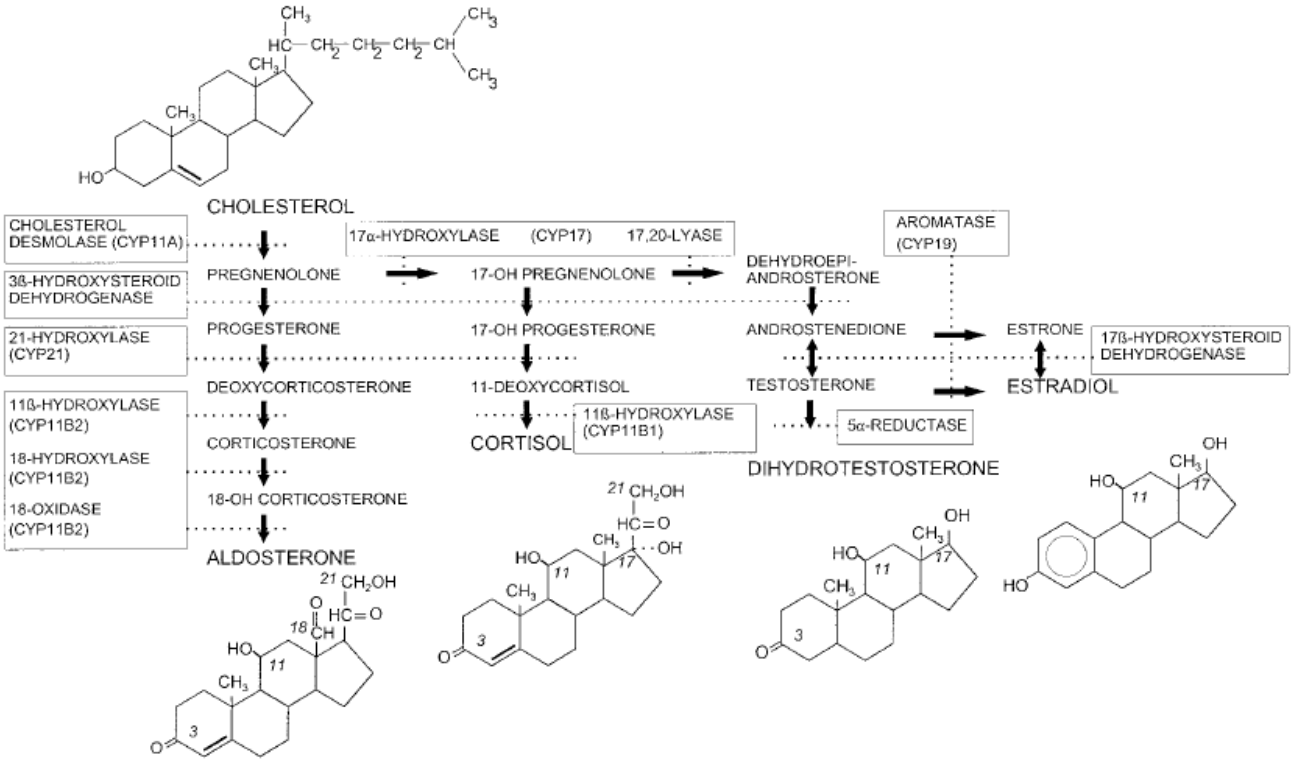
- The goals of therapy for classic 21OHD are to replace the hormonal deficits, while adequately suppressing the androgen excess
- Risk of iatrogenic Cushing syndrome.
- Near-normalization of AD in both men and women and of testosterone in women indicates adequate control in most circumstances
- Mineralocorticoid replacement is generally maintained but occasionally becomes unnecessary in adults, possibly due to extra-adrenal 21-hydroxylation of adrenal-derived progesterone

Steroid continuation during pregnancy	One retrospective series found high rates of pregnancy loss in women with nonclassic 21OHD, but this rate was lower in women who were treated with glucocorticoids.

	For this reason, glucocorticoids (hydrocortisone) are often continued throughout gestation, particularly in women who conceive while taking glucocorticoids.

Role of elective adrenalectomy

- Bilateral adrenalectomy has been performed in selected patients with severe forms of 21OHD, in whom hyperandrogenism was difficult to control despite generous glucocorticoid replacement or in order to avoid their associated side effects.
- The ensuing primary adrenal insufficiency, however, is more tenuous than 21OHD and mandates strict adherence to lifelong glucocorticoid and mineralocorticoid replacement, in order to prevent potentially fatal adrenal crises
- Complete absence of epinephrine and DHEA are additional theoretical concerns, but the consequences of these deficiencies remain unknown.



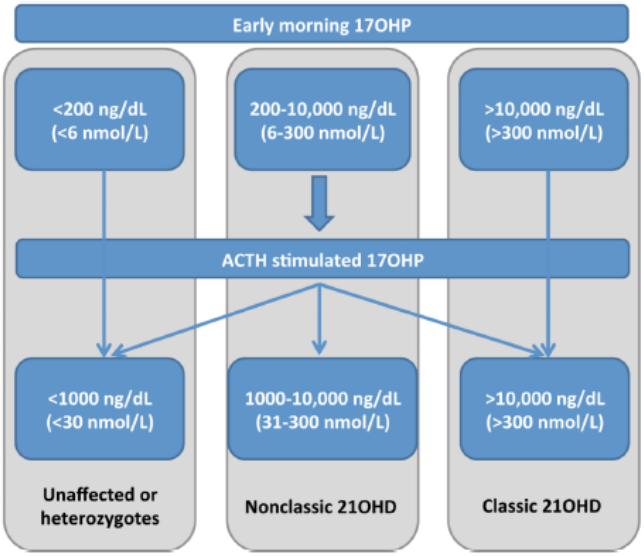
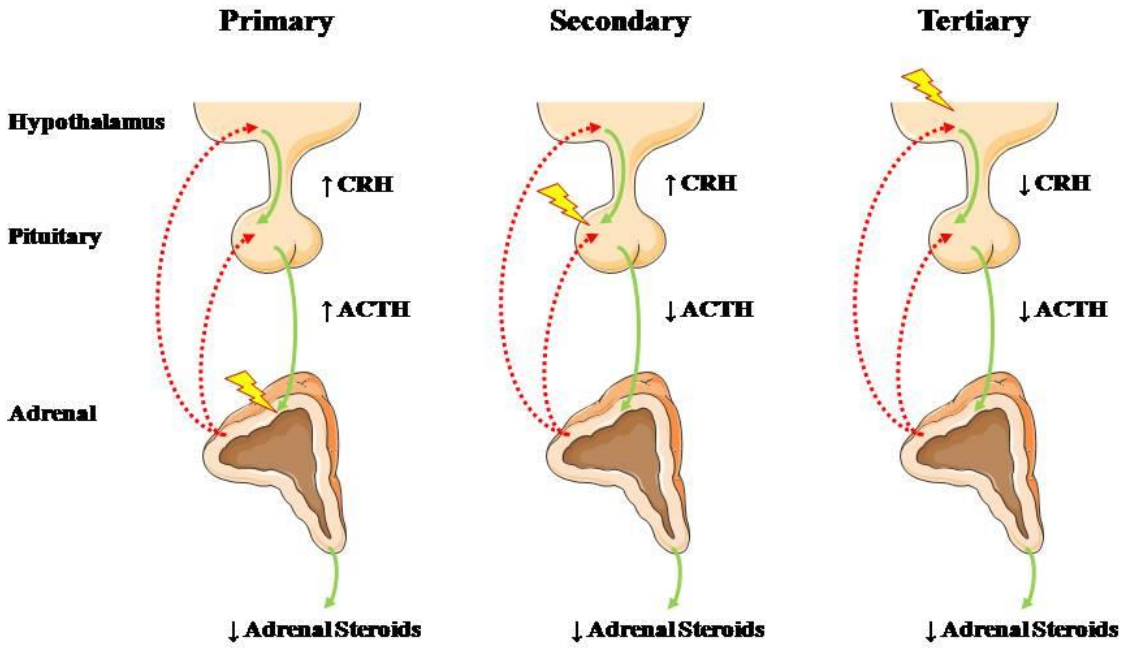


Figure 3.
Schematic evaluation of 21OHD based on baseline and stimulated 17OHP values.

ADRENAL INSUFFICIENCY

1



What to do with short term steroid exposure
• Any patient with <3 weeks of glucocorticoid treatment is unlikely to have clinically significant adrenal suppression. If the medical

condition allows it, glucocorticoid treatment can be stopped acutely.
** Major stress within 1 week of stopping steroids should however be covered with glucocorticoids.

Exceptions to the above general rule….

1. Patients with other possible reasons for adrenal insufficiency
2. Received >40mg prednisolone (or equivalent)
3. Evening doses of hydrocortisone (greater HPA suppression due to perturbations of the diurnal rhythm)
4. Short courses prescribed within 1 year of cessation of long term therapy

Long term steroids

Supraphysiological doses of steroids refers to >5mg of prednisone or equivalent of glucocorticoid

Dose reduction depends on disease activity. (if dx has resolved, reduce prednisone by 2.5mg every 3-5days till a dose of 5mg prednisone steroid equivalent is reached.
↓
Once a daily equivalent dose of 5mg is reached (rate of reduction should be slower to allow recovery of HPA axis)
↓
Consider switching to PO hydrocortisone (average BSA estimate of 20mg daily in the morning only)
This has a shorter half life and allows recovery of the axis. (less prolonged suppression of ACTH)
↓
Daily hydrocortisone dose should be reduced by 2.5mg every 1-2weeks or as tolerated until a dose of 10mg is reached.
↓
After this 2-3 month period of taper, a 9AM cortisol is checked 24hours after the last dose of hydrocortisone.
↓

a) If cortisol is >10mcg/dl then hydrocortisone can be stopped and cortrosyn test performed
b) If cortisol is <10mcg/dl then continue hydrocortisone 10mg for another 2-3months and repeat 9AM cortisol

When basal cortisol is >14mcg/dl, stop regular hydrocortisone and administer in emergency only. Supplemental stress dose steroids during intercurrent illness are not required.

Hydrocortisone	15-25	2-3
Prednisone	5-7.5	2
Prednisolone	4-6	2
Dexamethasone	0.25-0.5	1

Clinical features of anabolic steroid abuse	
Musculoskeletal	• Increased muscle mass
Reproductive	• **Low testosterone, FSH, LH** • **Testicular atrophy** • Decreased spermatogenesis • Normal libido & erectile function (during use) • Decreased libido, impotence (during withdrawal)
Endocrine	• Increased LDL, decreased HDL cholesterol
Hematologic	• **Erythrocytosis**
Psychological	• Affective symptoms • Aggression
Dermatologic/breast	• Acne • Gynecomastia

FSH = follicle-stimulating hormone; **LH** = luteinizing hormone; **LDL** = low-density lipoprotein; **HDL** = high-density lipoprotein.

PHEOCHROMOCYTOMAS AND PARAGANGLIOMAS

Important concepts in physiology

- The medulla can be considered a sympathetic nervous system ganglion, which, in response to preganglionic sympathetic neuron stimulation, release of acetylcholine and its **binding to a cholinergic receptor in chromaffin cells**, stimulates the production and release of catecholamines.

- It is extremely vascular and consists of large chromaffin cells arranged in a network. It is made of 2 cell types called pheochromocytes , which are epinephrine-producing (more numerous) and norepinephrine-producing cells.
- These cells synthesize and secrete the catecholamines epinephrine (in greater amounts) , norepinephrine and, to a lesser extent, dopamine.
- **Catecholamines** are amino acid–derived hormones, synthesized from the **amino acid tyrosine**

Synthesis Pathway
Hydroxylation of **tyrosine** to 3,4-dihydroxyphenylalanine (L -dopa) by the enzyme tyrosine hydroxylase. This enzyme is found in the cytosol of catecholamine-producing cells and is the main control point for catecholamine synthesis **Decarboxylation of L -dopa to dopamine by the enzyme dopa decarboxylase in a reaction that requires pyridoxal phosphate as a**

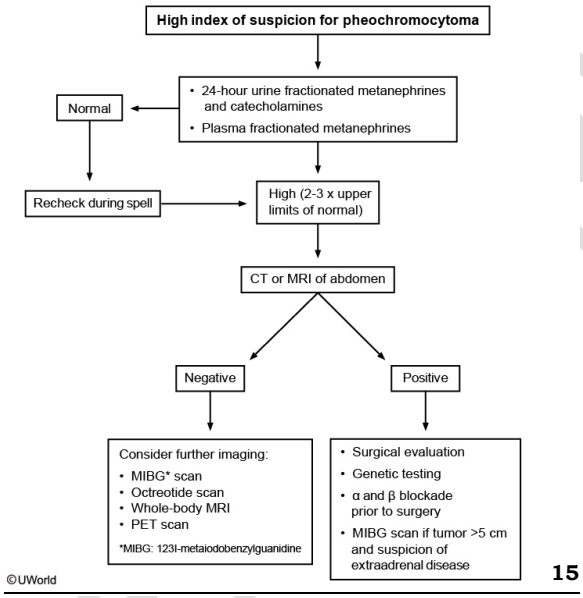
cofactor. This end product is packaged into secretory vesicles

Hydroxylation of dopamine to norepinephrine by the enzyme dopamine β-hydroxylase, a membrane-bound enzyme found in synaptic vesicles that uses vitamin C as a cofactor. Th is reaction occurs inside the secretory vesicles.

Methylation of norepinephrine to epinephrine by the enzyme phenylethanolamine N-methyltransferase. The activity of this cytosolic enzyme is modulated by adjacent adrenal steroid hormone production, underscoring the importance of radial arterial flow from the cortex to the medulla.

In the cytoplasm, epinephrine is converted to metanephrine and norepinephrine is converted to normetanephrine
by the enzyme catechol- O -methyltransferase (COMT)

Phaechromocytoma workup



15

Contrast enhanced CT -- features suggestive of pheochromocytoma
On dual-phase contrast-enhanced CT, pheochromocytomas can also be distinguished from other adrenal masses 1)_ **Higher intensity during the arterial phase**, with enhancement levels **greater than 10 HU** (usually more than 20 HU is diagnostic) 2)_**Washout less than 50% at the end of 10 minutes** (it is important to note that adrenal cancers also have limited washout)

[15] To be of any value an education should prepare for life's work.

*** In case of high fat content, adrenal pheochromocytoma may also resemble adrenal adenomas*

secondary hypertension

Hypertension is "essential or idiopathic" in nearly 85% of patients, while approximately 15% have secondary hypertension.

Secondary hypertension commonly presents at a young age and is severe, multidrug resistant, and may be associated with target organ damage disproportionate to the degree and duration of hypertension.

Who should be evaluated for secondary hypertension

1. Young age of onset (<30 years)
2. Presence of paroxysms and hypokalemia in a patient with hypertension
3. labile hypertension
4. severe hypertension
5. resistant hypertension (uncontrolled blood pressure despite use of ≥3 antihypertensives of different classes in optimal doses, including a diuretic)
6. Hypertension associated with clinical stigmata of a specific disorder (e.g., Cushing's syndrome, MEN2, NF1, GRS) or adrenal mass should also be evaluated.

Diagnosis	Clinical clues
Renovascular hypertension	Recurrent episodes of flash pulmonary edema
	Renal bruit
	Abnormal urine analysis
	Elevation in serum creatinine ≥30% after administration of angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB)
Pheochromocytoma/ Paraganglioma (PPGL)	Paroxysms of headache, palpitations, and sweating
	Postural drop in blood pressure
	Mucosal neuroma, Marfanoid habitus
	Neurofibromas, cafe-au-lait macules, retinal angiomas
Primary aldosteronism	Diastolic hypertension, hypokalemia-related symptoms, metabolic alkalosis
Cushing's syndrome	Classical stigma of Cushing's syndrome
	Hypertension with hypokalemia
Glucocorticoid resistance syndrome	Features of androgen excess
	Hypertension with hypokalemia

The term **"pheochromocytoma"** is derived from the Greek words phaios **("dusky"),** chroma **("color")** and cytoma **("tumor")**
it refers to the dark staining that occurs when intracellular catecholamines are treated with chromium salts.

Catecholamine-secreting tumors arising from the **adrenal medulla (chromaffin tissue)** are called as pheochromocytoma, and they constitute **85% of catecholamine-secreting tumors.**

- Paragangliomas are extra-adrenal tumors arising from glomus cells or chromaffin tissue present in paraganglia, a tissue located in the vicinity of ganglia. Head and neck regions have parasympathetic paraganglia and consist of glomus cells, while chest, abdomen, and pelvis have sympathetic paraganglia and comprises of chromaffin tissue.

- Both glomus cell and chromaffin tissue are derivatives of neural crest cells.

- Head and neck paragangliomas arising from glomus cells of parasympathetic paraganglia are usually nonfunctional
- Paragangliomas arising from chromaffin tissue of sympathetic paraganglia present in the chest, abdomen, and pelvis are usually functional (catecholamine secreting).

Characters	Pheochromocytoma	Sympathetic paraganglioma	Parasympathetic paraganglioma
Functionality	Usually functional	Usually functional	Rarely functional (<1%)
Location	Adrenal medulla	Mediastinum, abdomen, and pelvis	Head and neck
Inheritance	Commonly sporadic	Commonly familial	Commonly familial
Malignant potential	Low	High	High

Pathophysiology Pearl

Conversion of norepinephrine to epinephrine in adrenal medulla is mediated by the enzyme phenylethanolamine N-methyltransferase (PNMT), which is induced by cortisol secreted from the adrenal cortex.

The clinical implication of this fact is that all **epinephrine-secreting tumors arise from the adrenal medulla**, whereas all **functioning paragangliomas secrete only norepinephrine**, as they lack PNMT and its paracrine induction by cortisol.

Headache is present in 90%, **sweating and tachycardia** in 60–70%, and all three in only 30% of patients. The specificity of this triad is around 90%.

Etiology	Norepinephrine	Epinephrine	Dopamine
Sporadic pheochromocytoma	+++	++	±
Paraganglioma	+++	–	±
MEN-related pheochromocytoma	+	+++	±
VHL-related pheochromocytoma	+++	+	±
Malignant pheochromocytoma/ paraganglioma	+++	+	++

Parameters	MEN2A	MEN2B
Gene defect	RET proto-oncogene in extracellular component	RET proto-oncogene in intracellular component
Medullary thyroid carcinoma	Virtually all	Virtually all
Pheochromocytoma	50%	50%
PHPT	20–30%	None
Mucosal neuromas	Absent	Present (98%)
Cutaneous lichen amyloidosis	5%	Absent
Intestinal ganglioneuromas	Absent	Present
Marfanoid habitus	Absent	Present

Clinical Pearl

All patients with medullary thyroid cancer (MTC) should be evaluated for pheochromocytoma prior to thyroid surgery. This is because 6–8% of patients even with apparently sporadic MTC may harbor pheochromocytoma

Von Hippel–Lindau disease

- autosomal dominant disorder
- bilateral pheochromocytoma and/or paraganglioma**
- nonfunctioning pancreatic islet cell tumor
- hemangioblastomas of cerebellum, brainstem or spinal cord,
- retinal angiomas
- clear cell renal cell carcinoma

**predominantly produce norepinephrine due to the under-expression of the enzyme PNMT.

VHL Screening guidelines (from VHL alliance)
Annual screens, 16 years + • Physical examination by physician informed about VHL. • Dilated eye/retinal examination with indirect ophthalmoscope by ophthalmologist informed about VHL. • Quality ultrasound and at least every other year when not pregnant, an MRI scan) of abdomen with and without contrast to assess kidneys, pancreas, and adrenals. • Test for fractionated metanephrines, especially normetanephrine in "plasma free metanephrines" blood test or 24- hour urine test. Abdominal MRI or MIBG scan if biochemical abnormalities found.
Every 2-3 years, 16 years + - MRI scans should be ordered as no less than a 1.5T MRI with and without contrast of brain, cervical, thoracic, and lumbar spine, with thin cuts through the posterior fossa, and attention to inner ear/petrous temporal bone to rule out both ELST and hemangioblastomas of the neuraxis. - Audiology assessment by an audiologist.
During Pregnancy (for women with VHL)

• Regular retinal checkup to anticipate potentially more rapid progression of lesions.

• Test for pheo early, mid, and again late pregnancy to ensure no active pheo during pregnancy or especially labor and delivery.

• During the 4th month of pregnancy, MRI—without contrast—to check on any known lesions of the brain and spine. If known retinal, brain, or spinal lesions, consider C-section

Catecholamines are metabolized within the tumoral cells to intermediate metabolites (epinephrine to metanephrine and norepinephrine to normetanephrine).
Measurement of fractionated metanephrine denotes estimation of metanephrine and normetanephrines separately, either in plasma or in urine.

The measurement of either urine or plasma metanephrine and normetanephrine is preferred for the diagnosis of PPGL as *intra-tumoral catecholamine metabolism is continuous and metanephrine and normetanephrine are intermediate products of catecholamine metabolism.* A level >3 times the upper limit of normal is considered diagnostic.

Tests	Sensitivity (%)	Specificity (%)
Plasma free metanephrine and normetanephrine	96–100	85–89
Plasma epinephrine and norepinephrine	84	81
24 h urinary metanephrine and normetanephrine	98	98
24 h urinary epinephrine and norepinephrine	86	88
24 h urinary VMA	66	94

Sample for **plasma metanephrines and normetanephrines** should be taken in supine position, after being recumbent for 30 min. This is done as upright posture results in activation of sympathetic nervous system, thereby resulting in increased release, metabolism, and clearance of catecholamines. **Sampling in upright position has been shown to increase the incidence of false-positive results by 2.8-fold.**

Table 3. Clinical Findings Associated with Syndromic PPGL

Multiple endocrine neoplasia type 2A	Medullary thyroid cancer, primary hyperparathyroidism, and cutaneous lichen amyloidosis
Multiple endocrine neoplasia type 2B	Medullary thyroid cancer, mucocutaneous neuromas, skeletal deformities (eg, kyphoscoliosis or lordosis), joint laxity, myelinated corneal nerves, and intestinal ganglioneuromas (Hirschsprung disease)
von Hippel-Lindau syndrome	Hemangioblastoma (involving the cerebellum, spinal cord, or brainstem), retinal angioma, clear cell renal cell carcinoma, pancreatic neuroendocrine tumors and serous cystadenomas, endolymphatic sac tumors of the middle ear, papillary cystadenomas of the epididymis and broad ligament
Neurofibromatosis type 1	Neurofibromas, multiple café-au-lait spots, axillary and inguinal freckling, iris hamartomas (Lisch nodules), bony abnormalities, central nervous system gliomas, macrocephaly, and cognitive deficits

Medications and biochemical testing in PPGL

Discontinue 2 weeks prior to test	• Tricyclic antidepressants, selective serotonin reuptake inhibitor (e.g., fluoxetine) • Decongestants, paracetamol, β-blockers and nonselective α-blockers • (Phenoxybenzamine), α-methyldopa, and Labetalol
Can be continued	• Calcium channel blockers • ACE inhibitors/ARBs • Selective α-1 blockers, and diuretics
Do not DIScontinue	• **Clonidine** (falsely elevates metanephrines)

Table 6. Protocol for Clonidine Suppression Test

Principle	Clonidine is an α_2-adrenoreceptor agonist that inhibits neuronal norepinephrine release in patients without PPGL but not in patients with autonomous tumoral secretion of catecholamines by a PPGL.
Indication	To discriminate patients with mildly elevated test results for plasma normetanephrine due to increased sympathetic activity from patients with elevated test results due to a PPGL.
Pretest condition	Withdraw sympatholytic drugs before testing (eg, β-blocker) at least 48 h before testing. The test is carried out with patient in the supine position. The test is cancelled if baseline blood pressure is <110/60 mm Hg or in volume-depleted patients.
Procedure	A venous cannula is placed in an antecubital vein. After 20 min of supine rest, a first blood sample is drawn. Clonidine is administered orally at a dose of 300 μg/70 kg body weight. Blood pressure and heart rate are measured at regular intervals before and during the test. Three hours after drug administration, a second blood sample is drawn. The tubes with blood samples are immediately placed on ice. Blood samples are analyzed for plasma normetanephrine.
Interpretation	An abnormal test result indicating a PPGL includes an elevation of plasma normetanephrine at 3 h after clonidine administration and a less than 40% decrease in levels compared with baseline.

Localization of source of catecholamine excess

anatomic imaging	CT and MRI
functional scans	123I-MIBG and 18F-FDG–PET

** *certain medications, such as opioids, tricyclic antidepressants, and anti-hypertensives like labetalol, can also affect MIBG uptake, leading to less intense or false-negative scans.*

Endocrine Society Guidelines recommend using 18F-FDG PET scan as a preferred modality of functional imaging in patients with metastatic disease

123 I-MIBG is useful to identify patients with metastatic PPGL because MIBG avid lesions indicate that these patients may benefit from treatment with therapeutic doses of 131 I-MIBG

Imaging modality	Sensitivity (%)	Specificity (%)
Ultrasonography	83–89	60
CT	98	92
MRI	93–100	50
^{123}I-MIBG	77–90	95–100
^{18}F-FDG–PET	89	96

indications for functional imaging in patients with pheochromocytoma/paraganglioma

- adrenal pheochromocytoma >5 cm
- All paragangliomas irrespective of size
- multicentric disease
- recurrent disease
- metastatic disease when therapy with 131 I-MIBG

Table 9. Presurgical Medical Preparation

Drug	Starting Time	Starting Dose	Final Dose[b]
Preparation 1			
Phenoxybenzamine	10–14 d before surgery	10 mg b.i.d.	1 mg/kg/d
or Doxazosine	10–14 d before surgery	2 mg/d	32 mg/d
Preparation 2			
Nifedipine[a]	As add-on to preparation 1 when needed	30 mg/d	60 mg/d
or Amlodipine[a]	As add-on to preparation 1 when needed	5 mg/d	10 mg/d
Preparation 3			
Propranolol	After at least 3–4 d of preparation 1	20 mg t.i.d.	40 mg t.i.d.
or Atenolol	After at least 3–4 d of preparation 1	25 mg/d	50 mg/d

Abbreviations: b.i.d., twice daily; t.i.d., three times daily.

[a] Add when blood pressure cannot be controlled by α-adrenoceptor blockade (preparation 1).

[b] Higher doses usually unnecessary.

Medications used for symptom management and preprocedural blockade.

Drug	Classifications	Doses	Recommended use
α-Blockers			
Phenoxybenzamine (Dibenzyline)	Long lasting, irreversible, and noncompetitive	10 mg 1-3 times daily	First choice for α-adrenoceptor blockade
Prazosin (Minipress)	Short-acting, specific, and competitive	2-5 mg 2-3 times daily	• When phenoxybenzamine is not available
Terazosin (Hytrin)	Short-acting, specific, and competitive	2-5 mg/d	• For patients who cannot tolerate phenoxybenzamine
Doxazosin (Cardura)	Short-acting, specific, and competitive	2-8 mg/d	• For patients with mild hypertension
β-Blockers			
Atenolol (Tenormin)	Cardioselective	12.5-25 mg 2-3 times daily	
Metoprolol (Lopressor)	Cardioselective	25-50 mg 3-4 times daily	To control tachyarrythmia caused by catecholamines or alpha-blockade
Propranolol (Inderal)	Nonselective	20-80 mg 1-3 times daily	
Calcium channel blockers			
Amlodipine (Norvasc)		10-20 mg/d	• To provide additional blood pressure control for patients on alpha blockers • For patients who cannot tolerate alpha blockers • For patients with intermittent hypertension
Nicardipine (Cardene)		60-90 mg/d	
Nifedipine (Adalat)	Extended-release action	30-90 mg/d	
Verapamil (Covera-HS and Calan-SR)	Extended-release action	180-540 mg/d	
Catecholamine synthesis inhibitors			
Metyrosine (Demser)		250 mg every 8-12 h for a total dose of 1.5-2 g/d	To provide additional blood pressure control for patients on adrenoceptor blockade

preoperative management of pheochromocytoma/paraganglioma

- Preoperative management should focus on the control of blood pressure and appropriate volume expansion
- Patients who are normotensive should also be administered α-blockers to prevent hypertensive crisis during surgery
- **Nonselective α-blocker, phenoxybenzamine, or selective α-1 blocker, prazosin,** are used for preoperative α-blockade *
- After achieving adequate α-blockade, **salt ad lib (>5 g/day) and β-blockers** should be added to counteract the **orthostatic hypotension** and **tachycardia** induced by α-blockade, respectively
- β-blockers should be used only after adequate α-blockade is achieved **
- Effective β-blockade is considered when heart rate is 60–70 per minute (sitting) and 70–80 per minute (standing).
- **Calcium channel blockers** may be required if blood pressure is not controlled despite the use of α-and β-blockers.
- Target blood pressure of <130/80 mmHg (seated) and systolic blood pressure >90 mmHg on standing should be achieved prior to surgery.
- **Labetalol should be avoided** as it has more potent β-blocking activity than α-blocking activity (β : α = 5:1).

* Adequate α-blockade is suggested by nasal stuffiness, appearance/worsening of orthostatic hypotension, and tachycardia.Patients should receive α-blockade for at least 7 days prior to surgery to minimize hypertensive surges intraoperatively and to allow intravascular volume repletion with salt ad lib and fluid

** it might precipitate hypertensive crisis due to unopposed α-adrenergic action resulting in vasoconstriction

Anesthesia considerations in PPGL

Preferred Agents	• Propofol, etomidate, or barbiturates in combination with synthetic opioids
Agents to avoid	• atropine and anesthetics like fentanyl, ketamine, • morphine, halothane, and desflurane

Table 2. Medications That Are Implicated in Adverse Reactions in Patients with Pheochromocytoma and That Can Precipitate a Crisis

Class of Drugs	Examples
Dopamine D2 receptor antagonists (including some antiemetic agents and antipsychotics)	Metoclopramide, sulpiride, amisulpride, tiapride, chlorpromazine, prochlorperazine, droperidol
β-Adrenergic receptor blockers[a]	Propranolol, sotalol, timolol, nadolol, labetalol
Sympathomimetics	Ephedrine, pseudoephedrine, fenfluramine, methylphenidate, phentermine, dexamfetamine
Opioid analgesics	Morphine, pethidine, tramadol
Norepinephrine reuptake inhibitors (including tricyclic antidepressants)	Amitriptyline, imipramine,
Serotonin reuptake inhibitors (rarely reported)	Paroxetine, fluoxetine
Monoamine oxidase inhibitors	Tranylcypromine, moclobemide, phenelzine
Corticosteroids	Dexamethasone, prednisone, hydrocortisone, betamethasone
Peptides	ACTH, glucagon
Neuromuscular blocking agents	Succinylcholine, tubocurarine, atracurium

[a] Although most case reports on β-adrenergic receptor blockers pertain to nonselective blockers, selective β_1-blockers may also precipitate a crisis because at higher doses they may lose β_1-selectivity.

	Location	Other related tumor conditions	First-choice radiopharmaceutical	Second-choice radiopharmaceutical
SDHB	Adrenal/extradrenal	GISTs, RCCs, and pituitary adenomas	^{68}Ga-DOTA-SSAs	^{18}F-FDG
SDHD	Adrenal/extradrenal	GISTs, RCCs, and pituitary adenomas	^{68}Ga-DOTA-SSAs	^{18}F-FDG
SDHC	Adrenal/extradrenal	GISTs, RCCs	^{68}Ga-DOTA-SSAs	^{18}F-FDG
FH	Adrenal/extradrenal	Skin and uterine leiomyomas, RCCs, uterine leiomyosarcomas and ovarian mucinous cystadenomas	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
VHL	Adrenal/extradrenal	RCCs, CNS hemangioblastomas, pancreatic and testicular tumors	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
EPAS1/HIF2A	Adrenal/extradrenal	Somatostatinomas	^{18}F-FDOPA	^{18}F-FDG
MEN2	Adrenal	MTC, parathyroid adenomas, or hyperplasia	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
NF1	Adrenal	Neurofibromas, peripheral nerve sheath tumors, and gliomas	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
TMEM127	Adrenal	RCCs	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
MAX	Adrenal/extradrenal	Renal oncocytomas	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs

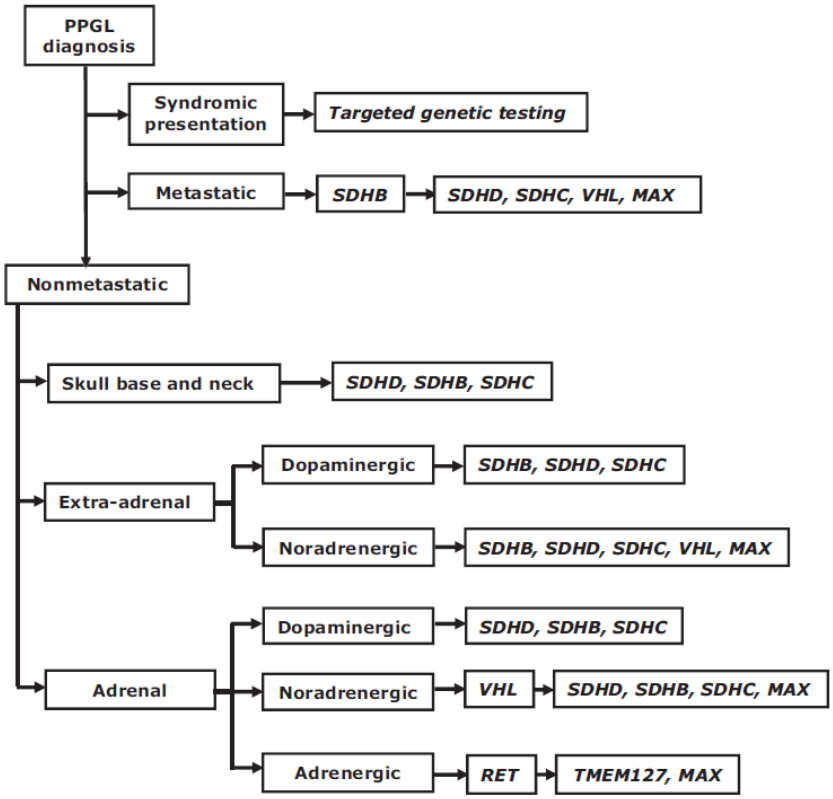


Figure 1. Decisional algorithm for genetic testing in patients with a proven PPGL. Dopaminergic, noradrenergic, and adrenergic phenotypes are defined as significant productions of respective 3-methoxytyramine, normetanephrine, and metanephrine relative to combined production of all three metabolites.

Predicting Tools for Malignant PPGL

Most PPGLs are benign, about 10% of pheochromocytomas and 25% of PGL are malignant.

- Several **markers** (Ki-67 index, expression of heat-shock protein 90, activator of transcription3, pS100 staining, increased expression of angiogenesis genes, and N-terminal truncated splice isoform of carboxypeptidase E)
- Pheochromocytoma of adrenal gland scaled score.

Both have a suboptimal correlation to malignant behavior

⊕ **Independent risk factors for metastatic disease**

- presence of *SDHB* mutations
- extra-adrenal location
- size of primary tumor > 5 cm (in *SDHB*-related PPGLs over 3.5 cm)
- younger age of initial diagnosis of PPGL and elevated 3-MT levels

PPGL typically metastasize to lungs, liver, bones, and lymph nodes and patients with metastatic disease suffer from diminished quality of life due to localized pain caused due to metastasis, consequences of catecholamine excess and of course, treatment side effects

Therapeutic options for PPGL

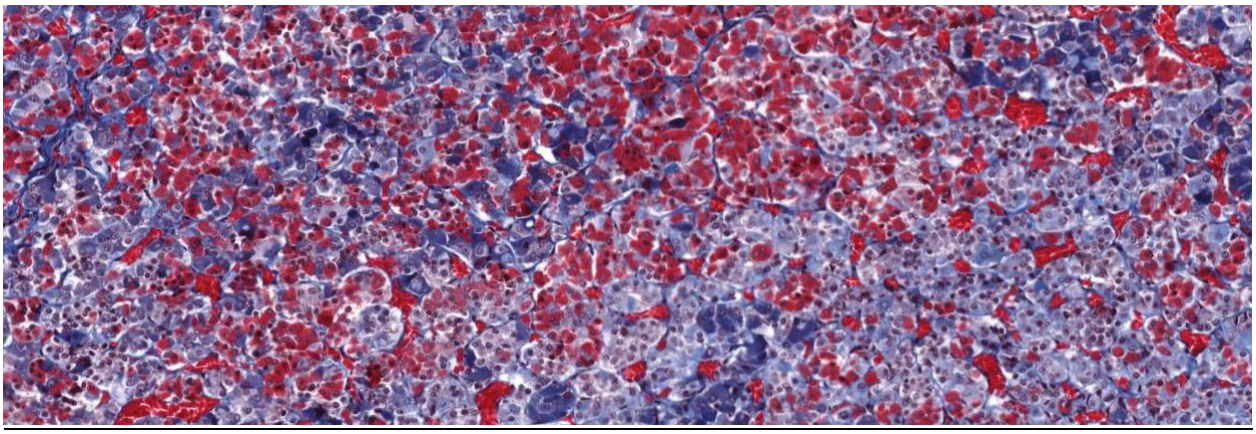
- **Medical management**
- **Surgical** -- curative for recurrent or limited metastatic tumors/ debulking for extensive dx
- **Radiation** -- external radiation or radiotherapy with I-131 MIBG
- Traditional **chemotherapy** with cyclophosphamide,vincristine and dacarbazine (increased risk of excess catecholamines when tumor cells get destroyed in the first 24hrs -- monitor in ICU)
- **Molecular targeted therapies** -- Sunitinib (TKI) or everolimus (mTOR inhibitors) -- mixed results

Practice Points

1. PPGLs are neural crest-derived tumors, and currently more than 40% have a known genetic cause. Thus, all patients with PPGLs should be considered for genetic testing. Recently new syndromes were described associated with these tumors: Carney-Stratakis and Pacak-Zhuang syndromes.
2. Genetic testing should be based on several considerations: syndromic features, family history, age at diagnosis, multifocal and metastatic presentation, tumor location, and a specific biochemical phenotype.
3. PPGLs are tumors that are mainly diagnosed based on the measurement of plasma or urinary metanephrine and 3-MT since 30% of these tumors do not secrete catecholamines.
4. Patients with metastatic disease should undergo appropriate genetic testing based on the biochemical profile and tumor location.

5. Computed tomography (CT) is the first-choice imaging modality. Magnetic resonance imaging (MRI) is recommended in patients with metastatic PPGL, for detection of skull base and neck PGLs, in patients with surgical clips that cause artifacts when using CT, in patients with an allergy to CT contrast, and in patients in whom radiation exposure should be limited (children, pregnant women, patients with known germline mutations and those with recent excessive radiation exposure).
6. 18F-FDOPA or 68Ga DOTATATE scanning is preferred functional modality in patients with primary solitary or metastatic disease.
7. 123I-MIBG scintigraphy as a functional imaging modality in patients with metastatic PPGL detected by other imaging modalities when radiotherapy using 131I-MIBG is planned.
8. All patients with a hormonally functional PPGL should undergo preoperative blockade with α-adrenoceptor blockers followed by β-adrenoceptor blockade as the first choice to prevent perioperative cardiovascular complications for 7-14 days.
9. Minimally invasive adrenalectomy is recommended for most adrenal PPGLs and open resection for large or invasive PPGLs to ensure complete resection and avoid local recurrence.
10. Multidisciplinary teams at centers with appropriate expertise to ensure favorable outcome should treat all patients with PPGL.

PITUITARY DISORDERS



Pituitary Disorders	10% of Exam
Prolactin	<2%
Hyperprolactinemia	
Normoprolactinemic galactorrhea	
Growth hormone	2%
Acromegaly	
Deficiency	
Thyroid-stimulating hormone (TSH)	<2%
Thyroid-stimulating hormone–secreting adenoma	
Hyperplasia secondary to longstanding primary hypothyroidism	
Thyroid-stimulating hormone deficiency	
Gonadotropins	<2%
Gonadotroph pituitary tumors	
Hypogonadotropic hypogonadism	

Nonsecreting pituitary tumors	<2%
Adrenocorticotropic hormone (ACTH)	<2%
Cushing's disease	
ACTH deficiency	
Hypopituitarism	<2%
Clinical presentation	
Causes	
Tumors	
Pituitary apoplexy	
Sheehan's syndrome	
Hemochromatosis	
Lymphocytic hypophysitis	
Sarcoidosis	
Traumatic brain injury	
Iatrogenic (radiation, surgery)	
Treatment	
Adjustment of growth hormone according to insulin-like growth factor 1 levels	
Monitoring of thyroid with free thyroxine (T4)	
Clinical adjustment of glucocorticoids	
Empty sella syndrome	<2%
Antidiuretic hormone (ADH)	<2%
Diabetes insipidus	
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	
Craniopharyngioma	<2%
Pituitary incidentaloma	<2%

Table 1. Causes of Acquired Adult Hypopituitarism

- **Neoplastic**
  - Pituitary adenoma
  - Craniopharyngioma
  - Meningioma
  - Cysts (Rathke's cleft, arachnoid, epidermoid, dermoid)
  - Germinoma
  - Glioma
  - Astrocytoma
  - Ganglioneuroma
  - Paraganglioma
  - Teratoma
  - Chordoma
  - Pituicytoma
  - Ependymoma
  - Pituitary carcinoma
  - Metastases
- **Treatment of sellar, parasellar, and hypothalamic diseases**
  - Surgery
  - Radiotherapy
- **Infiltrative/inflammatory disease**
  - Autoimmune (lymphocytic hypophysitis, pituitary and POUF-1 antibodies)
  - Hemochromatosis
  - Granulomatous (granulomatosis with polyangiitis, sarcoidosis)
  - Langerhans cell histiocytosis
  - Giant cell granuloma
  - Xanthomatous hypophysitis
- **Infectious**
  - Bacterial
  - Fungal
  - Parasites
  - Tuberculosis
  - Syphilis
- **Vascular**
  - Pituitary tumor apoplexy
  - Sheehan's syndrome
  - Intrasellar carotid artery aneurysm
  - Subarachnoid hemorrhage
- **Traumatic**
  - Head injury
- Medications
  - Opiates (primarily gonadotropin ACTH, GH)
  - GCs (ACTH only)
  - Megestrol acetate (ACTH only)
  - Somatostatin analogs (GH, ACTH, TSH)
  - CTLA-4 blockers (ACTH, TSH, LH/FSH)
- Empty sella
- Idiopathic

Abbreviation: CTLA-4, cytotoxic T-lymphocyte antigen 4. [Derived from Carmichael JD. Anterior Pituitary Failure, Melmed S, editor, The Pituitary 3rd edition, Elsevier; 2011:343–381 with permission, © Elsevier (64).]

Table 2. Clinical Manifestations of Hypopituitarism

Symptom/Sign	Pituitary Trophic Hormone Deficiency
General	
Fatigue, weakness	ACTH, TSH, LH/FSH, GH
Weight gain	TSH
Weight loss	ACTH
Decreased exercise capacity	ACTH, TSH, LH/FSH, GH
Impaired sleep quality	TSH, LH/FSH, GH
Depression	TSH, GH, LH/FSH
Cognitive decline	ACTH, TSH, ?GH
Cold intolerance	TSH
Skin	
Pallor	ACTH, LH/FSH
Dry skin	ACTH, TSH
Thinning hair, loss of body hair	ACTH, TSH, LH/FSH
Cardiovascular/metabolic	
Hypertension	TSH, GH
Hypotension, particularly orthostatic	ACTH
Bradycardia	TSH
Decreased lean body mass, increased fat mass	GH
Hyperlipidemia	TSH, GH
Insulin resistance, impaired glucose tolerance	TSH, GH
Hypoglycemia	ACTH
Impaired cardiac function	ACTH, TSH, GH
Premature atherosclerosis	TSH, GH
Pulmonary	
Shortness of breath, dyspnea on exertion	ACTH, TSH
Gastrointestinal	
Anorexia	ACTH
Nausea/vomiting	ACTH
Diarrhea/loose stools	ACTH
Constipation	TSH
Musculoskeletal	
Muscle weakness	ACTH, TSH, LH/FSH, GH
Osteoporosis, fractures	ACTH, TSH, LH/FSH, GH
Renal	
Increased thirst	ADH
Polyuria, nocturia	ADH
Reproductive	
Oligo/amenorrhea	ACTH, TSH, LH/FSH
Erectile dysfunction	LH/FSH
Low libido	LH/FSH
Hot flashes	LH/FSH
Infertility	LH/FSH
Vaginal dryness	LH/FSH

Derived from S. Melmed and J. L. Jameson: Disorders of the anterior pituitary and hypothalamus. In: Jameson JL, ed. *Harrison's Endocrinology*. 2nd ed. Chap 2. New York, NY: McGraw-Hill Professional; 2010:16–49 (65), with permission.

Table 3. Dynamic Tests for Diagnosing Suspected Hypopituitarism

Hormone Test	Procedure	Interpretation/Expected Normal Response
GH		
Insulin tolerance	Administer insulin, 0.05–0.15 U/kg iv. Sample blood at − 30, 0, 30, 60, 120 min for GH and glucose.	Glucose should drop <40 mg/dL, (2.2 mmol/L). GH should be >3–5 μg/L. Cutoffs for GH response are BMI related.
GHRH[a] + arginine	Administer GHRH, 1 μg/kg (max 100 μg) iv followed by an arginine infusion 0.5 g/kg (max 35 g) over 30 min. Sample blood at 0, 30, 45, 60, 75, 90, 105, and 120 min for GH.	Can give false normal GH response if GHD is due to hypothalamic damage (eg, after radiation). GH >4 μg/L, but cutoffs for GH response should be correlated to BMI. (Obesity may blunt GH response to stimulation.)
Glucagon	Administer glucagon, 1 mg (1.5 mg if weight >90 kg) im. Sample blood at 0, 30, 60, 90, 120, 150, 180, 210, and 240 min for GH and glucose.	GH >3 μg/L, but cutoffs for GH response should be correlated to BMI. (Obesity may blunt GH response to stimulation.)
ACTH		
Insulin tolerance	Administer insulin, 0.05–0.15 U/kg iv. Sample blood at −30, 0, 30, 60, and 120 min for cortisol and glucose.	Glucose should drop <40 mg/dL (2.2 mmol/L). Peak cortisol should be >500–550 nmol/L (>18.1–20 μg/dL) depending on assay.
Corticotropin standard dose (250 μg)	Administer ACTH 1–24 (cosyntropin), 250 μg im or iv. Sample blood at 0, 30, and 60 min for cortisol.	Cortisol should be at 30 or 60 min >500–550 nmol/L (>18.1–20 μg/dL) depending on assay.
Corticotropin low dose (1 μg)	Administer ACTH 1–24 (cosyntropin), 1 μg iv. Sample blood at 0 and 30 min for cortisol.	Cortisol should be at 30 min >500 nmol/L (18.1 μg/dL) depending on assay.
ADH		
Water deprivation test	Initiate fluid deprivation for 8h (starting from 8 AM). Weigh patient at beginning of testing, then measure weight and urine volume hourly during the test. Measure plasma and urine osmolality every 2–3 h. At 4 PM administer DDAVP 2 μg im and allow patient to drink freely. Notes: If plasma osmolality >305 mOsm/kg or if 3% loss of body weight with plasma osmolality >305 mOsm/kg, proceed to DDAVP administration earlier. If urine output has not decreased and/or urine osmolality/plasma osmolality ratio <2, but the plasma osmolality has not concentrated to >295 mOsm/kg, continue water deprivation for a further hour and measure plasma and urine osmolality. Offer DDAVP after this. Continue measuring urine osmolality hourly for the next 4 h (after DDVAP administration) and measure hourly urine volumes. Stop test if >3% weight loss occurs.	Plasma osmolality >295 mOsm/L with inappropriately hypotonic urine (urine osmolality/plasma osmolality ratio <2) during the fluid deprivation confirms DI (test is discontinued). After administering DDVAP, urine concentrates >800 mOsm/kg with central DI and <300 mOsm/kg with nephrogenic DI. With partial DI or primary polydipsia, urine concentrates partially during the water deprivation test (300–800 mOsm/kg), and further investigation is required including a prolonged water deprivation test or DDVAP therapeutic trial.

Table 4. Dose Equivalence for GCs

Equivalent Dose	GCs
20 mg	HC
5 mg	Prednisone
0.75 mg	Dexamethasone
4 mg	Methylprednisolone
5 mg	Prednisolone
25 mg	Cortisone

Table 6. Patient Monitoring After Initiating Adult GH Replacement

1. Measure IGF-1 6 weeks after initiating GH replacement, after dose escalations, and every 6 months thereafter.
2. Assess body weight, blood pressure, waist circumference, and BMI every 6 months.
3. Assess thyroid and adrenal function and replace or adjust replacement doses as indicated.
4. Assess metabolic profile including blood sugar and lipids every 6 months.
5. Assess BMD by DXA every 18 months.
6. Periodically assess residual pituitary mass via a pituitary MRI
7. Assess QOL.

Abbreviation: DXA, dual-energy x-ray absorptiometry. [Derived from S. Melmed: Idiopathic adult growth hormone deficiency. *J Clin Endocrinol Metab*. 2013;98:2187–2197 (167), with permission. ©The Endocrine Society.].

Table 7. Dose Comparisons of Available Desmopressin Formulations

	Melts	Tablets	Spray	Drops	Injections
Bioavailability	0.25% (95% CI, 0.21–0.31%)	0.16 ± 0.17%	6.0 ± 2.29%	Similar to spray?*	NA
Dose equivalence	60 μg	100 μg	2.5 μg	2.5 μg	NA
	120 μg	200 μg	5.0 μg	5.0 μg	<0.5 μg
	240 μg	400 μg	10.0 μg	10.0 μg	<1.0 μg

Abbreviations: *?, unclear; NA, not applicable. [Derived from Y. Oiso et al: Clinical review: treatment of neurohypophyseal diabetes insipidus. *J Clin Endocrinol Metab*. 2013;98:3958–3967 (183), with permission. © Endocrine Society.].

Pituitary incidentaloma

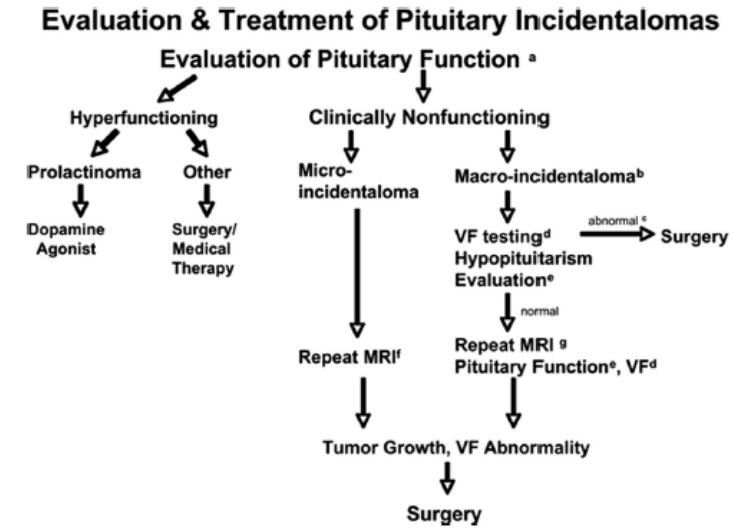
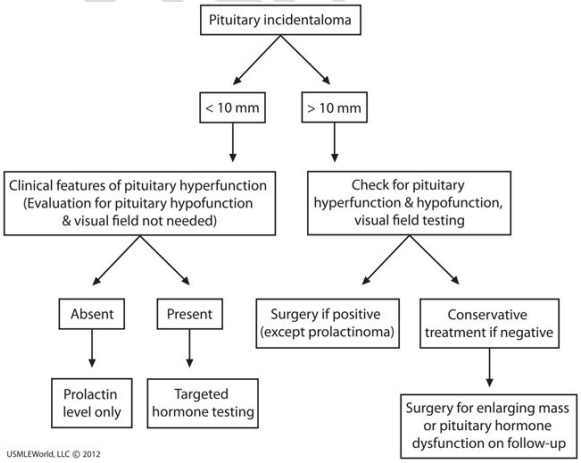


FIG. 1. Flow diagram for the evaluation and treatment of pituitary incidentalomas. a, Baseline evaluation in all patients should include a history and physical exam evaluating for signs and symptoms of hyperfunction and hypopituitarism and a laboratory evaluation for hypersecretion. b, This group may also include large microlesions (see *Section 2.1 Evidence*). c, The recommendation for surgery includes the presence of abnormalities of VF or vision and signs of tumor compression (*Section 3.1*); surgery is also suggested for other findings (see *Section 3.2*). d, VF testing is recommended for patients with lesions abutting or compressing the optic nerves or chiasm at the initial evaluation and during follow-up. e, Evaluation for hypopituitarism is recommended for the baseline evaluation and during follow-up evaluations. This is most strongly recommended for macrolesions and larger microlesions (see *Section 1.3*). f, Repeat MRI in 1 yr, yearly for 3 yr, and then less frequently thereafter if no change in lesion size. g, Repeat the MRI in 6 months, yearly for 3 yr, and then less frequently if no change in lesion size. [Modified from Molitch ME: *J Clin Endocrinol Metab* 80:3–6, 1995 (49).]

- Small lesions 2-4mm require no further testing
- Lesions 5-9mm require follow up MRI in 12months to document stability
- Lesions >10mm should be evaluated for hyper/hypo function
- **Prevalence of incidentalomas is 10% of the population**



Differential Diagnosis of a thickened stalk

- Langerhans Cell Histiocytosis (Histiocytosis X)
- Sarcoidosis
- Dysgerminoma
- Infundulohypophysitis
- Metastasis
- Tuberculosis
- Lymphoma
- Infundibuloma

Symptoms of Sellar Metastases

- Diabetes insipidus
- Hypopituitarism
- Retroorbital pain or headache
- Visual field deficits
- CN Palsies -- III,IV,V1,V2,VI
- Anorexia, nausea and vomiting.

Causes of hyperprolactinemia

Physiologic
- Pregnancy
- Breast feeding
- Stress

Pathologic
- Pituitary adenoma & macroprolactinoma
- Hypothalamic disease with ↓dopamine secretion (e.g., malignancy, sarcoidosis)
- Drugs (e.g., antidepressants, antipsychotics, metoclopramide)
- Hypothyroidism
- Chest wall injury (including herpes zoster)
- Chronic kidney disease
- Following generalized tonic-clonic or partial complex seizure

16

[16] It is astonishing with how little reading a doctor can practise medicine, but it is not astonishing how badly he may do it.

TABLE 1. Etiology of hyperprolactinemia

- Physiological
  - Coitus
  - Exercise
  - Lactation
  - Pregnancy
  - Sleep
  - Stress
- Pathological
  - Hypothalamic-pituitary stalk damage
    - Granulomas
    - Infiltrations
    - Irradiation
    - Rathke's cyst
    - Trauma: pituitary stalk section, suprasellar surgery
    - Tumors: craniopharyngioma, germinoma, hypothalamic metastases, meningioma, suprasellar pituitary mass extension
  - Pituitary
    - Acromegaly
    - Idiopathic
    - Lymphocytic hypophysitis or parasellar mass
    - Macroadenoma (compressive)
    - Macroprolactinemia
    - Plurihormonal adenoma
    - Prolactinoma
    - Surgery
    - Trauma
  - Systemic disorders
    - Chest—neurogenic chest wall trauma, surgery, herpes zoster
    - Chronic renal failure
    - Cirrhosis
    - Cranial radiation
    - Epileptic seizures
    - Polycystic ovarian disease
    - Pseudocyesis
- Pharmacological
  - Anesthetics
  - Anticonvulsant
  - Antidepressants
  - Antihistamines (H_2)
  - Antihypertensives
  - Cholinergic agonist
  - Drug-induced hypersecretion
  - Catecholamine depletor
  - Dopamine receptor blockers
  - Dopamine synthesis inhibitor
  - Estrogens: oral contraceptives; oral contraceptive withdrawal
  - Neuroleptics/antipsychotics
  - Neuropeptides
  - Opiates and opiate antagonists

Adapted from Melmed and Kleinberg (28).

Indications for treatment of prolactinoma	
Females	• Presence of classic symptoms (e.g., amenorrhea and galactorrhea) • Infertility without classic symptoms • Osteoporosis and risk for bone loss • Acne and hirsutism
Males	• Hypogonadism and gynecomastia • Osteoporosis and risk for bone loss
Both Sexes	• Enlargement of adenoma

Prolactinoma (Essential Pearls)

1. Large macroadenoma with marginally elevated prolactin -- ?hook effect → dilution of sample
2. High risk for CSF leak after dramatic response to dopamine agonist therapy -- > Send Beta-2 transferrin
3. Risk for apoplexy with initiation of therapy
4. Worsening of visual field defects without evidence of enlargement or apoplexy on MRI should raise the possibility of a tethered chiasm -- STOP dopamine agonist -- refer to Neurosurgery!

Cystic Prolactinoma -- what to do?

Drainage if visual field defects.
Small without compression of chiasm -- medical therapy (majority respond to therapy)

Acromegaly

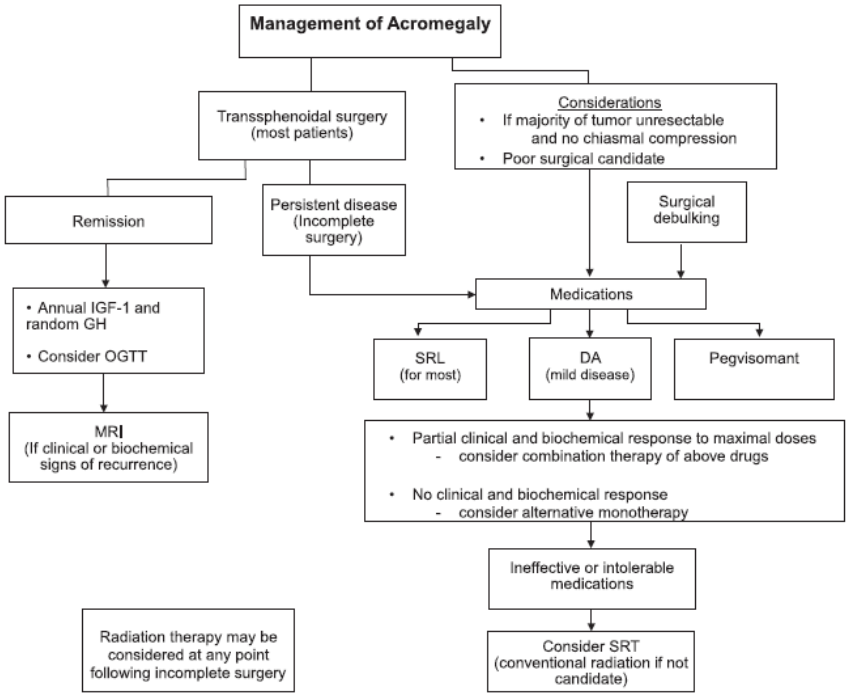
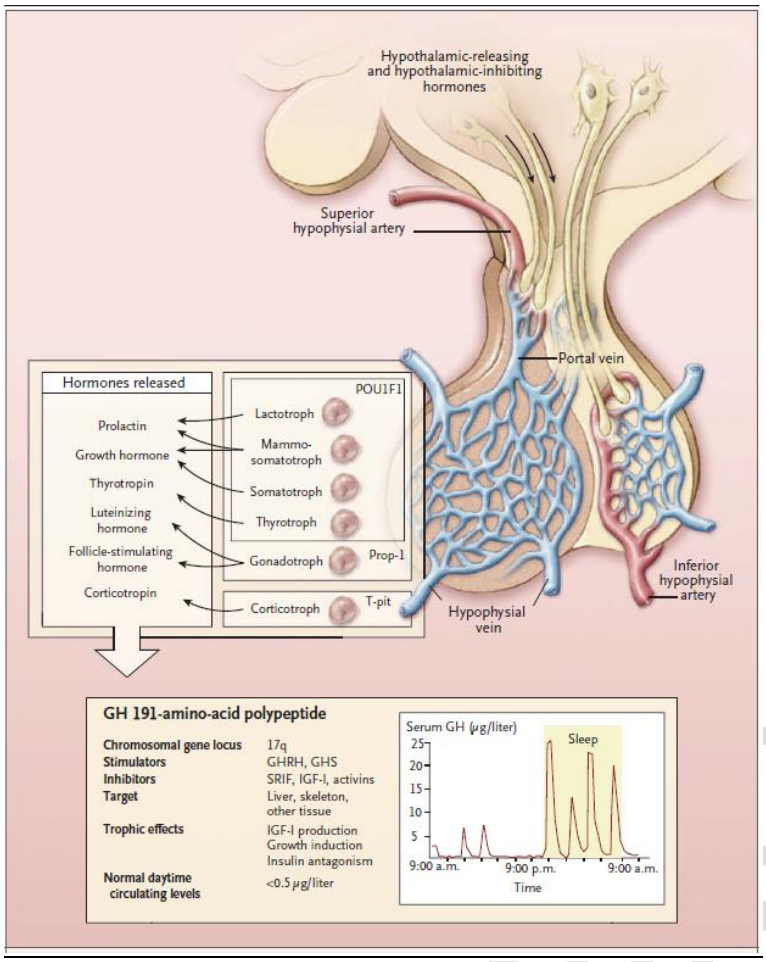


Figure 1. Treatment considerations in the approach to a patient with acromegaly. This approach refers to management of a patient with a pituitary adenoma. DA, dopamine agonist; OGTT, oral glucose tolerance test.



- IGF-1 levels do not fluctuate, unlike GH.
- Levels of IGF-1 can however decrease with age.
- Preferred screening test for acromegaly
- Confirmatory test : 75g oral glucose load. Patients without acromegaly have a decrease in GH levels <1ng/dL (within two hours)
-

Dysglycemia in GH excess

- Dysglycemia is present in approximately 50% of patients with acromegaly (diabetes 10–15% and prediabetes 20–40%).
- It is more prevalent in those who have long duration of disease, higher GH levels, and family history of diabetes. Diabetes in acromegaly occurs despite GH-mediated β-cell hyperplasia

Mechanism of dysglycemia in acromegaly

- **Acromegaly is characterized by chronic GH and IGF1 excess, and these hormones have opposing effects on glucose metabolism; IGF1 has insulin like effects, whereas GH has insulin-antagonistic properties; the effects of GH predominates over IGF1.**
- GH antagonizes the action of insulin at the liver, skeletal muscle, and adipocytes, and this results in increased hepatic glucose output due to augmented glycogenolysis and gluconeogenesis
- reduced uptake of glucose into muscle and adipocytes, and increased lipolysis

- Hyperglycemia associated with acromegaly is frequently severe and diffi cult to treat

Evaluate for GH excess in resistant diabetes.

Common clinical features of untreated acromegaly	
Local tumor effect	Pituitary enlargement, visual field defects, headache, cranial nerve defects
Musculoskeletal/Skin	Gigantism, mal-occluded jaw, arthralgias/arthritis, proximal myopathy, hyperhidrosis, skin tags, carpal tunnel syndrome
Cardiovascular	Cardiomyopathy, hypertension, heart failure, valvular disease (eg, mitral and aortic regurgitation)
Pulmonary/GI	Sleep apnea, narcolepsy, colon polyps/cancer, diverticulosis
Enlarged organs	Tongue, thyroid, salivary glands, liver, spleen, kidney, prostate
Endocrine	Galactorrhea, decreased libido, diabetes mellitus, hyperparathyroidism, hypertriglyceridemia

** Almost every organ in body requires GH–IGF1 for their growth and proliferation.

- The only exceptions are brain and eye, as their growth is GH–IGF1
- independent

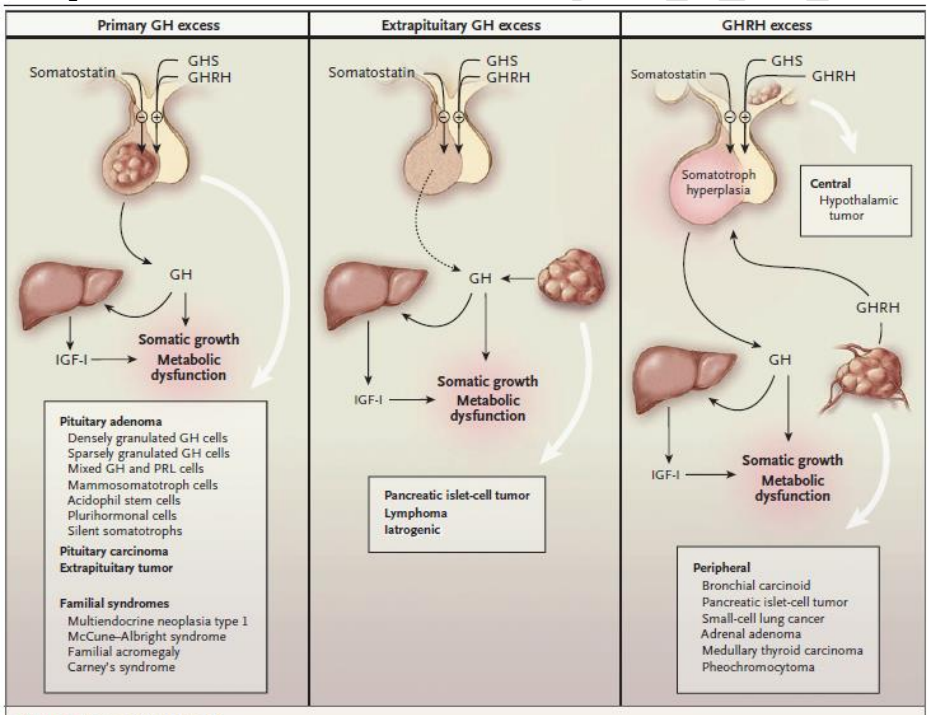


Figure 2. Causes of Acromegaly.
In most patients, acromegaly is caused by excessive production of growth hormone (GH) or GH-releasing hormone (GHRH). In rare cases, the disease is associated with familial syndromes, including multiple endocrine neoplasia type 1, the McCune–Albright syndrome, familial acromegaly, and Carney's syndrome (see Table 2 in the Supplementary Appendix). GHS denotes growth hormone secretagogues, and PRL prolactin.

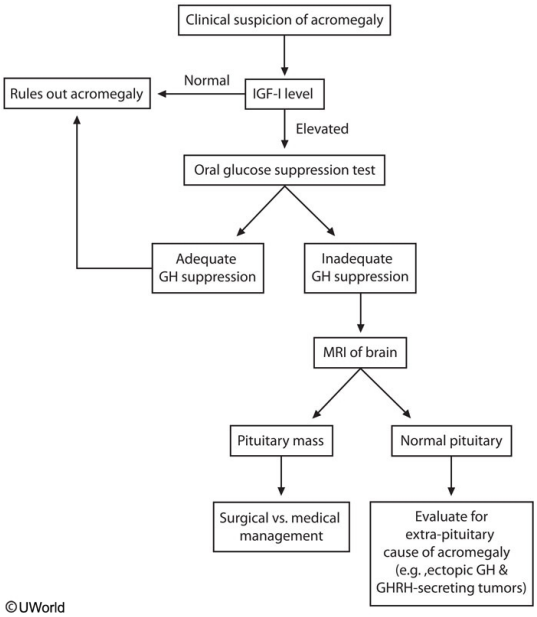
Table 1. Clinical Features of Acromegaly.

Local tumor effects	**Visceromegaly**
Pituitary enlargement	Tongue
Visual-field defects	Thyroid gland
Cranial-nerve palsy	Salivary glands
Headache	Liver
Somatic systems	Spleen
Acral enlargement, including thickness of soft tissue of hands and feet	Kidney
	Prostate
Musculoskeletal system	**Endocrine and metabolic systems**
Gigantism	Reproduction
Prognathism	Menstrual abnormalities
Jaw malocclusion	Galactorrhea
Arthralgias and arthritis	Decreased libido, impotence, low levels of sex hormone–binding globulin
Carpal tunnel syndrome	
Acroparesthesia	Multiple endocrine neoplasia type 1
Proximal myopathy	Hyperparathyroidism
Hypertrophy of frontal bones	Pancreatic islet-cell tumors
Skin and gastrointestinal system	Carbohydrate
Hyperhidrosis	Impaired glucose tolerance
Oily texture	Insulin resistance and hyperinsulinemia
Skin tags	Diabetes mellitus
Colon polyps	Lipid
Cardiovascular system	Hypertriglyceridemia
Left ventricular hypertrophy	Mineral
Asymmetric septal hypertrophy	Hypercalciuria, increased levels of 25-hydroxyvitamin D_3
Cardiomyopathy	Urinary hydroxyproline
Hypertension	Electrolyte
Congestive heart failure	Low renin levels
Pulmonary system	Increased aldosterone levels
Sleep disturbances	Thyroid
Sleep apnea (central and obstructive)	Low thyroxine-binding–globulin levels
Narcolepsy	Goiter

Unusual presentations of acromegaly?

- Malocclusion of jaw
- diabetic ketoacidosis
- pituitary apoplexy
- CSF rhinorrhea
- Facial asymmetry (fibrous dysplasia in McCune–Albright syndrome)
- tonsillomegaly
- recurrent nasal obstruction (nasal polyp)
- severe hirsutism, entrapment neuropathy
- dilated cardiomyopathy
- cutis verticis gyrata
- frontal lobe syndrome (antesellar extension of tumor or anterior cerebral artery spasm due to apoplexy).[17]

[17] When the hopeless attempt is made to cram the work of two years into a six months' session, with results only too evident to your examiners.



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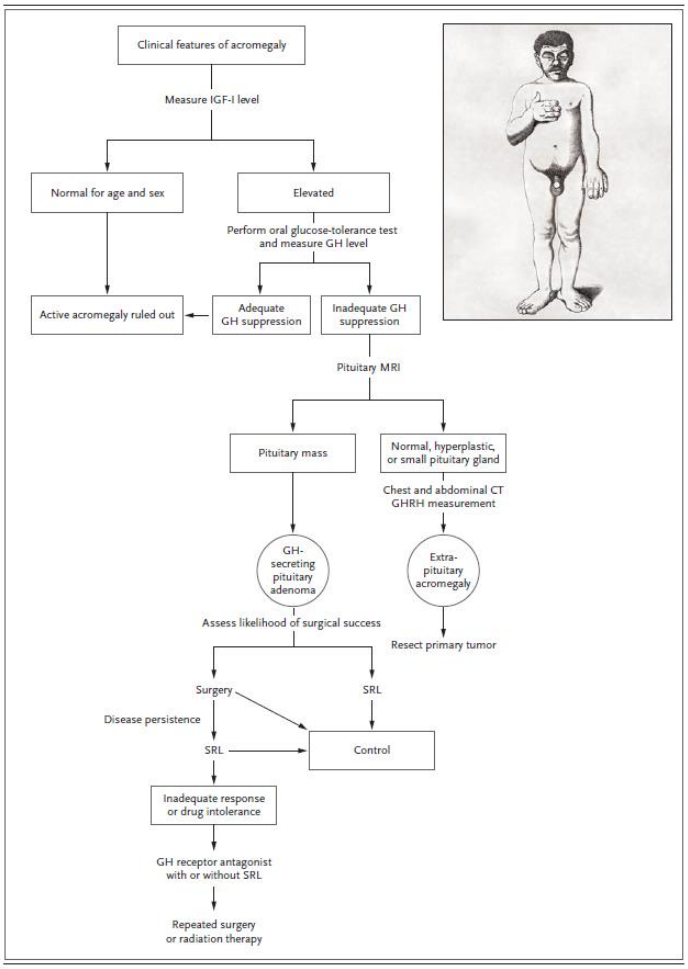


Management of Acromegaly/GH excess

best screening test for the diagnosis of acromegaly is serum insulin like growth factor 1 (IGF1), with a sensitivity of 97% and specificity of 90%.

- long half-life (12–15 h)
- secreted in a non-pulsatile manner
- serum IGF1 has a log-linear relationship with circulating GH levels.

IGF1 production is facilitated by FT4, insulin, testosterone and estrogen(low levels) and inhibited by cytokines.
The **causes of low IGF1 in patients with acromegaly** include uncontrolled diabetes mellitus, hypothyroidism, hypogonadism, hepatic or renal failure, malnutrition, systemic illness,
catabolic states, and oral estrogen therapy.

Confirmatory test for acromegaly : inability to suppress serum GH <1g/mL after 75g oral glucose load.
** reasons for non-suppressible GH after an oral glucose load. Uncontrolled diabetes, hypothyroidism, puberty, pregnancy, depression, chronic liver or renal disease, and anorexia nervosa.

Non-suppressed GH and low/normal IGF1	Suppressed GH and high IGF1
Poorly controlled DM	Mild acromegaly
Hypothyroidism	Immediate postoperative period
Oral contraceptive use	Post-radiotherapy
Liver failure	Hyperthyroidism
Renal failure	
Hyperthyroidism	
Early recurrence after surgery	
Somatostatin analogue therapy	
Dopamine agonist therapy	
Pegvisomant therapy	

* IGFBP3 may be useful in case of discrepancy between GH and IGF1. also in cases of uncontrolled DM.
** Optimize blood glucose (not necessarily HbA1C prior to testing).

Who should be screened for acromegaly

- Screening is recommended in patients with typical signs and symptoms of acromegaly.
- type 2 diabetes mellitus, hypertension, sleep apnea syndrome, debilitating arthritis, carpal tunnel syndrome, and hyperhidrosis

Further evaluation after confirmation of diagnosis

- serum calcium, phosphorus
- blood glucose
- lipid profile
- Hormonal profi le include
- T4 , TSH, 0800 h cortisol, testosterone/estradiol, and prolactin
- Contrast enhanced MRI sella should be done to localize ***
- EKG
- Colonoscopy at baseline
- DXA in hygogonadal patients

*** No adenoma on sellar imaging differentials : Silent apoplexy, ectopic GHRH-secreting NET, McCune-Albright syndrome, ectopic pituitary adenoma (sphenoid sinus location). Majority
of these patients have **macroadenoma (75–80%),** while the rest have microadenoma (20–25%).

Surgical Management of GH excess

Transsphenoidal surgery is the primary modality of therapy in all patients with acromegaly, irrespective of tumor size. The surgical cure rate is 80–90% in patients with microadenoma and 50% in macroadenoma.

preoperative cardiac evaluation, airway assessment, adequate replacement therapy for pituitary hormone deficiencies, and optimal blood glucose and blood pressure control

Factors predicting poor response to surgery and/or medical therapy

- Young age at onset
- GH > 40ng/ml
- Large and invasive tumors (eg. involvement of cavernous sinus)
- AIP gene mutation
- Sparsely granulated tumors on histology (hyperintense on T2 weighted MRI)
- Over expression of proliferative indices like Ki67, p53 and pituitary transforming gene (PTTG)
- Reduced expression of somatostatin receptors subtype 2 and 5, predicts poor response to somatostatin analogues.

Prediction of remission post surgery

1. A postoperative day 1 fasting serum GH level <2 ng/mL is predictive of clinical and biochemical remission at 5 years.
2. GH–GTT can be performed as early as the 1st week postoperatively, and nadir GH level <1 ng/ml is predictive of remission in 98% individuals at 5years.

NB: However, immediate postoperative assessment of GH (random or GH–GTT) may be influenced by surgical stress-induced increase in GH secretion; hence the current guidelines do not favor this approach

Clinical assessment	Soft tissue regression
	Disease activity (e.g., hyperhidrosis, seborrhea, headache, arthralgia)
	Visual field and acuity
Biochemical assessment	IGF1 and random GH
	GH following glucose load if random GH >1 ng/ml
	T_4, 0800 h cortisol, prolactin, testosterone/estradiol
MR imaging	If disease is biochemically active

Cure vs controlled disease vs active disease

CURE

- resolution of symptoms and signs
- Normalization of age-adjusted IGF1
- Random GH<1ng/ml
- Restoration of GH suppressibility after glucose load i.e <0.4ng/ml
- Preservation of other pituitary hormone
- Complete removal of disappearance of the tumor

CONTROLLED DISEASE

- resolution of symptoms and signs
- normalization of age-adjusted IGF1
- random GH <1 ng/ml
- nadir GH <0.4 ng/ml after glucose load

ACTIVE DISEASE

- Elevated age-adjusted IGF1
- random GH >1 ng/ml
- nadir GH after glucose load >0.4 ng/ml
- with or without clinical signs or symptoms of acromegaly

Indications for medical therapy in GH excess

- *high risk* for surgery due to multiple comorbidities
- *Invasive macroadenoma* (e.g., parasellar extension) *without mass effects*
- *McCune–Albright syndrome* either because of absence of tumor (**constitutive activation of Gsα subunit**) or difficult surgery due to **cranial fibrous dysplasia**.

NB: Medical treatment as a primary modality should be discouraged in patients with
microadenoma, where the cure rate after surgery is 80–90%.

Management of active disease after transsphenoidal surgery

- Repeat surgery
- Medical therapy (somatostatin receptor ligands, dopamine agonists and GH receptor antagonist eg. pegvisomant)
- Radiotherapy

*** in clinical practice, redo surgery should be considered wherever it is feasible. Otherwise, radiotherapy with interim medical therapy should be offered to a patient with persistent disease.

Medical therapy in GH excess

Somatostatin receptor ligands	Octreotide and lanreotide
Mechanism of action	• Affinity for somatostatin receptor subtype 2 and 5. Affinity for subtype 2 is 10x higher (the dominant subtype expressed in somatotropinomas) • Suppress the release of GH via inhibition of cAMP • Antiproliferative action through cell cycle arrest • Karyhorrhexis • Impaired angiogenesis
Pan-somatostatin	Pasireotide*

receptor ligand inhibition	• High affinity for somatotropin receptor subtypes 1,2,3,5 (predominant affinity for subtype 5) • Higher rates of IGF1 normalization, but similar rates of GH normalization when comparing pasireotide to octreotide. • Hyperglycemia is its major side effect • DOC for sparsely granulated somatotropinomas which are resistant to conventional SRL (high subtype 5)

* This difference in GH and IGF1 response can be explained by the additional effect of pasireotide on hepatocytes (which express SSTR 1, 3, and 5 subtypes) and greater inhibitory effect on insulin secretion (as insulin also mediates IGF1 generation)

somatostatin receptor ligands (SRL)

Octreotide	• IM injection once a month • Initial dose is 20mg monthly • Increase to 30-40mg per month if IGF1 doses not normalize within 3 months.
Lanreotide	• 30mg every 7-14days IM • 60-120mg q4-6 weeks as autogel or depot
Side effects of somatostatin analogues	• Gastrointestinal discomfort • Gallstone disease • dysglycemia
Pegvisomant	• Preferred if hyperglycemia develops on somatostatin receptor ligand therapy. • SRL therapy-resistant acromegaly

"Somatostatin receptor ligand resistance" in acromegaly is defined as failure to reduce serum **GH and IGF1 levels to <50%** or **tumor shrinkage <20%** or increase in tumor size despite optimal treatment with **somatostatin ligands for at least 1 year.**

Dopamine receptor agonists

Cabergoline	**Mechanism** • Dopamine, through its action on the hypothalamus, causes GH release by increasing GHRH and, through its action on the pituitary gland, inhibits GH release. • In the physiological state, hypothalamic action of DA predominates, thereby increasing GH secretion, which is exploited in testing GH

	reserve • D2 receptors are overexpressed on somatotropinoma, and DAs directly inhibit GH release through its action on the pituitary gland thereby overcoming the hypothalamic effects.
Role in management	Cabergoline normalizes GH and IGF1 only in <15% of patients, without significant reduction in tumor size.
Indications	• mildly elevated IGF1 • adjunctive therapy after surgical debulking • interim period following radiotherapy • suboptimal response to somatostatin receptor ligand therapy
Side effect	Valvulopathy

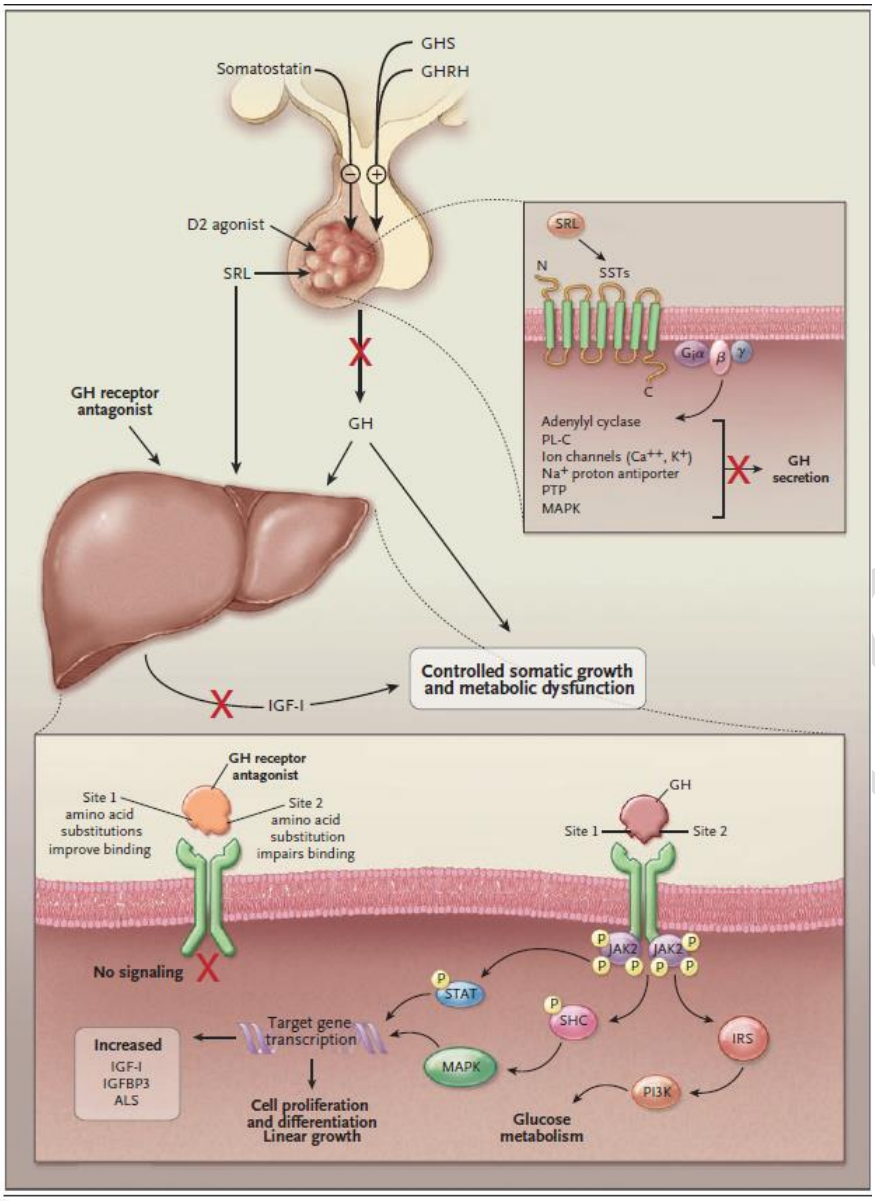
Pegvisomant

- Adverse effects associated with pegvisomant therapy are **hepatotoxicity** and **lipodystrophy**
- monitor liver function test monthly for the initial 6 months after starting pegvisomant and biannually thereafter.
- Pegvisomant should be avoided in patients with large tumors abutting the optic chiasm or any other vital structures (increase in size of tumor in 3-5% of patients).

Advantages of SLR and Pegvisomant combination therapy

- Effective control of GH and IGF1 levels
- Decreased incidence of dysglycemia
- Lesser requirement of pegivosomant dose
- Reduction in risk of increase in tumor size

** NB: Higher incidence of transaminitis.



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Radiotherapy treatment options in GH excess

	Stereotactic radiosurgery	**Conventional radiotherapy (fractionated)**
Mode of delivery	single sitting delivery, targeted therapy to the tumor tissue (resulting in lesser probability of	multiple small doses or radiation

[18] It goes without saying that no man can teach successfully who is not at the same time a student.

	damage to surrounding brain parenchyma)	
Indications/Contraindications	• Avoid SRS when the optic pathway is involved, since it is sensitive to single large doses of radiation.	• substantial residual tumor burden (tumor size >3cm) • tumor is too close to the optic chiasm (within 5mm).
Remission	mean time for the achievement of remission is 2 years after SRS	5–10 years with conventional radiotherapy.

Radiation induced Brain Injury

Presentation	• Seizures • Cognitive dysfunction • Rapid vision loss • Altered sensorium • Rarely secondary malignancies
Risk factors	• Old age • Functioning pituitary tumors (e.g acromegaly and cushings disease) • External beam radiation and radiation dose exceeding 2 Gy per fraction
Mechanisms	• Free radical mediated tissue injury • Progressive vascular damage • Direct brian tissue injury by radiation
Treatment	• Glucocorticoids • Mannitol • antiepileptics
Evaluation	MRI findings are nonspecific (shrinkage of brain volume, ventricular dilatation, periventricular hyperintense areas on T1WI, cerebral edema and necrosis)

Pregnancy and GH excess

Diagnosis	• Nonsuppressible GH after glucose load and mildly elevated IGF1 occur in normal pregnancy due to placental production of GH. • Serum IGF1 is highly elevated and establishes diagnosis
Natural hx	Acromegaly does not worsen due to relative GH-resistant state in the setting of higher estrogren levels.
Neonatal outcome	GH and IGF1 do not cross the placenta, therefore no direct deleterious effect on neonatal outcome
Overall pregnancy outcome	GH-IGF1 excess associated comorbidities such as hyperglycemia and HTN need to be aggresively treated.
Monitoring	Visual field testing and acuity
Indications for treatment	Worsening headache or compressive symptoms Tx : surgery or somatostatin analogues/cabergoline

ADULT GROWTH HORMONE DEFICIENCY

Effects of growth hormone deficiency (AGHD) Acquired or inherited
• Increased cardiovascular mortality • Increased central adiposity • Hyperlipidemia • Osteoporosis • Decreased QoL • Psychologic dysfunction

Pattern of hormonal deficiencies with compressive pituitary lesions

1. Low evoked GH
2. Low gonadotropins
3. Low TSH…and finally
4. Low ACTH

Causes of acquired growth hormone deficiency

Trauma -- traumatic sports, military personnel
CNS infection
Radiation
CVA -- stroke, subarachnoic hemorrhage
Surgery

Tumors
- Pituitary adenoma
- Craniopharyngioma
- Rathke's cleft cyst
- Glioma
- Metastatic

Infiltrative/granulomatous
- Histiocytosis
- Sarcoidosis
- Tuberculosis
- Hypophysitis -- immune checkpoint inhibitors

Cryptic
- Transcription factor antibodies
- Subtle structural changes

Likely of growth hormone deficiency is 100% between 3-4 central pituitary hormone deficiencies (Hartman, JCEM in 2002)

Assessment of growth hormone deficiency.
Growth hormone stimulation

1) Insulin tolerance testing -- 0.1units/kg IV regular insulin. Growth hormone cut off of 5ug/l. (GOLD Standard)
2) Arginine/GHRH -- Not available
3) Glucagon stimulation -- Glucagon 1mg IM, 1.5mg if >90kg . GH cut off of 3ug/l. Available.

Endocrine society guidelines - Growth hormone deficiency

1. If GHD is suspected, perform GH stimulation test
2. Use appropriately controlled BMI cut offs to assess peak GH values
3. In patients with clear cut features and three other pituitary hormone deficits, biochemical testing is not recommended when IGF-1 is low.

Effect of growth hormone replacement
● Lean body mass increases ● Fat mass decreases ** *Evidence Salomon. NEJM 1989* ● All fractures - vertberal and nonvertebral fractures reduced! ● Improved QoL markers ● Improved mortality outcomes ** evidence not as rigorous

** Estrogen blocks GH action - women tend to require a higher dose. Same for OCPs

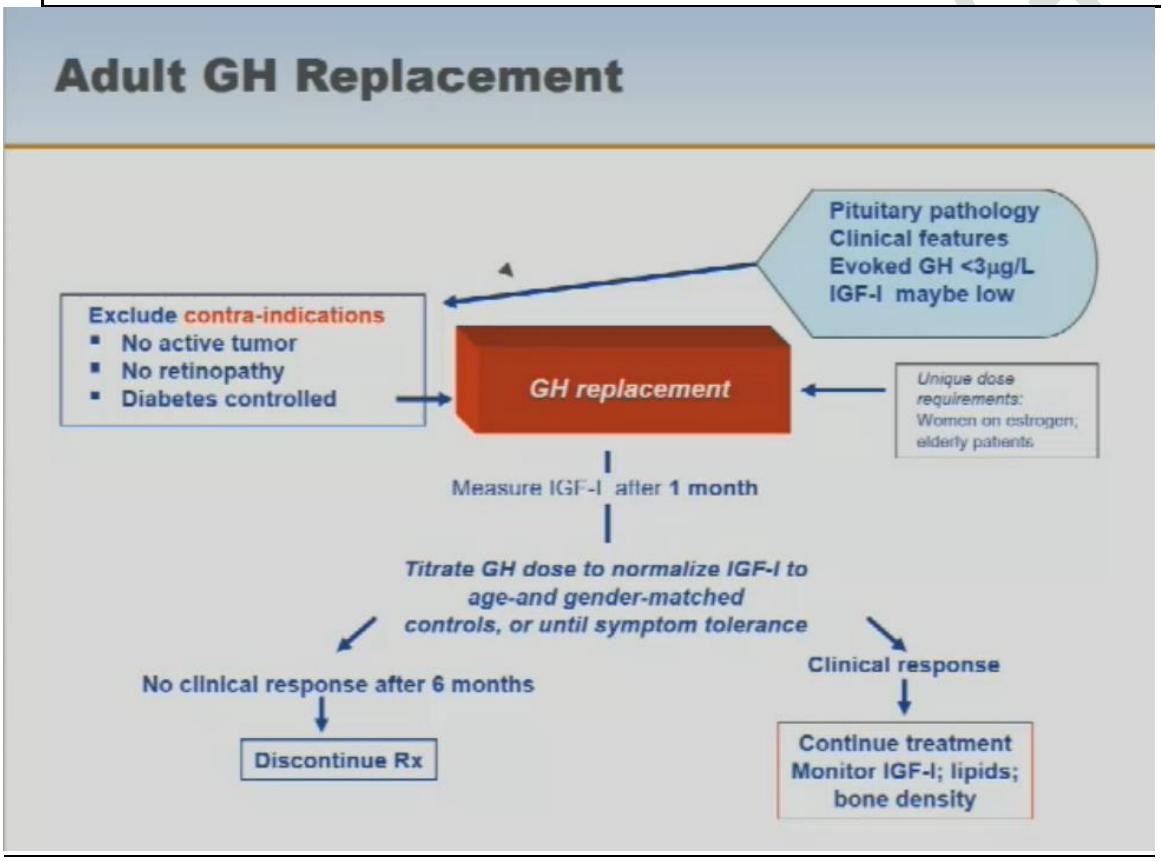
Guidelines for Adult GHD GH Replacement

Pre-Rx:	Elicited GH response IGF-1, glucose, lipids Replacement of other hormone deficits Pituitary imaging Body composition
Dose:	0.15-0.3 mg/day Monthly increment 0.01-0.15 mg/day
Monitor:	IGF-1 (dose titration) Lipids, glucose Weight, body composition, quality of life
Side effects:	Edema, arthralgia, myalgia, parasthesia
Dosage considerations:	Avoid weight-basing Women require **more** GH Elderly require **less** GH Doses higher with oral estrogens
Contraindications:	Malignancy, intracranial hypertension, retinopathy

Side effects of Growth hormone replacement

1) **COMMON**
- Fluid retention
- Arthralgias
- Myalgias
- Headache

2) **RARE**
- Hypertension
- Hyperglycemia
- anorexia



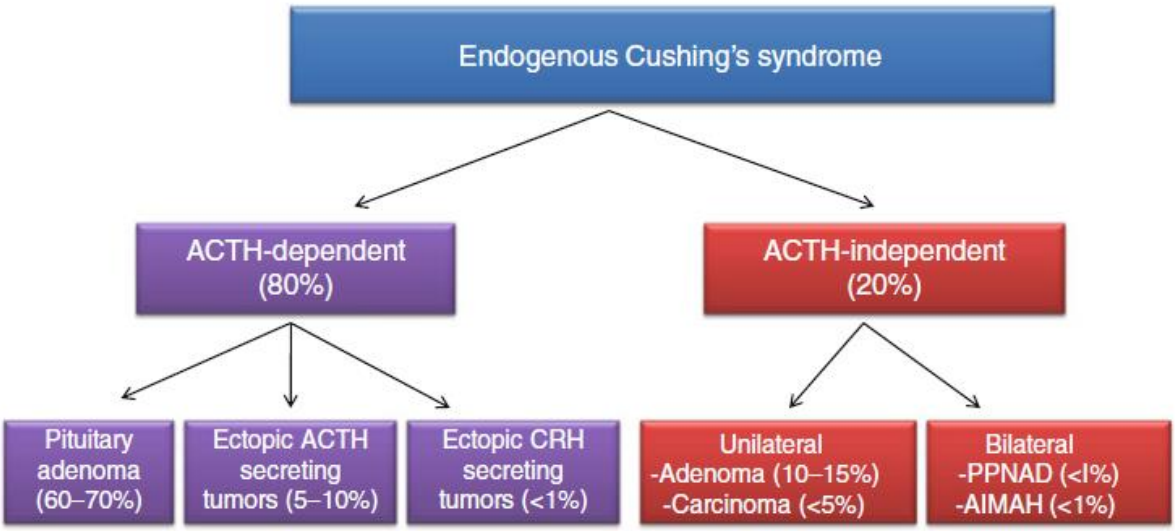
IGF-1 half life of 36hrs
GH half life of 10minutes

CUSHINGS SYNDROME

Patients with low ACTH levels <5pg/mL have an ACTH independent, cortisol secreting adrenal mass. CT of the adrenals should be ordered

High ACTH levels means a **pituitary adenoma** or **ectopic ACTH production**. Pituitary adenoma's are most common cause of high ACTH cushings syndrome, thus an MRI of the pituitary should always be ordered in this setting.

Cushing's syndrome is a disorder of **chronic glucocorticoid excess** and is characterized by features of protein catabolism along with varying signs and symptoms. The most common cause of Cushing's syndrome is exogenous administration of glucocorticoids



Primary pigmented nodular adrenocortical disease (PPNAD)
ACTH-independent macronodular adrenal hyperplasia (AIMAH)

Cushing's disease is the most common cause of endogenous Cushing's syndrome. Approximately 90% of patients with Cushing's disease have microadenoma, while macroadenoma contributes to the rest.

Hypercortisolemia in the absence of clinical features of Cushing's syndrome

- stress (hospitalization, surgery, and pain),
- intense chronic exercise
- Malnutrition
- anorexia nervosa
- cortisol-binding globulin (CBG) excess states

Pseudo - Cushing ' s syndrome

a group of reversible disorders with subtle symptoms and signs of Cushing's syndrome and hypercortisolism with anomalous response to dexamethasone suppression tests.

- Morbid obesity,
- Depression
- Alcoholism
- metabolic syndrome
- poorly controlled diabetes
- polycystic ovarian disease are associated with pseudo-Cushing's syndrome.

Cyclical Cushing's syndrome

characterized by periods of waxing and waning symptoms and signs of hypercortisolemia and anomalous results of cortisol dynamic tests. It is biochemically defined as presence of three peaks and two troughs of cortisol secretion over a period of time (usually weeks to months).

Mechanism	periodic hormonogenesis is a commonly purported mechanism; periodicity in hormone biosynthesis may be due to **recurrent hemorrhage in the tumor** or **early programmed tumoral cell death**.
location	pituitary (54%), ectopic (26%), or even with adrenal Cushing's (11%).
Diagnostic testing *	require frequent monitoring with 24hr urine free cortisol or late-night salivary cortisol

***** Dexamethasone suppression test (DST) is not preferred

Subclinical Cushing's syndrome

- Subclinical Cushing's syndrome is characterized by *lack of specific symptoms and signs of Cushing's syndrome, but with evidence of autonomous glucocorticoid secretion.*
- commonly *diagnosed during evaluation for an adrenal incidentaloma.*
- diagnostic cutoff for subclinical Cushing's syndrome following 1 mg overnight dexamethasone suppression test (ONDST) is **0800h cortisol > 5 µg/dl**, with a specificity of 100%, instead of **>1.8 µgm/dl as in overt Cushing's syndrome**
- Suppressed dehydroepiandrosterone sulfate (DHEAS) and ACTH are surrogate evidences for the presence of subclinical Cushing's syndrome.

Causes of weight loss in Cushings Syndrome

- adrenocortical carcinoma,
- ectopic Cushing's syndrome
- uncontrolled diabetes
- concurrent infections like tuberculosis
- endogenous depression.
- ACTH and TSH co-secreting adenoma
- McCune–Albright syndrome

Clinical Clues to etiology of Cushings Syndrome

Exogenous Cushings Syndrome	• History of administration of glucocorticoids • presence of florid manifestations of protein catabolism • absence of hyperpigmentation, and lack of virilization (androgen-mediated)
Pituitary ACTH dependent CS	• Insidious onset of disease • female gender, young age • presence of hyperpigmentation (palmar creases, mucosal surface, scar tissue site) • features of cortisol and androgen excess
Ectopic Cushings Syndrome* **	• Rapid onset of disease, middle age, male gender • Severe proximal muscle weakness • Hyperpigmentation • hypokalemia, metabolic alkalosis • lack of features of protein catabolism • signs of underlying disease
Adrenocortical Carcinoma	• Rapid onset of disease • extremes of age (either <10 or >50 years) • lack of hyperpigmentation • presence of hirsuitism/virilization

*** bronchial carcinoids usually behave like pituitary Cushing's syndrome but may have additional features like flushing, diarrhea, and bronchospasm.

Physiology of cortisol secretion

Cortisol secretion peaks at 0400–0800h and troughs at 2300–2400h, and this diurnal rhythm is established by 2–3 years of age. Diurnal variation of cortisol secretion prevents sustained hypercortisolemia, which may be detrimental to neuronal function and sleep.

Liddle's Protocol

Liddle's protocol was first described in 1960 and is also called as "adrenal suppression tests." It includes sequential **low-dose dexamethasone suppression test (LDDST)** followed by **high-dose dexamethasone suppression test (HDDST)** in patients with suspected Cushing's syndrome.

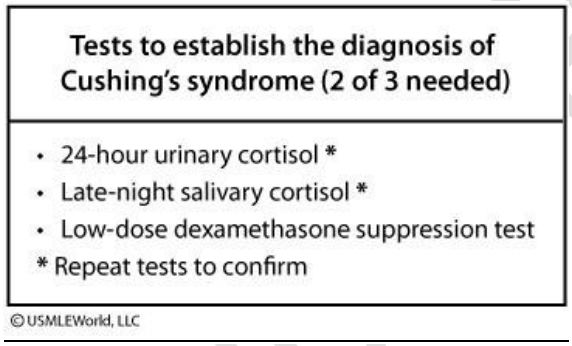
Dexamethasone in cortisol dynamic tests

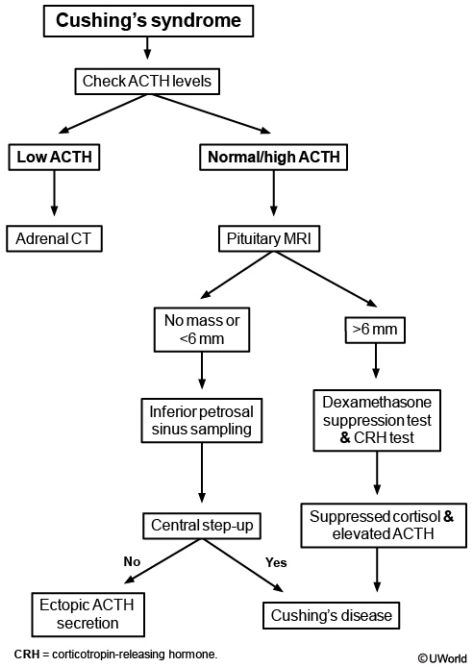
- Dexamethasone is the most potent glucocorticoid in suppressing hypothalamo–pituitary–adrenal axis (17 times more potent than hydrocortisone).

- It easily crosses the blood–brain barrier as it does not bind to cortisol-binding globulin (CBG).
- It has no cross-reactivity to hydrocortisone and other metabolites; therefore, it does not interfere with cortisol assay.

Overnight Dexamethasone suppression test (procedure)

Procedure	• Administer 1mg of dexamethasone b/n 2300-2400h • Sampling of serum cortisol b/n 0800-0900h
Rationale	• Dexamethasone is administered between 2300 and 2400h to inhibit the ACTH secretion, which starts at 0300h and peaks by 0700h
Diagnosis	• The cutoff for diagnosing endogenous hypercortisolemia is > 1.8 µg/dl with a sensitivity of 95% and a specificity of 80%. • The HPA axis recovers within 24 h after the administration of a single dose of 1 mg dexamethasone.





Interference with testing (DST)

False Positive DST	• **pseudo-Cushing's syndrome**, pregnancy, chronic kidney disease, glucocorticoid resistance syndrome, and acute stress • drugs that either **increase dexamethasone metabolism** like rifampicin, phenytoin, phenobarbitone, carbamazepine, and pioglitazone or **increase CBG** like estrogen, mitotane, and tamoxifen. • **marked intra-individual variation** in the absorption and metabolism of dexamethasone can also result in false- positive ONDST.
False Negative DST	• **cyclical Cushing's syndrome**, exogenous Cushing's syndrome, • **drugs that inhibit the metabolism of dexamethasone** like ritonavir, itraconazole, cimetidine, fluoxetine, and diltiazem

Factors interfering with Cushing's syndrome screening tests	

Overnight dexamethasone suppression test (false positive results)	• ↑ cortisol-binding globulin (e.g., estrogen, mitotane)
	• ↑ dexamethasone metabolism
	  • Anticonvulsants (e.g., phenytoin, carbamazepine, phenobarbital)
	  • Rifampicin
	  • Rifapentine
	  • Pioglitazone
	• Depression, alcoholism

Increased 24-hour urinary free cortisol	• Carbamazepine • Fenofibrate • Synthetic glucocorticoids • Licorice
Late-night salivary cortisol	• Men > age 60 may have elevated levels • Erratic sleep-wake cycles may cause false positive results

Clinical utility of midnight serum cortisol in Cushings Syndrome evaluation

Loss of circadian rhythm is the earliest biochemical abnormality in the evolution of Cushing's syndrome; thus, estimation of midnight serum cortisol may be used as an alternative screening test for the diagnosis of Cushing's syndrome in certain situations.

1. Patients with a high index of suspicion for Cushing's syndrome, but UFC/ONDST is negative.
2. Patients with a low index of suspicion for Cushing's syndrome, but UFC/ONDST is positive.
3. Patient on anticonvulsant medications with a non-suppressible dexamethasone suppression test.

Diagnostic cutoffs (for salivary or serum cortisol) in this setting…

Low index of suspicion	**High Index of suspicion**
A sleeping midnight serum cortisol < 1.8 µg/dl *	A sleeping midnight serum cortisol > 1.8 µg/dl **
An awake midnight serum cortisol < 7.5 µg/dl *	An awake midnight serum cortisol > 7.5 µg/dl **

* effectively rules out Cushing's Syndrome

** increases the probability of Cushings Syndrome

Parameters	Pituitary Cushing's syndrome	Ectopic Cushing's syndrome
Clinical features	Insidious onset	Rapid onset (except for bronchial carcinoids)
		Presence of features related to underlying disease
Hypokalemia	Rare	Present
Metabolic alkalosis	Rare	Present
ACTH	High, >20 but <90 pg/ml	Very high, >90 pg/ml
HDDST	Suppressible	Non-suppressible
CRH stimulation test	Positive	Negative
IPSS (basal) Central/peripheral ACTH ratio	>2	<1.4
IPSS with CRH stimulation Central/peripheral ACTH ratio	>3	<3
MRI sella	Adenoma localized	Normal

What is the rationale of high-dose dexamethasone suppression test ?

- **HDDST** is helpful in discriminating varying etiologies of Cushing's syndrome. In normal individuals, ACTH is suppressed even by 1 mg of dexamethasone.
- However, in pituitary Cushing's syndrome, the **negative feedback control of ACTH is set at a higher level than normal.** Therefore, higher doses are required to suppress ACTH in pituitary Cushing's syndrome.
- Patients with ectopic Cushing's syndrome and large invasive pituitary macroadenoma do not show this responsiveness, even at higher doses of dexamethasone possibly because their *threshold is set at a much higher level than in pituitary Cushing's syndrome.*

What is the rationale for IPSS

- Inferior petrosal sinus drains 80% of venous blood from pituitary and is thus the most appropriate site for ACTH sampling to localize the source of ACTH excess.
- Each half of pituitary drains into its corresponding inferior petrosal sinus, and in nearly 60% of individuals, venous drainage is symmetrical; thereby, it helps in lateralization of tumor. CRH-stimulated IPSS improves the specificity of test, and ovine CRH is preferred over human CRH, as it is more potent.

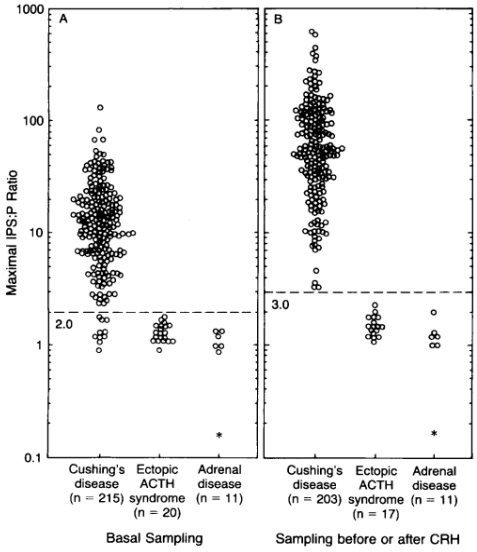


Figure 1. Maximal Ratio of Adrenocorticotropin Concentration in Plasma from One Inferior Petrosal Sinus to the Concentration in Peripheral Blood (IPS:P) in Patients with Cushing's Syndrome.

During basal sampling (Panel A), the maximal ratio was ≥2.0 in 205 of 215 patients with confirmed Cushing's disease but below 2.0 in all patients with ectopic adrenocorticotropin (ACTH) syndrome or primary adrenal disease. Panel B shows that all patients with Cushing's disease who received CRH had maximal ratios of ≥3.0, whereas all patients with ectopic adrenocorticotropin syndrome had ratios of <3.0.

The asterisks represent five patients with primary adrenal disease in whom adrenocorticotropin was undetectable in peripheral-blood plasma before and after CRH administration.

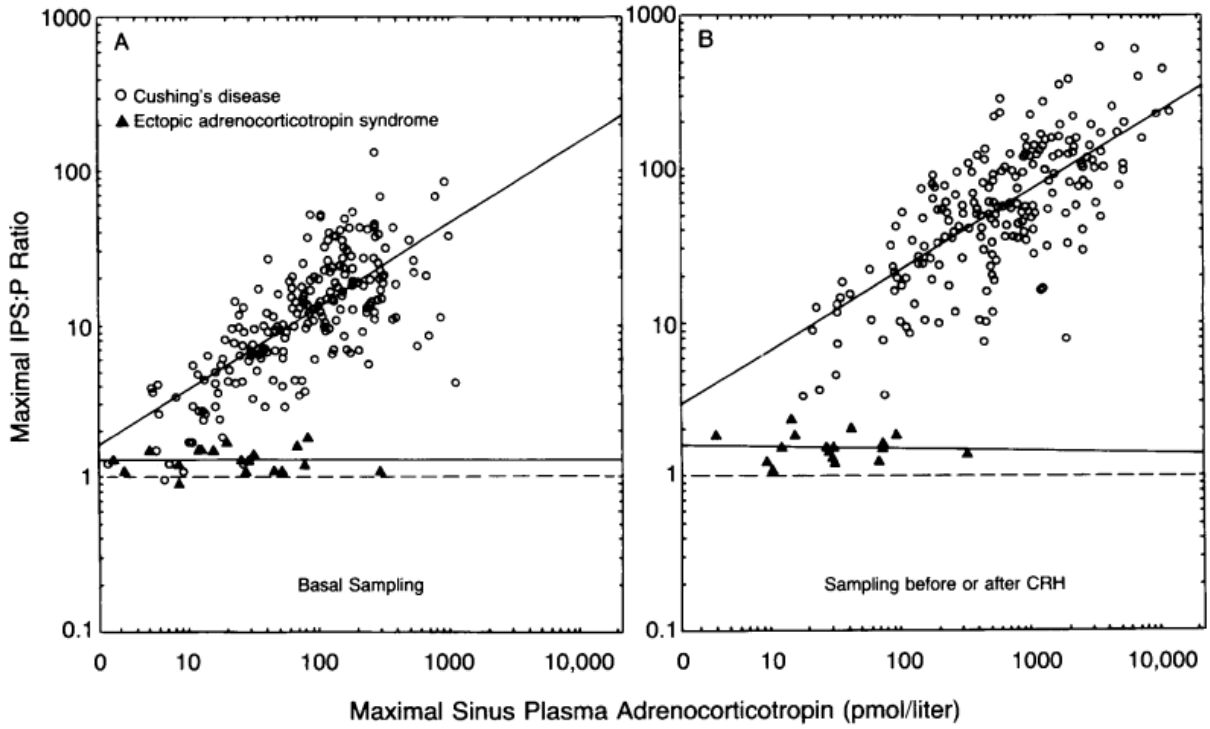


Figure 2. IPS:P Adrenocorticotropin Ratio in Relation to Petrosal Sinus Plasma Adrenocorticotropin Concentration in Patients with Cushing's Syndrome.

**** If facility for IPSS is not available, then internal jugular vein sampling is an alternative, but the data available are not encouraging.**

Medical management of Cushing's Syndrome

The role of medical therapy in Cushing's syndrome is limited because of its low efficacy, adverse side effects, and the need for lifelong therapy

1. patients with failure to localize the source of ACTH excess
2. Persistent disease after surgery
3. preoperative preparation
4. interim period after radiotherapy
5. presence of concurrent comorbidities which renders patient at high risk for surgery, and patient refusal for surgery.

DRUG	Mechanism of action	Side effects
Ketoconazole**	• Ketoconazole is an imidazole derivative and inhibits cytochrome 450-dependent enzymes in adrenal steroid biosynthetic pathway; particularly side chain cleavage, 17,20-lyase, and 11-β hydroxylase • **cytostatic effect with a t½ of 8–12 h**	• **transaminitis** • Hyperbilirubinemia • adrenal insufficiency. • decreased libido and gynecomastia in males.
Pasireotide	• somatostatin receptor analogue which acts on receptor subtypes **SSTR 1** , **SSTR 2** , **SSTR 3** , and **SSTR 5** , with the highest binding affinity for SSTR 5 (highly expressed by Corticotropinoma) .	• **hyperglycemia**

**** other cytostatic therapies available are aminoglutethimide, and metyrapone.**

** The advantages with combined medical therapy are rapid achievement of eucortisolemia, reduction in doses of individual drug thus limiting the adverse effects, and the ability to **target multiple sites**, e.g., pituitary **(somatostatin/dopamine type 2 receptor agonist i.e cabergoline)**, adrenal **ketoconazole/mitotane/metyrapone**), and peripheral glucocorticoid receptors **(mifepristone)**

Indications for bilateral adrenalectomy in patients with Cushing ' s syndrome

- AIMAH and PPNAD.
- ectopic Cushing's syndrome with persistent hypercortisolemia despite removal of primary tumor

- unresectable/metastatic tumor
- occult ectopic ACTH-secreting tumor

Why not to prefer bilateral adrenalectomy in all patients with pituitary Cushing ' s syndrome ?

- need for lifelong glucocorticoids, mineralocorticoid and DHEAS replacement
- risk of adrenal crisis in poorly compliant patients
- lack of adrenomedullary response to stress.
- future risk of **Nelson's syndrome** requiring regular ACTH monitoring and pituitary imaging

Severe hypercortisolism is an endocrine emergency and, if the UFC level is greater than fivefold the normal level, prophylactic treatment is advised; anticoagulation agents are used to prevent deep venous thrombosis and trimethoprim-sulfamethosazole is recommended for prevention of Pneumocystis jirovecii

A rare case of ectopic ACTH independent CS caused by ovarian steroid cell tumor, NOS

NELSON SYNDROME

Nelson's syndrome refers to growth of corticotropinoma after total bilateral adrenalectomy in a patient with pituitary Cushing's syndrome, regardless of previous pituitary surgery.

Mechanism of Nelson Syndrome

After a bilateral adrenalectomy is performed **cortisol levels are no longer normal**. This increases **CRH production** because it is not suppressed within the hypothalamus anymore. The **increased CRH levels promote the growth of the tumor.**

Predictors of Nelson Syndrome

- presence of de novo or residual corticotropinoma prior to **total bilateral adrenalectomy (TBA)**
- increase in ACTH >100 pg/ml in the first year post TBA
- aggressive histological variant of corticotropinoma
- lack of adjuvant radiotherapy after TBA
- lack of glucocorticoid receptor expression and greater tumor aggressiveness (as demonstrated by increased mitoses and Ki67-immunopositive nuclei) may contribute to the genesis of Nelson's adenoma

The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline - 2008

Who should be tested for Cushings Syndrome

- Patients with **unusual features for age** (e.g. osteoporosis, hypertension)
- Patients with multiple and progressive features, particularly those who are more predictive of Cushing's syndrome
- Patients with **adrenal incidentaloma** compatible with adenoma
- Children with decreasing height percentile and increasing weight.

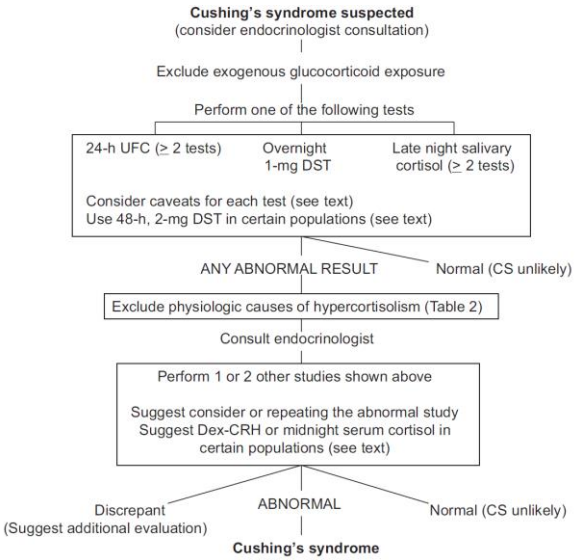
Caveat: A thorough drug history to exclude excessive exogenous glucocorticoid exposure leading to iatrogenic Cushing's syndrome before conducting biochemical testing

Recommended testing

- Urine free cortisol (UFC; at least two measurements)
- Late-night salivary cortisol (two measurements)
- 1-mg overnight dexamethasone suppression test (DST)
- Longer low-dose DST (2 mg/d for 48 h)

Not Recommended

- Random serum cortisol or plasma ACTH levels
- Urinary 17-ketosteroids
- Insulin tolerance test
- Loperamide test
- Tests designed to determine the cause of Cushing's syndrome (e.g. pituitary and adrenal imaging, 8 mg DST).



Cushings Testing in Special populations/considerations

pregnancy	use of UFC and against the use of dexamethasone testing in the initial evaluation of pregnant women
epilepsy	recommend against the use of dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone clearance and recommend instead measurements of nonsuppressed cortisol in blood, saliva, or urine
Renal failure	1-mg overnight DST rather than UFC for initial testing for Cushing's syndrome in patients with severe renal failure
Cyclic Cushings syndrome	UFC or midnight salivary cortisol tests rather than DSTs
Adrenal incidentaloma	1-mg DST or late-night cortisol test, rather than UFC

Symptoms	Signs	Overlapping conditions
Features that best discriminate Cushing's syndrome; most do not have a high sensitivity		
	Easy bruising	
	Facial plethora	
	Proximal myopathy (or proximal muscle weakness)	
	Striae (especially if reddish purple and > 1 cm wide)	
	In children, weight gain with decreasing growth velocity	
Cushing's syndrome features in the general population that are common and/or less discriminatory		
Depression	Dorsocervical fat pad ("buffalo hump")	Hypertension[b]
Fatigue	Facial fullness	Incidental adrenal mass
Weight gain	Obesity	Vertebral osteoporosis[b]
Back pain	Supraclavicular fullness	Polycystic ovary syndrome
Changes in appetite	Thin skin[b]	Type 2 diabetes[b]
Decreased concentration	Peripheral edema	Hypokalemia
Decreased libido	Acne	Kidney stones
Impaired memory (especially short term)	Hirsutism or female balding	Unusual infections
Insomnia	Poor skin healing	
Irritability		
Menstrual abnormalities		
In children, slow growth	In children, abnormal genital virilization	
	In children, short stature	
	In children, pseudoprecocious puberty or delayed puberty	

Treatment options for Cushings Disease

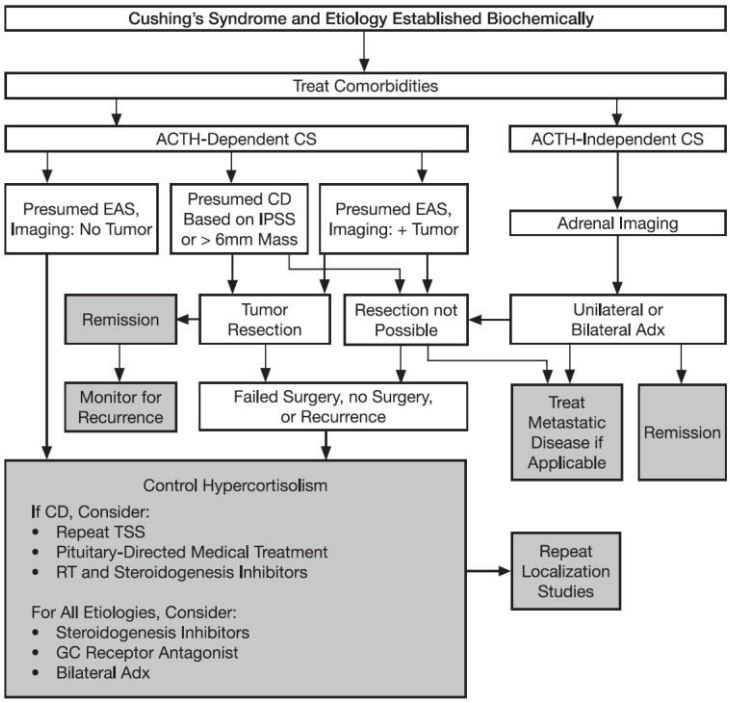
First line treatment	• initial resection of primary lesion(s) underlying **Cushing's disease (CD)**, **ectopic and adrenal** (cancer, adenoma, and bilateral disease) etiologies, unless surgery is not possible or is unlikely to significantly reduce glucocorticoid excess • **localizing and resecting ectopic ACTH-secreting tumors with node dissection as appropriate.** • transsphenoidal selective adenomectomy (TSS) by an experienced pituitary surgeon as the optimal treatment for CD in pediatric and adult patients. • We recommend surgical resection of bilateral adrenal disorders and suggest medical therapy to block aberrant hormone receptors for bilateral macronodular adrenal hyperplasia (BMAH)
Post surgery recommendations	• measuring serum sodium several times during the first 5–14 days after transsphenoidal surgery. • free T4 and prolactin within 1–2 weeks of surgery, to evaluate for overt hypopituitarism. • postoperative pituitary magnetic resonance imaging (MRI) scan within 1–3 months of successful TSS. • late-night salivary or serum cortisol in patients with eucortisolism after TSS, including those cases where eucortisolism was established by medical treatment before surgery.
Second line treatment	• **bilateral adrenalectomy** for occult or metastatic ectopic ACTH secretion (EAS) • **repeat transsphenoidal surgery,** particularly in patients with evidence of incomplete resection, or a pituitary lesion on imaging.

	• RT/radiosurgery in patients who have failed TSS or have recurrent CD.

Medical therapy for Cushings Disease

steroidogenesis inhibitors	• second-line treatment after TSS in patients with CD either with or without RT/radiosurgery • primary treatment of EAS in patients with occult or metastatic EAS • adjunctive treatment to reduce cortisol levels in adrenocortical carcinoma
pituitary-directed	Patients with CD who are not surgical candidates or who have persistent disease after TSS
Glucocorticoid antagonists	**diabetes or glucose intolerance who are not surgical candidates or who have persistent diseaseafter TSS.**

Drug	Pros	Cons	Dose[a]
Steroidogenesis inhibitors			
Ketoconazole[b]	Quick onset of action	Adverse effects: GI, hepatic dyscrasia (death), male hypogonadism; requires acid for biological activity; DDIs	400–1600 mg/d; every 6–8 h dosing
Metyrapone[b]	Quick onset of action	Adverse effects: GI, hirsutism, HT, hypokalemia; accessibility variable across countries	500 mg/d to 6 g/d; every 6–8 h dosing
Mitotane[c]	Adrenolytic, approved for adrenal cancer	Slow onset of action; lipophilic/long half-life, teratogenic; adverse effects: GI, CNS, gynecomastia, low WBC and T_4, ↑ LFTs; ↑ CBG, DDIs	Starting dose, 250 mg; 500 mg/d to 8 g/d
Etomidate	Intravenous, quick onset of action	Requires monitoring in ICU	Bolus and titrate
Pituitary-directed			
Cabergoline		Adverse effects: asthenia, GI, dizziness	1–7 mg/wk
Pasireotide[d]		Most successful when UFC <2-fold normal; sc administration; adverse effects: diarrhea, nausea, cholelithiasis, hyperglycemia, transient ↑ LFTs; ↑ QTc	600–900 μg twice daily
Glucocorticoid receptor-directed			
Mifepristone[e]		Difficult to titrate (no biomarker); abortifacient; adverse effects: fatigue, nausea, vomiting, arthralgias, headache, hypertension, hypokalemia, edema, endometrial thickening	300–1200 mg/d



GLUCOCORTICOID REPLACEMENT THERAPY

Women on OCPs, should have baseline morning cortisol >20
Glucocorticoid replacement therapy

- Hydrocortisone 10-12mg/m2 in 2-3 divided doses
- Prednisone 3-6mg daily in divided doses.

Human growth hormone increases conversion of cortisol to cortisone. May require more steroid replacement.

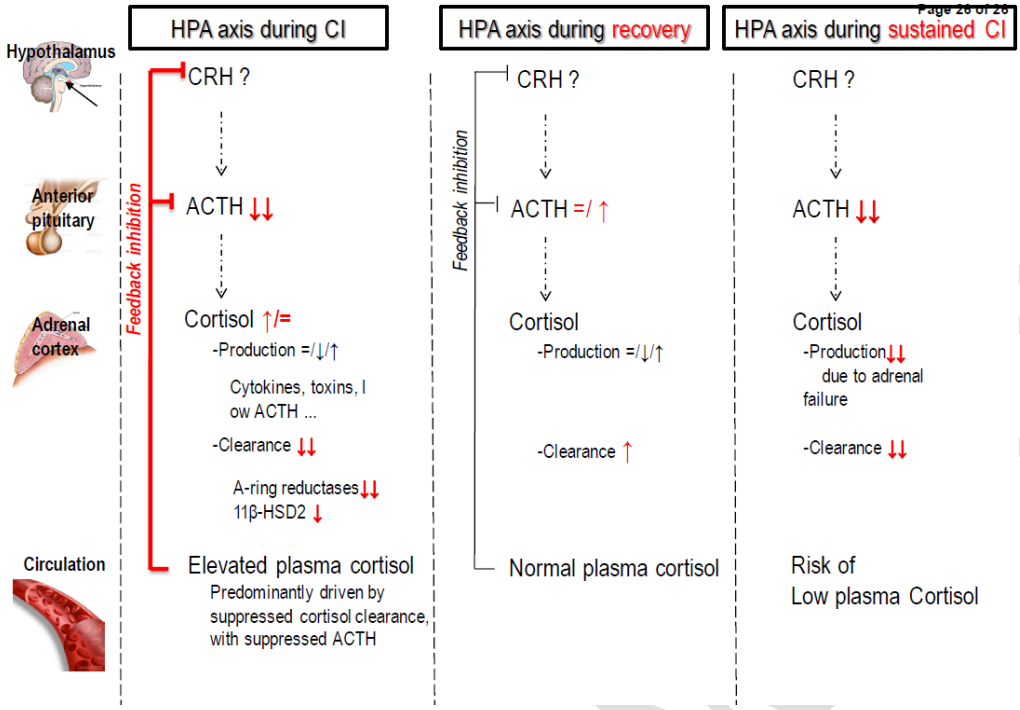
- There is no physiologic prednisone replacement dose and its use is discouraged in patients with adrenal insufficiency.

- Patients on steroid replacement therapy for AI need careful clinical surveillance for signs and symptoms of glucocorticoid excess (cardiometabolic profile, bone density)
- Primary adrenal insufficiency is a serious problem requiring life long glucocorticoid and mineralocorticoid therapy 5-10% annual risk of adrenal crises
- ACTH levels should not be used to assess the adequacy of glucocorticoid replacement in PAI; however low levels (<20pg/ml) may suggest over-replacement
- Parenteral hydrocortisone available (SC also works, not just IM)

Teaching points

1. Total serum cortisol in seriously ill patients may underestimate biologic cortisol effect, free cortisol may provide better insight into physiology.

2. Relative adrenal insufficiency in critical illness is fake news. The adrenal glands do not fatigue, but we assault the HPA axis with many medications that decrease its functional capacity.



Initiating or adjusting glucocorticoid therapy

Dose adjustment	• Weight • Age • Use of concurrent medications (phenytoin,rifampin,barbiturates,mitotane)
	• **Sense of wellbeing** • **Normalcy of blood pressure** • **Heart rate and temp** • **Symptoms such as nausea, vomiting, anorexia, dizziness.**
Adverse effects of steroids	• Hypertension • Hyperglycemia • Electrolyte abnormalities • Muscle and skin changes

Clinical pearls : adrenal insufficiency

Effect of increased potency and longer acting	• Mineralocorticoid activity decreases. Eg.

synthetic glucocorticoid	dexamethasone and methylprednisolone
Stress doses of 200-300mg for any procedure of medical illness	• No benefit to extensive duration of dosing • No benefit to excessive dosing >200-300mg/d
Side effects of high doses(acutely)	• Hyperglycemia • Immunosuppression • Accelerated protein catabolism • Poor wound healing • Hypertension • Volume overload • Acute corticosteroid-induced psychosis
Need for mineralocorticoid	• Production of cortisol returns to normal within 24-48h after surgery • Not required in patients with secondary or tertiary AI • Not required Primary AI with more than 50mg/d of hydrocortisone.

TABLE 1. CAUSES OF PRIMARY AND SECONDARY ADRENAL INSUFFICIENCY.

PRIMARY ADRENAL INSUFFICIENCY	SECONDARY ADRENAL INSUFFICIENCY
SLOW ONSET	
Autoimmune adrenalitis (alone or as a component of type I or II autoimmune polyglandular syndrome*)	Pituitary or metastatic tumor†
Tuberculosis	Craniopharyngioma†
Adrenomyeloneuropathy	Pituitary surgery or radiation
Systemic fungal infections (e.g., histoplasmosis, cryptococcosis, blastomycosis)	Lymphocytic hypophysitis†
AIDS (opportunistic infections with cytomegalovirus, bacteria, or protozoa; Kaposi's sarcoma)	Sarcoidosis†
Metastatic carcinoma (lung, breast, kidney), lymphoma	Histiocytosis X†
Isolated glucocorticoid deficiency (often familial)	Empty-sella syndrome
	Hypothalamic tumors†
	Long-term glucocorticoid therapy
ABRUPT ONSET	
Adrenal hemorrhage, necrosis, or thrombosis in meningococcal or other kinds of sepsis, in coagulation disorders or as a result of warfarin therapy, or in antiphospholipid syndrome	Postpartum pituitary necrosis (Sheehan's syndrome)
	Necrosis or bleeding into pituitary macroadenoma
	Head trauma, lesions of the pituitary stalk†
	Pituitary or adrenal surgery for Cushing's syndrome (transient)

*Type I autoimmune polyglandular syndrome consists mainly of adrenal insufficiency, hypoparathyroidism, and mucocutaneous candidiasis. Type I autoimmune polyglandular syndrome consists mainly of adrenal insufficiency, autoimmune thyroid disease, and insulin-dependent diabetes mellitus.

†Diabetes insipidus is often present.

TABLE 2. CLINICAL MANIFESTATIONS OF ADRENAL INSUFFICIENCY.

Primary and secondary adrenal insufficiency

Tiredness, weakness, mental depression
Anorexia, weight loss
Dizziness, orthostatic hypotension
Nausea, vomiting, diarrhea
Hyponatremia, hypoglycemia, mild normocytic anemia, lymphocytosis, eosinophilia

Primary adrenal insufficiency and associated disorders

Hyperpigmentation
Hyperkalemia
Vitiligo
Autoimmune thyroid disease
Central nervous system symptoms in adrenomyeloneuropathy

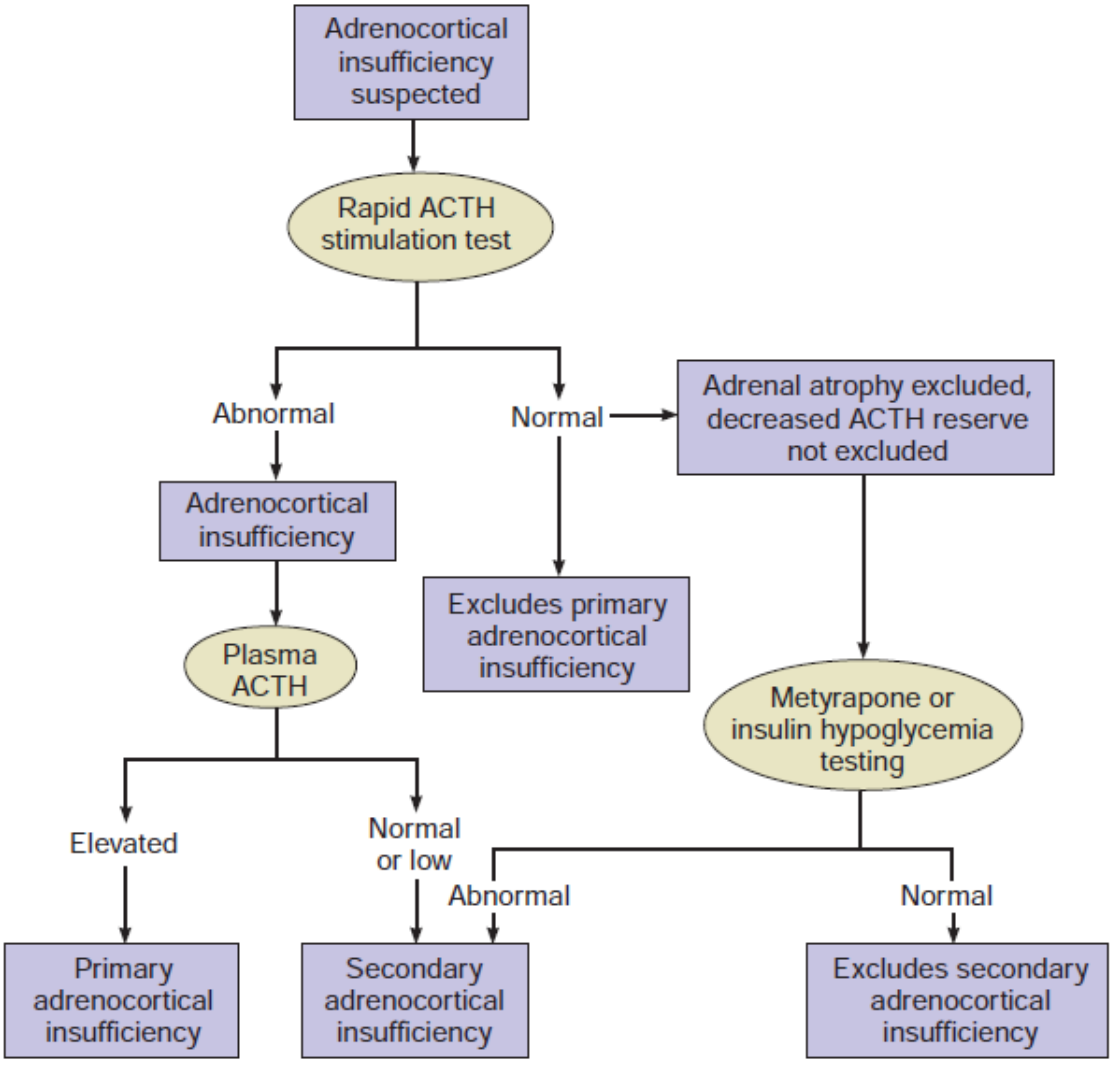
Secondary adrenal insufficiency and associated disorders

Pale skin without marked anemia
Amenorrhea, decreased libido and potency
Scanty axillary and pubic hair
Small testicles
Secondary hypothyroidism
Prepubertal growth deficit, delayed puberty
Headache, visual symptoms
Diabetes insipidus

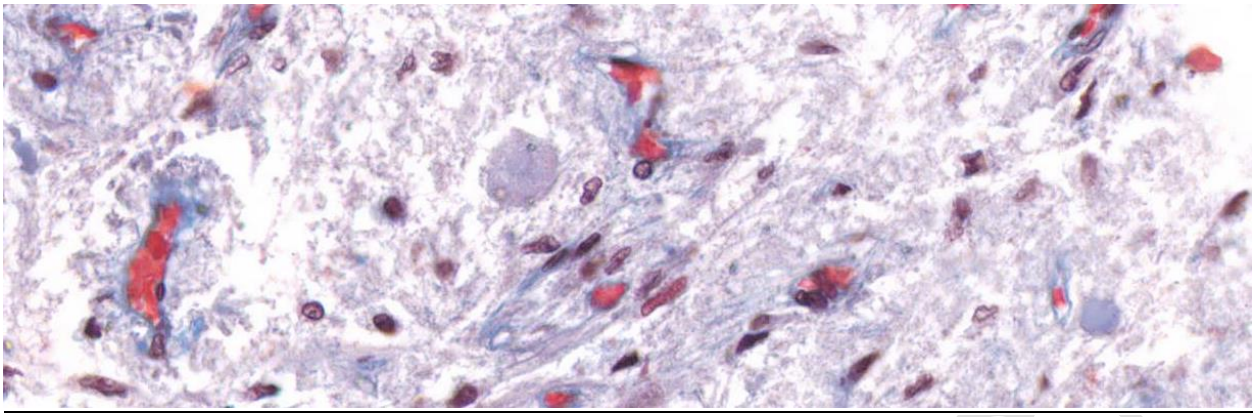
REASON FOR TEST	HORMONE TEST	NORMAL RANGE	INTERPRETATION RESULT	REFERENCE
Rule out adrenal insufficiency	Measurement of basal plasma cortisol between 8 and 9 a.m.	Plasma cortisol, 6–24 μg/dl	If plasma cortisol ≤3 μg/dl, adrenal insufficiency confirmed; if ≥19 μg/dl, adrenal insufficiency ruled out	Grinspoon and Biller[23]
	Conventional corticotropin test	Basal or post-corticotropin plasma cortisol, ≥20 μg/dl	Insufficient increase in plasma cortisol in most cases of adrenal insufficiency	May et al.,[3] Oelkers et al.,[4] Grinspoon and Biller[23]

In the absence of DHEA supplements a normal DHEA-sulphate conclusively rules out adrenal insufficiency. No need for dynamic testing (ITT etc). J Clin Endocrinol Metab. 2003;88(11):5293-8298

Risk of hypothalamic-pituitary-adrenal suppression with chronic glucocorticoid therapy	
No risk (No perioperative stress-dose steroids required)	• Daily **morning** dose of prednisone <5 mg (or its equivalent) for any period • Any dose of any glucocorticoid for <3 weeks • Prednisone 10 mg (or its equivalent) every other day
Intermediate or unknown risk (Preoperative evaluation of HPA axis recommended)	• Daily **morning** dose of prednisone 5-20 mg (or its equivalent) for >3 weeks • Daily **evening** doses of prednisone <5 mg (may disrupt diurnal variation) • Prior longer duration or higher doses of glucocorticoids in the past year • Inhaled glucocorticoids for >3 weeks, or ≥3 intra-articular or spinal glucocorticoid injections within past 3 months
High risk (Stress-dose glucocorticoids recommended during perioperative period)	• Daily prednisone ≥20 mg (or its equivalent) for >3 weeks • Any patient taking glucocorticoids who has Cushingoid features (eg, buffalo hump, central obesity, moon face, weight gain)



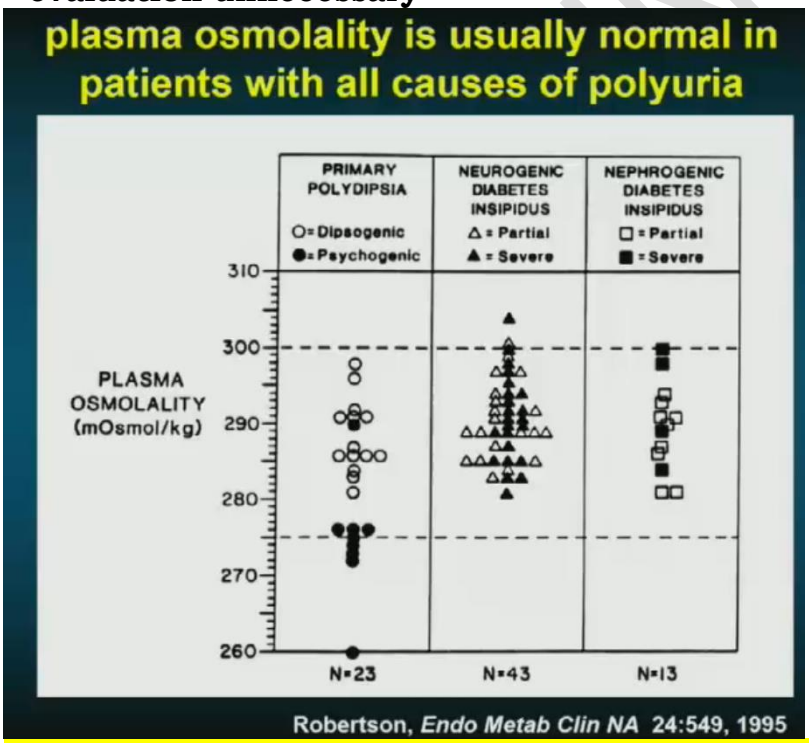
Diabetes Insipidus



Diabetes insipidus (Diagnostic criteria)

Hypotonic Polyuria	• **24 hour urine volume >50ml/kg under conditions of ad lib intake** • **Urine specific gravity <1.010, Urine Osm <300mOsm/kg H2O** • **Absence of solute diuresis (dipstick negative for glucose)**

**** failure to meet any of these criteria (24hr urine) renders further evaluation unnecessary**



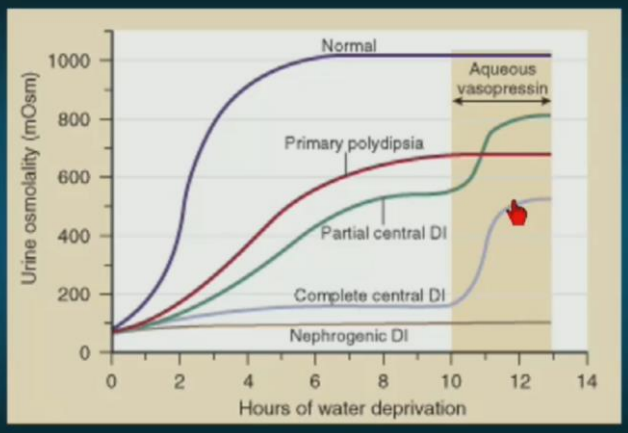
Serum hypoosmolarity in the setting of polyuria almost always clinches the diagnosis of primary polydipsia

Serum hyperosmolarity in the setting of polyuria clinces the diagnosis of neurogenic/central diabetes insipidus

water deprivation tests

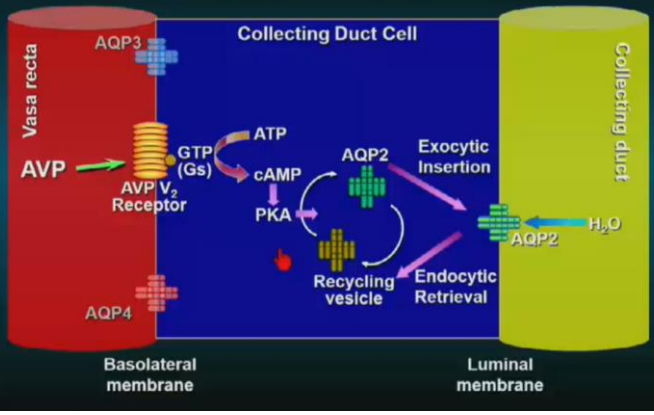
1. overnight (outpatient):
   - withhold all fluids after dinner until the next morning
   - measure AM serum [Na^+] and urine osmolality
   - Uosm >800 eliminates DI, >600 effectively does in most cases as well
2. formal (inpatient):
   - withhold all fluids until BW decreases by 3-5%, urine osmolality plateaus X 2-3 successive measurements, or serum [Na^+] >145 mmol/L
   - administer AVP (5 U) or dDAVP (1 µg) sc and follow urine osmolality and volume for 2 more hours
   - Uosm increase >50% following AVP/dDAVP indicates central DI, <10% indicates nephrogenic DI, intermediate responses (10-50%) are equivocal

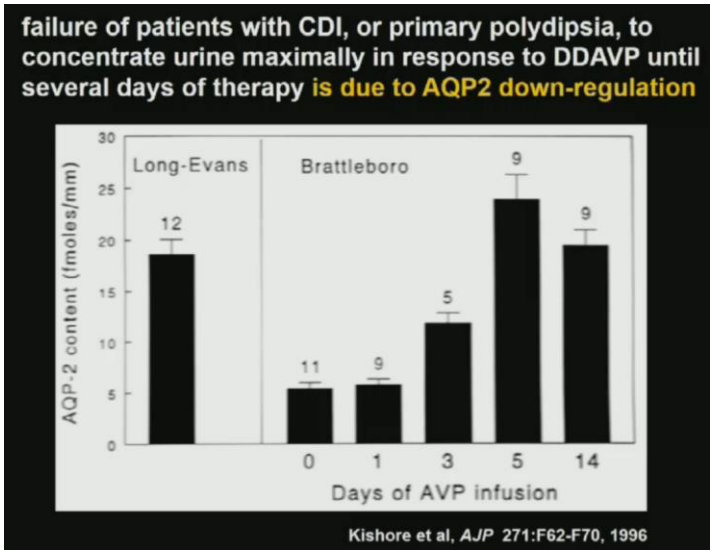
water deprivation test: interpretation



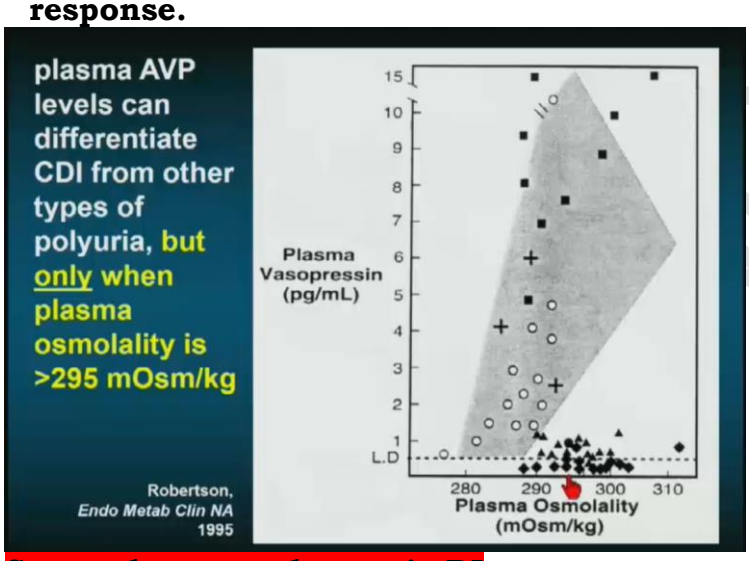
Verbalis, Posterior Pituitary.
In: Cecil Textbook of Medicine, 4th edition, 2011

AVP regulation of water reabsorption from renal tubular cells

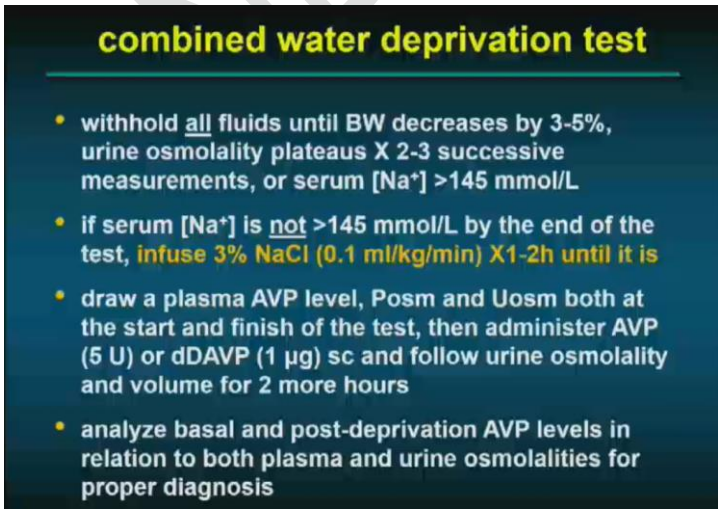


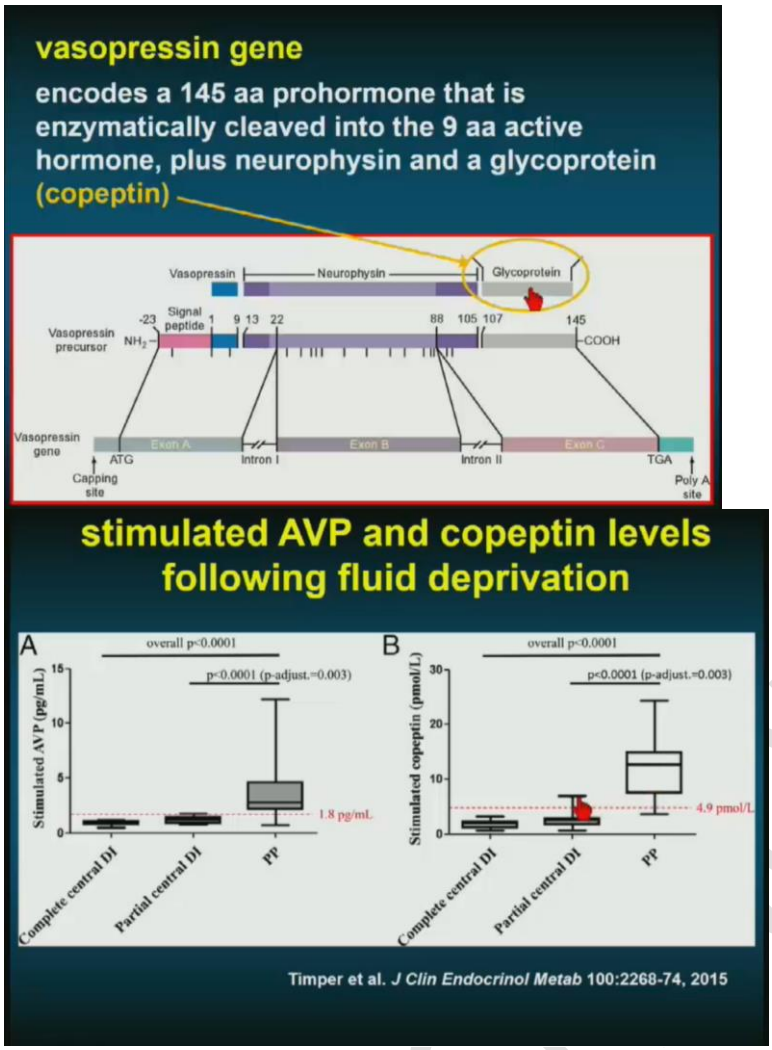


Remember : In primary polydipsia and patients with central DI. There is downregulation of aquaporin 2 receptors. Takes 3-5 days for full response.

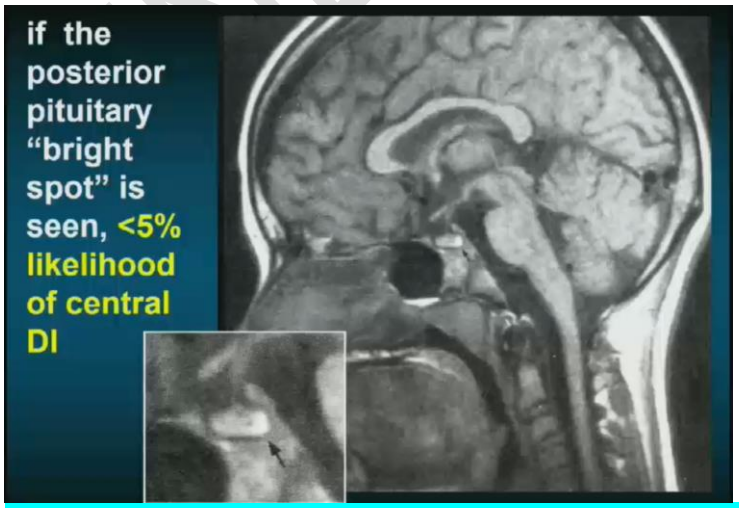


Square box = nephrogenic DI
Circle = primary polydipsia
Triangle = central DI





T1-weighted images the MRI produces a bright spot in the sella caused by stored hormone in neurosecretory granules in the posterior pituitary. The bright spot is present in approximately 80% of normal subjects and is absent in most patients with diabetes insipidus. Some studies have reported a bright spot in patients with clinical evidence of diabetes insipidus

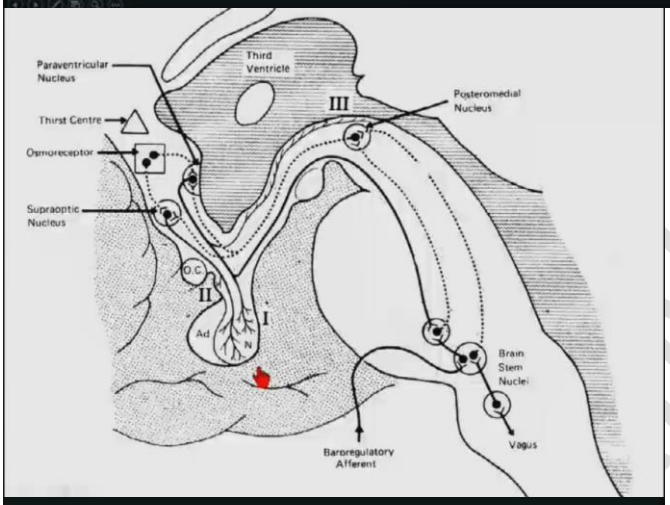


Elderly, diabetes mellitus patients, dehydrated patients may lose the

posterior pituitary bright spot. It's absence means pretty much nothing.

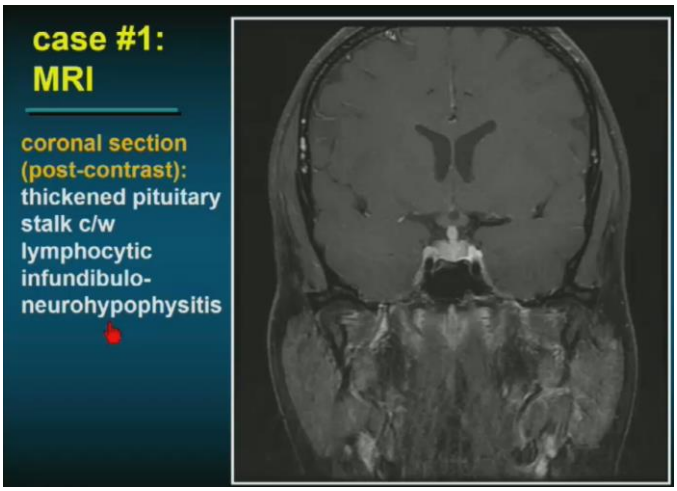
central (neurogenic) DI

- rare, prevalence <1:25,000
- hypothalamic lesion in ~40-50% (tumor, sarcoidosis, histiocytosis)
- pituitary lesions are generally not sufficient to cause DI until postoperatively
- idiopathic in 20-50% (probable autoimmune process in most of these)
- genetic <5% (often delayed onset)

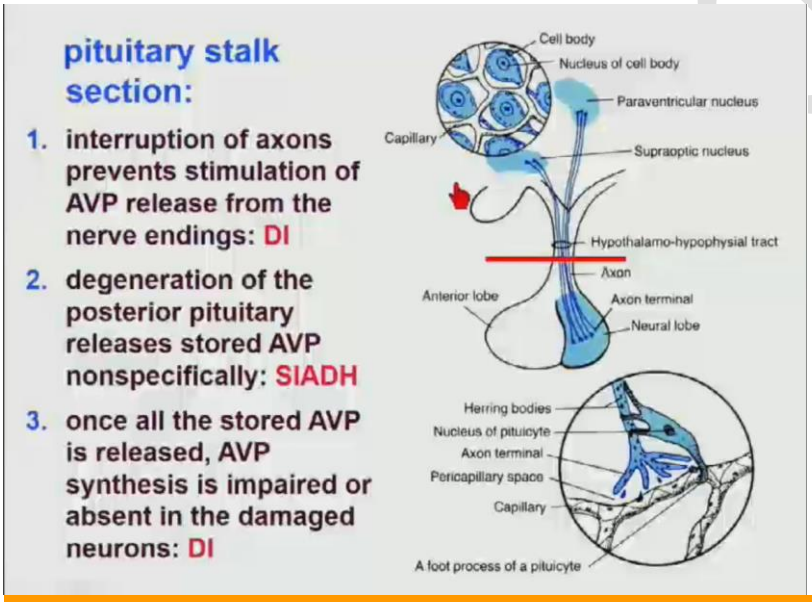


DI with an intrasellar lesion

- metastatic tumor (lung, breast, lymphoma)
- pituitary apoplexy
- rapidly enlarging pituitary tumor (usually hemorrhage without full apoplexy picture)
- pituitary abcess



Lymphocytic Infundibulo-neurohypophysitis
• Thickened pituitary stalk, it usually regresses in size from 5-10years • Rarely a thickened stalk might be due to malignancy (infiltrating like a germinoma. Will need to be followed over time)



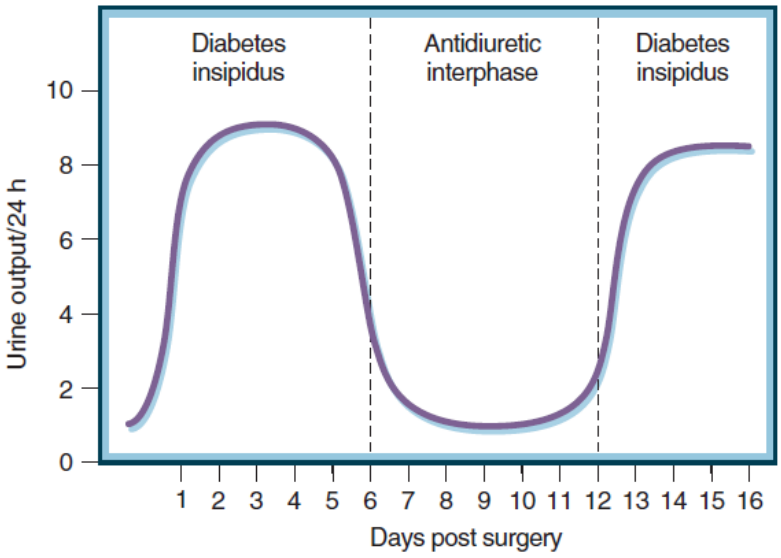
If there is complete stalk section patients may exhibit a pattern known as triphasic diabetes insipidus

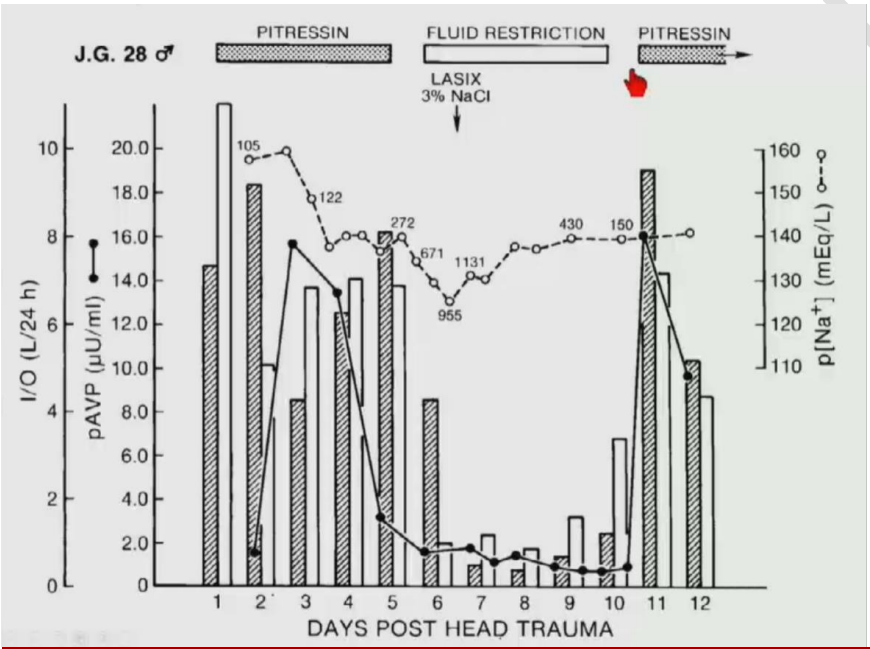
Phase 1 : The *first phase is diabetes insipidus* with onset within the first 24 hours of surgery and is thought to be due to axon shock and inability of action potentials to be propagated from the cell body to the axon terminals in the posterior pituitary.

Phase 2: *antidiuretic phase,* which was originally described as a normal interphase but is not normal

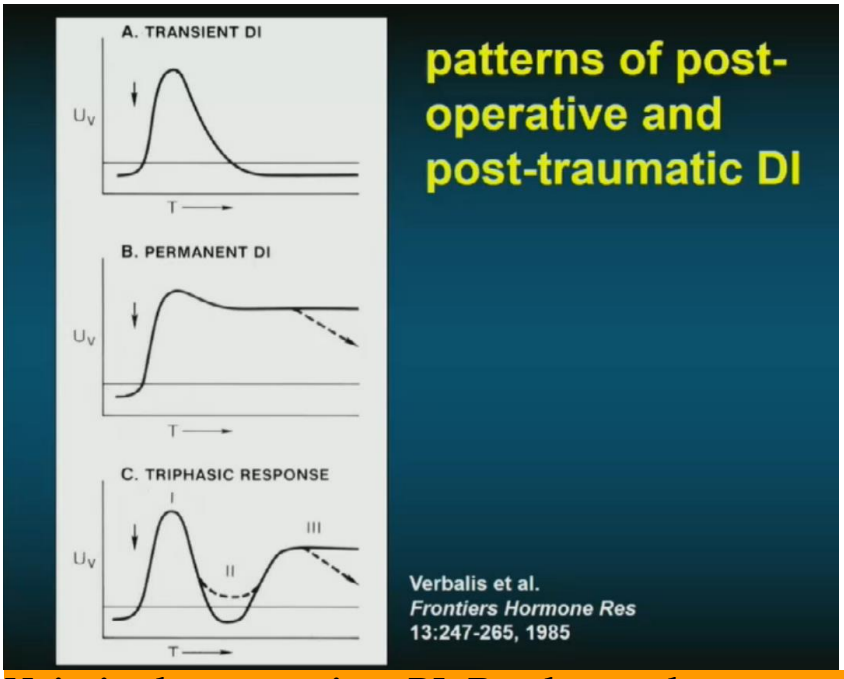
and is thought to be due to unregulated release of vasopressin from the store of hormone in the degenerating axons of the posterior pituitary. Because the release of vasopressin in this phase is unregulated, excess administration of fluids will produce hyponatremia and SIADH **(Watering hole, evolution..prey and predator. 1 week supply)**

Phase 3: When the *entire hormone content has been released* diabetes insipidus returns, constituting the third phase. The course of diabetes insipidus may be permanent, or subsequently it may resolve to partial or clinically inapparent disease.

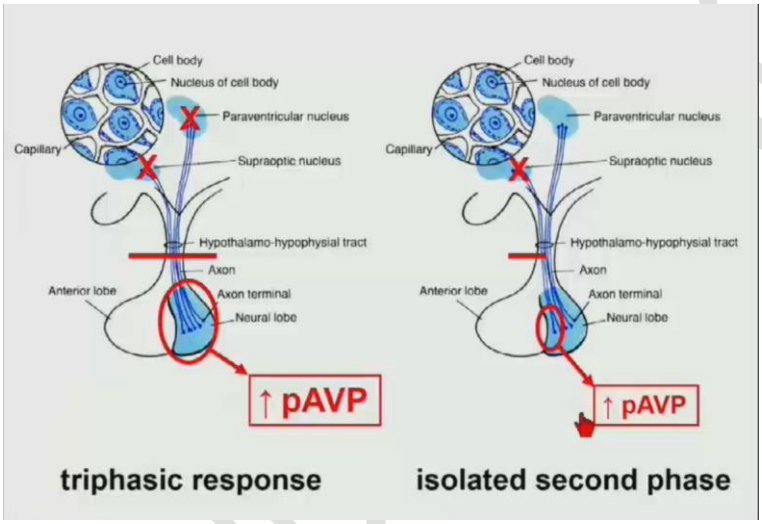




***** Above illustration of post traumatic triphasic response (Case report. Verbalis)**



Majority have transient DI. Rarely may have permanent DI. 4-6% have a triphasic response



Treatment

1) Desmopression

desmopressin a synthetic analogue of vasopressin in which the substitution of D-arginine

markedly reduces pressor activity and removing the terminal amine increases the half-life

an agent nearly 2000 times more specific for antidiuresis than naturally occurring L-arginine vasopressin

- dose of desmopressin is given and the patient is allowed to drink fluid ad lib. A decrease in urine volume is noted in 1 to 2 hours, and the total duration of action will usually be 6 to 18 hours.

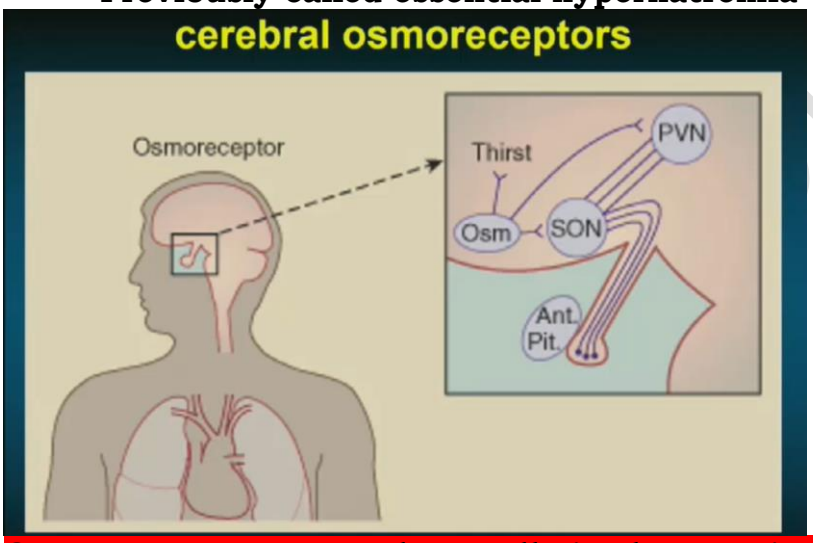
- When a dose is sufficient to elicit a stable therapeutic response, further increasing the dose (e.g., doubling the dose) produces only a moderate increase in duration of a few hours.
- a satisfactory schedule is achieved with a modest dose and the maximum dose rarely exceeds 0.2 mg orally or 20 µg intranasally (two sprays) given two or three times a day (usually three times a day for tablets and twice for intranasal spray).

DDAVP DOSING (as per Verbalis lecture)

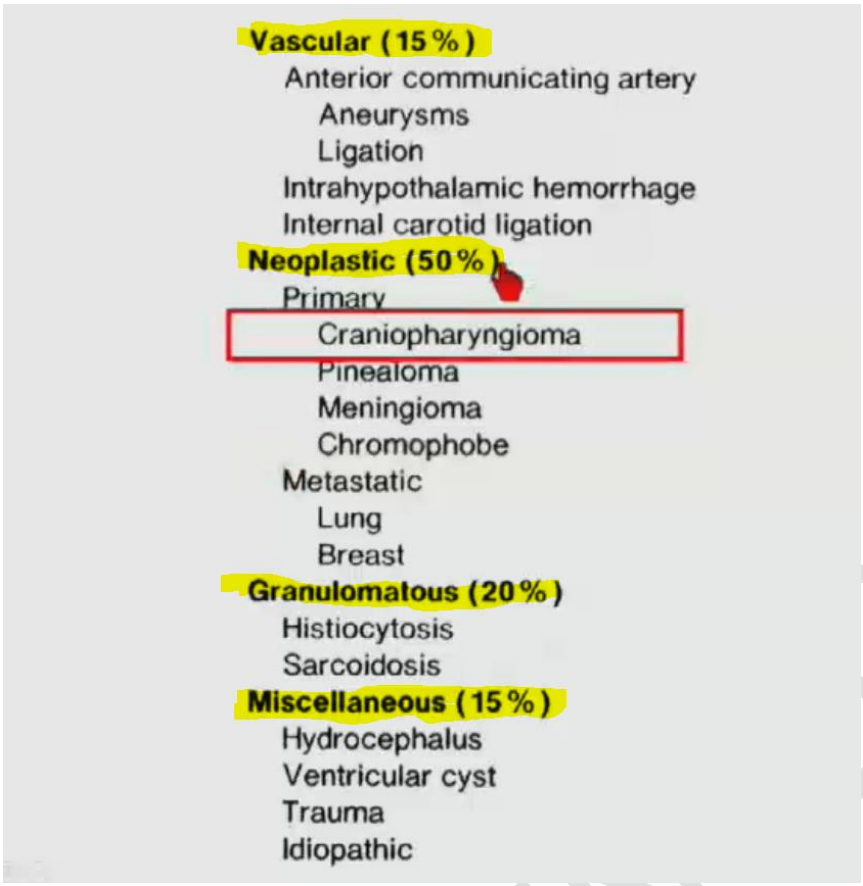
Starting dose	1mcg SC Q12H
Maximally allowed dose (research)	2mcg SC Q12H

Adipsic Diabetes insipidus : Board Pearl

- **Patient with Central DI, urine osmolarity high but still persistently hypernatremic**
- **Previously called essential hypernatremia**



Osmoreceptors. Located rostrally in the anterior wall of the 3rd ventricle.

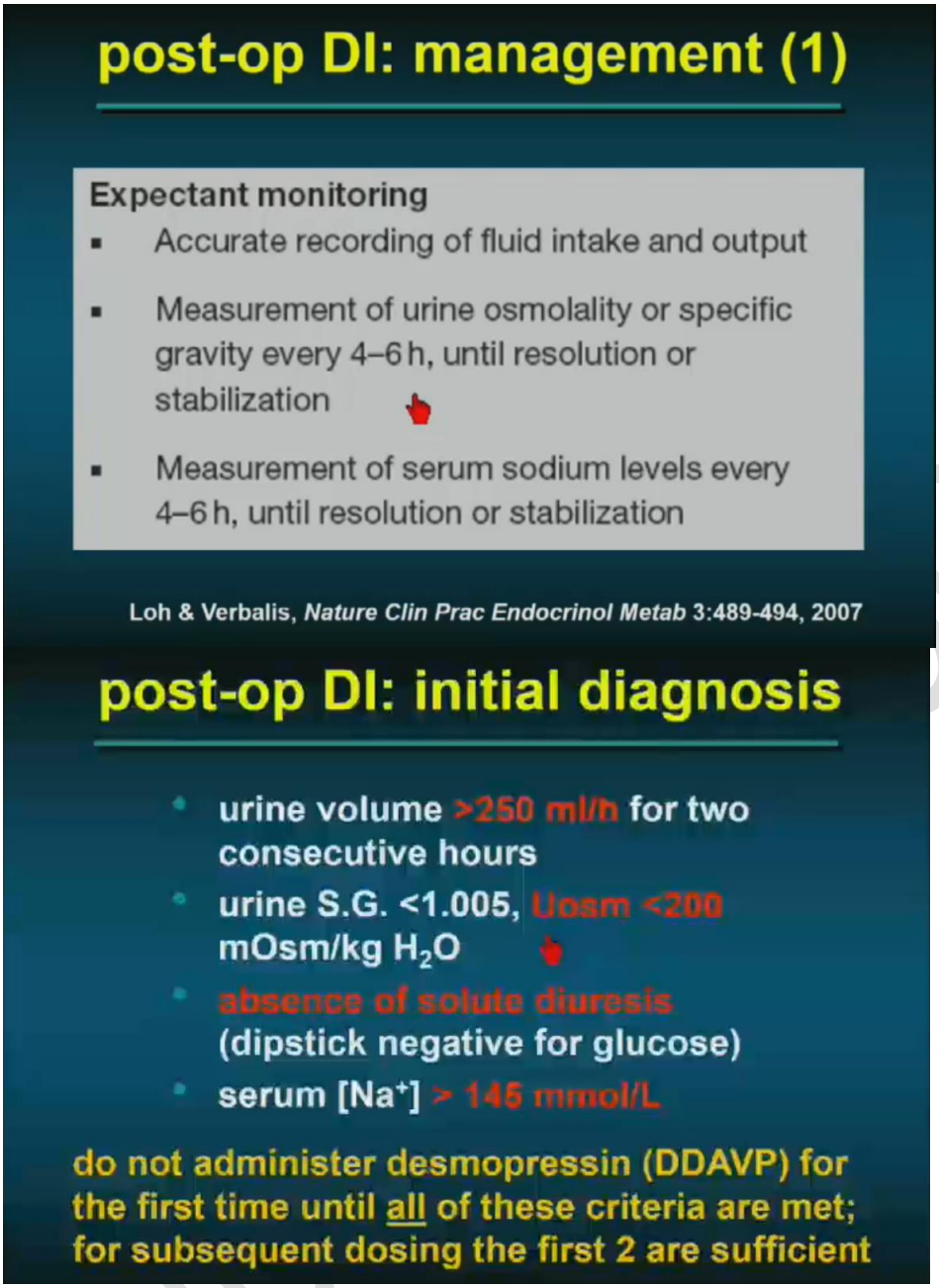


Therapeutic Agents for Treatment of Diabetes Insipidus

1. Water
2. Water-retaining agents
   a. L-Arginine vasopressin
   b. Desmopressin, 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin
   c. Chlorpropamide
   d. Carbamazepine*
   e. Clofibrate*
   f. Indomethacin
3. Natriuretic agents
   a. Thiazide diuretics
   b. Amiloride
   c. Indapamide

*Not recommended.

- The major action of **chlorpropamide** is on the renal tubule to increase the hydroosmotic action of residual vasopressin,but the agent can produce significant antidiuresis even in patients with severe hypothalamic/neurohypophyseal diabetes insipidus.
- The usual dose is 250 to 500 mg/day with a response noted in 1 to 2 days and a maximum antidiuresis in 4 days.
- possibility of severe hypoglycemia.

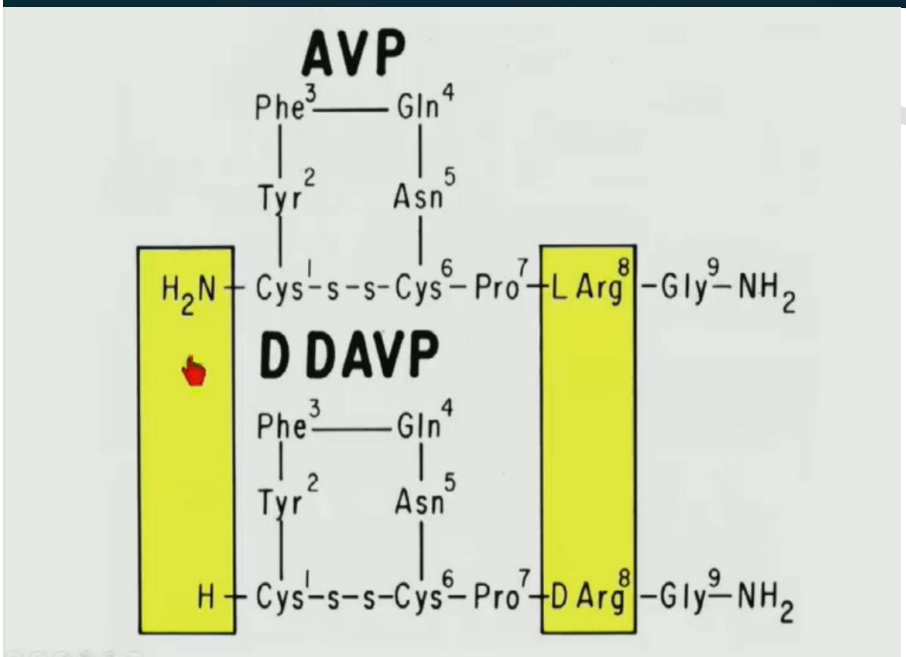

post-op DI: management (1)
Expectant monitoring
Accurate recording of fluid intake and output
Measurement of urine osmolality or specific gravity every 4–6 h, until resolution or stabilization
Measurement of serum sodium levels every 4–6 h, until resolution or stabilization
Loh & Verbalis, Nature Clin Prac Endocrinol Metab 3:489-494, 2007
post-op DI: initial diagnosis
urine volume >250 ml/h for two consecutive hours
urine S.G. <1.005, Uosm <200 mOsm/kg H2O
absence of solute diuresis (dipstick negative for glucose)
serum [Na+] > 145 mmol/L
do not administer desmopressin (DDAVP) for the first time until all of these criteria are met; for subsequent dosing the first 2 are sufficient

post-op DI: management (2)

Antidiuretic hormone therapy

- Desmopressin given intravenously or subcutaneously at an initial dose of 1–2 µg
- Repeat the desmopressin dose when urine output is 200–250 ml/h for ≥2 h with urine specific gravity <1.005 or urine osmolality <200 mOsm/kg H_2O

Loh & Verbalis, *Nature Clin Prac Endocrinol Metab* 3:489-494, 2007



desmopressin dosing

parenteral (sc or iv)

- 1-2 mcg q 12 h

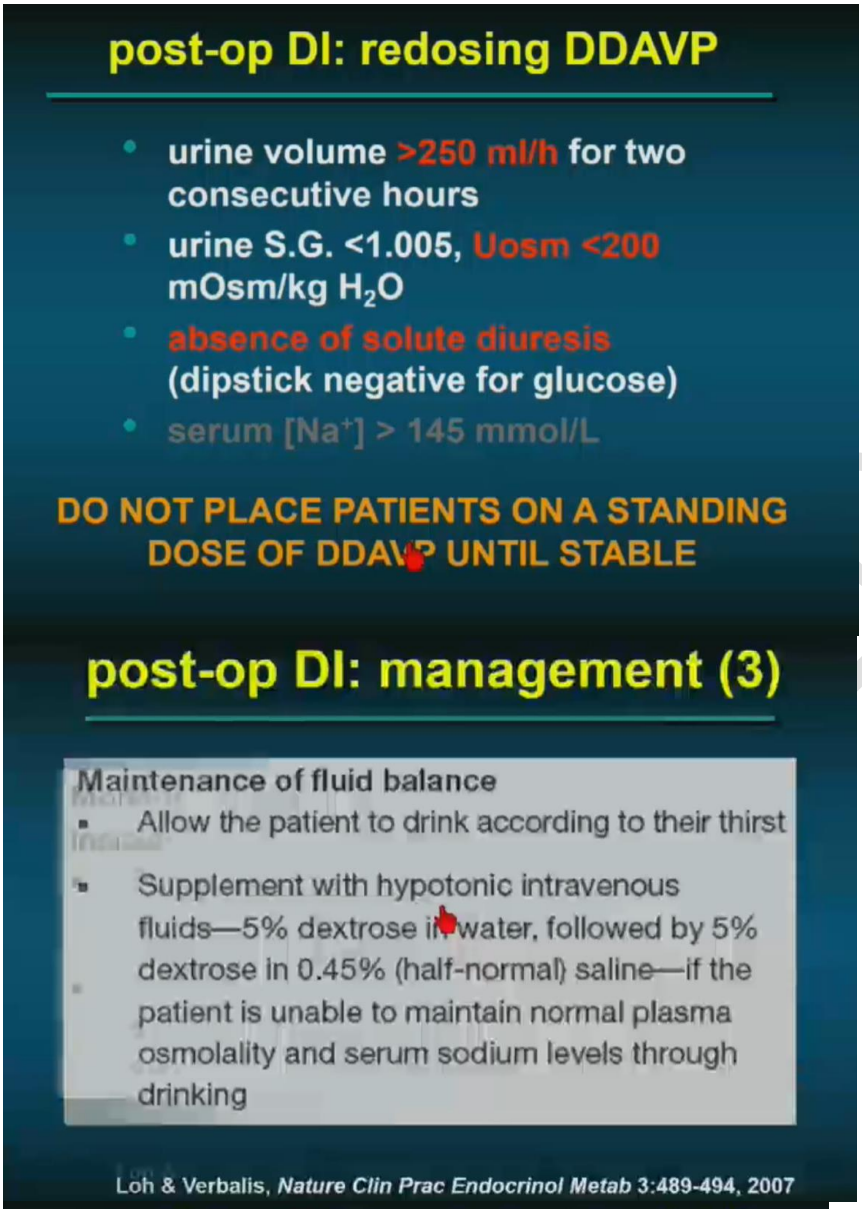
intranasal

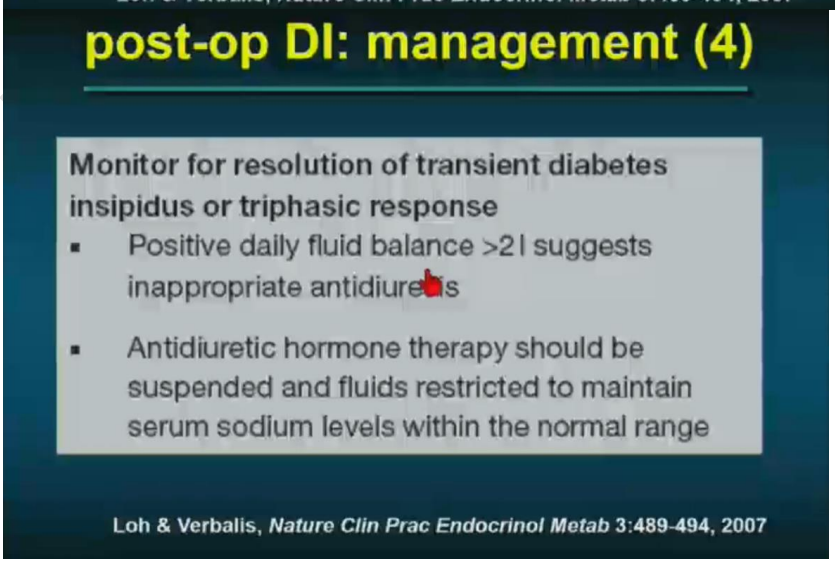
- 10-20 mcg q 8-12h

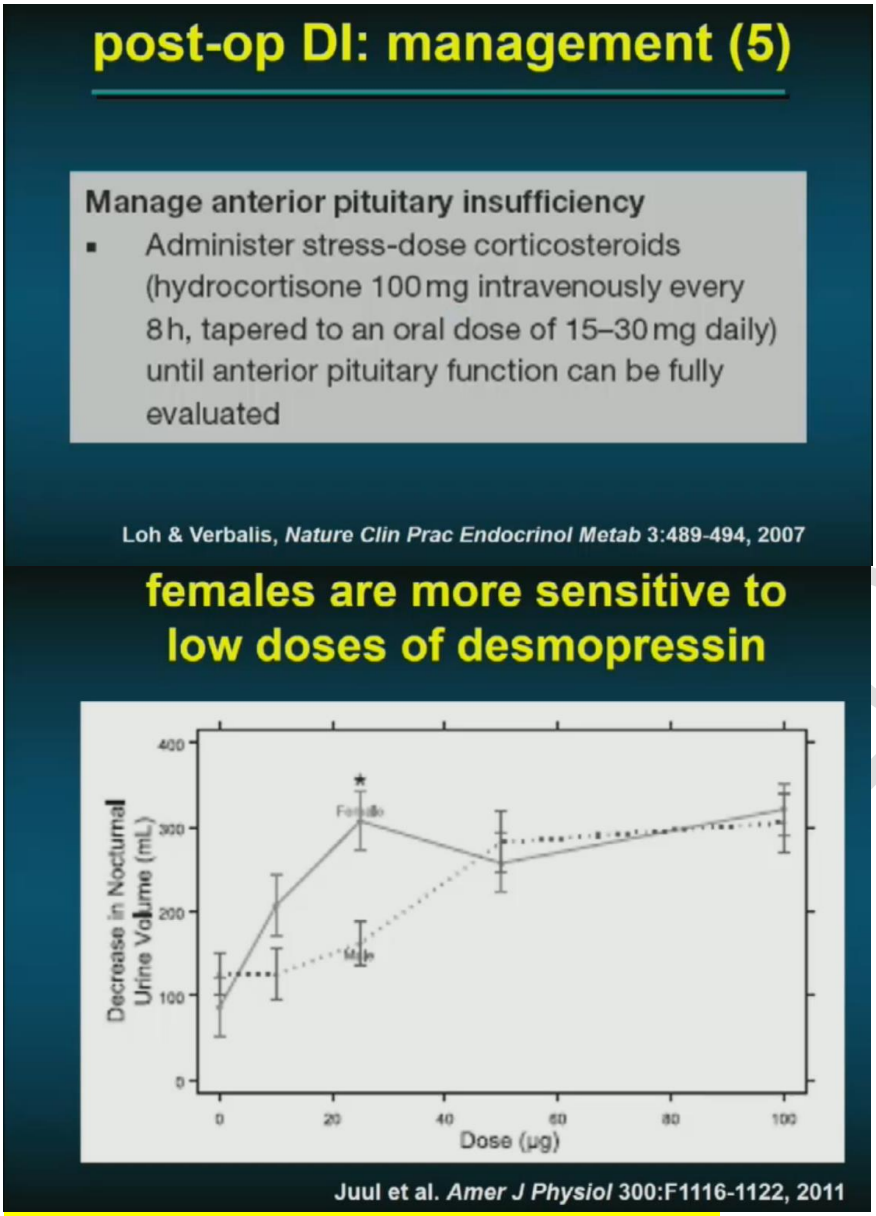
oral

- 100-200 mcg (0.1-0.2 mg) q 6-8 h
- 1 h before or 2 h after meals

99% of DDAVP is destroyed in the GI tract. NB : stimulation of peptidases destroy the DDVAP. ***







BOARD PEARL : NSAIDs and Desmopressin

- over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit the action of prostaglandin E2.
- Prostaglandin E has a limiting action on vasopressin-induced water uptake by enhancing the retrieval of aquaporin 2 from the plasma membrane and returning it to the intracellular pool.
- NSAIDs inhibit prostaglandin E2 and prolong the time the water channels remain in the membrane, thus increasing the duration of action of administered desmopressin.

Because elderly persons may have an increased use of NSAIDs, patients with diabetes insipidus should be specifically informed of the risk of developing hyponatremia when taking an NSAID with desmopressin.

SODIUM DISORDERS : FOCUS ON SIADH (PROF. VERBALIS)

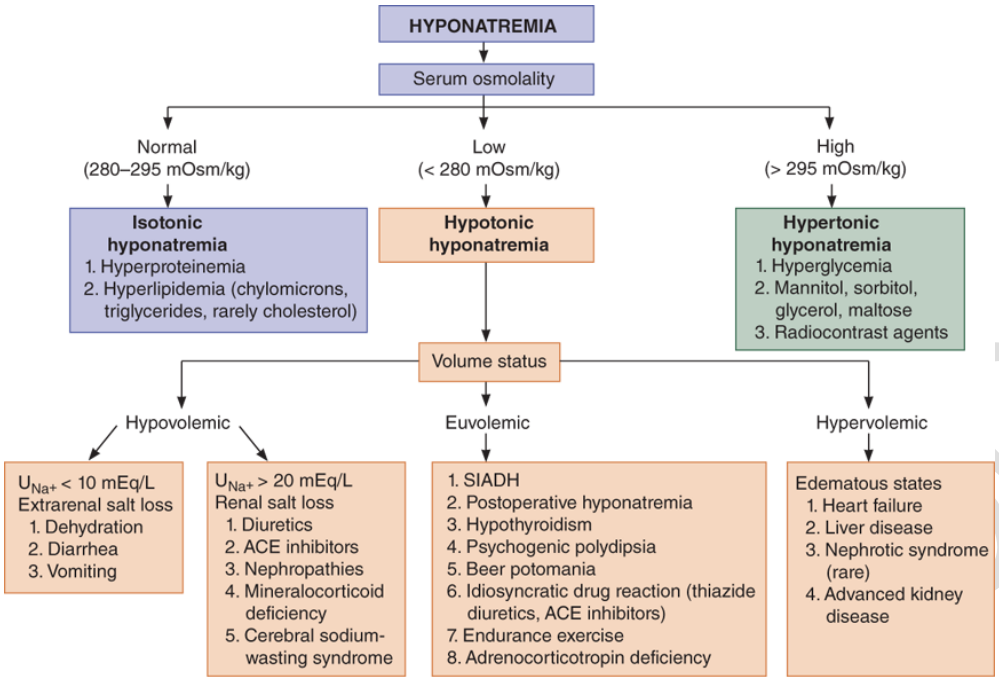
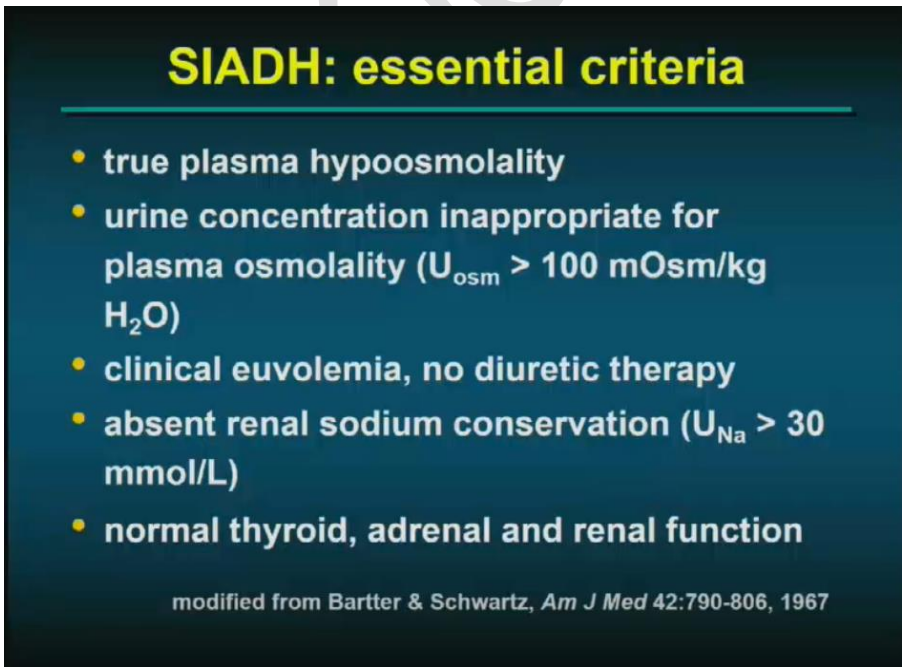
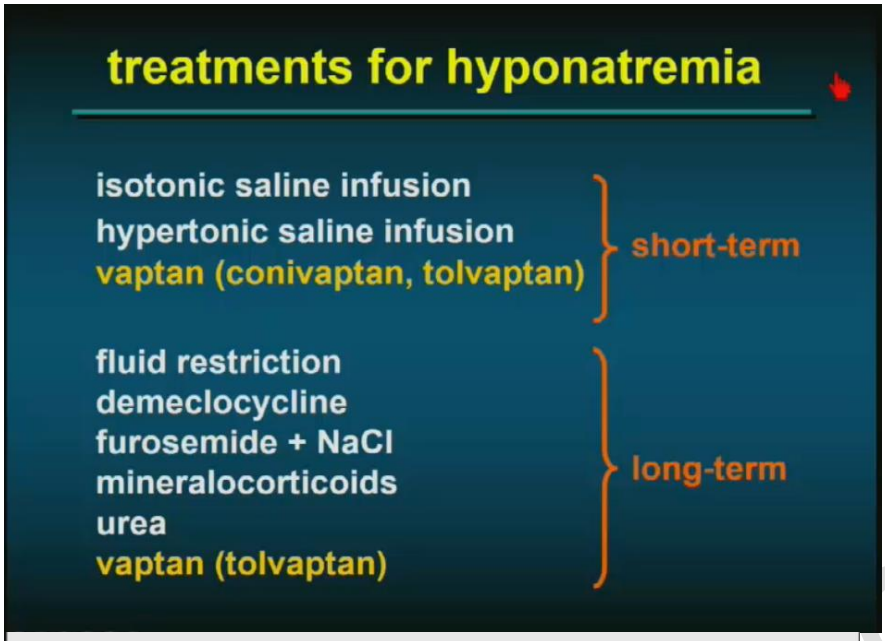


Table 2 Criteria for Diagnosing SIADH

Decreased effective osmolality of the extracellular fluid (P_{osm} <275 mOsmol/kg H_2O).
Inappropriate urinary concentration (U_{osm} >100 mOsmol/kg H_2O with normal renal function) at some level of plasma hypo-osmolality.
Clinical euvolemia, as defined by the absence of signs of hypovolemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites).
Elevated urinary sodium excretion (>20-30 mmol/L) while on normal salt and water intake.
Absence of other potential causes of euvolemic hypo-osmolality: severe hypothyroidism, hypocortisolism (glucocorticoid insufficiency).
Normal renal function and absence of diuretic use, particularly thiazide diuretics.

H_2O = water; kg = kilogram; mmol = millimole; mOsmol = milliosmole; P_{osm} = plasma osmolality; SIADH = syndrome of inappropriate antidiuretic hormone secretion; U_{osm} = urine osmolality.




treatments for hyponatremia
isotonic saline infusion
hypertonic saline infusion
vaptan (conivaptan, tolvaptan)
short-term
fluid restriction
demeclocycline
furosemide + NaCl
mineralocorticoids
urea
vaptan (tolvaptan)
long-term

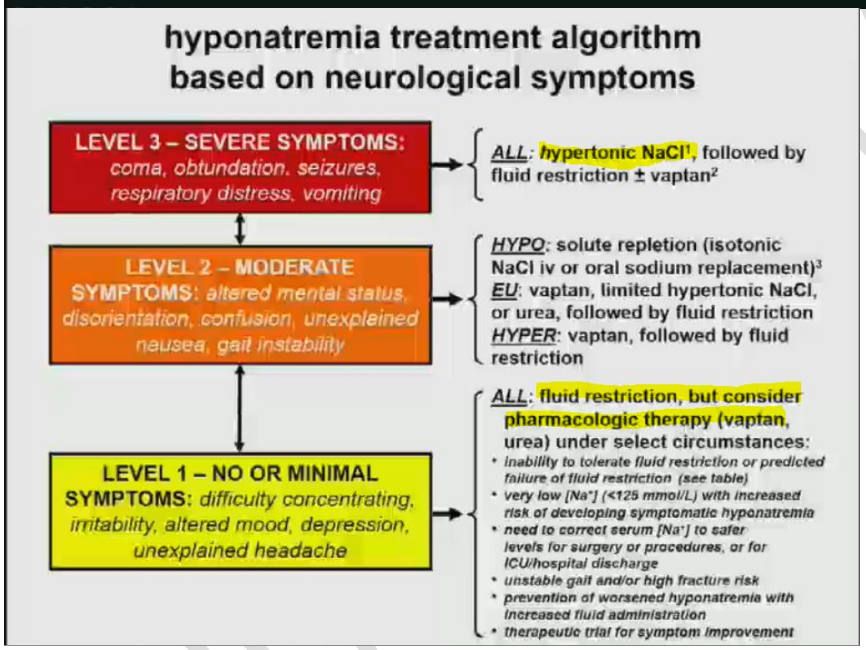

hyponatremia treatment algorithm
based on neurological symptoms
LEVEL 3 – SEVERE SYMPTOMS: coma, obtundation, seizures, respiratory distress, vomiting
ALL: hypertonic NaCl[1], followed by fluid restriction ± vaptan[2]
LEVEL 2 – MODERATE SYMPTOMS: altered mental status, disorientation, confusion, unexplained nausea, gait instability
HYPO: solute repletion (isotonic NaCl iv or oral sodium replacement)[3]
EU: vaptan, limited hypertonic NaCl, or urea, followed by fluid restriction
HYPER: vaptan, followed by fluid restriction
LEVEL 1 – NO OR MINIMAL SYMPTOMS: difficulty concentrating, irritability, altered mood, depression, unexplained headache
ALL: fluid restriction, but consider pharmacologic therapy (vaptan, urea) under select circumstances:
inability to tolerate fluid restriction or predicted failure of fluid restriction (see table)
very low [Na+] (<125 mmol/L) with increased risk of developing symptomatic hyponatremia
need to correct serum [Na+] to safer levels for surgery or procedures, or for ICU/hospital discharge
unstable gait and/or high fracture risk
prevention of worsened hyponatremia with increased fluid administration
therapeutic trial for symptom improvement

Table 5 General Recommendations for Employment of Fluid Restriction and Predictors of the Increased Likelihood of Failure of Fluid Restriction

General recommendations:

- Restrict all intake that is consumed by drinking, not just water.
- Aim for a fluid restriction that is 500 mL/d below the 24-hour urine volume.
- Do not restrict sodium or protein intake unless indicated.

Predictors of the likely failure of fluid restriction:

- High urine osmolality (>500 mOsm/kg H_2O).
- Sum of the urine Na^+ and K^+ concentrations exceeds the serum Na^+ concentration.
- 24-hour urine volume <1500 mL/d.
- Increase in serum Na^+ concentration <2 mmol/L/d in 24-48 hours on a fluid restriction of ≤1 L/d.

D = day; H_2O = water; K = potassium; kg = kilogram; L = liter; mL = milliliter; mmol = millimole; mOsm = milliosmole; Na = sodium.

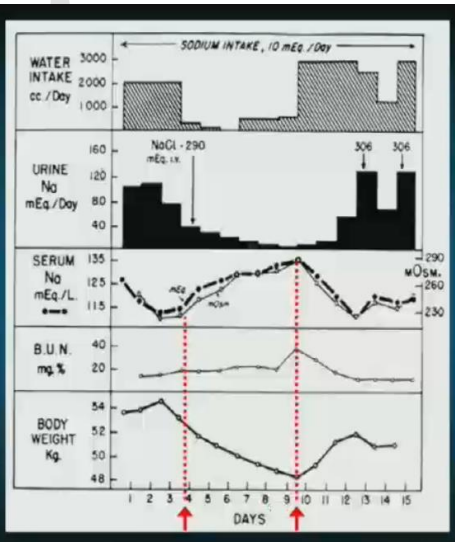
use of urine electrolytes to predict stringency of fluid restriction

urine/plasma electrolyte ratio	recommended fluid consumption
>1.0	0 mL
0.5–1.0	Up to 500 mL
<0.50	Up to 1 L

Furst H et al. *Am J Med Sci* 319:240-244, 2000

fluid restriction

- fluid restriction in patients with SIADH corrects hyponatremia by only 1-2 mmol/L/day, even when severe (<500 ml/day)
- in addition, fluid restriction is poorly tolerated because of increased thirst, with subsequent poor compliance



Adapted from Schwartz WB et al. *Am J Med* 23:529-542, 1957

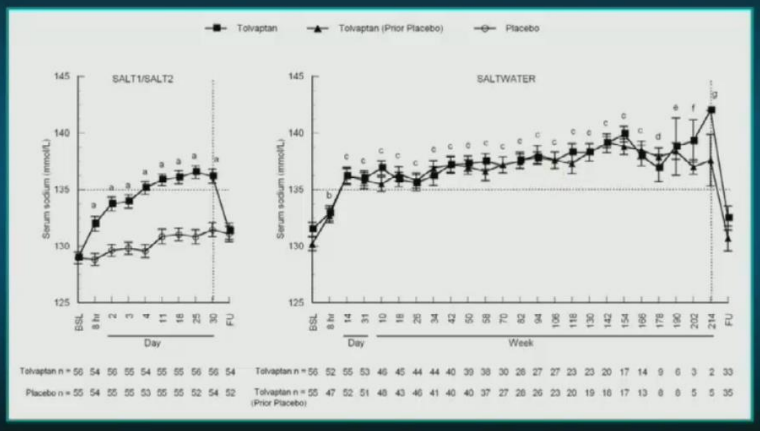
diuresis:

increased excretion of urine by the kidney; includes water and typically increased solute excretion as well

aquaresis:

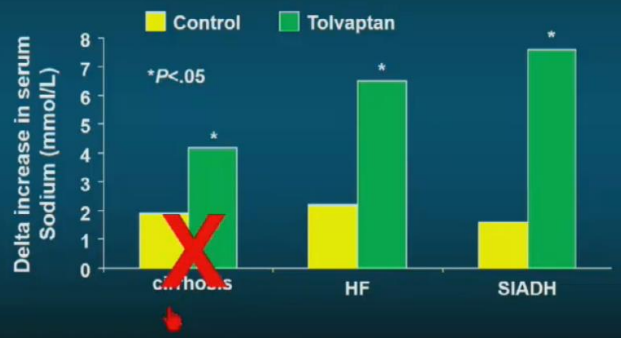
increased excretion of water by the kidney without increased solute, i.e., electrolyte-sparing excretion of free water by the kidney

tolvaptan: salt-water open label extension study



Berl et al. *J Am Soc Nephrol* 4:705-712, 2010

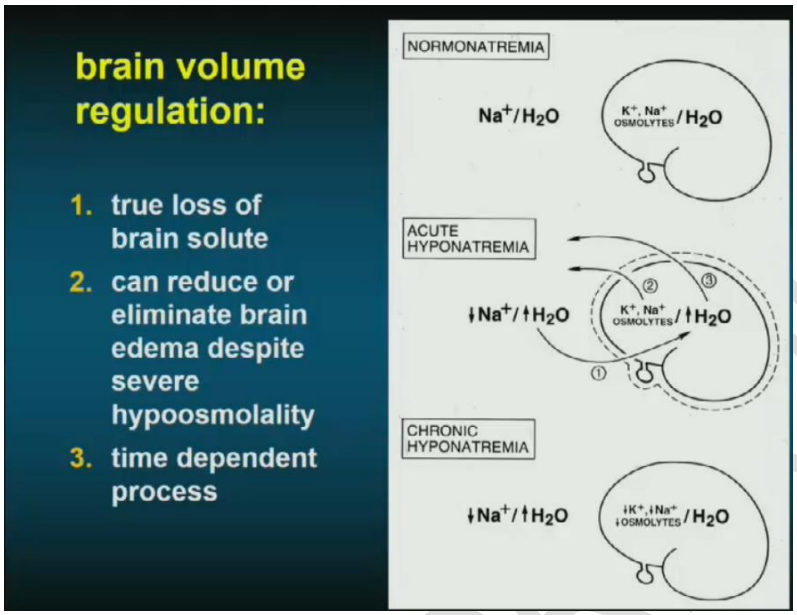
SALT: mean increases in serum [Na^+] after 30 d in patients with cirrhosis, HF, and SIADH

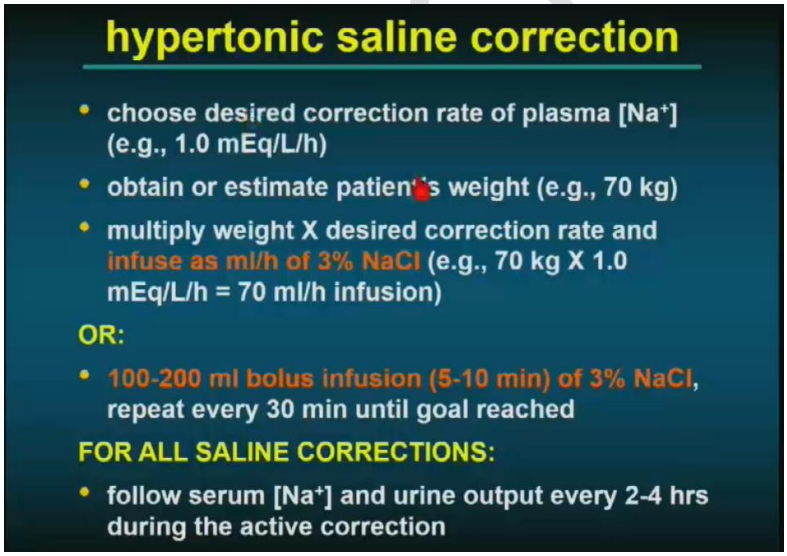


Schrier et al. *NEJM* 355:2099-2112, 2006

High risk for osmotic demyelination syndrome	**1. Serum sodium <105mmol/L** **2. Hypokalemia** **3. Alcoholism** **4. Malnutrition** **5. Advanced liver disease**

DO NOT COMBINE VAPTANS and Hypertonic saline within 24hrs of each other.





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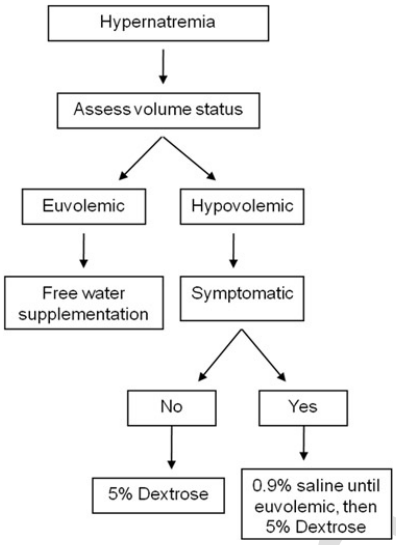
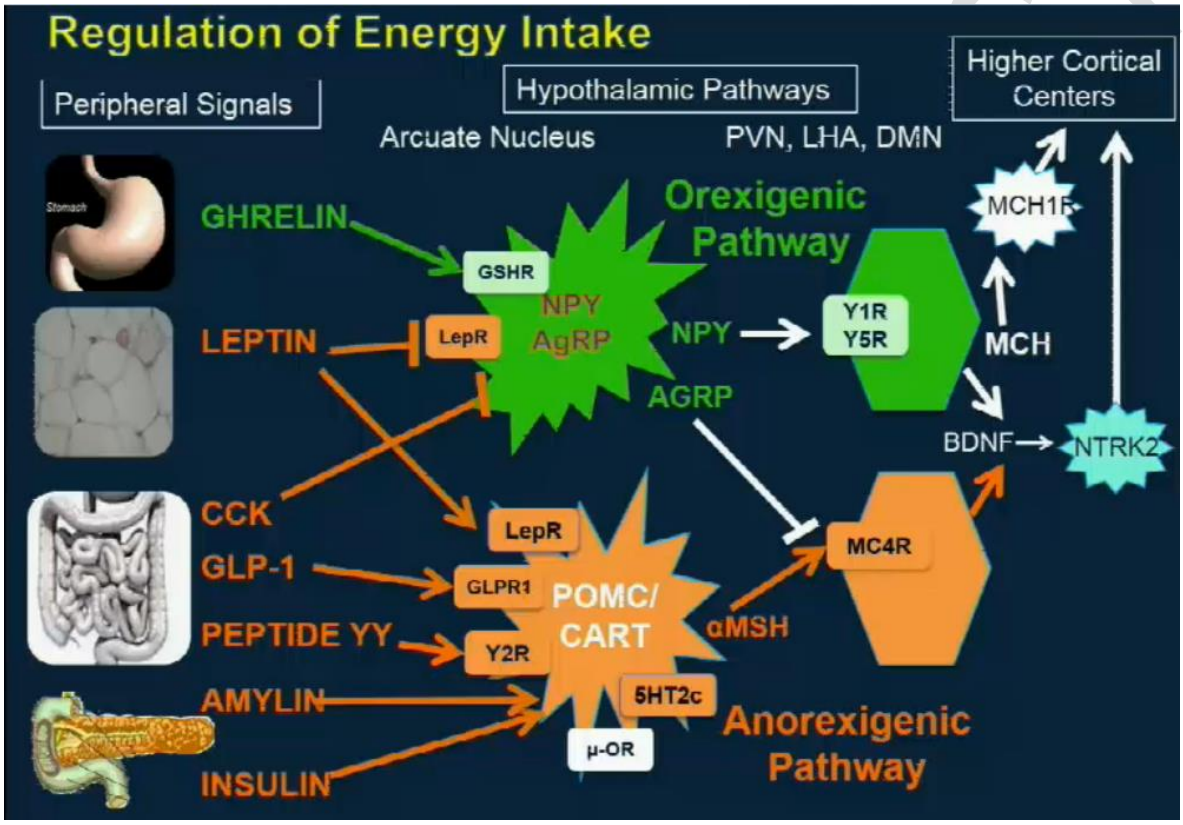
Predictors of the likely failure of fluid restriction:

- High urine osmolality (>500 mOsm/kg H_2O).
- Sum of the urine Na^+ and K^+ concentrations exceeds the serum Na^+ concentration.
- 24-hour urine volume <1500 mL/d.
- Increase in serum Na^+ concentration <2 mmol/L/d in 24-48 hours on a fluid restriction of ≤1 L/d.

D = day; H_2O = water; K = potassium; kg = kilogram; L = liter; mL = milliliter; mmol = millimole; mOsm = milliosmole; Na = sodium.



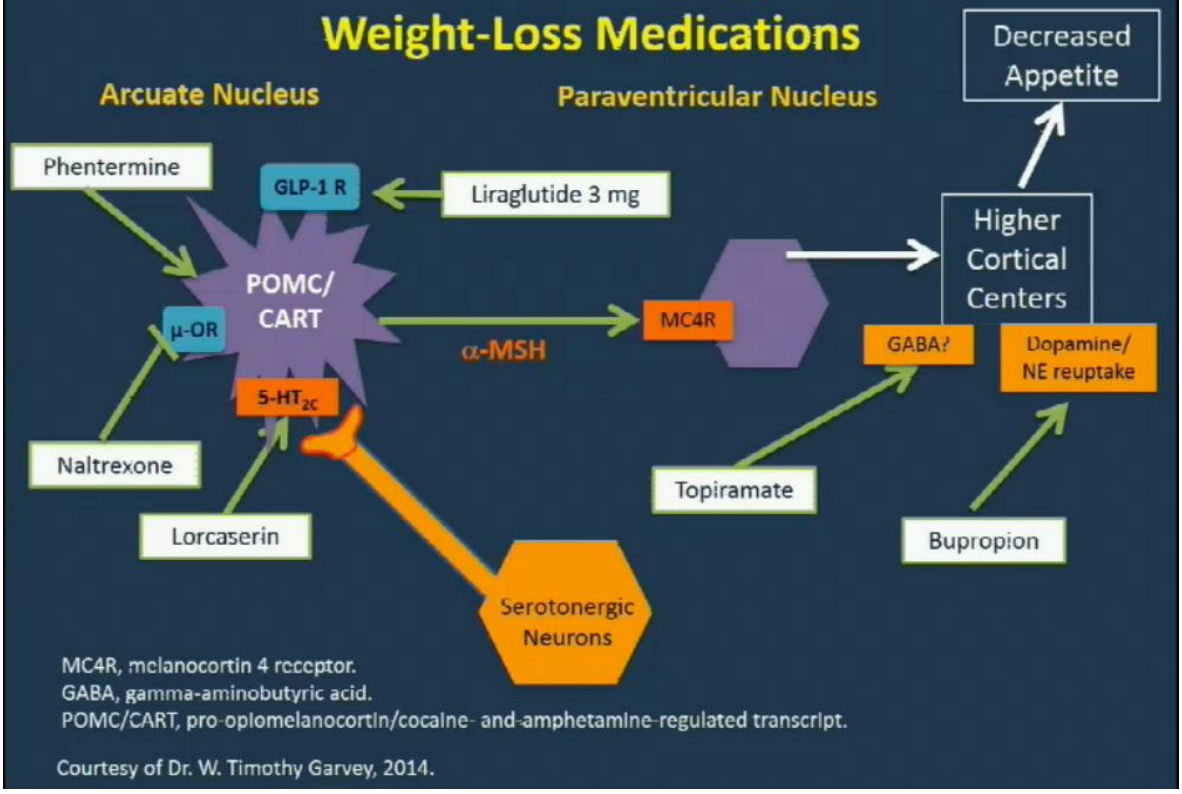
OBESITY



Two pathways underlying obesity --- orexigenic pathway (increase food intake) and anorexigenic pathway (reduce food intake)

Agents	Action	Approval
	Previously available	
Phentermine	• Sympathomimetic	• 1959
Orlistat	• GI lipase inhibitor	• 1997
	Recently Approved	
Phentermine/ Topiramate ER	• Sympathomimetic/Anticonvulsant (GABA receptor modulation?)	• Approved, Summer 2012
Lorcaserin	• 5-HT_{2C} serotonin receptor agonist	• Approved, Summer 2012
Naltrexone ER/ Bupropion ER	• Dopamine/noradrenaline reuptake inhibitor/Opioid receptor antagonist	• Approved, September 2014
Liraglutide 3 mg	• GLP-1 receptor agonist	• Approved December 2014

Actions of Recently Approved Weight-Loss Medications



MC4R, melanocortin 4 receptor.
GABA, gamma-aminobutyric acid.
POMC/CART, pro-opiomelanocortin/cocaine- and-amphetamine-regulated transcript.

Courtesy of Dr. W. Timothy Garvey, 2014.

Therapeutic Weight Loss Reduces Complications

OBESITY COMPLICATION	% weight loss required for therapeutic benefit	Notes	References
Diabetes Prevention	3% to 10%	Maximum benefit 10%	DPP (Lancet, 2009) SEQUEL (Garvey et al. 2013)
Hypertension	5% to >15%	BP still decreasing >15%	Look AHEAD (Wing, 2011)
Dyslipidemia	3% to >15%	TG still decreasing at >15%	Look AHEAD (Wing, 2011)
HbA1c	3% to >15%	HbA1c still decreasing at >15%	Look AHEAD (Wing, 2011)
NAFLD	10%	Improves steatosis, inflammation, mild fibrosis	Assy et al, 2007; Dixon et al, 2004; Anish et al, 2009
Sleep Apnea (AHI)	10%	Little benefit at < 5%	Sleep AHEAD (Foster, 2009) Winslow et al, 2012
Osteoarthritis	5-10%	Improves symptoms and joint stress mechanics	Christenson et al, 2007 Felson et al, 1992; Aaboe et al, 2011
Stress Incontinence	5-10%		Burgio et al, 2007 Leslee et al, 2009
GERD	5-10% women 10% men		Singh et al, 2013 Tutuljan R, 2011
PCOS	5-15% (>10% optimal)	Lowers androgens, improves ovulation, increases insulin sensitivity	Panidis D et al, 2008 Norman et al, 2002 Moran et al, 2010

Preferred Weight Loss Medications in Patients with Obesity and Hypertension

Hypertension

Preference	Obesity Medication	References & Notes	Clinical Monitoring
1st	Phentermine/ Topiramate ER	BP decreased by 3.2/1.1 mmHg placebo subtracted (1)	Monitor heart rate
1st	Liraglutide 3 mg	BP decreased by 2.8/0.9 mmHg placebo subtracted (21)	Monitor heart rate
1st	Orlistat	BP decreased by 2.1/1.0 mmHg placebo subtracted at 1 year (12)	
2nd	Lorcaserin	BP decreased by 0.6/0.5 mmHg placebo subtracted at 1 year (15)	
3rd	Naltrexone ER/ Bupropion ER	No change from baseline despite weight loss (17) or decrements less than observed in placebo (SBP -1.3 vs 3.0; DBP 1.4 vs 2.8) despite greater weight loss with drug (19).	BP lowering is not commensurate with degree of weight loss. Monitor heart rate and BP
	Naltrexone ER/ Bupropion ER	Contraindicated if Blood Pressure is uncontrolled.	

1. Gadde KM et al. Lancet. 2011 Apr 16;377(9774):1341-52
12. Torgerson JS et al. Diabetes Care. 2004 Jan;27(1):155-61
15. Smith SR et al. N Engl J Med. 2010;363(3):245-256
17. Greenway FL et al. Lancet. 2010; 376(9741):595-605
19. Wadden TA et al. Obesity (Silver Spring). 2011 Jan;19(1):110 20
21. Pi-Sunyer X et al. N Engl J Med. 2015;373(1):11-22

Preferred Weight Loss Medications in Patients with Prediabetes and/or Metabolic Syndrome

Diabetes Prevention / Metabolic Syndrome / Prediabetes

Preference	Obesity Medication	References & Notes
1st	Phentermine/ Topiramate ER	Highly effective (3); 79% reduction in DM at 2 years. Lowers systolic BP by 7.2 mmHg while decrease in diastolic NS. Lowers TG and raises HDL
1st	Liraglutide 3 mg	Highly effective (26); 72% reduction in DM at 3 years. Lowers systolic BP by 2.8 mmHg while decrease in diastolic NS. Lowers TG and raises HDL
2nd	Orlistat	Moderately effective (12); 45% reduction in DM at 4 years. Lowers BP by 4.9/2.6 mmHg. Lowers LDL and raises HDL
2nd	Lorcaserin	Moderately effective (16); 36% reduction in DM at 1 year. Lowers BP by 2.2/1.8 mmHg. Lowers TG and raises HDL
3rd	Naltrexone ER/ Bupropion ER	Insufficient data for DM prevention.

3. Garvey WT et al. Diabetes Care. 2014 Apr;37(4):912-21
12. Torgerson JS et al. Diabetes Care. 2004 Jan;27(1):155-61
16. Nesto R et al. Postgrad Med. 2016 May;128(4):364-70
26. Le Roux CW et al. Lancet 2017;389(10077):1399-409

Primary Causes
- Genetic causes
  - Monogenic disorders
    - Melanocortin-4 receptor mutation
    - Leptin deficiency
    - POMC deficiency
  - Syndromes
    - Prader-Willi
    - Bardet-Biedl
    - Cohen
    - Alström
    - Froehlich

Secondary Causes
- Neurological
  - Brain injury
  - Brain tumor
  - Consequences of cranial irradiation
  - Hypothalamic obesity
- Endocrine
  - Hypothyroidism[a]
  - Cushing syndrome
  - GH deficiency
  - Pseudohypoparathyroidism
- Psychological
  - Depression[b]
  - Eating disorders
- Drug-Induced
  - Tricyclic antidepressants
  - Oral contraceptives
  - Antipsychotics
  - Anticonvulsants
  - Glucocorticoids
  - Sulfonylureas
  - Glitazones
  - β blockers

Gut hormone regulation of appetite, food intake and insulin secretion

Pancreatic polypeptide- fold peptides

- Neuropeptide Y
- Peptide tyrosine-tyrosine PYY and Pancreatic polypeptide (both are gut hormones)

Peptide YY (PYY)	• PYY is processed in circulation by DPP-4 > active peptide then acts on the hypothalamus as a

	satiety signal. (has anorexigenic effects of normal weight and obese) • High levels of PYY post GI surgery may explain long term maintenance of weight loss.
Pancreatic polypeptide	• PP is regarded as part of the "ileal brake," which slows the transit of food through the gut. • PP slows gastric emptying, inhibits pancreatic exocrine secretion and reduces gallbladder contraction. • *Main stimulus of PP release is the ingestion of food*

Incretins

Incretins are gut-derived factors that stimulate insulin release and are produced by *selective posttranslational cleavage of proglucagon*, a 160-residue peptide, expressed in the **α-cells of the pancreas** and **L cells of the intestine** and the **CNS.**

What is the incretin effect?
Which is the enhanced secretion of insulin in response to oral administration of glucose compared with intravenous administration of glucose

GLP-1	• GLP-1 is released in the gut in proportion to ingested calories -- it has anorexigenic effects. • *Reduction in gastric emptying and a suppression of gastric acid secretion* • Obese individuals have been reported to elicit delays in the postprandial release of GLP-1, and thus present with reduced circulating levels of the peptide

Glucose-dependent insulinotropic polypeptide (GIP)	• Along with GLP-1, GIP acts as an incretin to potentiate glucose-stimulated insulin release
	• direct **anabolic effects on adipose tissue**, including
	  ○ stimulation of glucose import
	  ○ fatty acid synthesis
	  ○ Lipogenesis
	  ○ inhibition of lipolysis

- GLP-1 is released in the gut in proportion to ingested calories -- it has anorexigenic effects.

Ghrelin

Ghrelin is a 28-amino acid peptide hormone produced predominantly in the stomach and is the only known orexigenic gut hormone.

- Binds to growth hormone secretagogue receptor and is expressed in NPY neurons of the hypothalamus.

Fasting state	**Levels increase** -- encouraging food intake
Post prandial state	**Levels decrease** • Expected postprandial fall in circulating ghrelin levels is attenuated, or even absent in obese people • ghrelin has a role in the pathophysiology of obesity • ghrelin antagonism may be a promising strategy to treat obesity.

***Ghrelin may be useful to reverse pathological states of cachexia*

Amylin -- Islet amyloid polypeptide (IAPP)

- Amylin decreases postprandial blood glucose levels through inhibition of gastric emptying and suppression of glucagon secretion
- *Activation of a mylin receptors in the area postrema in the brain induces satiety and leads to decreased food intake*

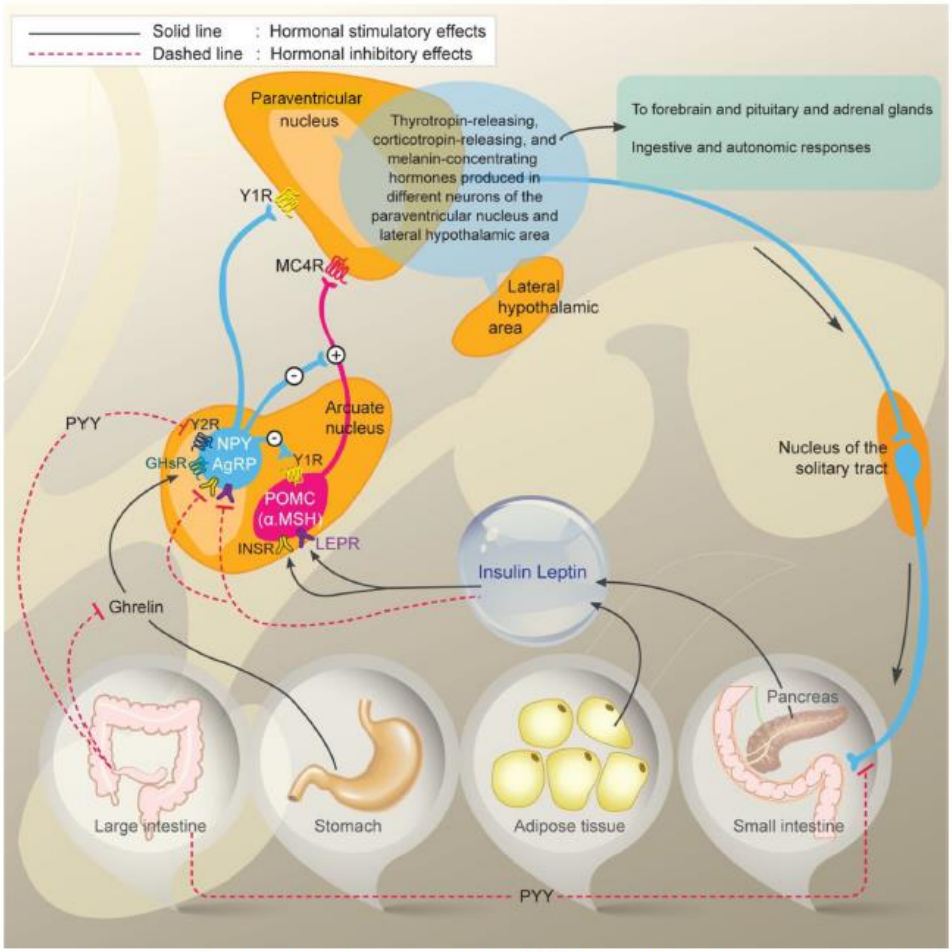


Figure 1. Interactions among hormonal and neural pathways that regulate food intake and body-fat mass. α-MSH, α-melanocyte-stimulating hormone; GHsR, GH secretagogue receptor; INSR, insulin receptor; LEPR, leptin receptor; MC4R, melanocortin receptor type 4; Y1R, Y1 receptor; Y2R, Y2 receptor. [Adapted from J. Korner and R. L. Leibel: To eat or not to eat - how the gut talks to the brain. *N Engl J Med.* 2003;349:926–928 (24), with permission. © Massachusetts Medical Society.]

Table 2. Advantages and Disadvantages Associated with Weight Loss Medications

Drug	Advantages	Disadvantages
Phentermine	Inexpensive ($) Greater weight loss[a]	Side effect profile No long-term data[b]
Topiramate/phentermine	Robust weight loss[a] Long-term data[b]	Expensive ($$$) Teratogen
Lorcaserin	Side effect profile Long-term data[b]	Expensive ($$$)
Orlistat, prescription	Nonsystemic Long term data[b]	Less weight loss[a] Side effect profile
Orlistat, over-the-counter	Inexpensive ($)	Less weight loss[a] Side effect profile
Natrexone/bupropion	Greater weight loss[a] Food addiction Long-term data[b]	Side effect profile Mid-level price range ($$)
Liraglutide	Side effect profile Long-term data[b]	Expensive ($$$) Injectable

[a] Less weight loss = 2–3%; greater weight loss = >3–5%; robust weight loss = >5%.
[b] Long term is 1–2 years.

Obesity Management

Orlistat inhibits pancreatic lipase to reduce fat absorption and increase fecal fat excretion.

Table 4. Pharmacotherapy for Obesity in the United States (December 2014)

Drug (Generic)	Dosage	Mechanism of Action	Weight Loss Above Diet and Lifestyle Alone, Mean Weight Loss, % or kg[a]; Duration of Clinical Studies	Status	Common Side Effects	Contraindications
Phentermine resin	AdipexP (37.5 mg), 37.5 mg/d Ionamin (30 mg), 30–37.5 mg/d	Norepinephrine-releasing agent	3.6 kg (7.9 lb); 2–24 wk	Approved in 1960s for short-term use (3 mo)	Headache, elevated BP, elevated HR, insomnia, dry mouth, constipation, anxiety Cardiovascular: palpitation, tachycardia, elevated BP, ischemic events Central nervous system: overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychosis Gastrointestinal: dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances Allergic: urticaria Endocrine: impotence, changes in libido	Anxiety disorders (agitated states), history of heart disease, uncontrolled hypertension, seizure, MAO inhibitors, pregnancy and breastfeeding, hyperthyroidism, glaucoma, history of drug abuse, sympathomimetic amines
Diethylpropion	Tenuate (75 mg), 75 mg/d	Norepinephrine-releasing agents	3.0 kg (6.6 lb); 6–52 wk	FDA approved in 1960s for short-term use (3 mo)	See phentermine resin	See phentermine resin
Orlistat, prescription (120 mg)	120 mg TID	Pancreatic and gastric lipase inhibitor	2.9–3.4 kg (6.5–7.5 lb), 2.9–3.4%; 1 y	FDA approved in 1999 for chronic weight management	Decreased absorption of fat-soluble vitamins, steatorrhea, oily spotting, flatulence with discharge, fecal urgency, oily evacuation, increased defecation, fecal incontinence	Cyclosporine (taken 2 h before or after orlistat dose), chronic malabsorption syndrome, pregnancy and breastfeeding, cholestasis, levothyroxine, warfarin, antiepileptic drugs
Orlistat, over-the-counter (60 mg)	60–120 mg TID	Pancreatic and gastric lipase inhibitor	2.9–3.4 kg (6.5–7.5 lb), 2.9–3.4%; 1 y	FDA approved in 1999 for chronic weight	See Orlistat, prescription	See Orlistat, prescription

Drug (Generic)	Dosage	Mechanism of Action	Weight Loss Above Diet and Lifestyle Alone, Mean Weight Loss, % or kg[a]; Duration of Clinical Studies	Status	Common Side Effects	Contraindications

Orlistat, over-the-counter (60 mg)	60–120 mg TID	Pancreatic and gastric lipase inhibitor	2.9–3.4 kg (6.5–7.5 lb), 2.9–3.4%; 1 y	FDA approved in 1999 for chronic weight management	See Orlistat, prescription	See Orlistat, prescription
Lorcaserin (10 mg)	10 mg BID	5HT2c receptor agonist	3.6 kg (7.9 lb), 3.6%; 1 y	FDA approved in 2012 for chronic weight management	Headache, nausea, dry mouth, dizziness, fatigue, constipation	Pregnancy and breastfeeding **Use with caution:** SSRI, SNRI/MAOI, St John's wort, triptans, buproprion, dextromethorphan
Phentermine (P)/ topiramate (T)	3.75 mg P/23 mg T ER QD (starting dose) 7.5 mg P/46 mg T ER daily (recommended dose) 15 mg P/92 mg P/T ER daily (high dose)	GABA receptor modulation (T) plus norepinephrine-releasing agent (P)	6.6 kg (14.5 lb) (recommended dose), 6.6% 8.6 kg (18.9 lb) (high dose), 8.6%; 1 y	FDA approved in 2012 for chronic weight management	Insomnia, dry mouth, constipation, paraesthesia, dizziness, dysgeusia	Pregnancy and breastfeeding, hyperthyroidism, glaucoma, MAO inhibitor, sympathomimetic amines
Naltrexone/ bupropion	32 mg/360 mg 2 tablets QID (high dose)	Reuptake inhibitor of dopamine and norepinephrine (bupropion) and opioid antagonist (naltrexone)	4.8%; 1y (Ref. 79)	FDA approved in 2014 for chronic weight management	Nausea, constipation, headache, vomiting, dizziness	Uncontrolled hypertension, seizure disorders, anorexia nervosa or bulimia, drug or alcohol withdrawal, MAO inhibitors
Liraglutide	3.0 mg injectable	GLP-1 agonist	5.8 kg; 1 y (Ref. 30, 31)	FDA approved in 2014 for chronic weight management	Nausea, vomiting, pancreatitis	Medullary thyroid cancer history, multiple endocrine neoplasia type 2 history

A. OBESITY

- Post bariatric surgery care - Endocrine society guidelines
  i. Prevention and treatment of weight regain
    - a technically proficient surgical team, accredited by national certifying organization, and and integrated medical support team able to provide dietary instruction and behavior modification postoperatively and long term.
    - Remitting weight gain - if GI tract intact consider further surgical manipulation. If not intact multidisciplinary team should consider all options, such as patient education, behaviour modification, additional weight loss therapies or revisionary surgery.

Causes and prevention of WR
Causes
Noncompliance with dietary and lifestyle recommendations
Physiological factors (variations in response to surgery)
Surgical failure
Prevention
Optimizing patient selection criteria
Realistic preoperative expectations
Consideration of benefits of bypass *vs.* restrictive procedures
Adherence to scheduled visits

    - Causes
      - Mechanical problems such as band slippage or pouch and stomal dilation could potentially

impair gastric neural signals driving satiety sensations to the CNS, favoring increased food intake.
    - No conclusive evidence that WR is due to surgical factors
    - Psychological factors and eating disorders can also promote WR
- Prevention and tx of WR (weight regain)
    - preoperative realistic expectation
    - adherence to scheduled visits
    - complanc with nutritional recommendations
        - low glycemic load, moderately high protein diet combined with physical activity has been shown to be effective in treating WR in short term
        - Promoting adherence and collecting food records, monitoring body weight and participation in support groups
    - maintenance of regular physical activity of at least 150 min/wk
    - periodic assessment to prevent or treating eating or other psychiatric disorders

Lifestyle Interventions

- Diabetes Prevention Program
- Look AHEAD
- National Weight Control Registry

Weight Effects of Common Medications[1]

Medication	Weight Gain Associated With Use	Alternatives (Weight Reducing in Parentheses)
Diabetes medications	Insulin, sulfonylureas, TZDs, mitiglinide, sitagliptin?[a]	(Metformin, acarbose, miglitol, pramlintide, exenatide, liraglutide, SGLT-2 inhibitors)
Hypertension medications	α-Blocker?, β-blocker?	ACE inhibitors?, calcium channel blockers?, angiotensin-2 RAs
Antidepressants and mood stabilizers	Amytriptyline, doxepin, imipramine, nortriptyline, trimipramine, mirtazapine, fluoxetine?, sertraline?, paroxetine, fluvoxamine	(Bupropion), nefazodone, fluoxetine (short term, sertraline, <1 year)
Oral contraceptives	Depot progesterone	Barrier methods, IUDs

? represents uncertain/under investigation.

KNOWN MECHANISMS OF ACTION OF WEIGHT LOSS MEDICATIONS (BOARD PEARL)

Medication	Mechanism of Action	FDA Approval
Phentermine (Adipex®)	Stimulant appetite suppressant (sympathomimetic)	1959 Short-term (<6 mo)
Orlistat (Xenical®, Alli®)	Blocks intestinal fat absorption	1999 Long-term treatment 2007 Over-the-counter
Phentermine/topiramate (Qysmia®)	Appetite suppressant (sympathomimetic/activates GABA receptors)	2013 Long-term treatment
Lorcaserin (Belviq®)	Appetite suppressant (selective 5HT2c receptor blocker)	2013 Long-term treatment
Bupropion/naltrexone (Contrave®)	Appetite suppressant (NE/dopamine reuptake inhibitor, opioid receptor antagonist)	2014 Long-term treatment
Liraglutide 3.0 mg (Saxenda®)	Appetite suppressant (GLP-1 receptor agonist)	2014 Long-term treatment

MONOGENIC FORMS OF OBESITY WITH CHILDHOOD ONSET

Gene Symbol	Gene Name	Prevalence	Pathophysiology	Characteristics
A. *MC4R*	Melanocortin 4 receptor	5%	Loss of satiety, hyperphagia	Increased growth Tall for age Increased lean mass
B. *LEP*	Leptin	<1%	Leptin secreted by adipocytes – acts centrally to promote satiety; proportional to fat mass	Hyperphagia Hypothyroidism Hypogonadism Impaired immune function
C. *LEPR*	Leptin receptor	< 1%	Receptor to mediate effects of the adipose hormone leptin	Same as above for leptin
D. *POMC*	Proopiomelanocortin	1%	Regulates energy expenditure and appetite; POMC cleaved into peptides including α-MSH and ACTH	Hyperphagia ACTH deficiency Adrenal insufficiency Hypopigmentation

Gene Symbol	Gene Name	Prevalence	Pathophysiology	Other Characteristics
SIM1	Single-minded homolog 1	2%	Loss of satiety, hyperphagia	Increased lean mass Developmental delay Autistic like features Autonomic dysfunction Increased RQ
BDNF	Brain derived neurotrophic factor	<1%	Loss of satiety, hyperphagia	Speech and language delay Hyperactivity Impaired memory Impaired nociception
TRKB	Tyrosine kinase receptor	<1%	Loss of satiety, hyperphagia	Speech and language delay Hyperactivity Impaired memory Impaired nociception
PC1/3	Proconvertase 1/3	<1%	Loss of satiety, hyperphagia	Hypopigmentation Impaired prohormone Neonatal enteropathy

GENETICS OF ADULT ONSET OBESITY

Gene Symbol	Gene Name	Mechanism
FTO	FTO, alpha-ketoglutarate dependent dioxygenase	Largely unknown, increased food intake
IRS1	Insulin receptor substrate 1	Higher BMI, ↑CAD, ↓TG, ↑HDL, ↓insulin, ↑adiponectin
TLR4	Toll like receptor 4	Higher BMI, may work via microbiome
MC4R	Melanocortin 4 receptor	Severe childhood obesity, rare
HHIP	Hedgehog interacting protein	Higher BMI, ↓T2D, ↑HDL

- Common adult obesity is a complex disorder with both genetic and environmental influences
- More than 100 genetic variants contribute to obesity
- Explain <5% of variation in adult BMI

Medication	Mechanism of Action	Notes
A. Lorcaserin (Belviq®)	Appetite suppressant (selective 5HT2c receptor blocker)	Selective for 5HT2C not 5HT2B receptors; does not increase blood pressure, heart rate or cause valvular heart disease
B. Phentermine ER (Adipex®)	Stimulant appetite suppressant (sympathomimetic)	Sympathomimetic may increase blood pressure and heart rate, and risk of tachyarrhythmias
C. Phentermine/topiramate (Qysmia®)	Appetite suppressant (sympathomimetic/activates GABA receptors)	Sympathomimetic may increase blood pressure and heart rate and risk of tachyarrhythmias
D. Liraglutide 3.0 mg (Saxenda®)	Appetite suppressant (GLP-1 receptor agonist)	Increases heart rate by average or 2-3 beats/min 34% heart rate increase by ≥10 beats/min 5% heart rate increase by ≥20 beats/min
E. Diethypropion	Stimulant appetite suppressant (sympathomimetic)	Sympathomimetic may increase blood pressure and heart rate and risk of tachyarrhythmias

Weight-Promoting	Weight-Neutral	Weight Loss
Paroxetine (SSRI, most weight gain)	Imipramine (tricyclic)	Fluoxetine (SSRI)
Amitriptyline (tricyclic)	Sertraline (SSRI)	Bupropion (NE/Dopa RI)
Nortriptyline (tricyclic)	Citalopram (SSRI)	
Mirtazapine (NA/SR receptor blocker)	Escitalopram (SSRI)	
Duloxetine (SNRI)		
Venlafaxine (SNRI)		

Weight-Promoting	Weight-Neutral	Weight Loss
β-Adrenergic blockers (HTN, CAD)	ACE Inhibitors (HTN)	GLP-1 receptor agonists (diabetes)
Insulin/insulin analogues (diabetes)	ARBs (HTN)	SGLT-2 inhibitors (diabetes)
Insulin secretagogues (SU, meglitinides)	Calcium channel blockers (HTN)	
Thiazolidinediones (diabetes)	Metformin (diabetes)	
Antihistamines (allergy)	DPP-4 inhibitors (diabetes)	
Glucocorticoids	α-Glucosidase Inhibitors (diabetes)	
Antipsychotics	Statins/HMG-CoA reductase inhibitors	
Hormonal contraceptives	Fibrates	
Antidepressants	Antidepressants	Antidepressants

MISCELLANEOUS RELEVANT CLINICAL TRIALS, NEUROENDOCRINE TUMORS. ETC

MULTIPLE ENDOCRINE NEOPLASIA (MEN)

-- A **heterogeneous group of autosomal dominant inherited disorders** characterized by the presence of **tumors involving ≥2 endocrine organs**, either synchronous or metachronous, in a same patient.

Multiple endocrine and other organ neoplasia (MEON) syndrome

-- Disorders which are associated with multiple endocrine as well as non-endocrine neoplasia

- Carney's complex
- Von Hippel–Lindau disease
- Neurofibromatosis type 1

MEN syndrome	Endocrine organs involved	Associated features
MEN 1	Parathyroid: hyperplasia/ adenoma	Lipoma, collagenoma, angiofibroma, gastric carcinoid, meningioma
	Pituitary: prolactinoma, somatotropinoma	
	Pancreas: gastrinoma, insulinoma	
	Adrenal: nonfunctional adrenal hyperplasia and adenoma	
	Thyroid: thyroid nodule, MNG	
MEN 2A	Thyroid: MTC	Cutaneous lichen amyloidosis
	Parathyroid: hyperplasia/ adenoma	Hirschsprung disease
	Adrenal: pheochromocytoma	
MEN 2B (MEN3)	Thyroid: MTC	Mucosal neuroma, marfanoid habitus, and slipped capital femoral epiphysis
	Adrenal: pheochromocytoma	
MEN 4	Parathyroid: adenoma	Reproductive organ neoplasia
	Pituitary: adenoma	
	Pancreas: NET	

MNG multinodular goiter, *MTC* medullary thyroid carcinoma, *NET* neuroendocrine tumor

MEN1 gene

- **MEN1 is a tumor suppressor gene** which is **located on chromosome 11q13**
- It consists of 10 exons which encodes 610 amino acid protein termed as Menin
- **Regulates transcription**, **genome stability**, **cell division**, and **proliferation**.

Knudson hypothesis

- Inheritance of a **germ-line MEN1 mutation** predisposes an individual to develop a tumor after acquisition of somatic mutation which may be a point mutation or more commonly a deletion.
- This results in loss of heterozygosity in the involved tissue, thereby

leading to tumor formation
- The first-degree relatives of the patients with MEN1 have 50 % risk of developing the disease and can often be identified by MEN1 mutational analysis

Parathyroid gland is the most common endocrine organ involved, and **parathyroid hyperplasia/adenoma is seen in 95 % of patients with MEN1 syndrome**. Pancreatic neuroendocrine tumors (NET) occur in 40–70 % of MEN1 patients.

Who should be screened for MEN1 syndrome

- **≥2 MEN1-associated endocrine tumors** (parathyroid, pancreatic, and pituitary tumor)
- **asymptomatic first-degree relatives of an individual with MEN1 mutation**
- ≥2 MEN1-associated endocrine tumors that are not part of classical triad of parathyroid, pancreatic, or pituitary tumor
- **PHPT <30 years of age**
- **Multiglandular parathyroid disease**
- Gastrinoma
- **Multiple pancreatic neuroendocrine tumor**

When to suspect MEN1 syndrome in a patient who presents with single endocrine gland involvement.

- **PHPT <30 years of age**
- **Multiglandular parathyroid disease**
- **Multiple ulcerations at unusual sites** (second part of the duodenum and jejunum)

⊕ The investigations required for the detection of other endocrine organ involvement include estimation of **serum gastrin**, **fasting plasma glucose**, **insulin and C-peptide**, **prolactin**, and **chromogranin A**.
⓵ further corroborated with **genetic analysis for MEN1 gene mutation**

Screening recommendations for MEN-1

Endocrine tumor	Age to screen (years)	Biochemistry (annually)	Imaging
Parathyroid	8	Calcium and iPTH	–
Gastrinoma	20	Gastrin	–
Insulinoma	5	Fasting glucose and C-peptide	–
Nonfunctional pancreatic NET	<10	Chromogranin A	MRI, CT, or endoscopic ultrasound (annually)
Anterior pituitary	5	Prolactin, IGF1	MRI (3 yearly)
Adrenal	<10	Unless symptomatic or tumor size >1 cm	CT (annually)
Thymic and bronchial carcinoid	15	–	CT or MRI (annually)

Cutaneous manifestations in patients with MEN1 syndrome

- lipomas
- facial angiofibromas
- collagenomas

Characteristics of gastrinomas with MEN1 syndrome

- Usually small (<5 mm) and are frequently multiple
- **"Gastrinoma triangle"** formed by confluence of cystic and common bile duct superiorly, junction of second and third portion of the duodenum inferiorly, and junction of the neck and body of the pancreas medially

Nonfunctioning pancreatic neuroendocrine tumor in MEN 1 syndrome

- NET is present in 20–55% of patients with MEN1 syndrome
- Usually recognized late in the course of disease
- **Majority of these tumors are malignant** and result in high morbidity and mortality.
- **Endoscopic ultrasound** is the most sensitive modality to **localize** these pancreatic neuroendocrine tumors
- **Somatostatin receptor scintigraphy** is useful to detect **metastatic disease**

-- Treatment options

- **Surgical resection** is recommended for tumor >1 cm in size or tumor <1 cm but rapidly growing (doubling of tumor size over 3–6 months interval)
- **Tyrosine kinase inhibitors** and **mTOR inhibitor** (mammalian target of rapamycin)

Multiple Endocrine Neoplasia Type 2 Syndrome

- An **autosomal dominant inherited disorder** characterized by multiple endocrine organ involvement of **neural crest origin.**

RET proto-oncogene

-- RET **(REarranged during Transfection)** proto-oncogene is the only gene known to be associated with MEN2 syndrome

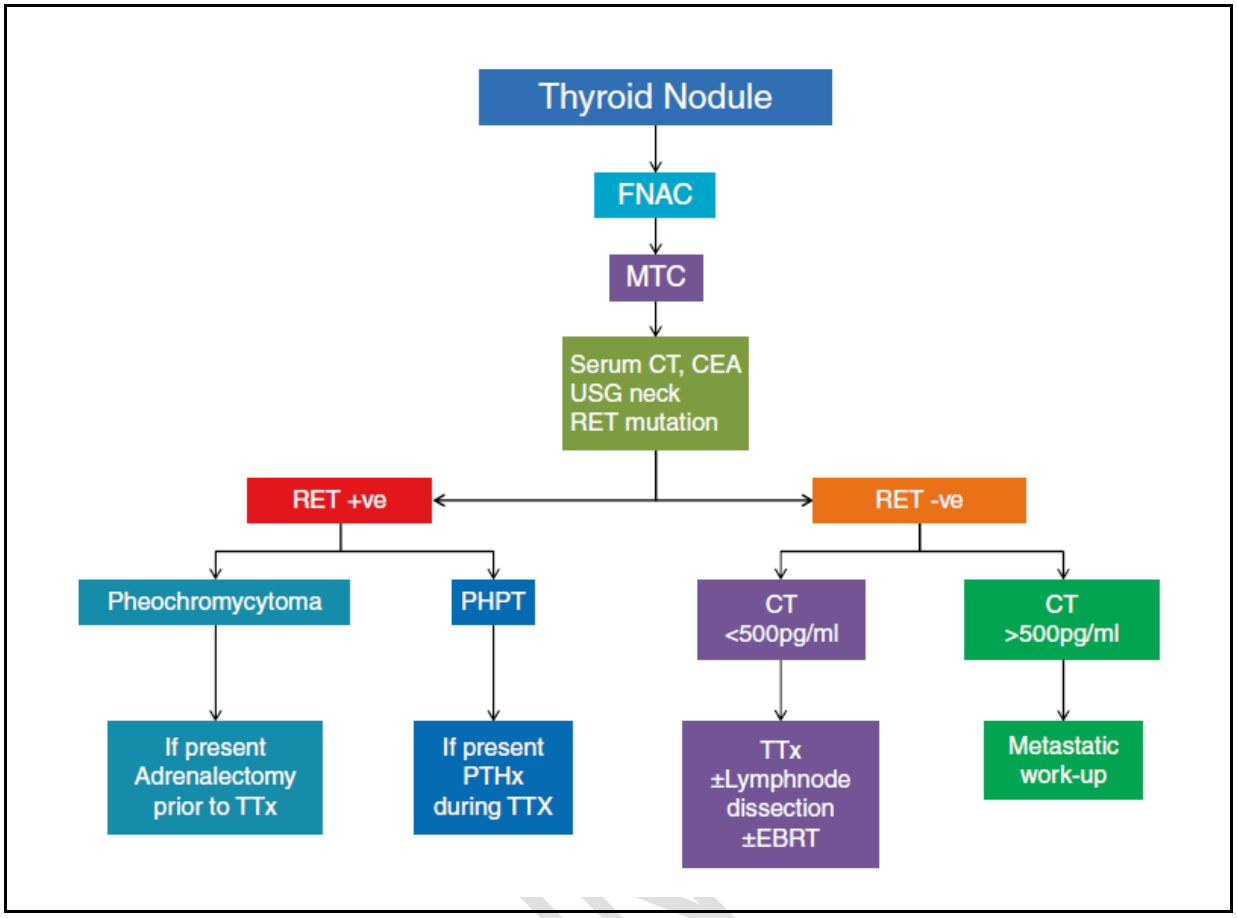
- This gene is located on chromosome 10q11.2 and **encodes receptor tyrosine kinase family**
- **Constitutive activation of this receptor** and consequent downstream signaling result in unrestricted cell growth and proliferation
- Cells-derived from the neural crest, branchial arch, and urogenital system express RET proto-oncogene
- **Gain-of-function mutations of RET proto-oncogene** result in tumorigenesis in these organs
- MEN2A, MEN2B, and FMTC have RET **proto-oncogene germ-line mutations** (ALMOST ALL!)
- Approximately 50 % of patients with **sporadic MTC have somatic RET mutations**

MEN2A syndrome

- **Medullary thyroid carcinoma (MTC)** is usually present in almost all patients (100 %)
- **Pheochromocytoma** is present in 30–50%
- **PHPT** in 10–20 % of patients
- cutaneous lichen amyloidosis, Hirschsprung disease

How to suspect MEN2A syndrome?

- MTC is the most common and the earliest presenting manifestation of MEN2A syndrome
- **Presence of diffuse or nodular goiter and recurrent diarrhea in a euthyroid young individual (<35 years of age) should raise a suspicion of MTC**
- young individual with goiter and cervical lymphadenopathy



⇧⇧ Causes of high serum calcitonin other than MTC

- chronic renal failure
- Hashimoto's thyroiditis
- PHPT
- prostate and lung cancer
- Mastocytosis
- neuroendocrine tumors
- DPP4 inhibitors, GLP1 agonists and proton pump inhibitors
- Ingestion of food (entero-calcitonin axis)
- Presence of heterophile antibodies interfere with the assay

** **lack of rise in serum calcitonin levels in response to calcium and pentagastrin differentiates these disorders from MTC**

* serum calcitonin level should be measured in the fasting state

causes of low serum calcitonin in patients with MTC

- Low serum calcitonin levels in patients with MTC may occur as a result of "hook effect" (prozone phenomenon) or poorly

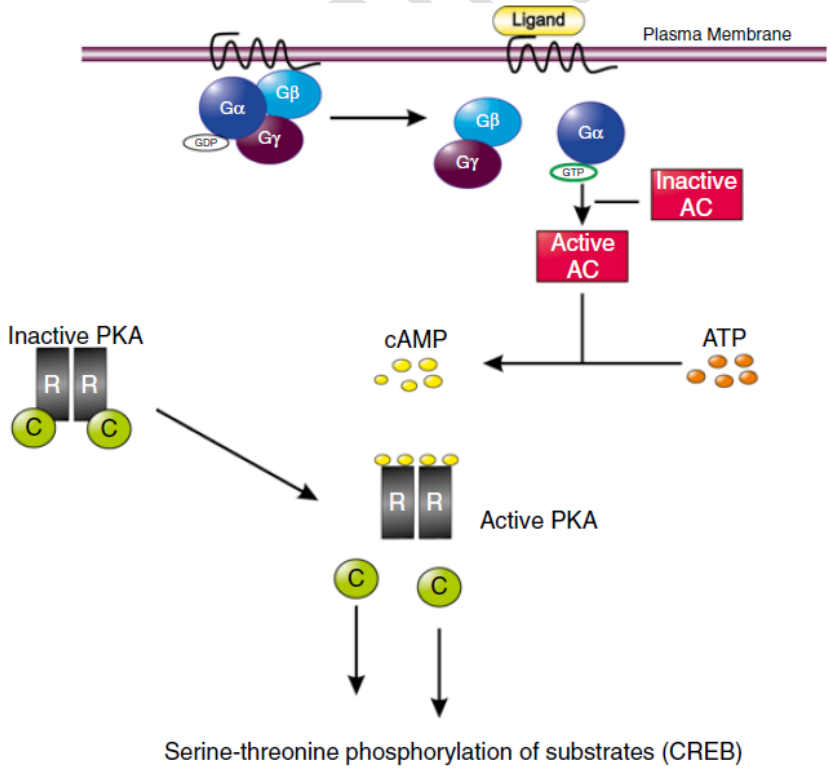
differentiated tumor
- **CEA** levels may be helpful in monitoring the progression of disease in patients with **poorly differentiated MTC**

What is MEN4 syndrome?

3 % of patients with PHPT and pituitary adenoma who simulates MEN1 syndrome but are negative for MEN1 gene mutation are reclassified as MEN4 syndrome.

What is Carney's complex?

- autosomal dominant inherited disorder
- small pigmented cutaneous and mucosal lesions (lentigines)
- **cardiac myxomas**
- multiple endocrine neoplasias including primary pigmented nodular adrenal disease (**PPNAD**), pituitary adenoma, and nodular goiter
- **non-endocrine tumors** like fibroadenoma of the breast and testicular tumors



Protein kinase A (PRKA) is an enzyme which is ubiquitously expressed and is
involved in cell growth and proliferation in cyclic AMP-responsive tissues

MUTATION IN PRKA -- tumorigenesis in cAMP-responsive tissues in patients with Carney's complex.

NEUROENDOCRINE TUMORS

- Neuroendocrine tumors (NETs) are rare, slow growing neoplasms characterized by their ability to store and secrete different peptides and neuroamines
- Some of these substances cause specific clinical syndromes while others are not associated with specific syndromes or symptom complexes.
- There is no "ideal neuroendocrine tumor marker" but according to the presentation, the sensitivity and specificity of each marker varies and it is possible to choose those of greatest value for each clinical syndrome.
- The annual incidence of neuroendocrine tumors (NETs) has risen to 40-50 cases per million

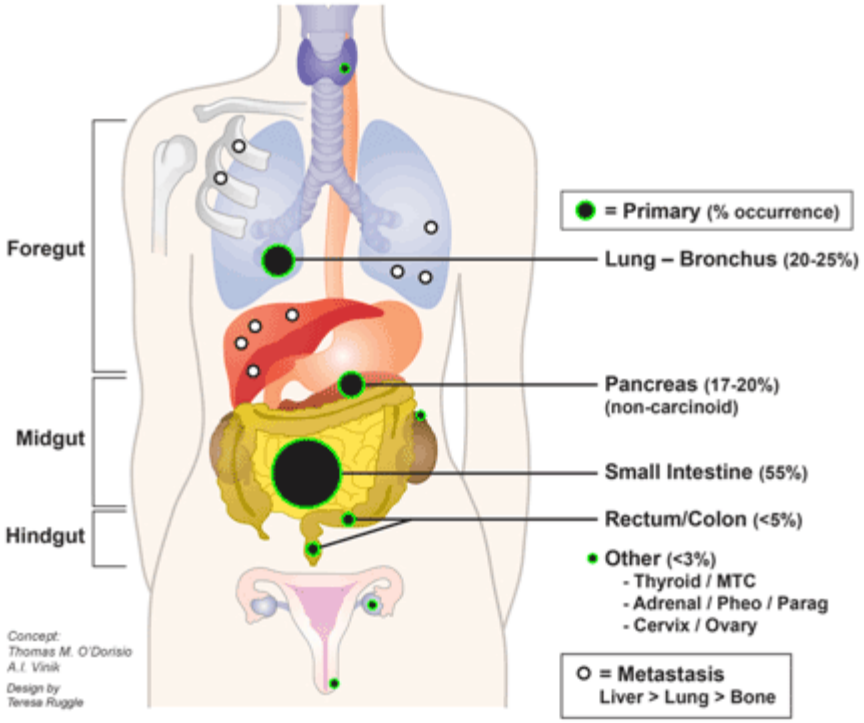
Distribution by subtype

- **50% of neuroendocrine tumors** in clinical practice are the **carcinoid variety** and are found incidentally at operation, after metastasis has occurred, in the small intestine (especially the appendix).
- The remaining fraction comprises approximately **50% gastrinomas**, **30% insulinomas**, **13% VIPomas**, **5 to 10% glucagonomas**, and, rarely, **less than 5% neurotensinomas, somatostatinomas, and ectopic hormone-secreting tumors**

Nonfunctional NETs - the ultimate masquerade
With better immunohistochemical stains for endocrine cells, especially for neuron-specific enclose (NSE), chromogranin, synaptophysin, and receptors for somatostatin, there is increasing recognition that tumors masquerading as **carcinomas of liver, small cell carcinoma of the lung**, and others, are in reality neuroendocrine tumors

****** Most of these nonsecretory tumors actually store and secrete **pancreatic polypeptide (PP)**, but because it has so little, if any, in the way of biologic activity, the tumor often remains silent until it is quite large

Figure 1: Anatomical Distribution of Neuroendocrine Tumors



What is Pasarro's triangle?
60% of pancreatic gastrinomas are concentrated in Pasarro's Triangle, an area subtended by the head of pancreas, gastric antrum, and first portion of the duodenum.

Characteristics of neuroendocrine tumors
• Rare • Usually small, <1 cm • Slow growing, months to years, "cancer in slow motion" • Usually metastasize before becoming symptomatic, often when tumor is >2 cm • Expression is episodic, may be silent for years • Symptoms mimic commonplace conditions and often are misdiagnosed • Complex diagnosis, rarely made clinically, requiring sophisticated laboratory and scanning techniques.

Features of carcinoid syndrome	
Clinical manifestations	• Skin: flushing, telangiectasias, cyanosis • Gastrointestinal: diarrhea, cramping • Cardiac: valvular lesions (right > left side) • Pulmonary: bronchospasm • Miscellaneous: Niacin deficiency (dermatitis, diarrhea & dementia)
Diagnosis	• Elevated 24-hour urinary excretion of 5-HIAA • CT/MRI of abdomen & pelvis to localize tumor • OctreoScan to detect metastases • Echocardiogram (if symptoms of carcinoid heart disease are present)
Treatment	• Octreotide for symptomatic patients **&** prior to surgery/anesthesia • Surgery for liver metastases

Incidence of antipsychotic side effects			
2nd generation antipsychotic	**Weight gain/ metabolic syndrome**	**EPS**	**Prolonged QTc**
Aripiprazole	Low	Low	Low
Olanzapine	Very high	Low	Low
Risperidone	High	High	High
Ziprasidone	Low	Low	High
Clozapine	Very high	Low	Low

Clinical features of lithium toxicity	
Drugs that ↑ lithium levels	• Diuretics • NSAIDs • SSRIs • ACE inhibitors and ARBs • Non-dihydropyridine calcium channel blockers (eg, verapamil) • Antiepileptics (eg, carbamazepine, phenytoin)
Clinical presentation	• Neurologic: confusion, agitation, vertigo, ataxia and/or neuromuscular excitability (eg, irregular coarse tremors, fasciculations, myoclonic jerks) • Cardiac: bradycardia and prolonged QTc interval • Nephrogenic diabetes insipidus • Severe toxicity (lithium level 2.5 - 3.5 mEq/L): seizures, encephalopathy, coma

Indications & contraindications for influenza vaccination	
Live attenuated intranasal vaccine	**Indications** • Healthy individuals age 2-49 years
	Contraindications • Age <2 or ≥50 • Immunosuppressed patients (eg, HIV with $CD4^+$ cell count<200/μL) & close contacts • Chronic cardiovascular, pulmonary, neurologic/neuromuscular, neurologic, or metabolic (eg, diabetes, renal insufficiency) diseases • History of Guillain-Barré syndrome following previous influenza immunization • Pregnant women • Children/adolescents on long-term aspirin • Severe allergy to vaccine or its components (eg, egg allergy)
Inactivated vaccine	**Indications** • Individuals age ≥6 months
	Contraindications • Severe allergy to vaccine or its components (eg, egg allergy)

Recommended vaccines for adults		
	Age 19-64	**Age ≥65**
Td/Tdap	Tdap once as substitute for Td booster, then Td every 10 years	
Influenza	Annually	
Pneumococcus	**PPSV23 alone** • Chronic heart, lung, or liver disease • Diabetes, current smokers, alcoholics **Sequential PCV13 + PPSV23 (very high risk patients)** • CSF leaks, cochlear implants • Sickle cell disease, asplenia • Immunocompromised (eg, HIV, malignancy) • Chronic kidney disease	**Sequential PCV13 + PPSV23** • 1 dose of PCV13 followed by PPSV23 in 6-12 months

CSF = cerebrospinal fluid; **PCV13** = 13-valent pneumococcal conjugate vaccine;
PPSV23 = 23-valent pneumococcal polysaccharide vaccine;
Td = tetanus-diphtheria toxoid booster; **Tdap** = tetanus-diphtheria-pertussis.

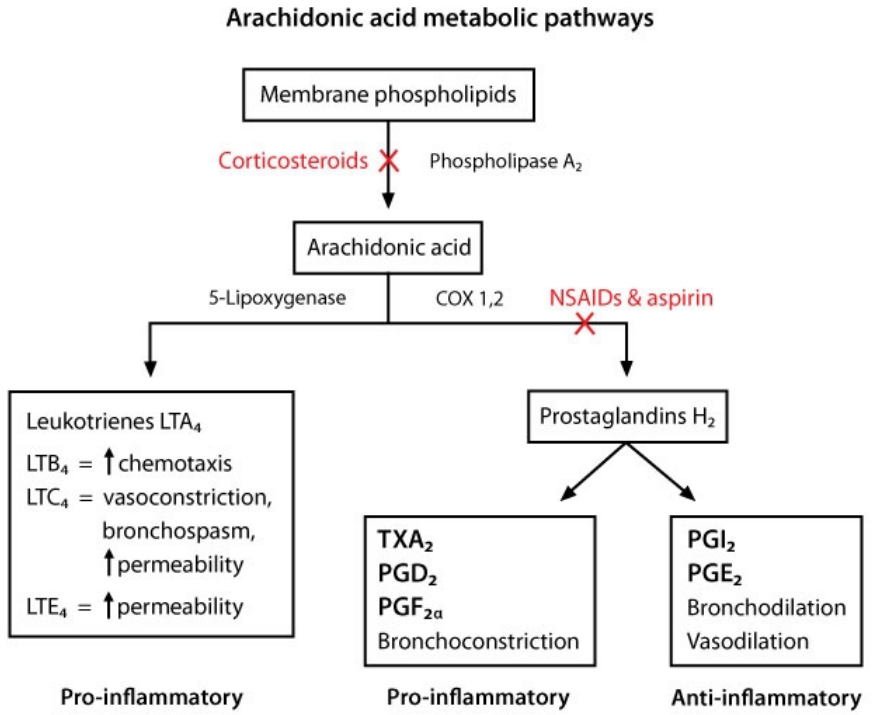
Pneumococcal vaccination guidelines

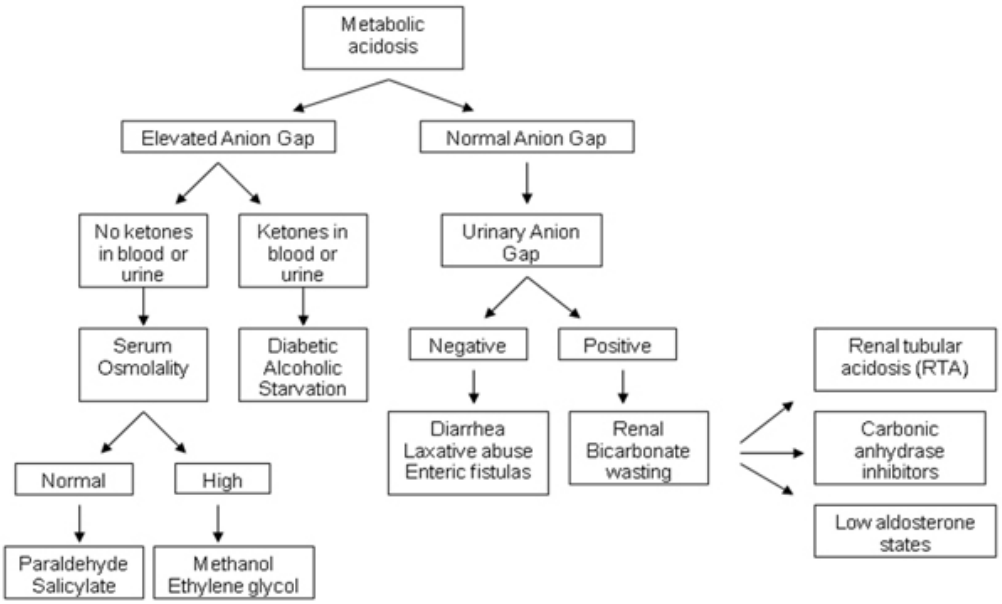
Pneumococcal vaccination in adults		
Average risk	Age ≥65	**Sequential PCV13 + PPSV23** (1 dose of PCV13 followed by PPSV23 6-12 months later)
Elevated risk	• Chronic heart, lung, or liver disease • Diabetes • Current smokers, alcoholics	**PPSV23 alone**, then sequential PCV13 & PPSV23 at age 65
Very high risk	• CSF leaks, cochlear implants • Sickle cell disease, asplenia • Immunocompromised (eg, HIV, malignancy) • Chronic kidney disease	**Sequential PCV13 + PPSV23** • **No prior PPSV23**: 1 dose of PCV13 followed by PPSV23 at least 8 weeks later • **History of prior PPSV23**: 1 dose of PCV13 ≥1 year after previous PPSV23 **Revaccination** (PPSV23) 5 years later & at age 65

CSF = cerebrospinal fluid; **PCV13** = 13-valent pneumococcal conjugate vaccine; **PPSV 23** = 23-valent pneumococcal polysaccharide vaccine.

Differential diagnosis of myopathy			
Disorder	**Clinical features**	**ESR**	**CK**
Glucocorticoid-induced myopathy	• Progressive proximal muscle **weakness** & atrophy **without pain** or tenderness • Lower-extremity muscles are more involved	Normal	Normal
Polymyalgia rheumatica	• Muscle **pain & stiffness** in the shoulder & pelvic girdle • Tenderness with decreased range of motion at shoulder, neck & hip • **Responds** rapidly **to glucocorticoids**	↑	Normal
Inflammatory myopathies	• Muscle pain, tenderness & proximal muscle weakness • **Skin rash** & **inflammatory arthritis** may be present	↑	↑
Statin-induced myopathy	• Prominent muscle pain/tenderness with or without weakness • Rare rhabdomyolysis	Normal	↑
Hypothyroid myopathy	• Muscle pain, cramps & weakness involving the proximal muscles • Delayed tendon reflexes & myoedema • Occasional rhabdomyolysis • **Features of hypothyroidism** are present	Normal	↑

CK = creatine kinase; **ESR** = erythrocyte sedimentation rate.





LANDMARK TRIALS (SUMMARY OF THE EVIDENCE)

Study	Diabetic Patients	Diabetic Nephropathy		Diabetic Retinopathy		Diabetic Neuropathy	
DCCT/EDIC	1441 type 1 diabetes patients (mean age 27 ± 7 years, mean disease duration around 2 to 3 years in primary prevention cohort and around 8 to 9 years in secondary prevention cohort) and mean duration of study of 6.5 years in the initial study; post-trial follow-up ranged from 6.5 to 17 years	↓	↓	↓	↓	↓	↓
UKPDS	3867 newly diagnosed type 2 diabetic patients (median age 54 years, interquartile range 48–60 years) studied over 10 years and another 10 years post-trial follow-up	↓	↓	↓	↓	↔	No data
Kumamoto	110 Japanese type 2 diabetic patients (mean age around 47–52 years, mean disease duration around 6–7 years in primary cohort and around 10 years in secondary prevention cohort) for a treatment period of 6 years and another 8 years of post-trial follow-up	↓	↓	↓	↓	↓	↓
ADVANCE	11,140 type 2 diabetic patients (mean age of 66 years, mean disease duration of 8 years, 46% from Europe & 37% from Asia, median HbA_{1c} at baseline was 7.2%, goal of HbA_{1c} for intensive arm ≤6.5%, median follow-up of 5 years)	↓		↔		↔	
ACCORD	10,251 type 2 diabetic patients in United States and Canada (mean age of 62 years, mean disease duration of 10 years, median HbA_{1c} at baseline was 8.1%, goal of HbA_{1c} for intensive arm <6%, premature termination after 3.7 years of treatment due to higher mortality in the intensive treatment group)	↓		↓		↓	
VADT	1,791 type 2 diabetic patients from United States (mean age of 60 years, mean disease duration of 11.5 years, median HbA_{1c} at baseline was 9.4%, goal of HbA_{1c} for intensive arm <6%, median duration of follow-up of 5.6 years)	↓		↔		↔	
VA Feasibility Trial	153 type 2 diabetic patients (mean only, mean age of 60 years, mean disease duration of 8 years) were treated for 2 years	↓		No data		No data	

Initial Study Follow up study ↓ Decreased risks ↔ No increased or decreased risks

PART II - BOARD REVIEW

1) Antihyperglycemic agents associated with improved cardiovascular outcomes

- Liraglutide (LEADER trial)
- Empagliflozin (EMPAREG OUTCOME)
- Pioglitazone (PRO-ACTIVE)

2) Biochemistry associated wih hypoglycemia mediated by a non-islet cell tumor and describe the mechanism underlying this phenomenon.

- Non-islet cell hypoglycemia - -- a rare complication of malignancy. Epithelial tumors like HCC or mesenchymal tumors like fibrosarcoma. Rare case reports of adrenocortical carcinoma.
- Increased glucose use and inhibition of hepatic glucose release due to secretion of incompletely processed IGF-2 (also termed big IGF-2) by the tumor
- Hypoglycemia workup > *low serum insulin, low c-peptide and low B-OH butyrate*
- "Big" IGF-2 or IGF-2 to IGF-1 ratio measurement.

Treatment of IGF-2 mediated hypoglycemia -- what does not work
● Unresponsive to somatostatin analogues and diazoxide.

Multiple treatment options - debulking surgery, 10% dextrose infusion, glucagon infusion, human Growth hormone, glucocorticoids and continuous NG feeding.
Growth hormone : increase IGF-binding protein and acid labile subunit, which can bind IGF-2 and prevent interaction with the insulin receptor

3) HDR syndrome as a cause of hypoparathyroidism

- HDR syndrome (hypoparathyroidism, sensorineural deafness and renal disease) - rare genetic disorder inherited in an autosomal dominant pattern.
- Also known as Barakat syndrome

Evaluation of hypocalcemia

Autosomal Dominant hypocalcemia	● Activating mutation of CASR gene ● Shifts the set point of CASR so the PTH is not released at calcium [] that normal trigger PTH release ● Increased urinary calcium excretion ● Usually asymptomatic
Pseudohypoparathyroidism	● Mutations in GNAS gene** ● Low calcium, high phosphate and elevated PTH levels due to organ resistance to PTH. ** imprinted based on whether it is maternally or paternally inherited
Autoimmune	● Also referred to as Autoimmune

polyglandular syndrome type 1	polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome • Mutations in the AIRE gene (expressed in the parathyroid glands, thymus,pancreas, adrenal cortex and fetal liver)
Wilson disease	• Mutations in ATP7B -- encodes hepatic Cu transport • Defect in cellular copper transport • Accumulation of copper in the liver, brain and other tissues including parathyroids

4.) Storage of insulin

Tips on handling insulin -- consumersafety.org
• Do not keep insulin in hot places (such as a car) • Do not keep in a freezer • Do not leave insulin in direct sunlight • Do not use beyond expiration date • *Unused insulin should be stored in a refrigerator. Once insulin is opened and used, the vial or pen should be kept at room temperature, below 86F (30 C). Any unused insulin in a pen or vial should be discarded after 28days.*

5.) Side effects of androgen deprivation therapy.

Androgen deprivation therapy with bilateral orchiectomy, GnRH analogues (leuprolide), antiandrogen (flutamide), CYP17 inhibitors of adrenal androgen synthesis (Abiraterone)

NCCN guidelines recommend SC Denosumab to prevent fractures in men on ADT

6.) Approach to Ketosis prone diabetes mellitus

- KPD heterogenous disorder that is intermediate in features between type 1 and type 2 diabetes.
- Almost always obese and have a family history of T2DM.
- Common in ethnic minorities
- Aß classification

A+B- and A-B- = are distinct immunologically but are considered to have T1DM
A +B+ and A-B+ = typical of T2DM

7.) Non PTH mediated hypercalcemia

Mechanism of action of steroids
- Reduce intestinal absorption of calcium - Inhibit 1α hydroxylase activity in granulomas (via role of IL- and IFN-gamma) *No effect on renal 1a OH activity.*

8.) Mechanism of action of mifepristone

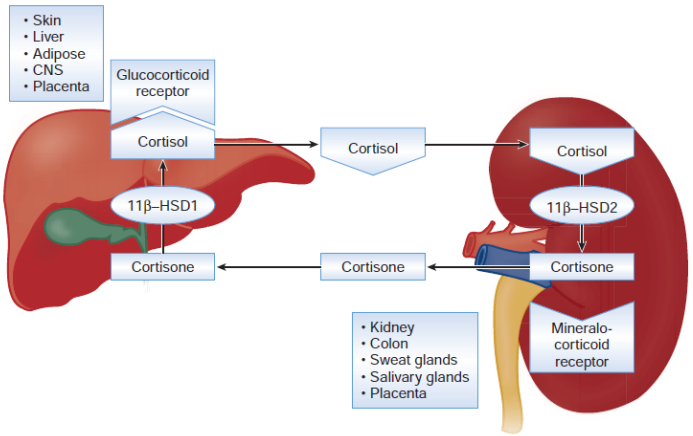


FIGURE 9–8 Cortisol-cortisone shunt. Contrasting functions of the isozymes of 11β-HSD. 11β-HSD2 is an exclusive 11β-dehydrogenase that acts in classical aldosterone target tissues to exclude cortisol from otherwise nonselective mineralocorticoid receptors. Inactivation of cortisol also occurs in placenta. 11β-HSD1 is a predominant 11β-reductase in vivo that acts in many tissues to increase local intracellular glucocorticoid concentrations and thereby maintain adequate exposure of relatively low affinity glucocorticoid receptors to their ligand.

Cortisol is a potent mineralocorticoid receptor agonist and circulates in blood at concentrations ranging from 100 to 1000 fold higher than that of aldosterone.

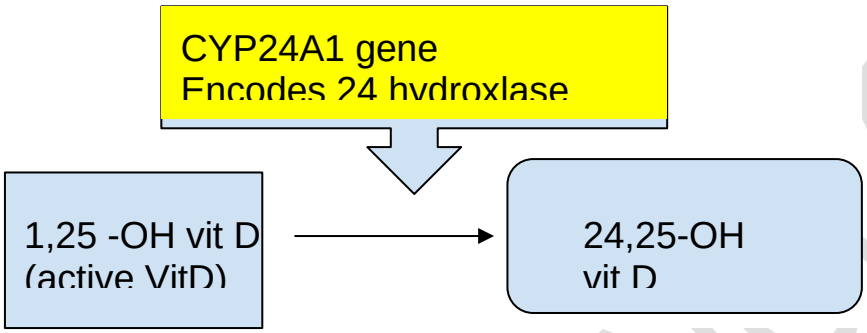
Renal 11BHSD-type2 enzyme inactivates cortisol into cortisone, this minimizes the effect of cortisol on the mineralocorticoid receptor (specificity spillover)

Pseudohyperaldosteronism -- a clinical syndrome of mineralocorticoid receptor excess (HTN and hyperkalemia) in which renin and aldosterone are appropriately suppressed

Mechanism of action of mifepristone	• **Progesterone receptor antagonist and glucocorticoid receptor antagonist** • Blocks the GCR and reduce effects of Cushings syndrome • Increased activation of the MCR (excess cortisol substrate …leading to specificity spillover)

Side effects of mifepristone	• **Hypertension** and increased urinary potassium excretion • **Hypokalemia** (treat with spironolactone and potassium supplements) • Endometrial hypertrophy (spotting and bleeding) • Adrenal insufficiency (cortisol levels are high and nondiagnostic)

9.) Inactivating Mutation in the CYP24A1 gene - A rare cause of non-PTH mediated hypercalcemia



- Idiopathic infantile hypercalcemia
- Adult onset nephrocalcinosis and nephrolithiasis
- Raised or borderline-high calcium,suppressed PTH and high 1,25-OH Vitamin D
- Measure 24,25-OH vitamin D levels
- Treatment -- avoidance of calcium and vitamin D.

10.) Weight loss recommendations (Dietary therapy)

Hypocaloric diet	• A very low-calorie diet (less than 800Kcal/day) • Recommended when rapid weight loss is necssary for a specific reason such as undergoing surgery. (requires close medical supervision and px with BMI>30) • Women lose 1.5-2.0kg per week and men lose 2.0-2.5kg per week • Patients lose on the average 20kg at 12 weeks • Most plans include full meal replacements with either protein shakes or bars. • Increased risk of electrolyte imbalance,volume depletion,fatigue,constipation and gallstones. (monitor q1-2weeks)
Pharmacotherapy	• Not applicable for short term weight loss

	• Phentermine (3.6kg weight loss at 24weeks) • Lorcaserin (3.6kg weight loss at 12months) • Liraglutide (5.8kg at 12months)
Low carbohydrate diet	• Limits carbohydrate intake to less than 60g per day. • No prescribed energy restriction • 3.2 to 12kg weight loss at 6 months

11.) Radiographic evaluation of adrenal incidentaloma

characteristic	Benign adenoma	Adrenal metastasis	pheochromocytoma	Adrenocortical carcinoma
Appearance	Smooth countours, homogenous	Irregular outline heterogenous	Heterogenous,vascular	Irregular
Size and function	<4cm, unilateral	Variable size, often bilateral	Variable can be bilateral	Usually >4cm
Density	Low unenhanced CT attenuation values (<10 Hounsfield units)	High attenuation value (>20 HU)	>20HU	>20HU

IV contrast	Rapid washout (>50% washout 10min after contrast)	Delayed washout (<50% washout 10mins after contrast)	Delayed washout	Delayed washout

** If noncontast CT demonstrates a small <4cm adrenal mass with density <10HU , then evaluation of contrast washout is not required.
Lipid rich core = density of <10HU

12.) How does testosterone replacement cause oligospermia

Increases negative feedback inhibition of FSH

13.) When to consider a thionamide holiday in Graves disease

Thionamide treatment for 12-18months

High risk of relapse after a thionamide holiday
- Large goiters
- Higher free T4 levels, translating into higher MMI requirements
- Men
- Smoking of cigarettes
- Degree of TRAb elevation at the end of te initial period of treatment

14.) Exercise and insulin sensitivity.

Precautions with exercise
• Optimal glucose level during exercise is 120 to 180mg/dl • If pre-exercise glucose is **less than 100-120mg/dl**, patient should **ingest 15 to 30grams** of rapid-acting carbohydrates and have carbs readily available during exercise. • Intensive exercise should be avoided if the glucose level is greater than 250mg/dl (increased risk of counter regulatory hormone release) • **Hypoglycemia can occur during and for up to 18hours after moderate or intensive exercise**. • For T1DM patients who have exercised for at least 60minutes during the day had a lower risk of nocturnal hypoglycemia if a temporary basal rate of 20% was used during sleep hours.

15.) Hypophosphatasia

- A rare, inherited and sometimes life-threatening metabolic disorder that arises from loss-of-function mutations in the gene that encodes the tissue nonspecific isoenzyme of alkaline phosphatase.

- Defective mineralization of bone and teeth in the presence of low activity of serum and bone alkaline phosphatase.

- Serum concentrations of pyridoxal 5-pyrophosphate and vitamin B6 are both increased.

Clinical features of hypophosphatasia
• Rickets and osteomalacia • Fractures • Early loss of both primary and secondary dentition. • Seizures • Nephrocalcinosis and chronic pain • Treatment -- DO NOT use bisphosphonates (act as a substrate for ALP due to similar conformation to inorganic pyrophosphate). SC asfotase alfa is now approved by US FDA for patients with infantile or juveline onset disease.

16.) Role of tyrosine kinase inhibitiors in radioiodine-refractory thyroid cancer

For patients with differentiated thyroid cancer
- 15% have distant metastasis at the time of presentation
- 6-20% develop metastases during follow up.

What is radioiodine refractory disease?? -- no consensus definition
- Poor avidity of tumors on radioiodine scans
- Disease progression despite radioactive iodine uptake in the 6-12months after therapy.

*** radioiodine refractory differentiated thyroid cancer often has an indolent phase with stable or slow growth.

Indicators of poor response to radioiodine therapy
• Age older than 40years • Large tumor burden • Hurthle-cell histology • Poorly differentiated tumors • FDG-avid on PET scan

US FDA approved sorafenib and lenvatinib (first like agents for progressive differentiated thyroid cancer that is refractory to radioiodine)

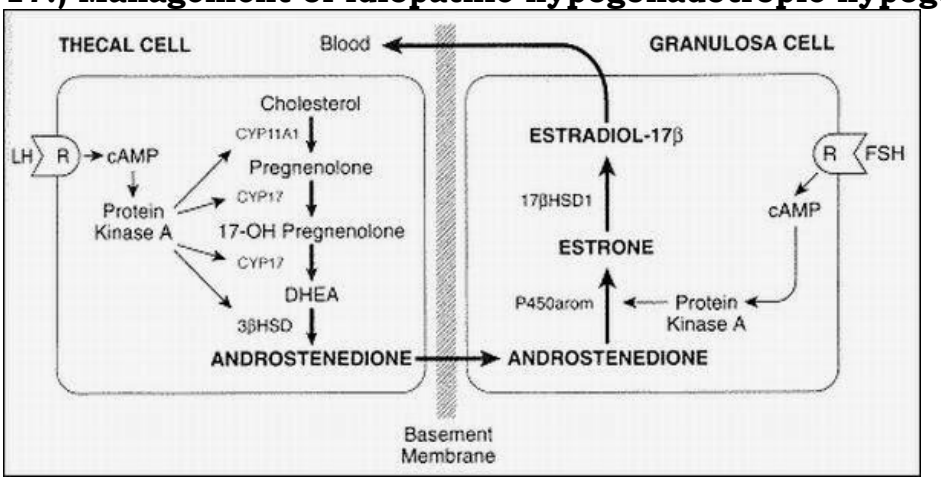
Sorafenib

- Orally active TKI with multiple targets (BRAF,VEGFR 1 and 2)
- Also used in metastatic RCC and HCC
- DECISION TRIAL -- improvements in median progression free survical from 5.8months in placebo to 10.8months in sorafenib arm.

Lenvatinib

- Orally active TKI targetting VEGFR1 and 2,FGFR1,2,3 and 4, RET (Rearranged during transfection) and PDGFR.
- SELECT trial -- improved progression free survival from 3.6 months in placebo group to 18.3months in treatment group.

17.) Management of idiopathic hypogonadotropic hypogonadism



Two cell - two gonadotropin hypothesis

Idiopathic hypogonadotropic hypogonadism = primary amenorrhea due to GnRH deficiency

** Kallmann syndrome if associated with Anosmia.

Therapy includes **pulsatile GnRH** and exogenous gonadotropin therapy with **human menopausal gonadotropins.**

Human menopausal gonadotropins
• These are highly purified urinary preparations of LH and FSH • LH is required to stimulate the theca cells to produce androstendione • FSH is required to stimulate the granulosa cells to convert androstendione into estradiol.

Pulsatile GnRH
● Stimulates both LH and FSH in a physiologic manner ● Clinical use is limited by relative lack of availability

Recombinant FSH
● Highly purified FSH preparation -- causes proliferation of granulosa cells and follicle growth ● In the absence of LH, there would be no androgen precursor to aromatize to estradiol. No proliferation of the endometrium - this makes pregnancy impossible.

Clomiphene citrate
● **Useful in secondary hypothalamic amenorrhea, but not primary amenorrhea from GnRH deficiency** ● Clomiphene citrate is a selective estrogen receptor modulator with a hypothalamic site of action ● It blocks the estrogen receptor in a patient with an intact hypothalamic-pituitary-ovarian axis ● This leads to compensatory increase in GnRH secretion > increased LH and FSH

17.) Medical therapy for obesity

Indications
● BMI >30 ● BMI >27 with comorbidities such as diabetes mellitus, hypertension or sleep apnea.

18.) Abnormal thyroid function tests -- Errors with immunoassays

Disagreement between the clinical and biochemical assessment of a patient's thyroid status.

Falsely elevated TSH	**Falsely elevated free T4**
- Macro TSH - Anti-animal antibodies	- Nonesterified free fatty acids - Heterophilic antibodies

- Heterophilic antibodies	- Iodothyronine antibodies

** daily biotin requirements of 30-100mcg...supplements contain up to 10mg
High biotin causes errors in assays using competitive assay/sandwich assay (using a biotin-steptavidin signaling system)

19.) Apparent mineralocorticoid excess

- Glycyrrhizic acid (present in licorice) suppresses the RAS system due to alternative mineralocorticoid activation.
- Inhibition of 11BHSD-type 2 (in the kidney) prevents conversion of "normal" cortisol into cortisone (inactive metabolite). Excess cortisol activates the mineralocorticoid receptor.

- Low renin, low aldosterone state
- Hypertension and hypokalemia

20.) Evaluation of thyrotroph hyperplasia and hyperprolactinemia in the setting of primary hypothyroidism

Causes of pituitary hyperplasia! No discrete adenoma seen on a large pituitary gland

- Physiologic -- peripuberty, perimenopause
- Pathologic -- thyrotroph cell hyperplasia due to long standing primary hypothyroidism

Mechanism	• Low circulating thyroid hormone leads to increased hypothalamic release of thyrotropin-releasing hormone. • Thyrotroph-cell hyperplasia > increase in serum TSH • Hyperprolactinemia (TRH is a strong prolactin-releasing factor)

21) Thyroid metastasis

- Metastasis to the thyroid gland from nonthyroid sites is an uncommon clinical presentation -- overall incidence is estimated at 2%
- RCC and lung cancer are the most common cancers.
- Present with signs and symptoms identical to those of patients with primary thyroid disease.

22.) Osteogenesis imperfecta

- Inherited connective tissue disorder of type 1 collagen.
- Mutations in the COL1A1 and COL1A2 genes
- Type 1 collagen is a constituent of bone,ligaments,skin and sclera.

- Patients are prone to fractures and osteoporosis - monitor bone densitometry every 2 years.
- Well studied agent is IV pamidronate q3monthly

23.) Weight loss medication with appetite suppression effects

- Phentermine+Topiramate ER

Phentermine reduces norepinephrine uptake
Topiramate is a GABA receptor modulator.

24.) Management of sulfonylurea induced hypoglycemia

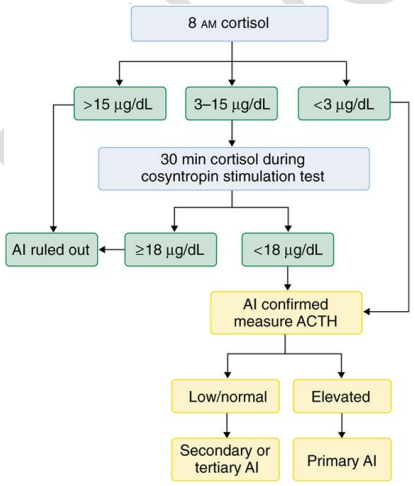
1) IM glucagon or infusion of 50% Dextrose
2) If hypoglycemia recurs, additional D50% followed by D5 or D10% infusion
3) Off-label US FDA indication -- SC Octreotide 50mcg q6h if hypoglycemia is recurrent

Most patients need 1 or 2 doses of octreotide to completely resolve hypoglycemia.

25.) **ACTH stimulation test in the setting of TBI**
In central adrenal insufficiency due to traumatic brain injury cortrosyn stimulation does not have a clinical utility in the acute setting.

Why??? - It would take several weeks of reduced ACTH secretion to cause adrenocortical atrophy that would result into a reduced serum response during an ACTH stimulation test.

26.) Cortrosyn (cosyntropin) stimulation test



- Cosyntropin (Cortrosyn) stimulation test (CST), which can be performed at any time during the day.
- Intravenous or intramuscular injection of 250 µg cosyntropin with plasma cortisol before and 30 and 60 minutes after the injection.
- A normal response is a plasma **cortisol concentration higher than 18 µg/dL at 30 minutes**. *Most individuals with normal adrenal function achieve much higher cortisol levels at*

	60 minutes after cosyntropin injection ● The standard-dose CST is excellent for excluding primary adrenal insufficiency.

The insulin tolerance test (ITT) and metyrapone test are generally used for the evaluation of patients suspected to have secondary adrenal insufficiency.

Contraindications of ITT
- Older patients (>65 years)
- Acute illnness
- Seizure disorders
- Cardiovascular-cerebrovascular disease.

27.) Management of prolactinoma in pregnancy.
- ESC guidelines -- in general dopaminergic agonist therapy can be withdrawn after 2 years of response (clinical,biochemical and radiologic)
- Tapering should be done gradually and monitoring of serum prolactin done

Effect of prolactinoma on tumor size

Basal PRL levels gradually increase throughout the course of pregnancy
This has generally been attributed to the stimulatory effect of the hormonal milieu of pregnancy, primarily estrogenic, on the pituitary lactotrophs.
There is a gradual increase in the number of pituitary lactotrophs during pregnancyand by term,
PRL levels may be increased ten-fold to levels over 200 ng/ml. These elevated PRL levels found at term prepare the breast for lactation.
The lactotroph cell hyperplasia occurring during pregnancy is reflected on MRI scans which show a gradual increase in pituitary volume over the course of gestation, beginning by the second month and peaking the first week postpartum with a final height reaching to almost 12 mm in some cases

Are dopaminergic agonists teratogenic?
● No teratogenic or other untoward effects of bromocriptine cabergoline on pregnancy have been noted when these drugs were stopped within a few weeks of conception ● The incidence of malformation in the offspring of women treated with either drug is not greater than that found in the general population

28.) Mechanisms of hypercalcemia of malignancy

1. Ectopic prodcution of PTHrP causing humoral hypercalcemia of malignancy
2. Secretion of cytokines or osteoclast activating factors causing local osteolysis-mediated hypercalcemia
3. Overproduction of 1,25-OH vitamin D due to activation of 1a hydroxylase activity by lymphoma
4. Ectopic production of "authentic PTH" -- extemely rare (few case reports)

HHM due to PTHrP production	Local osteolytic hypercalcemia
• **Accounts for 80% of cases** • Squamous cell ca of lung,head/neck,esophagus and cervix • Breast cancer	• **Second most common cause** • Multiple myeloma • Some forms of lymphoma • Leukemia • Breast cancer

** PTHrp is a poor stimulus for 1a hydroxylation compared with PTH. This results in a typically low or normal 1,25-OHvitD in HHM.

FGF-23 mediated hypophosphatemia
• A phosphaturic factor > renal phosphate wasting • Overproduced in autosomal dominat hypophosphatemic rickets • Tumor induced osteomalacia -- a paraneoplastic syndrome typically associated with indolent mesenchymal tumors. •

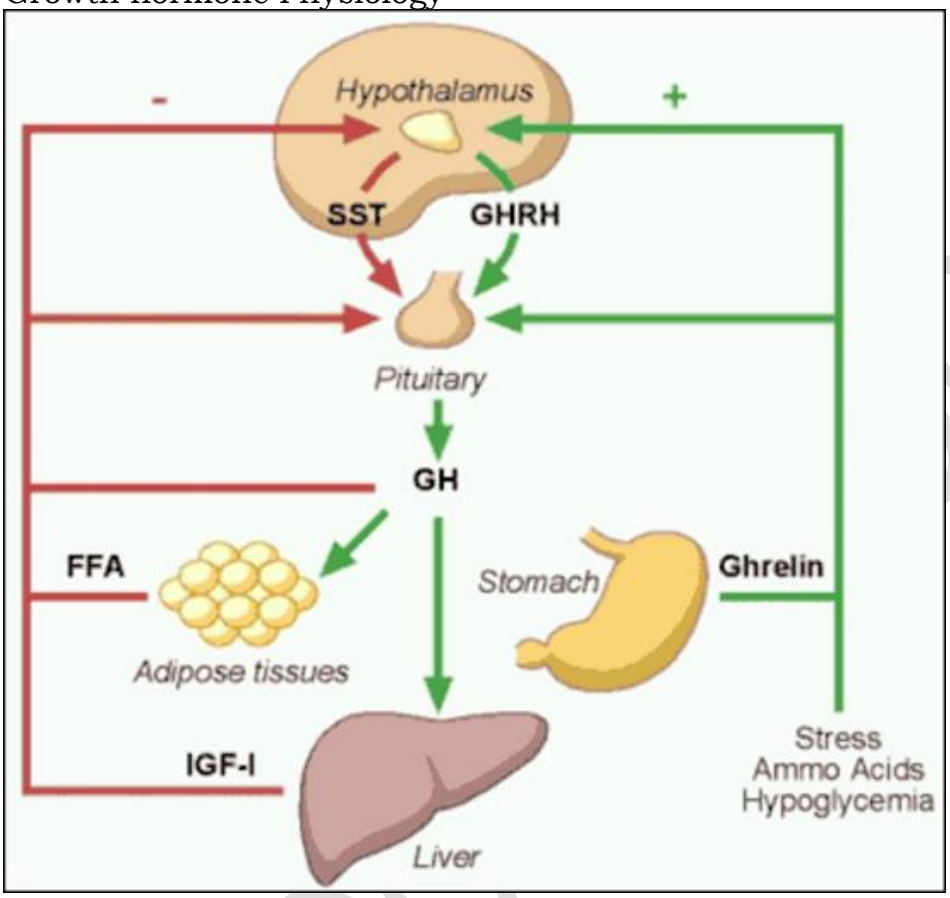
29.) Growth hormone deficiency in adults.

- Radiation therapy to the brain and skull base can cause hypopituitarism
- GH deficiency can be present despite the presence of real GH deficiency
- A test that directly stimulates the somatotroph cells (GHRH+arginine stimulation test) may be normal in the first few years
- Tests which evaluate the whole axis (ITT or glucagon test) are more likely to be abnormal at an earlier time.

GH deficiency cannot be diagnosed by these methods!
IGF-1 is bound to IGFBP3 and acid labile subunit. Secretion of both

proteins is GH-dependent
IGF-1,IGFBP3 and Acid labile subunit are NOT useful in diagnosing GH deficiency

Growth hormone Physiology



30.) Reason for treating central adrenal insufficiency prior to initiating thyroid hormone replacement in patients with panhypopituitarism

1. Thyroid hormone increases basal metabolic rate
2. Increased hepatic metabolism and renal clearnce of cortisol

31.) Acetaminophen interference with CGM
Recent pilot study; 1g ingestion of acetaminophen resulted in random blood glucose ranges from 85-400mg/dl in non-diabetic patients.

32. Transgender medicine and Gender Dysphoria ## HIGH YIELD BOARD QUESTIONS

Transgender Men -- effects of testosterone replacement therapy
• Lower voice • Facial and body hair

- Increased strength
- Cessation of menstruation
- Acne
- Increased hemoglobin
- Increased sexual desire
- Clitoral growth and pain

Goal of testosterone replacement, should be targeted to the median testosterone level +/- 100ng/dl of a cisgender man of the same age.

Important research findings in patients with Gender dysphoria

- Testosterone results in reduction in gender dysphoria (similar findings in transgender women on estorgen and anti-androgen therapy)
- First 1-2 years of therapy is associated with an average weight gain of 2.2-3.5kg. Gain of lean mass and loss of fat mass
- Menses stop by 6 months (reduced levels of estrogen, LH and FSH)
- Stromal hyperplasia of the ovaries -- typically larger than those of nontransgender women.

33.) Renal impairment and selection of oral hypoglycemic agents

DPP4 inhibitors	• Sitagliptin requires dosage adjustment based on renal insufficiency • Linagliptin does not require dosage adjustment
Pioglitazone	• Does not have unchanged drug or active metabolites that are renally cleared. • Given salt and water retention > CHF.. it should be used with caution in renal insufficiency
Metformin	• Eliminated unchanged by the kidney, but levels become elevated when estimated GFR is below 30ml/min per 1.73m2 • Higher levels leasd to inhibition of pyruvate dehydrogenase,increased pyruvate to lactate and increased risk of lactic acidosis. **<u>2016 US FDA labeling</u>** 1. Start metformin only if GFR is >45 2. Continue metformin with period assessment when it falls between 30-45 3. STOP metformin when GFR <30
Sulfonylureas	• Risk of prolonged hypoglycemia in patients with renal insufficiency

	• Not recommened with GFR <60
SGLT-2 inhibitors	• May lead to hypotension and worsening renal function • Initiation of canagliflozin is not recommended when the estimated GFR is below 45 • Contraindicated when GFR is below <30 mL/min per 1.73m2

34.) Immune Checkpoint inhibitors

- **CTLA-4** (cytotoxic T lymphocyte-associated protein 4) inhibitor -- ipilimumab
- **PD-1** (programmed cell death protein 1) inhibitors -- nivolumab and pembrolizumab
- **PD-L1** (programmed cell death 1 ligand) inhibitors -- atezolizumab, avelumab

Immune checkpoint molecules have an important function in regulating immune response: after binding to their
ligands, these proteins can initiate either inhibitory or stimulatory pathways that modulate T-cell function.

Both CTLA-4 and PD-1 play a key role in the maintenance of immunological tolerance to self-antigens, preventing autoimmune disorders

Endocrine dysfunctions are among the most common (immune related adverse events) irAEs that have been reported in clinical trials with ICIs, including **hypothyroidism, hyperthyroidism, hypophysitis, primary adrenal insufficiency (PAI), and insulin-deficient diabetes (IDD).**

Ipilimumab associated hypophysitis results in symmetrically enlarge pituitary gland and stalk thickening with generalized enhancement with contrast.

Immediate institution of glucocorticoids -- Previously treated with high dose steroids 1mg/kg of prednisone . Current recommendation is to start physiologic steroids only.

35.) **What is Pendred's syndrome?**

An autosomal recessive condition which includes **nerve deafness with goitre due to a defect of iodine binding.** Patients are usually euthyroid

36.) Features of **Familial hypercholesterolemia**

- Autosomal dominant condition
- Increased low density lipoprotein, due to reduced numbers of the LDL-receptor
- Tendon xanthomata (not palmar xanthomata which occur in Type III hyperlipidemia)

37.) **Biochemical Features of Anorexia nervosa**

- Patients with anorexia nervosa frequently manifest **impaired glucose tolerance**. The mechanism of this is not entirely understood, but in its most severe form it can result in diabetes.
- **Cortisol levels are elevated and acquired growth hormone resistance** occurs, resulting in raised basal and pulse levels compared to healthy individuals.
- Luteinising hormone (LH) and follicle-stimulating hormone (FSH) would be low and LH response to luteinising hormone-releasing hormone (LHRH) is impaired when weight loss is severe. This results in low androgen levels.
- Hypokalaemia, hypoalbuminaemia, anaemia, leukopaenia, and raised serum carotene.

38.) Kallmann syndrome

- Kallmann syndrome may arise due to abnormalities of the KAL-1 or KAL-2 gene (encoding anosmin-1 and FGF-1).
- Whilst the majority of cases are sporadic, perhaps up to 50% of cases are due to genetic inheritance.
- Kallmann presents with hypothalamic gonadotrophin-releasing hormone deficiency and deficient olfactory sense - hyposmia or anosmia.
- FISH, using a specific chromosomal probe is currently the best means of a genetic diagnosis of this condition.

39.) Glycemic index

Glucose is the gold standard of high glycaemic index (GI) against which all others are compared.

The GI index of these sugars is:

- Maltose - 100
- Sucrose - 80
- Lactose - 50
- Fructose - 25.

40.) **Pituitary incidentalomas have a prevalence of about 10% in post-mortem/imaging studies.** They are split into two categories:

- Macroadenomas - those that measure >10 mm, and
- Microadenomas - those that measure <10 mm.

All patients should have a thorough history and examination and then there should be a baseline pituitary profile, including looking for hypersecretion. Patients should have a dedicated pituitary MRI with gadolinium (unless contra-indicated). All patients with radiological evidence of the adenoma abutting or involving the optic chiasm should have formal visual fields carried out.

Follow-up/surveillance for those not undergoing surgery is:

- Macroadenomas - Repeat MRI in 6 months and then annually for 3 years, after which frequency can be reduced. Biochemical testing of pituitary function and hypersecretion at 6 months and then one year.
- Microadenomas - Repeat MRI in one year and then 1-2 yearly for 3 years, after which frequency can be reduced. Biochemistry should not be routinely repeated unless there is growth on MRI or new symptoms.

41.) **Amyloid polypeptide on pancreatic histology**
The presence of amyloid polypeptide on pancreatic histology is highly suggestive of type 2 diabetes.

Although the primary defect in type 2 diabetes is insulin resistance, loss of insulin secretory function over time does occur in patients with type 2 diabetes, and reduction in beta cell mass due to amyloid deposition may partly account for this

42.**) Glycemic index of foods**

The 'second meal effect' of a low GI food is well recognised. A low GI dinner the evening before can help reduce the glycaemic load following breakfast the next day.

Food may have a lower GI if it includes fat but this does not make it preferable to eat. GI is affected by the quantity eaten. Some of this is due to an effect on gastric emptying.

Some vegetables may have a high GI but they are usually very low in carbohydrate and high in micronutrients. Vegetables are good for you and should not be avoided.

The area under the glucose response curves used when calculating GI is proportional to the amount of carbohydrate but not equal for all GI levels, since effects of metabolism may alter the amount of glucose extracted.

Low GI	**High GI**

Granary and 'bitty' bread	White and wholemeal bread
Basmati and quick cook rice	Other rice
Boiled potatoes	Jacket potato
Mashed potato	Cornflakes
Sweet potatoes	Rice crispies
Porridge	
No added sugar muesli	
Fruit and fibre	
Pasta	
Noodles	

Foods containing different carbohydrates have different effects on post-prandial glucose concentration depending on how quickly that carbohydrate is broken down and digested.

Those foods containing rapidly digestible carbohydrates will result in a greater peak in blood glucose than those foods that are digested slowly.

The glycaemic index is a ranking system for carbohydrates based on their effect on blood glucose levels, with lower numbers attributed to those foods that are more slowly absorbed.

The glycaemic index (GI) of a food may vary depending on how the carbohydrate is cooked, for example, boiled potatoes have a lower GI than jacket potatoes (50-70/150 g versus 60-80/150 g) but also different varieties of potatoes may carry different GI values.

Bread may carry different GI values depending on the relative proportions of the ingredients used by different manufacturers. Different types of bread will carry different GI values (for example baguettes higher than sliced bread).

The type of food in the rest of the meal may also have a bearing on the post-prandial glucose level.

For example, eating baked beans with a jacket potato slows gastric emptying and therefore will delay absorption compared with eating a jacket potato with cheese, for example.

In the question above, beef lasagne has the lowest GI value (35-45) and would therefore be associated with the lowest post-prandial rise in blood glucose.

Further revision points you may which to consider:

- Why is the control of post-prandial blood glucose important?
- What are the mechanisms in place to control post-prandial glucose in a non-diabetic?
- What factors may delay gastric emptying?
- Where can you find out information regarding glycaemic index of foods?
- Be able to rank common foods in order of glycaemic index.

43.) Diabetes Insipidus -- management with thiazide diuretics.

The effect of thiazide diuretics in nephrogenic diabetes insipidus (DI) is thought to be mediated by a hypovolaemia-induced increase in proximal sodium and water reabsorption. This diminishes water delivery to ADH-sensitive sites in the collecting tubule, thus reducing urine output. In this situation thiazides are considered the primary mode of intervention after following a low salt, low protein diet.

Amiloride is usually considered for control of nephrogenic DI where lithium must be continued. It is important to recognise, however, that extracellular volume may decrease, meaning that lithium dose should be reduced. Desmopressin is only likely to have a small positive impact, if any, on nephrogenic DI. In patients who fail to respond to thiazides alone, NSAIDs can be added in.

Following a low protein, low solute diet can significantly impact on urine output, reducing it by up to 2 L per day. The high salt diet mentioned here is therefore clearly inappropriate.

44.) Contraindications to pioglitazone

In adults with type 2 diabetes, do not offer or continue pioglitazone, if they have any of the following:

- heart failure or history of heart failure
- hepatic impairment
- diabetic ketoacidosis
- current, or a history of, bladder cancer
- uninvestigated macroscopic haematuria.

45.) Factors that suggest a poor prognosis in thyroid cancer include:

- increasing age
- male sex
- poorly differentiated histological features, and
- distant spread.

46.) Sulfonylureas and drug-drug interaction

As a result of drug interaction hypoglycaemia may be potentiated when a sulfonylurea is used concurrently with agents such as:

- Long-acting sulfonamides
- Tuberculostatics
- Phenylbutazone
- Clofibrate
- Monoamine oxidase (MAO) inhibitors
- Coumarin derivatives
- Salicylates
- Probenecid
- Propranolol
- Cimetidine
- Disopyramide, and
- Angiotensin converting enzyme inhibitors.

Gliclazide is a sulphonylurea drug with an intermediate half life of around 11 hours. It is extensively metabolised within the liver by CYP2C9. Within the circulation, gliclazide is highly bound to plasma proteins, about 94%. Renal clearance accounts for only 4% of total drug clearance.

Therefore gliclazide action can be potentiated predominantly by two mechanisms:

- Displacement of the drug from plasma proteins to give more free (unbound) drug - some agents such as aspirin can do this, and
- Intereference with the hepatic metabolism of the drug.

Fluconazole has a low level of plasma protein binding and it is excreted by the kidney. However, it is also a potent inhibitor of CYP2C8 and CYP2C9 and can thus interact with gliclazide and other sulphonylureas (for example, glimepiride, glibenclamide, tolbutamide and glipizide).

47.) Laron's syndrome is due to a GH receptor defect with impaired IGF-1 production. It is an autosomal recessive condition, characterised by short stature and reduced incidence of cancer and diabetes.

48.) Careers opportunities are affected by insulin use in diabetes mellitus and it is important to know these restrictions in order that you can provide appropriate advice to your patient.

- Any employment in the armed forces, fire service or police force is not permissible unless already a member of the armed forces.
- Offshore work also is not an option

49.) Pseudohyperaldosteronism due to licorice ingestion

11bHSD is responsible for the conversion of cortisol to the inactive cortisone, preventing activation of the mineralocorticoid receptor by cortisol but permitting activation by aldosterone.

Both liquorice and carbenoxolone inhibit 11bHSD and produce pseudohyperaldosteronism with hypertension and hypokalaemia yet appropriately low renin and aldosterone concentrations.

50.) **Diabetic nephropathy**

Diabetic nephropathy develops in approximately 40% of patients with type 1 diabetes and in 5% to 40% of patients with type 2 diabetes. Without intervention nephropathy is likely to deteriorate with the development of macroalbuminuria. In association with the latter, renal function declines about 10% per year, ending in end-stage renal disease.

Proven interventions in the treatment of nephropathy include ACE inhibitors, low dietary protein and improved glycaemic control.

The evidence for good glycaemic control in the treatment of microalbuminuria in patients with type 1 diabetes suggests no clear benefit [DCCT]). However, meta-analyses of the effects of ACEi on the development of nephropathy in type 1 diabetics show an albumin excretion rate 50% lower at two years in treated versus untreated patients.

The evidence for a low protein diet exists for overt proteinuria but not microalbuminuria.

51.) DAFNE programme

DAFNE(dose adjustment for normal eating) was developed as a structured patient education programme for adults with type 1 diabetes. It allows patients to count acrbohydrates and adjust insulin doses accordingly. It is a 5 day course, relying on 'DAFNE rules' to aid dose adjustment. Patients must be on basal-bolus regimen and be willing to test 5 times per day and share their data.

52.) **Drug drug interaction and thyroid hormone replacement**

Raloxifene is recognised to reduce absorption of levothyroxine. It increases thyroxine-binding globulin, leading to a reduction in levels of free thyroxine. Other agents known to inhibit thyroxine absorption include:

- iron
- calcium
- aluminium hydroxide
- cholestyramine
- colestipol, and
- sucralfate.

Tamoxifen and oestrogen are also recognised to increase levels of thyroxine-binding globulin.

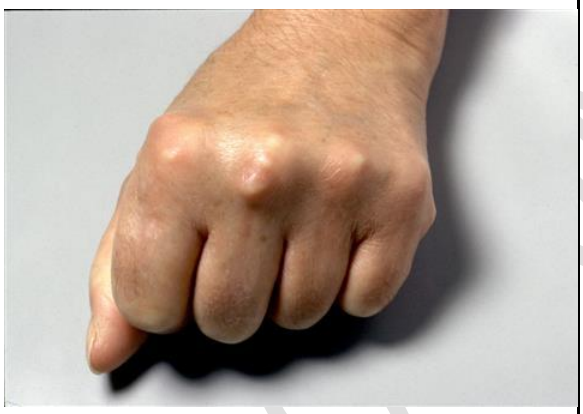
Phenytoin and carbamazepine are recognised to increase hepatic metabolism of thyroxine, although more modern anti-epileptics such as levetiracetam and lamotrigine do not. Similarly, other treatments for osteoporosis apart from raloxifene, such as risedronate and denosumab, do not affect thyroxine metabolism.

53.) Assessment of growth hormone and ACTH/cortisol reserve, especially when insulin-induced hypoglycaemia is contraindicated. This is a good assessment of GH reserve. Cortisol results should be interpreted with caution in light of the clinical picture.

Contraindications of ITT include:

- ischaemic heart disease
- epilepsy
- untreated hypothyroidism (impairs the GH and cortisol response)

54.) type IIa hyperlipidaemia.

	This picture shows tendinous xanthomata which are virtually pathognomonic of familial hypercholesterolaemia. Tendon xanthomata commonly affect the Achilles tendons and the tendons overlying the metacarpophalangeal (MCP) joints in the hands. Less common sites include the extensor hallucis longus and triceps tendons. Histologically, the xanthomata consist of accumulations of cholesterol deep within the tendon with associated fibrous tissue. The skin overlying the lesion is usually normal, although if there is inflammation in the tendon, there may be overlying erythema. This is an autosomal dominant disorder of chromosome 19 causing a mutation in the LDL receptor. There are homozygous and heterozygous forms. Heterozygosity occurs in one in 500 people. Homozygosity is much rarer and is associated with earlier onset of

	premature vascular disease, even in childhood.

The cardinal features of the metabolic syndrome include:

- the hypertension
- central adiposity
- hyperlipidaemia
- "fatty liver" (we presume his raised transaminases are due to this and/or alcohol)
- pre-diabetes.

The XENDOS study revealed that orlistat, in combination with diet, will reduce the risk of diabetes in these obese patients by 38% more than just diet alone plus placebo.

	The retinal photograph shows multiple areas of retinal haemorrhage and a circinate of hard exudates in the area of the macula. This raises the possibility of diabetic maculopathy with macular oedema. As such options for intervention include focal laser photocoagulation or intravitreal VEGF inhibitors such as bevacizumab. Out of the two options, intravitreal VEGF is usually preferred. Triamcinalone has also traditionally been used as a therapy for macular oedema, although response to intervention is often transient, and the treatment ineffective. I**ncreasing insulin dose to drive tighter glycaemic control or increasing BP lowering therapy will be ineffective in reducing risk of serious visual loss.** Peripheral laser therapy is useful in reducing overall VEGF production and risk of neovascularisation, although it would not meet the immediate needs of intervention here.

	Vitrectomy is considered in patients who fail to respond to VEGF or laser therapy.

55.) **Optimal conditions for calcitonin testing**
A number of drugs used chronically are known to elevate serum calcitonin. These include proton-pump inhibitors, corticosteroids, and beta-blockers

56.)

Interpretation of AVS

Description	Formula	Interpretation
Selectivity index (SI)	$cortisol_{side}$ / $cortisol_{inferior\ vena\ cava}$	Values higher than cut-off confirm that blood sample is properly collected from adrenal vein
Lateralization index (LI)	(aldosterone* / cortisol*) / (aldosterone# / cortisol#)	Values higher than cut-off confirm lateralized aldosterone excess.

* – results from side with higher concentration. # – results from side with lower concentration.

- lateralisation index greater than 2 -- indicates the possibility of unilateral disease.
- contralateral suppression index (A/C ratio on lower side divided by A/C in IVC) -- Less than 0.5 is supportive of unilateral disease.

57. Diabetic amyotrophy

- Diabetic amyotrophy is thought to be a form of neuropathy but may occur due to inflammation rather than chronically poor glycaemic control. There is higher incidence amongst type 2 diabetics.
- Diabetic amyotrophy often affects the femoral nerve, lumosacral plexus or lumbar roots.
- Clinical symptoms include pain in the hip, buttock or thigh with associated weakness. There is often little sensory loss. Plantar responses may be flexor or extensor. EMG shows multifocal denervation in paraspinous & leg muscles.
- Partial or complete resolution occurs with control of hyperglycaemia.

58.) subclinical hypothyroidism and abnormal lipids

A hypercholesterolaemia with hypertriglyceridaemia is frequently associated due to impaired lipoprotein lipase function.

The dyslipidaemia may well resolve following the appropriate replacement with thyroxine.

59.) Hyperlipidemia

 This milky looking serum sample is due to hyperchylomicronaemia/hypertriglyceridaemia and is a consequence of deficiency of lipoprotein lipase (LPL)	Xanthomas, and lipaemia retinalis are features and pancreatitis and gout occur. It can occur as the primary condition due to a rare autosomal recessive loss of LPL, or more commonly is secondary to diseases such as: • Pancreatitis • Hypothyroidism • Type 1 diabetes • Alcoholism, and • Cushing's syndrome.

60.) **Causes of hyperprolactinemia**

Dromperidone	Cimetidine
dopamine antagonist	cimetidine produces hyperprolactinaemia only when given intravenously (IV)

61.) **Carcinoids**

Rare presentations	• Cushing's syndrome is only seen in approximately 1-2% of lung neuroendocrine tumours • lung carcinoid is the commonest cause of extra-pituitary related acromegaly
More common presentation	• local symptoms of carcinoid are much more likely here, with bleeding due to the very vascular nature of carcinoid tumours.
Classical carcinoid syndrome	• occurs in less than 10% of patients with carcinoid tumours but • tumours of the small intestine, appendix and

	proximal small bowel
Location -- foregut carcinoid tumours	Pancreas - VIPoma - Zollinger-Ellison syndrome - MEN-1 syndrome (pancreatic NETs predominate)

62.) Diagnosis of Growth Hormone deficiency

Gold standard for diagnosis	Insulin tolerance test**
Suitable alternative	GHRH/arginine
What not to use!	• IGF-1 levels can be used as marker of growth hormone levels, but are not diagnostic Conditions of spuriously decreased IGF-1 levels • *nutritional deficiencies* • *chronic kidney* • *liver disease* • *high doses of oestrogen.*

** Board pearl (contraindicated in cases of epilepsy,IHD,untreated hypothyroidism)

63.) What are the features of pseudohypoparathyroidism

- biochemistry shows a **hypocalcaemia with hyperphosphataemia** being usual but **elevated PTH due to resistance to parathormone (PTH).**
- **mutation of the PTH receptor** with **abnormality of the Gs alpha subunit** with reduced cyclic adenosine monophosphate (cAMP) production following a PTH infusion.
- Phenotypic features (short stature, low IQ and shortened fourth and fifth metacarpals)

64.) Polycystic ovary syndrome

- raised LH:FSH ratio
- insulin resistance (raised fasting insulin isn't measured in clinical practice.)
- hyperandrogenism as evidenced by *raised androstenedione and slightly raised testosterone.*

65) Why screen for celiac disease in T1DM patients.

Clinical presentation	• variable in its presentation and need

	not always be associated with a significantly abnormal bowel habit. • Although 3-4 loose and pale bowel motions is typical, bowel habit will depend on gluten intake. • Stool of normal colour and consistency does not exclude a diagnosis
Anemia	• Diffuse disease process affecting the small bowel Coeliac disease may cause malabsorption of iron and folate causing and anaemia with either micro- or macrocytosis. • Sometimes the MCV may be 'normal' due to a deficiency of both causing a **bimodal distribution of red cell volumes which has an average in the normal range**. If patients have additional reasons to be deficient in either folate or iron (e.g. menorrhagia in women) then that may dominate the clinical picture.
When to screen ♀	• young patient with nutritional deficits (B12, folate, iron) then you should check antibodies.

♀ = screen guidelines for T1DM patients**. VIDE SUPRA!**

66.) Modalities for treating hyperthyroidism

- **Long-term remission following antithyroid drugs is of the order of 15%**, with the vast majority relapsing. Thus, frequently, radio-iodine is advocated as a primary treatment - particularly for multi-nodular or toxic solitary nodules.
- **Approximately 80% will have long-term hypothyroidism following radio-iodine.**
- Goitre shrinkage may occur in up to 30% following RAI
- No evidence of increased risk of thyroid neoplasia or gastric neoplasia following radioactive iodine (RAI)

67.) Drug induced hyperglycemia

Nicotinic Acid	Nicotinic acid inhibits triglyceride synthesis, it may be that the increased availability of free fatty acids stimulates hepatic glucose output by increasing gluconeogenesis or replacing glucose as the primary energy source.

	Higher levels of fatty acids may also block glucose uptake by skeletal muscle.
Statins	A 2011 meta-analysis showed an increase risk of inducing diabetes in patients treated with intensive statin therapy, compared to moderate doses. However, discussion in the literature has suggested there may have been a number of confounding factors leading to increased diabetic risk in these patients. Regardless of this, it did not look at whether statins worsened HbA1c in established diabetics, and therefore you cannot extrapolate its findings to this question.

68.) **Biochemistry of type 2 diabetes mellitus**

- The characteristic features of type II diabetes is a marked hyalinisation of the islets which is due to infiltration by amyloid.
- The exact relationship between the two is not clear, but it appears that amyloid deposition is associated with reduced islet cell number and function.

69.) Diabetes prevention programme (DPP)

The **diabetes prevention programme (DPP)**, which reduced the incidence of type 2 diabetes by 58% in a cohort with impaired glucose tolerance, set a target of at least 7% weight loss and 150 minutes of medium intensity exercise per week for participants. Walking is the most commonly prescribed and the most likely to be a successful form of exercise on the basis of safety and accessibility.

70.) Insulin use in **Diabetes and exercise.**

With exercise, the patient may need to reduce his insulin dose pre-exercise by up to 25% and reduce the post-exercise by up to 25%. As his distance increases and the exercise therefore becomes high intensity, then he will need to take extra carbohydrate (CHO) before, or during, and after exercise.

Preparing for exercise	• A warm-up should consist of 5–10 min of aerobic activity (walking, cycling, etc.) at a low-intensity level. • Muscles should be gently stretched for another 5–10 min. Primarily, the muscles used during the active physical activity session should be

	stretched, but warming up all muscle groups is optimal. • silica gel or air midsoles as well as polyester or blend (cotton-polyester) socks to prevent blisters and keep the feet dry is important for minimizing trauma to the feet. *monitor closely for blisters* • A diabetes identification bracelet or shoe tag should be clearly visible when exercising.
General guidelines	• Avoid physical activity if fasting glucose levels are >250 mg/dl and ketosis is present, and use caution if glucose levels are >300 mg/dl and no ketosis is present. • Ingest added carbohydrate if glucose levels are <100 mg/dl. • Blood glucose monitoring before and after physical activity • Consume added carbohydrate as needed to avoid hypoglycemia. • Carbohydrate-based foods should be readily available during and after physical activity. • To better help with weight management, and avoid hypoglycemia, exercise should be scheduled post-meals when blood glucose levels are high
What do i do with my insulin dose?	• **may need to reduce insulin dose pre-exercise by up to 25% and reduce the post-exercise by up to 25%**

71.) **How to assess the first phase insulin response in type 2 diabetes mellitus.**

- Frequently sampled IV glucose tolerance test (FSIVGTT)
- The FSIVGTT allows for very rapid collection of blood for insulin estimation during the early period following glucose injection
- The first phase insulin response is lost very early in type 2 diabetes, and its restoration is important in dealing with post-prandial peaks of glucose and triglycerides.
- What the FSIVGTT does not take account of is the incretin effect - increased production of glucagon-like insulinotropic petide (GLP)-1 when carbohydrates are taken orally - which enhances insulin release.

72.) **VIPoma is a vasoactive intestinal polypeptide (VIP) secreting tumour occurring mainly in the pancreas**.

It is rarely a ganglioneuroblastoma (sympathetic chain or adrenal cortex).

Features include:

- secretory diarrhoea ('pancreatic cholera')
- weight loss
- dehydration
- abdominal colic
- cutaneous flushing
- raised plasma VIP
- urea+calcium
- raised plasma pancreatic polypeptide
- hypokalaemic acidosis (loss of alkaline secretions)
- achlorydia, and
- mildly raised glucose.

The normal functions of VIP are:

- increased intestinal secretion of water and electrolytes
- peripheral vasodilation
- inhibition of gastric acid secretion, and
- potentiates acetylcholine action on salivary glands.

73.) Alcohol use and hypoglycemia unawareness

· Alcohol inhibits gluconeogenesis, decreases peripheral hypoglycaemic responses and impairs perception of symptoms of hypoglycaemia.

· Alcohol is high in calories. However, it is not advisable to carbohydrate count.

· Alcohol increases blood glucose in the short term but lowers blood glucose for several hours after drinking.

Amiodarone induced thyrotoxicosis

Type 1 (Productive)	**Type 2 (Destructive)**
Type 1 is associated with pre-existing underlying thyroid pathology, where there is accelerated thyroid hormone synthesis secondary to iodide load. There is normal or high tracer up-take in radio-iodine uptake scan. It should be treated with anti-thyroid drugs.	Type 2 amiodarone induced thyrotoxicosis is due to the direct effect of amiodarone on the follicular cells, with breakdown of cells and therefore release of T4 and T3. There is reduced tracer uptake in radio-iodine uptake scan. *It will eventually result in hypothyroid stage prior to recovery.* Type 2 is treated with a trial of steroids.

74.) The role of "tight" glycemic control in the elderly population

The **Veterans' Affairs Diabetes Trial (VADT) study** tested the hypothesis that tighter glycaemic control in an elderly population reduced the risk of diabetes-related events in more than 1,000 patients managed by the Veterans Affairs Health System.

The study showed that tighter blood glucose control DID NOT reduce the risk of a range of endpoints associated with type 2 diabetes, including:

- ischaemic events
- amputation
- neuropathy, and
- retinopathy.

They did however, show **a reduction in the progression from normo- to micro- or macroalbuminuria**.

75.) NICE guidelines for Type 1 Diabetes Care

NICE guidelines suggest that coeliac disease be tested for at diagnosis and then 3 yearly thereafter.

Thyroid testing should occur annually. Clinical trials showed that 5 percent Type 1 diabetics have thyroid problems.

76.) Asymptomatic thyroglossal cysts

Observation in this case is suboptimal. *Cysts may become infected or become carcinomatous over time therefore not intervening with surgery is likely only to increase patient anxiety and drive repeated review in the clinic.*

77.) Features of anorexia nervosa

Phobic avoidance of normal weight
Relentless dieting
Self-induced vomiting
Laxative use
Excessive exercise
Amenorrhoea
Lanugo hair
Hypotension
Denial
Concealment
Over-perception of body image
Enmeshed families.

78.) Hyperthyroidism as a cause of atrial fibrillation

- Conversion to sinus rhythm frequently occurs spontaneously with treatment of hyperthyroidism.
- Digoxin is very rarely effective alone, but can be used in combination with propranolol(non-selective beta blocker) if it is ineffective as a single agent.
- **Electric or pharmacologic cardioversion** would only generally be attempted in patients who are **haemodynamically unstable** in whom other treatments have been unsuccessful.
- If AF persists, consideration should be given to anticoagulation in **patients who are at risk of embolic events** but this would not be the first treatment you would initiate.

79.) Interpretation of the high dose dexamethasone suppression test

8 mg dexamethasone suppression test --> **cortisol level suppresses by more than 50% indicates a pituitary source for ACTH**

80.) **Role of metformin in gestatational diabetes mellitus**

Starting with metformin	Evidence from large clinical studies supports the use of metformin as initial therapy after dietary modification in gestational diabetes
Neonatal outcomes	No impact on a composite of neonatal outcomes, although it did show a reduction in neonatal hypoglycaemia versus insulin
When to start basal-bolus	Fail to gain adequate control on metformin alone

81.) **Retreatment with RAI ablation**
The effect of radioactive iodine could take from six weeks to six months to fully manifest. The second dose of RAI is only considered six months after the first dose.

82.) Drugs causing hirsutism/hypertrichosis include:

- **minoxidil** (not moxonidine, a centrally acting anti-hypertensive)
- **phenytoin** (not valproate), and
- **Cyclosporin**

83.) Insulin response to intravenous glucose administration

The **first phase insulin response to intravenous glucose occurs rapidly between three to five minutes and lasts for approximately 10 minutes.**

As the fasting glucose increases, the first phase insulin response deteriorates, being almost absent when the fasting plasma glucose exceeds 144mg/dl.

The second phase begins at the time of commencement of glucose administration but does not become apparent until after 10 minutes.

This phase continues to increase slowly as long as the glucose level remains elevated. Again, when glucose tolerance deteriorates, this phase of insulin secretion also diminishes but not to the same extent as the first phase insulin response. The second phase persists in the absence of the first phase.

84.) **Autoimmune diabetes**

Risk of Type 1 diabetes in offspring in families where both parents have the disease.

- Risk is around 40%.
- Offspring of parents who both have Type 1 diabetes have a tendency to develop the disease at a younger age than their parents.

85.) **NASH and GLP-1**
Studies have shown liraglutide to be effective in resolving NASH (the LEAN study) and delaying diabetes (from the SCALE study programme).
LEAN STUDY : In this double-blind, randomised, placebo-controlled phase 2 trial, the longacting GLP-1 analogue, liraglutide, met the predefined primary endpoint and led to resolution of non-alcoholic steatohepatitis in (39%)
first randomised, placebo-controlled trial to report the effect of a GLP-1 analogue on liver histology in patients with non-alcoholic steatohepatitis

86.) leptin and obesity

Pathophysiology of leptin
• Leptin is synthesised within the **adipocyte** and **plasma concentrations are directly related to adipocyte (fat) mass.** • It **acts on receptors within the arcuate nucleus within the hypothalamus to produce satiety**. As such when patients reach a certain peripheral fat mass, **leptin acts as a lipostat to reduce food intake**. • However, leptin resistance is seen, hence patients can continue to accumulate weight and addition of leptin does not curb food intake.

87.) Diabetes mellitus and hyporeninemic hypoaldosteronism

hyporeninaemic hypoaldosteronism (type IV renal tubular acidosis)
• lowish sodium concentration and raised potassium • renal impairment • elderly diabetic patients • hyperkalaemia is usually mild but may be exacerbated by drugs such as beta-blockers and ACE inhibitors. • **Treatment** is usually successful with conservative measures such as stopping provocatory agents, a low potassium diet. Small doses of *fludrocortisone could be considered for refractory cases.*

88.) Dyslipidemia in primary biliary cirrhosis and other causes of cholestasis.

In prolonged cholestasis features include:

- Increased serum cholesterol
- A moderate increase in triglyceride
- Serum that is not lipaemic, and
- Reduced HDL levels.
- Palmar xanthomas
- Tuberous xanthomas (particularly on extensor surfaces)
- *Tendinous xanthomas are rare.*

Xanthomas usually only occur if cholestasis has persisted for more than three months. (Sometimes fat deposits may involve bone and peripheral nerves).

89.) **Worst prognostic feature of carcinoid syndrome**

- carcinoid heart disease have a dismal prognosis; most die of progressive right heart failure within one year after onset of symptoms
- The prognosis of patients with recognised carcinoid heart disease has improved over the past two decades and may be related to valve replacement surgery

90.) Diabetic nephropathy -- Prevalence

Risk of progression from diabetic nephropathy to ESRD depends on T1 or T2 DM status

50% for T1DM and 15% for T2DM

The majority of patients with diabetic nephropathy have type 2 diabetes, however this is due to higher prevalence of type 2

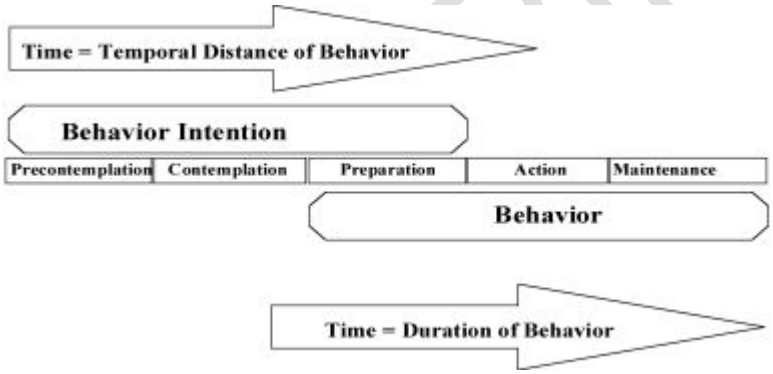
91.) **Facticious hyperthyroidism**

Thyroglobulin is the precursor of thyroid hormones, therefore if undetectable, indicates an *external source of thyroid hormone has been administered.*

92.) Conservative follow up of pituitary macroadenomas
- Eupituitary (nonfunctional tumor)
- No visual field defects (tumor distant from the pituitary)
- Stable size

93.) **Familial hypocalciuric hypercalcaemia**
- benign cause of hypercalcemia
- autosomal dominant inheritance with high penetrance
- mild hypercalcemia
- hypocalciuria
- a normal PTH level, and
- high-normal to frankly elevated serum magnesium levels.

94.) **Transtheoretical Model of Change**



A theoretical model of behavior change, which has been the basis for developing effective interventions to promote health behavior change

95.) Subclinical hyperthyroidism
If someone is less than 65 years old and has osteoporosis, then consider treating only if TSH is < 0.1 mu/l.
No treatment is required for subclinical hyperthyroidism despite having osteoporosis if TSH is 0.1 mu/l to 0.5 mul/l.

96.) Double diabetes
"Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m2 (23 kg/m2 for people from South Asian

and related minority ethnic groups) or above wants to improve their blood glucose control while minimising their effective insulin dose" -- NICE guidelines.

Bartter's syndrome
Bartter's syndrome is an autosomal recessive renal disorder, caused by a number of different mutations. • Presentation is often in childhood with gastrointestinal upset, failure to thrive and polyuria, but it can present in adolescence also. • The classic abnormalities seen on bloods are hypokalaemic alkalosis and elevated renin and aldosterone levels. The blood pressure is usually normal, and oedema is not a classic sign. Hyponatraemia and hypochloraemia may also be present. Urinary sodium, potassium and chloride are raised. • Treatment is aimed at preventing potassium wasting, for example with spironolactone and electrolyte supplements. Indomethacin is also effective, by inhibiting excess prostaglandin synthesis.

97. The diabetic Neuropathies

Generalised neuropathy	**Focal and multifocal neuropathy**
– hyperglycaemic neuropathy – symmetric distal polyneuropathy with/without autonomic neuropathy – acute painful sensory neuropathy variants	–cranial neuropathies –focal limb neuropathies –thoracolumbar radiculoneuropathy –lumbosacral

Clinical assessment in diabetic symmetricdistal polyneuropathy (DSDP)
• Look for any deformity, callus or foot ulcer, infection or fissure

- Absent ankle reflexes (mandatory)
- Test all sensory modalities starting at the toes and fingertips (in many diabetic screening clinics, vibration sensation and neurofilament sensitivity are the only modalities tested and this seems to be an effective part of a neuropathy screen)
- Weakness of small foot muscles (extensor hallucis longus and extensor digitorum brevis)
- Check resting pulse and blood pressure lying and standing
- Check peripheral pulses
- Look for retinopathy
- Check urine for protein

98.) SIGNAL TRANSDUCTION -- SUMMARY

cyclic adenosine monophosphate (cAMP) as the second messenger

- adrenaline
- growth hormone-releasing hormone (GHRH)
- glucagon
- luteinising hormone (LH)
- follicle stimulating hormone (FSH)
- parathyroid hormone (PTH), and
- thyroid-stimulating hormone (TSH).

mitogen-activated protein (MAP) kinase pathway

- Growth hormone
- Prolactin
- insulin

calcium/phosphoinositide

- Thyroid releasing hormone (TRH)
- gonadatrophin-releasing hormone (GnRH), and
- antidiuretic hormone (ADH).

cyclic guanosine monophosphate (cGMP)
Nitric oxide and atrial natriuretic peptide (ANP)

99.) Thionamide therapy and agranulocytosis
Agranulocytosis is rare, occurring in less than 1% of cases and sore throats are very common. It is not uncommon to see a drop in WCC associated with thionamides.

100.) Pseudohypoparathyroidism

- This is a group of disorders characterised by insensitivity to PTH.
- It is an autosomal dominant condition and is due to defects in the **gene (GNAS1)** encoding the **alpha subunit of the stimulatory G protein (Gsa)** contributing to at least three different forms of the disease: the severity of the condition may vary with generations.

Clinical features

- short stature
- stocky habitus
- obesity
- developmental delay
- round face
- dental hypoplasia
- brachymetacarpals
- brachymetatarsals, and
- soft tissue calcification/ossification
- Slipped femoral epiphysis

The diagnosis is confirmed with genetic analysis and with a failure of cyclic adenosine monophosphate (cAMP) rise following PTH.

101.) Relationship between Gardner's syndrome and Papillary thyroid cancer

- multiple small and large intestinal tumours and lipomas.
- Osteomas and fibromas are also seen.
- It is a rare familial condition that carries an increased risk of papillary carcinoma of the thyroid.

102.) **Parathyroid hormone has a number of direct effects:**

- it enhances the release of calcium from bones by binding to osteoblasts which stimulates the formation of osteoclasts, and
- it enhances reabsorption of calcium in the distal tubules.

103.) Thiazide diuretics and effect on glycemic control

Thiazides
• All thiazide diuretics inhibit sodium resorption in the beginning of the distal convoluted tubule. • At high doses, they cause an increase in serum glucose, lipids and uric acid, but these effects are small if low doses are used. • Higher doses should not be used for hypertension as they do not provide an incremental reduction in BP versus their side effect profile.

104.) **Indications for treatment of prolactinomas**

- infertility is an issue
- neurological symptoms
- bothersome galactorrhoea
- the patient is pubertal (as they will be hypogonadal), and
- longstanding hyperprolactinaemia has led to reduced bone mineral density.

➤ *Symptoms are due to hyperprolactinaemia and hypogonadism, due to the inhibition of GnRH by raised prolactin. Hyperprolactinaemia reduces bone mineral density but there is no evidence that it increases fragility fractures.*

Treatment of prolactinomas
Prolactinoma can be confirmed by response to dopamine-agonist. There should be normalisation of prolactin levels and reduction in adenoma size by 75%. **Cabergoline** (started at 0.25 mg twice weekly and up-titrated to 3 mg per week) is better tolerated but more expensive than **bromocriptine** (commenced at 1.25 mg OD and up-titrated to 2.5 mg TDS). MRI should be repeated at 2-3 months after commencing therapy and continued for at least 1 year. **Ideally prolactin levels should have**

normalised for at least 2 years prior to tapering down dose.

Antipsychotics and prolactinomas
• Patients with hyperprolactinaemia secondary to anti-psychotics should have the drug changed or stopped if possible, which is rarely the case. • If they can be stopped short-term it would be expected that prolactin levels would have normalised within 72 hours. • If drugs cannot be stopped then dopamine agonists should be avoided and a trial of OCP can be used *(in women of reproductive age)*

Prolactinomas and pregnancy
• Dopamine agonists should be stopped in pregnancy however 20% of macroadenomas will grow. • Patients should be monitored for symptoms and changes in visual fields. If there is change then MRI should be undertaken to confirm growth. • Options are to either restart dopamine agonists, have TSS or early delivery, or pre-emptively debulking of adenoma pre-conception.

105.) **Von Hippel Lindau Syndrome**

Von Hippel-Lindau (VHL)
• Autosomal dominant disease with mutation of VHL, a tumour suppressor gene affecting VEGF on chromosome 3. • The incidence is roughly 1 in 36,000 live births and it has over 90% penetrance by the age of 65. • Genetic testing is recommended in family members of an index case from 5 years.

Subtypes of VHL

Type 1 VHL is associated with tumours in eye, brain, spinal cord, kidney and pancreas.

Type 2 is associated with the following features, as well as phaeochromocytoma:

- Haemangioblastoma (HB) - commonly in cerebellum, treated with surgery
- Retinal angioma - these develop around age 10, may cause detachment/bleed, are are treated with laser
- Renal cyst and CA - main cause of death, multifocal, treated with surgery
- Phaeochromocytoma - affects 20% cases, 40% of which are bilateral
- Pancreatic neuroendocrine tumour - usually non-functioning.

DIAGNOSIS OF VHL

- Two or more haemangioblastomas (HB), or
- One HB and visual manifestation, or
- One HB or visual manifestation and positive family history.

Testing and Surveillance for VHL

- From 5 years old - palpation, urinalysis, 24 hour urinary catecholamines, fundoscopy, MRI abdomen
- From 10 years old - cerebral MRI.

- **Annually for affected** - examination, urinalysis, 24 hour urinary catecholamines, fundoscopy AND three yearly MRI brain + abdomen
- **Annually for 'at risk'** - examination, urinalysis, 24 hour urinary catecholamines, fundoscopy (from 5-60 years) AND MRI brain (from 5-40 years then 5 yearly until 60 years) & MRI abdomen (from 25-65 years).

106.) **Treatment of osteoporosis in the setting of Kallman's syndrome**

Testosterone replacement is the most appropriate intervention both to establish sexual function and promote an increase in BMD.

107.) **Subclinical hypothyroidism**

- 70 years old and TSH > 10 mu/l then consider treating with levothyroxine only if a patient has clear symptoms of hypothyroidism or high vascular risk. *(European thyroid association)*

108.) **Hypomagnesemic hypoparathyroidism associated with the use of proton-pump inhibitors**

patients who receive a diagnosis of "idiopathic" hypoparathyroidism should be asked about their medication history. We suggest that magnesium levels should be measured in patients receiving proton-pump inhibitors, particularly those with concomitant cardiac abnormalities.

109.) **Side effects of Human Growth Hormone**

Recombinant human growth hormone

- Raised ICP with normal MRI (a secondary form of *idiopathic intracranial hypertension* (IIH)) is thought to result from the antidiuretic effect of hGH and is most common in those patients who also have impaired renal homeostasis
- slipped upper femoral epiphysis (SUFE)
- Malignancies
- gynaecomastia
- impaired glucose metabolism
- Arthralgia

- Edema
- Rash and pain at injection site, transient fever.

110.) PPAR-gamma receptor

Peroxisome proliferator activated receptor gamma (PPAR gamma)
• **PPAR gamma is an intra-cellular receptor** that is activated by free fatty acids (which are the natural endogenous ligands) and the *thiazolinediones* such as pioglitazone. • *On ligand binding it associates with the retinoid X receptor and couples with deoxyribonucleic acid (DNA)* producing downstream gene activation with protein synthesis that controls adipocyte differentiation and function, and is also related to cellular anti-inflammatory effects.

111.) **Primary hyperaldosteronism**

Causes of primary hyperaldosteronism
• Conn's syndrome (adrenal adenoma) causes over 50% • Adrenal hyperplasia • Adrenal carcinoma (rare) • Glucocorticoid deficiency - also called **glucocorticoid-remediable aldosteronism**. Note that this is isolated glucocorticoid (cortisol) deficiency driving high ACTH levels and increased aldosterone production. Addison's disease is different as it involves both glucocorticoid and mineralocorticoid deficiencies.

Glucocorticoid-remediable aldosteronism (GRA), alternatively called **dexamethasone-suppressible hyperaldosteronism (DSH)** or **familial hyperaldosteronism type I**, a mineralocorticoid-excess state characterized by low PRA

Pathophysiology	• Under normal conditions, aldosterone

	production is regulated by the renin-angiotensin system and potassium balance • In GRA, aldosterone secretion is positively and solely regulated by ACTH, the renin-angiotensin system is suppressed, and there is an absence of the normal potassium induced increase in aldosterone secretion
Genetics	• GRA is inherited as an autosomal dominant trait that follows classic Mendelian genetics. • GRA is caused by a chimeric gene duplication that results from unequal crossing over between the highly hormologous 11b-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2) genes • This gene duplication results in **ectopic expression of aldosterone synthase activity in the cortisol producing zona fasciculata.**
Clinical presentation	• Moderate to severe hypertension with onset early in life. (Difficult to control HTN with conventional antihypertensive agents, late diagnosis due to normative BP in children) • Early, often fatal, cerebrovascular complications (hemorrhagic strokes) • Normokalemia in most patients unless tx with K-wasting diuretics. • Masquerades as essential hypertension
Diagnosis	• Patients with GRA have abnormal plasma aldosterone (PAC):PRA ratios (>30) • PRA will be suppressed unless mineralocorticoid antagonists (such as spironolactone) have been used as therapeutic agents • Therefore, nonsuppressed PRA levels in the absence of such therapies strongly argues against a diagnosis of GRA • The diagnosis of GRA is supported by dexamethasone suppression testing (DST) *A fall in aldosterone to nearly undetectable levels after low-dose DST (0.5 mg dexamethasone orally every 6 h over 2–4 days) in GRA is expected and reflects the sole control of aldosterone by ACTH in this disorder.*
Treament	• Smallest effective dose of shorter-acting agents such as prednisone or hydrocortisone • Another side effect of glucocorticoid

	suppression is hypoaldosteronism with salt wasting, hypotension, and hyperkalemia immediately after treatment is initiated. This occurs because aldosterone levels fall to nearly undetectable levels and the zona glomerulosa remains acutely hypofunctional as a result of chronic suppression of the renin-angiotensin system ● Spironolactone, a competitive antagonist of aldosterone for the mineralocorticoid receptor (effective monotherapy)

112.) **Necrobiosis lipoidica**

- Necrobiosis lipoidica is a disorder of collagen degeneration with a granulomatous response, thickening of blood vessel walls, and fat deposition.
- The exact cause of necrobiosis lipoidica is unknown, but the leading theory of necrobiosis lipoidica has focused on diabetic microangiopathy.
- Necrobiosis is often mistaken for eczema but rather than responding to steroids may actually deteriorate. Occasionally ulceration of the lesion may occur.
- Necrobiosis is typically painless.

113.) **This finding is common with nocturnal hypoglycemia?**

- Vivid dreams in this patient is nocturnal hypoglycaemia

114.) **Risk of progression of prediabetes**

A number of studies have looked at the absolute risk of progression from IGT to type 2 diabetes. The large and widely-quoted **Hoorn study which looked at 1342 Caucasian non-diabetic subjects** found that **33.8% progressed to type 2 diabetes over six years follow up**. This increased to **64.5% if individuals had both IGT and impaired fasting glycaemia (IFG).**

A similar rate of progression for individuals with IGT was Vaccaro who studied a Caucasian group in Italy.

115.) The role of GAD 65 antibody testing in Diabetes classification

- The presence of GAD autoantibodies would signify an autoimmune aetiology and their presence signifies a ten fold increased risk of developing insulin-dependent diabetes mellitus, being **found in 70-90% of type 1 diabetics**.

- **latent autoimmune diabetes in adults (LADA)** and constitutes approximately 10% of patients incorrectly labelled as type 2 diabetic.

116.) MUFAs -- Monounsaturated fats

Substituting monounsaturated for saturated fats in a diet lowers low density lipoprotein (LDL) cholesterol and triglycerides together with raised high density lipoprotein (HDL) cholesterol levels.

117.) Role of a high fiber diet

High fibre foods lower total and low density cholesterol levels through increased bile acid excretion and decreased hepatic production of cholesterol and fatty acids.

118.) **Alternative site testing (with glucometer)**

- Alternative site blood glucose testing such as forearms, abdomen, calf and thighs.
- Severe pain and discomfort in the fingers, resulting from the needle pricks necessary for blood glucose testing, is due to the high density of pain receptors and nerve fibre endings in the fingers

Diabetes Care 2002 Feb; 25(2): 337-341.

119.) **Transgender medicine**

The International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) offer clear criteria for the diagnosis of transsexualism in adults:

- A desire to live and be accepted as a member of the opposite sex, usually accompanied by a sense of discomfort with, or inappropriateness of, one's anatomic sex, and a wish to have surgery and hormonal treatment to make one's body as congruent as possible with one's preferred sex (ICD-10)
- Severe gender dysphoria, coupled with a persistent desire for the physical characteristics and social roles that connote the opposite biological sex (DSM-IV).

120.) **Hormone replacement therapy and menopause**

- Oestrogen only replacement is only appropriate for patients whose uterus has been removed due to the increased risk of endometrial cancer.
- Combined treatment with oestrogen and progesterone increases the risk of VTE, stroke, breast cancer, and cardiovascular disease.

- Protective effects include reduction in osteoporosis and colorectal cancers.

121.) **Adrenal incidentaloma's and screening for Cushings**

The European Society of Endocrinology Clinical Practice Guideline recommends that all patients with adrenal incidentalomas undergo a **1 mg overnight dexamethasone suppression test to exclude cortisol excess.**

- serum cortisol levels post dexamethasone (≤1.8 µg/dL) as a diagnostic criterion for the exclusion of autonomous cortisol secretion
- post-dexamethasone serum cortisol levels between (1.9-5.0 µg/dL) should be considered as evidence of "**possible autonomous cortisol secretion**"
- Cortisol levels post dexamethasone (>5.0 µg/dL) should be taken as evidence of "**autonomous cortisol secretion".**

122.) Typical antibody found in autoimmune adrenalitis (Addison's disease)
21 hydroxylase is the enzyme involved in the cholesterol steroid pathway and has been found to be present in **approximately 80% of cases**.

123.) Screening for growth hormone excess

- oral glucose tolerance test with growth hormone (GH) measurements

- Suppression of growth hormone concentrations below 2 mU/l would be expected in normal patients with non-suppression or paradoxical elevation seen in acromegaly.
- Elevated IGF-1 concentrations would be expected but this is not diagnostic.

124.) Management of VTACH in pheochromocytomas
Phenoxybenzamine

125.) **Graves' disease**

- Only 85% of patients with Graves' disease have positive antithyroid peroxidase antibodies
- A goitre may not be detectable clinically, and may only be seen on imaging

126.) **Elucidate the pathophysiologic mechanisms of hyperprolactinemia**

Hypothalamic stimulation	• primary hypothyroidism • adrenal insufficiency.
Medications (inhibit dopamine release, leading to reduced inhibition and therefore higher prolactin release)	• Neuroleptics - phenothiazines, haloperidol • Antihypertensives - calcium-channel blockers, methyldopa • Psychotropic agents - tricyclic antidepressants • Anti-ulcer agents - Hs antagonists • Opiates and opiate antagonists
Neurogenic (via autonomic nervous system)	• Chest wall injury • Breast stimulation • Breast feeding.
Physiological causes (via oestrogen stimulation)	• Pregnancy • Coitus • Exercise • Sleep • Stress.
Increased prolactin production	• Ovarian: polycystic ovarian syndrome • Pituitary tumours - adenomas, hypothalamic stalk interruption, hypophysitis
Reduced prolactin elimination	• Renal failure

	• Hepatic insufficiency

127.)_ Features of pituitary apoplexy

Apoplexy
• Pituitary apoplexy is caused by **acute haemorrhage or infarction of the pituitary gland**. A pituitary adenoma usually pre-exists. • The visual symptoms include reduced acuity, visual field impairment and ocular motility dysfunction. This is due to involvement of the optic nerve, chiasm and cavernous sinus • Predisposing factors include bromocriptine, head injury, pregnancy, irradiation and endocrine stimulation tests. • Endocrinologically, the main initial problem is a **lack of adrenocorticotropic hormone (ACTH)**, which results in a lack of cortisol and the features of an '**Addisonian crisis**', i.e. hypotension, hyponatraemia, hyperkalaemia and hypoglycaemia. Subacutely, there can be deficiency in thyroid stimulating hormone (TSH) and gonadotropins (LH and FSH).

128.) **Osteonecrosis of the jaw**

- Most cases have been associated with zoledronic acid and pamidronate given intravenously for metastatic bone disease.
- The reported incidence in patients with malignancy treated with these drugs is between 1.3-4.0%.
- The lesions usually heal with minimal surgical debridement, chlorhexidine mouthwashes, antibiotics and analgesia.

129.)_ **What thyroid malignancy is patients with Hashimoto's thyroiditis most predisposed to developing**

- Thyroid lymphoma associated with autoimmune thyroiditis (also known as Hashimoto's disease or lymphocytic thyroiditis).
- The risk is small and would certainly not be screened for, nor should it in patients with autoimmune thyroid disease.

130.) NICE guidance for growth hormone (GH) replacement recommends that paediatric clinic patients are considered for GH replacement for the following:

- Chronic renal failure
- Turner syndrome
- Prader-Willi syndrome
- SHOX (short stature homeobox-containing gene) deficiency
- Born small for gestation age with subsequent growth failure after 4 years, and

- Growth hormone deficiency.

131.)_ When should GH replacement be stopped in children.

- Less than 50% increase in growth velocity from baseline in the first year
- Poor concordance with medication
- Attained final height, or
- Close to final height and growth velocity is less than 2 cm/year.

132.) **Pegvisomant in acromegaly**

- growth hormone receptor antagonist
- leads to a dose-dependent increase in growth hormone levels

Biochemical features after initiation of pegvisomant

- gradual increase in serum growth hormone
- Increases in adenoma size
- Serum IGF-1 is reduced in a dose-dependent manner
- No significant change is expected in prolactin in response to pegvisomant treatment, although in patients who experience a significant increase in adenoma size, a small rise may be seen (stalk effect)

133.) **Indication for real- time continuous glucose monitoring**

- More than 1 episode a year of severe hypoglycaemia with no obviously preventable precipitating cause.
- Complete loss of awareness of hypoglycaemia.
- Frequent (more than 2 episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities.
- Extreme fear of hypoglycaemia.

134.) A stimulatory mutation of the Gs protein alpha subunit has been noted in approximately 30% of growth hormone (GH) secreting pituitary tumours.

135.)_ Addison's disease (primary hypoadrenalism) is associated with

- Low aldosterone secretion (leading to salt wasting)
- High plasma renin
- High adrenocorticotrophic hormone (ACTH)
- High lipotropin
- Elevated plasma vasopressin, and
- Angiotensin II.

136.)_ **Discriminatory findings which increase the pretest probablity of Cushing's**

Proximal myopathy, easy bruising and thin skin.

Elevated UFC has high sensitivity and specificity (above 95%) for the diagnosis of Cushing's syndrome. Another useful screening test would be the 1 mg overnight dexamethasone suppression test which has similar sensitivity and specificity.
137.) Gestational diabetes

Risk factors for gestational diabetes
• BMI >30 kg/m2 • Previous macrosomic baby (>4.5 kg) • Previous gestational diabetes • First-degree relative with diabetes, and • Ethnic origin (South Asian, Caribbean, Middle Eastern)

Most gestational diabetes will respond to changes in diet and exercise. Only 10-20% of women need oral hypoglycaemia agents or insulin therapy.

138.)_ Aetiology of osteoporosis

Endocrine diseases associated with osteoporosis are:

- Cushing's disease
- vitamin D deficiency
- thyrotoxicosis and
- hypogonadism.

Myeloma and lymphoma are also associated with reduced BMD.

Other associates include:

- rheumatoid arthritis
- renal failure
- corticosteroids
- early menopause
- slender habitus
- smoking
- lack of exercise
- family history
- age/sex, and

- excess alcohol.

139.)_ **Klinefelter's syndrome**

Klinefelter's syndrome as suggested by the hypergonadotropic hypogonadism and poor secondary sexual characteristics, plus tall stature and suggested poor academic record.

This is due to 47XXY and has no specific genetic pattern of inheritance.

140.) **Kallmann's syndrome**

- Evidence of hypogonadotrophic hypogonadism with a low testosterone and a relative low follicle-stimulating hormone (FSH) and luteinising hormone (LH).
- Often associated with anosmia.

141.)_ **Metformin Associated Lactic Acidosis (MALA)**

- The estimated prevalence of life threatening lactic acidosis is one to five cases per 100,000, with mortality in reported cases up to 50%. Traditionally, this complication has been thought of as secondary to an accumulation of the drug.
- Metformin is excreted unchanged in the urine, with the half life prolonged and renal clearance decreased in proportion to any decrease in creatinine clearance. This may occur chronically in chronic **renal impairment**, or acutely with dehydration, shock, and intravascular administration of iodinated contrast agents, all of which have the potential to alter renal function.
- **Tissue hypoxia also has a significant role**, and acute or chronic conditions that may predispose to this condition, such as sepsis, acute myocardial infarction, pulmonary embolism, cardiac failure and chronic liver disease, may act as triggers.

142.)_ **Amiodarone induced thyrotoxicosis**
Amiodarone contains **75 mg of iodine per 200 mg tablet.** In addition, the **half life is very long (100 days)** and can result in prolonged effects even after stopping therapy for several months.

143.) _ **Good food choices for hypoglycemia treatment**

- Foods with high content of fast acting sugars (glucose) are advised. These are often fruits and **juices such as orange, apple, soft drinks, honey and raisins.**
- Food with a **high fat content and are therefore poor choices for**

treating hypoglycaemia. -- (DO NOT ADVISE icecream, doughnut, chocolate bars)

144.)_ Nesidioblastosis in the setting of post gastric bypass surgery (RYGB)

- **Nesidioblastosis or islet cell hyperplasia** is a rare consequence of gastric bypass surgery. It presents as hyperinsulinaemic hypoglycaemia because of an overshoot of the response to a carbohydrate challenge.
- Patients complain of symptoms of hypoglycaemia **one to three hours after eating**.
- Calcium stimulation testing may be helpful in localising insulin release as coming from the pancreas, and in rare circumstances, patients may require a partial pancreatic resection.

➤ **Gastric dumping syndrome** is associated with slightly earlier hypoglycaemia, occurring some 15-30 minutes after eating

145.)_ **Indications of screening for a genetic condition as a cause for pheochromocytoma**

- Age <50years
- Extra adrenal tumors
- Bilateral tumors
- Malignancy

146.)_ **Secondary hyperthyroidism**

- **Elevated tri-iodothyronine (T3) and thyroxine (T4)** and **inappropriately *normal* TSH**. If free T4 and T3 are high, but TSH is normal or high, a pituitary MRI should be done to look for a pituitary mass **(TSH-secreting adenoma).**
- If there is no pituitary mass, but there is end-organ evidence of hyperthyroidism, a careful family pedigree should be obtained as well as genetic testing for the possibility of thyroid hormone resistance.
- Alpha subunit is also secreted in large amounts and measurement of this should yield an elevated **α-subunit :TSH ratio (usually 1:1).**
- The diagnosis should be suspected when TSH concentrations are not suppressed in the presence of hyperthyroidism.

147.)_ Causes of gynaecomastia include:

- Digoxin
- Cimetidine

- LHRH analogues, and
- Finasteride
- Spironolactone
- Ciclosporin
- Omeprazole
- Ramipril has very rarely been associated with gynaecomastia

148.)_ Causes of SIADH

- Pneumonia
- Meningitis
- Carcinoma (bronchial in particular)

149.)_ **Hypothyroidism and the importance of ruling out adrenal insufficiency**

In hypoadrenalism which is either primary or secondary, the addition of thyroxine can precipitate acute hypoadrenalism

150.)_ **Likely presenting symptom of phechromocytoma**
Episodic headache was present in 80%. It was usually of rapid onset, bilateral, severe, throbbing, and associated with nausea in about half of the cases.

Mayo clinic series by Thomas et al (JAMA 1966)

151) Diabetes complications and exercise

- **Untreated diabetic proliferative retinopathy carries a risk of haemorrhage** and therefore such patients should be advised to avoid strenuous exercise until adequately treated with photocoagulation therapy.
- Exercise is encouraged in peripheral vascular disease and ischaemic heart disease.

152.) **Carbohydrate counting**

Although some alcoholic drinks contain significant amounts of CHO, patients are usually advised not to count them given the risks of alcohol-induced hypoglycaemia.

153.) Hypoglycemia in the setting of a stable sulfonylurea dose, leading to hypoglycemia

- Glimepiride is metabolised by **CYP 2C9**
- **Fluconazole** on the other hand is an inhibitor of 2C9, as are **quinolones, sulphonamides and clarithromycin.**

154.) Bromocriptine or cabergoline and pregnancy

Largest body of data to support use in pregnancy is for bromocriptine, where no increase in either miscarriage or congenital malformation has been seen. It is generally recommended to discontinue therapy once successful pregnancy has been achieved.

155.) Kleinefelter's syndrome

Kleinefelter's is a congenital abnormality that causes primary hypogonadism. During meiotic division, there is non-disjunction of either parent's sex hormones resulting in 47,XXY genotype.

Clinical features include:

- small, firm testes
- in some cases micropenis
- low sperm count and infertility
- long bone abnormality results in longer limbs and tall stature, and
- gynaecomastia.

Patients are also more susceptible to autoimmune diseases such as SLE, rheumatoid arthritis, Sjorgren's syndrome, and diabetes mellitus.

Atrophy and damage to the seminiferous tubules and Leydig cells lead to low testosterone levels and high FSH and LH levels.

Diagnosis is generally made on karyotyping. The mainstay of treatment is androgen replacement. Some patients are able to have their own children using a combination of testicular sperm extraction and IVF.

156.) Importance of ACEi therapy in diabetes mellitus

Subjects with type 2 diabetes have a two- to fourfold increased cardiovascular mortality

- Studies such as UKPDS reveal that improving glycaemic control would reduce microvascular complications but this has no significant impact upon cardiovascular morbidity and mortality. However, lowering blood pressure significantly reduced morbidity from both microvascular and macrovascular disease.
- In this study angiotensin-converting enzyme inhibitors (ACEIs) compared with beta blockers the results were similar. But, the

HOPE study (using ramipril) suggested that mortality in patients at risk of cardiovascular disease (including diabetics) may be further reduced by the addition of an ACEI to their standard regime.
- ACEI may have a superior efficacy in delaying the progression of nephropathy.

157.) Cushings' evaluation

In the high dose dexamethasone suppression test, classically, the **cortisol should suppress to 50% of the level found after low dose dexamethasone in cases of pituitary dependent CS**. However 50% suppression is found on less than 80% of occasions and so is far from diagnostic.

Usually the cause of Cushing's disease is a pituitary microadenoma and this may not be seen on MR. However, the best way of distinguishing between ectopic and pituitary dependent CS is with inferior petrosal sinus sampling where a high gradient of ACTH from sinus compared with a peripheral sample is diagnostic of pituitary dependent disease.

158.) Carcinoid syndrome

- Neuroendocrine tumour with generally a reasonable prognosis despite widespread dissemination.
- The tumours usually express somatostatin receptors and good therapeutic response is usually seen following somatostatin analogue therapy (for example, octreotide).
- Standard chemotherapy has been shown to be ineffective.

159.) Diabetic retinopathy

- Scattered microaneurysms signify background diabetic retinopathy (DRn).
- Intraretinal microvascular abnormalities (IRMA) and soft exudates signify pre-proliferative retinopathy.
- Urgent referral to an ophthalmologist (seen within one week) is required if there is proliferative retinopathy or there is evidence of clinically significant macular oedema (hard exudates at the fovea).

160.) **When to consider autoimmune adrenalitis in a T1DM patient**

Type 1 diabetes is the weight loss, lethargy and reduced insulin requirements with increasing frequency of hypoglycaemic events.

161.) **Thyroid cancer and Graves' disease**

- Thyroid cancer associated with Graves' disease is not uncommon and usually due to papillary carcinoma and must be considered in

suspicious/expanding nodules rather than attributing purely to Graves' disease.
- Thyroid peroxidase antibodies are found in more than 70% of cases of Grave's disease

162.) **Nonclassical adrenal hyperplasia**

Congenital adrenal hyperplasia is caused by an inherited defect in the cortisol and/or aldosterone biosynthetic pathways. *Non-classical forms result from milder enzyme dysfunction* and *therefore manifest later in life (adolescence or adulthood).* The most common form is due to 21-hydroxylase deficiency, but it can also result from 11 beta hydroxylase deficiency. The clinical presentation may be indistinguisable from polycystic ovarian syndrome, with hirtusism being a dominant feature.

The synacthen stimulation test can evaluate adrenal gland function, and when 17-OHP levels are measured concurrently, can help to distinguish between PCOS and non-classical CAH. N-CAH due to 21-hydroxylase deficiency is diagnosed with the ACTH-stimulated 17-OHP levles. **If this is diagnosed, antiandrogens can be used to treat hirsutism, but glucocorticoids are generally not required.**

163.) Thyrotoxicosis (acute management)

Use of iodine preparations can bring rapid relief from symptoms of thyrotoxicosis by blocking release of thyroid hormone from the thyroid via negative feedback within hours of administration. Administration should be separated from thioamides by at least an hour. Use of iodine is useful to improve suitability for surgical thyroidectomy as the definitive intervention to control thyrotoxicosis.

Cholestyramine can further reduce circulating thyroid hormone by disrupting its enterohepatic circulation.

164.) Hemochromatosis

The main pointers towards a diagnosis of haemochromatosis here include

- elevated ferritin and transferrin saturation
- abnormal liver function tests (LFTs)
- presence of diabetes, and
- erectile dysfunction related to low testosterone.

165.) Management of diabetic postural hypotension in the setting of diabetic autonomic neuropathy

In patients who remain symptomatic with respect to postural hypotension despite TED stockings, or who fail to tolerate them, low-dose

fludrocortisone is an initial step, followed by midodrine in patients who fail to respond.

166.) **Acromegaly**

Acromegaly is caused by a growth hormone-producing adenoma in the anterior pituitary. Excessive growth hormone secretion causes increased growth of tissues such as bone, cartilage, connective tissue, viscera, and epithelial tissues.

Classical features include:

- Frontal bossing
- Enlarged jaw (macrognathia) and spacing of teeth
- Enlarged hands and feet - rings and shoes don't fit anymore
- Enlarged nose
- Enlarged tongue (macroglossia) - increases risk of sleep apnoea
- Hyperhidrosis
- Growth plates are fused so patients do not become taller, but hypertrophy of the joint cartilage can cause arthropathy
- Visceral enlargement - thyroid, heart, liver, lungs, and kidneys
- Increased incidence of colonic polyps
- Hyperinsulinism, insulin resistance, overt diabetes in 10 to 15 percent of cases

167.) Hypogonadotrophic hypogonadism -- suppressed luteinising hormone/follicle-stimulating hormone (LH/FSH) and a low oestradiol concentration.

168.) Albumin, a commonly used marker for nutritional status is surprisingly normal even in patients with severe anorexia nervosa.

169.) ADH physiology

- ADH is a nonapeptide manufactured in the paraventricular and supra-optic nuclei of the hypothalamus and released from the posterior pituitary.
- It acts on the collecting ducts improving water permeability and hence water retention.
- Carbamazepine as well as other agents such as thiazides and selective serotonin reuptake inhibitors (SSRIs) may potentiate its release.
- Ethanol usually inhibits release.

170.) vascular physiology

vasoconstriction	vasodilation
• ADH acts on the vasopressor receptors to cause vasoconstriction. • Endothelin is also a vasoconstrictor as is renin. • Somatostatin is also recognised to produce vasoconstriction of the splanchnic system.	• Calcitonin-gene related peptide causes vasodilatation.

- Diabetes, especially Type 2 diabetes, is associated with macrovascular disease.
- After a meal splanchnic blood flow is increased. If the mesenteric artery is occluded the lack of blood flow to the bowel will produce ischaemic type pain.

Pendred's disease
hypothyroidism, goitre and deafness.

Post menopausal state and bone health
• Calcium and vitamin D supplements are more likely to benefit women who are more than five years post menopause, as their intake is likely to be low. • Post menopausal women who wish to reduce the risk of osteoporosis should consume 1000-1500 mg of elemental calcium and 400-800 IU of vitamin D daily, ideally through calcium containing foods. • Excessive intake of calcium and vitamin D may cause adverse effects such as hypercalcaemia and hypercalciuria.

Bisphosphonates -- mechanism of action

Simple bisphosphonates such as clodronate and etidronate inhibit bone resorption through induction of osteoclast apoptosis.

Clodronate, and perhaps etidronate, triggers apoptosis by generating a toxic analogue of adenosine triphosphate, which then targets the mitochondria.

For **nitrogen-containing bisphosphonates**, the direct intracellular target is the **enzyme farnesyl-diphosphate synthase in the cholesterol biosynthetic pathway**.

Its inhibition suppresses a process called protein geranylgeranylation, which is essential for the basic cellular processes required for osteoclastic bone resorption.

Although nitrogen-containing bisphosphonates can induce osteoclast apoptosis, this is not necessary for their inhibition of bone resorption.

Microalbuminuria and diabetes

Microalbuminuria is defined as a urine albumin excretion of between 30-300 mg per 24 hours.

A concentration above 300 mg/24 hours signifies albuminuria and a concentration above 3.5 g/24 hours signifies overt proteinuria.

Microalbuminuria is not just an indicator of early renal involvement but it also identifies increased cardiovascular risk with an approximate twofold cardiovascular risk above the already increased risk in the diabetic population.

A useful surrogate of the total albumin excretion is the albumin: creatinine ratio. The urinary albumin:creatinine ratio is measured using the first morning urine sample where practicable.

Thyroid cancer

There are four main types of thyroid cancer (in order of frequency):

1. Papillary
2. Follicular
3. Medullary

4. Anaplastic.

Follicular thyroid carcinoma (FTC) is a well-differentiated tumour.

- In fact, FTC resembles the normal microscopic pattern of the thyroid. FTC originates in follicular cells and is the second most common cancer of the thyroid after papillary carcinoma.
- The most common presentation of thyroid cancer is an asymptomatic thyroid mass, or a nodule, that can be felt in the neck.

The staging of well-differentiated thyroid cancers is related to age for the first and second stages but not related for the third and fourth stages.

Younger than 45 years:

- Stage I - Any T, any N, M0 (Cancer is in the thyroid only).
- Stage II - Any T, any N, M1 (Cancer has spread to distant organs).

Older than 45 years:

- Stage I - T1, N0, M0 (Cancer is in the thyroid only and may be found in one or both lobes).
- Stage II - T2, N0, M0 and T3, N0, M0 (Cancer is in the thyroid only and is larger than 1.5 cm).
- Stage III - T4, N0, M0 and any T, N1, M0 (Cancer has spread outside the thyroid but not outside of the neck).
- Stage IV - Any T, any N, M1 (Cancer has spread to other parts of the body).

Surgery is the definitive management of thyroid cancer. Various types of operations may be performed.

Lobectomy with isthmectomy is the minimal operation for a potentially malignant thyroid nodule. Patients less than 40 years who have FTC nodules less than 1 cm, well defined, minimally invasive, and isolated may be treated with hemithyroidectomy and isthmectomy.

If feasible, subtotal thyroidectomy (small part of contralateral lobe retained) is preferable since it carries a lower incidence of complications (for example, hypoparathyroidism, superior and/or recurrent laryngeal nerve injury).

Approximately 10% of patients who have had total thyroidectomy (removal of all thyroid tissue preserving the contralateral parathyroid glands) demonstrate cancer in the contralateral lobe.

Total thyroidectomy

- > 40 years with FTC
- Any patient with bilateral disease.
- Any patient with a thyroid nodule and a history of irradiation

Some studies show lower recurrence rates and increased survival rates in patients who have undergone total thyroidectomy. This surgical procedure also facilitates earlier detection and treatment of recurrent or metastatic carcinoma.

Patients receive radioiodine four to six weeks after thyroidectomy to detect and destroy any metastases and any residual tissue in the thyroid.

External beam radiation is used in the management of FTC if the cancer cannot be resected, or if there is extension into adjacent structures. Radiotherapy may also be administered postoperatively to reduce the risk of local-regional recurrence. It may also be used palliatively to treat pain from bone metastases.

Chemotherapy with cisplatin or doxorubicin has limited efficacy. It may be employed when other treatment modalities have failed.

GLP-1 agonist therapy

NICE Guidelines for type 2 diabetes, only continue GLP1 mimetic therapy if the person with type 2 diabetes has had a **beneficial metabolic response**

- **a reduction of at least [1.0%] in HbA1c**
- **a weight loss of at least 3% of initial body weight in 6 months.**

Gynecomastia

Gynaecomastia is due to a perturbation in the testosterone to oestradiol ratio.

Neither hyperprolactinaemia nor hypopituitarism disturb this ratio and are rarely associated with gynaecomastia.

Unlike hyperthyroidism, hypothyroidism is not a cause. CAH is not a cause.

However, gynaecomastia may be a presenting symptom of a seminoma and may arise due to human chorionic gonadotropin (HCG) secretion.

Increased IGF-1 levels	Reduced IGF-1 levels
Pregnancy	• adult GHD • cirrhosis of the liver due to reduced synthesis • diabetes mellitus, and • starvation.

Current clinical trial data for hormone replacement therapy
• HRT **has not** been shown to reduce cardiovascular (CV) mortality or the incidence of stroke, nor does it cause regression of coronary plaques • HRT has been shown to have an increased CV morbidity in the WHI study • May increase HDL cholesterol • Increases triglycerides • It **does not raise** LDL cholesterol

Recombinant human growth hormone therapy
Unlike the old pituitary derived growth hormone (GH), recombinant human GH is not associated with CJD. RHGH therapy has been associated with headaches and idiopathic intracranial hypertension (IIH) probably due to the fluid retention associated with GH therapy.

Mechanism of action of finasteride

Finasteride is a 5 alpha-reductase inhibitor and inhibits the conversion of testosterone to the active DHT.

Primary hypogonadism	**Secondary hypogonadism**
serum testosterone concentration and the sperm count are below normal and the serum LH and FSH concentrations are above normal.	serum testosterone concentration and the sperm count are subnormal and the serum LH and FSH concentrations are normal or

	reduced.
More likely to be associated with a decrease in sperm production than in testosterone production. **Although many testicular diseases damage both the seminiferous tubules and the Leydig cells, they usually damage the seminiferous tubules to a greater degree.** As a consequence, the sperm count may be low, and the serum FSH concentration normal or high, yet the serum testosterone concentration remains normal.	In contrast, in secondary hypogonadism, there is a proportionate reduction in testosterone and sperm production.

Causes of primary hypogonadism in males can include congenital abnormalities and acquired diseases.

Congenital abnormalities:

- Klinefelter syndrome (and other chromosomal abnormalities)
- Mutation in the FSH and LH receptor genes
- Cryptorchidism
- Varicocele
- Disorders of androgen synthesis, and
- Myotonic dystrophy.

Acquired diseases:

- Infections (especially mumps)
- Radiation
- Alkylating agents
- Ketoconazole
- Glucocorticoids
- Environmental toxins
- Trauma
- Testicular torsion
- Autoimmune damage
- Chronic systemic illnesses
- Hepatic cirrhosis
- Chronic renal failure
- AIDS, and
- Idiopathic.

RAI treatment

RAI is associated with the induction of hypothyroidism in the majority of subjects by three months (70%) with 10% failing at the first dose at about 18 months.

Cortisol levels are increased in pregnancy, conditions of physical and emotional stress and drug therapy (oestrogens, oral contraceptives, amphetamines, cortisone, and spironolactone).

Post partum thyroiditis

- Occurs in approximately 5% of females and is associated with transient hyperthyroidism usually two to six months postpartum followed by hypothyroidism which also usually resolves but permanent hypothyroidism may occur.
- The exact aetiology is unknown but lymphocytic infiltration of the thyroid is typical, suggesting auto-immunity.
- Treatment for the hyperthyroidism is usually conservative as symptoms could resolve but, if required, beta-blockers are adequate.

FACTOIDS OF THYROID CANCER -- THE BAD AND UGLY

- **Anaplastic carcinoma** usually occurs in middle-aged and older patients with longstanding goitre.
- The gland may suddenly increase in size producing pressure symptoms, dysphagia or vocal cord paralysis.
- The tumour is resistant to therapy.
- Death from massive local extension usually occurs within 3-36 months.
- **Thyroid medullary carcinoma** is the next most aggressive, especially so in multiple endocrine neoplasia (MEN) 2B subjects, but less so in 2A subjects.
- **Lymphoma** may respond dramatically to irradiation.

Vitamin D resistant rickets

Vitamin D resistant rickets is inherited in an X-linked dominant manner.

Therefore an affected female will transmit the disease to 50% of her sons and 50% of her daughters.

An affected male will transmit the condition to all of his daughters but none of his sons.

Role of metformin in PCOS

Metformin has been shown to increase the rate of conception in PCOs through improved insulin sensitivity (although studies have not been powered to show a significant impact on pregnancy outcome)

Statin therapy and Diabetes mellitus

Lipid lowering therapy benefits patients with diabetes as much as those without diabetes in preventing macrovascular events in sub- group analyses but has no effect on microvascular events demonstrated so far. Adding fibrate may have an effect on retinopathy (FIELDS).

Acanthosis nigricans has a characteristic hyperpigmented, velvety surface. It frequently occurs in the axillae, groins and in the skin fold of the neck and occasionally on the dorsum of the hand.

Acanthosis nigricans is associated with:

- endocrine disease (acromegaly, Cushing's syndrome, insulin resistant diabetes mellitus)
- polycystic ovary syndrome, and
- paraneoplastic phenomenon (usually tumours of the GI tract, especially adenocarcinoma of the stomach).

Kallmann's syndrome is a common cause of hypogonadotrophic hypogonadism and inheritance is variable. Other associated abnormalities include midline defects particularly cleft palate, colour blindness, and deafness.

When suspected on the basis of the clinical presentation or physical findings, the diagnosis of congenital GnRH deficiency should be confirmed biochemically. The diagnosis requires the following findings:

- The demonstration of prepubertal serum concentrations of sex steroid hormones (serum testosterone in males or serum oestradiol in females).
- Low or normal serum LH and FSH concentrations (usually less than 4 to 5 IU/L) rather than the high concentrations expected with primary gonadal failure.
- Otherwise normal anterior pituitary function
-

Acquired hypertriglyceridemia

The commonest cause of a mild hypertriglyceridaemia is obesity secondary to a reduced efficacy of lipoprotein lipase activity and overproduction of VLDL.

Obesity (defined as a BMI above 30) is the commonest cause of hyperlipidaemia. Alcohol is probably a close second.

Other secondary causes of hypertriglyceridaemia include:

- pregnancy
- hypothyroidism
- diuretics, and
- Pancreatitis.

The specific features that would support a diagnosis of Graves' would include:

- Exophthalmos
- Thyroid bruit, and
- **Pretibial myxoedema.**

The latter is pathognomonic as exophthalmos may be a feature (rarely) of hashitoxicosis.

De Quervain's thyroiditis (also known as subacute thyroiditis or granulomatous thyroiditis) causes diffuse, tender enlargement of the thyroid gland. The thyroid enlargement is typically rapid, occurring over a period of days.

The syndrome often starts after a respiratory tract infection and it is likely that the condition has a viral aetiology (although no causative infectious agent has been found). Patients feel systemically unwell with myalgia, fever and prostration.

Plasma thyroid hormones are greatly elevated as is the erythrocyte sedimentation rate (ESR). There are often marked signs and symptoms of

thyrotoxicosis.

Radioiodine uptake is typically less than 1% at 24 hours (Tc 99m uptake is similarly low).

Treatment is usually bed rest and aspirin to reduce inflammation. Occasionally steroids are used to reduce inflammation.

After the thyroid is depleted of thyroid hormone, patients' serum levels of thyroxine (T4) and tri-iodothyronine (T3) decrease into the hypothyroid range. The hypothyroidism is usually mild but persists for two to four months. A few patients (~5%) remain hypothyroid and need longterm thyroid hormone replacement. Recurrences are uncommon.

The most likely associate of Graves' disease is vitiligo occurring in approximately 7% of cases.

It is important to appreciate that autoimmunity is relatively common in association with thyroid autoimmunity and include type 1 diabetes mellitus, Addison's, pernicious anaemia and Sjögren's.

GLP 1 Agonist therapy

Exenatide mimics the effect of the gut hormone GLP-1 (glucagon-like peptide 1) and has favourable effects on the metabolism of individuals with diabetes mellitus.

Exenatide suppresses appetite, inhibits glucose production in the liver, slows gastric emptying and stimulates insulin release. It does not increase insulin sensitivity which is achieved by drugs such as metformin and the glitazones.

In summary exenatide has the following metabolic effects

- Stimulates insulin release
- Inhibits glucose production by the liver
- Slows gastric emptying
- Suppresses appetite.

MODY

Monogenic forms of diabetes comprise a heterogous group of disorders that are caused by a single gene mutation, characterized by impaired insulin secretion.

5% of all diabetes is monogenic and affected individuals are often undiagnosed or misclassified as having T1 or T2DM

1. Young age at diagnosis (often under 25years)
2. Marked family history of diabetes in every generation due to autosomal dominant inheritance
3. Absence of obesity and signs of insulin resistance
4. Commonly mild hyperglycemia without the need for insulin therapy and negative results for B cell antibodies.

Confirmed by genetic testing

Ketosis-Prone Diabetes

Previously referred to as Flatbush diabetes, type 1b diabetes

20-50% of newly diagnosed African American or Hispanic patients

Patients present with DKA, predicting the duration of insulin therapy has been a therapeutic challenge.

AB classification system focusing on B cell autoimmunity (GAD-65 and Insulinoma associated protein 2 antibodies) and Beta cell function (c peptide levels).

The AB system accurately (99% sensitivity and 96% specificity) predicts the need for insulin therapy 12months after presentation with DKA.

CFRD

- Primary defect of insulin secretion due in part to autoimmune destruction of B cells (mainly) and also alpha cells in the pancreas, so both insulin and glucagon secretion are defective.
- CFRD correlates with poorer clinical status, reflected by reduced pulmonary function and nutritional status, increased frequency of acute pulmonary exacerbations and significant sputum pathogens
- Annual screening recommended beginning at 10years of age
- OGTT is the test of choice
- Insulin recommended for management. HBA1C can be used for monitoring (level of <5.5%)

How to switch from U100 insulin to U500 insulin

1) Check HBA1C at time of switch
2) If HBA1C is >8%; give 100% of the dose
3) If HBA1C is <8%, give 80% of the dose
4) Start either 60:40% or 40:30:30

Pediatric Endocrinology
Normal Puberty

HPA Axis activity (Uptodate)

- Active in utero and in 1st week of life
- It then becomes more active again during infancy, with peak activity between one and three months of age (levels comparable to early-mid puberty but no peripheral effects)
- Boys levels decrease to prepubertal by 6-9 months
- Girls, LH decrease same as boys but FSH can remain elevated up to 2 yrs of age.

PHYSIOLOGY AND ENDOCRINOLOGY OF PUBERTY

- Gonadarche is driven by an increase in the pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, resulting in increases in both frequency and amplitude of pulses of luteinizing hormone (LH) secretion,
- GnRH stimulates the gonadotroph cells of the anterior pituitary gland to secrete follicle-stimulating hormone (FSH) and LH, which in turn stimulate sex-steroidogenesis and eventually gametogenesis in the gonads.

Girls =

- FSH stimulates the growth of ovarian follicles and, in conjunction with LH, stimulates production of estradiol by the ovaries. *(reason why familial male limited precocious puberty can not occur in females)*

- Early in puberty, estradiol stimulates breast development and growth of the skeleton, leading to pubertal growth acceleration.

- Later in puberty, the interplay between pituitary secretion of FSH and LH, and secretion of estradiol by ovarian follicles leads to ovulation and menstrual cycles

- Estradiol also induces maturation of the skeleton, eventually resulting in fusion of the growth plates and cessation of linear growth.

Boys =

- LH stimulates the Leydig cells of the testes to produce testosterone, the high local concentration of which stimulates the growth of the seminiferous tubules, leading to an increase in testicular volume.

- FSH stimulates further growth of seminiferous tubules and increases in testicular volume.

- Testosterone also induces growth of the penis, deepening of the voice, growth of hair, and increases in muscularity. Some testosterone is converted to estradiol, which has the same effects on growth and skeletal maturation as in girls.

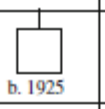
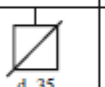
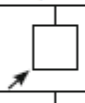
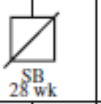
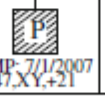
Licorice

- Chronic ingestion of licorice or licorice-like compounds (such as carbenoxolone) induces a syndrome with findings like those with the syndrome of apparent mineralocorticoid excess (AME): hypertension, hypokalemia, metabolic alkalosis, low plasma renin activity and low plasma aldosterone levels.
- as little as 50 g daily for two weeks, produce a rise in blood pressure in normal people.
- Licorice contains a steroid, glycyrrhetinic acid, that inhibits (both competitively and by reducing gene expression) 11-beta-HSD2, the same enzyme that is deficient in AME.
    - As in AME, normal levels of cortisol can markedly increase net mineralocorticoid activity in patients chronically ingesting licorice.
- The diagnosis is typically based upon the biochemical abnormalities and an elicited history of licorice ingestion.
    - Not always obvious: in some forms of flavored chewing gum, chewing tobacco, and tea. As noted above, urinary free cortisone and cortisol levels may help make the diagnosis, but such testing is not necessary if a history of licorice ingestion has been obtained.
- Cessation of licorice ingestion (or other source of glycyrrhetinic acid) is usually the only treatment necessary.
- Potassium supplements or a potassium-sparing diuretic may be initially required to treat hypokalemia but should not be needed once the effect of licorice has worn off (typically less than one week).

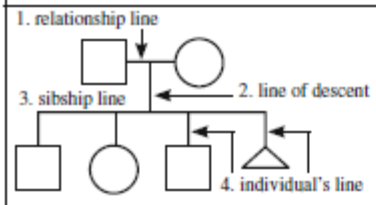
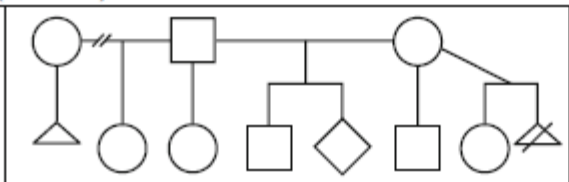
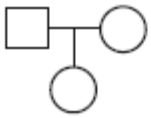
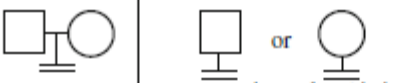
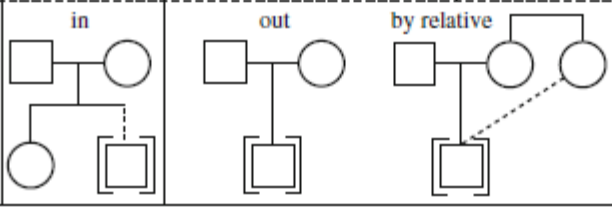
MEDICAL GENETICS

Standardized Human Pedigree Nomenclature

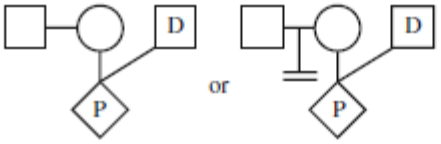
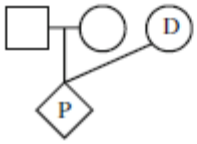
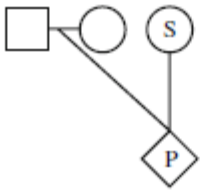
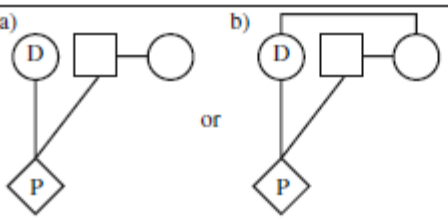
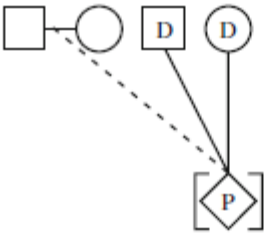
Instructions:
— Key should contain all information relevant to interpretation of pedigree (e.g., define fill/shading)
— For clinical (non-published) pedigrees include:
  a) name of proband/consultand
  b) family names/initials of relatives for identification, as appropriate
  c) name and title of person recording pedigree
  d) historian (person relaying family history information)
  e) date of intake/update
  f) reason for taking pedigree (e.g., abnormal ultrasound, familial cancer, developmental delay, etc.)
  g) ancestry of both sides of family
— Recommended order of information placed below symbol (or to lower right)
  a) age; can note year of birth (e.g., b.1978) and/or death (e.g., d. 2007)
  b) evaluation (see Figure 4)
  c) pedigree number (e.g., I-1, I-2, I-3)
— Limit identifying information to maintain confidentiality and privacy

	Male	Female	Gender not specified	Comments
1. Individual				Assign gender by phenotype (see text for disorders of sex development, etc.). Do not write age in symbol.
2. Affected individual				Key/legend used to define shading or other fill (e.g., hatches, dots, etc.). Use only when individual is clinically affected.
			With ≥2 conditions, the individual's symbol can be partitioned accordingly, each segment shaded with a different fill and defined in legend.	
3. Multiple individuals, number known				Number of siblings written inside symbol. (Affected individuals should not be grouped).
4. Multiple individuals, number unknown or unstated				"n" used in place of "?".
5. Deceased individual				Indicate cause of death if known. Do not use a cross (†)to indicate death to avoid confusion with evaluation positive (+).
6. Consultand				Individual(s) seeking genetic counseling/ testing.
7. Proband				An affected family member coming to medical attention independent of other family members.
8.Stillbirth (SB)				Include gestational age and karyotype, if known.
9. Pregnancy (P)				Gestational age and karyotype below symbol. Light shading can be used for affected; define in key/legend.

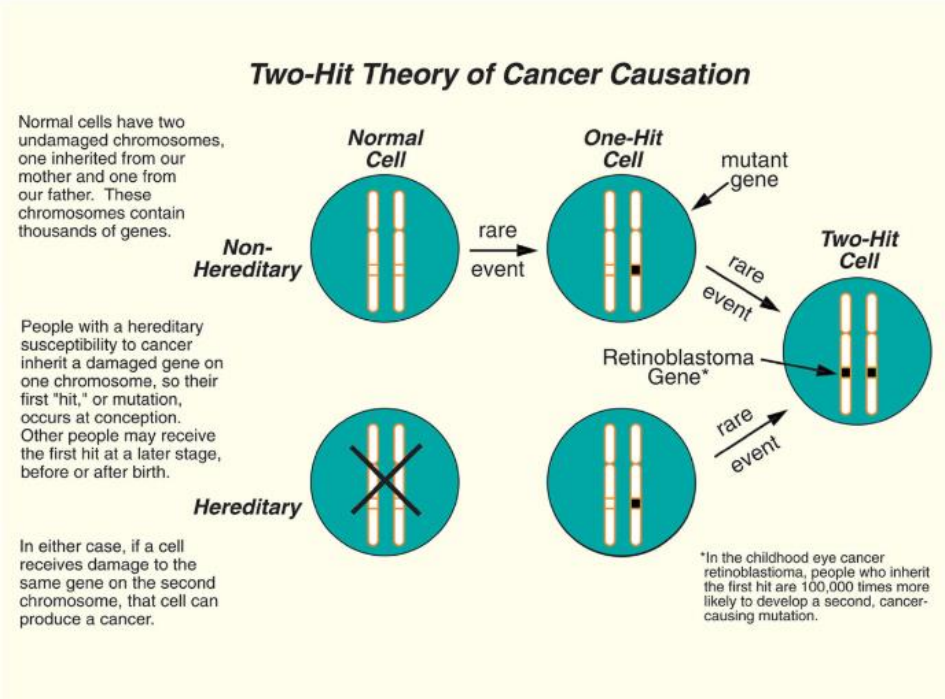
Pregnancies not carried to term	Affected	Unaffected	
10. Spontaneous abortion (SAB)			If gestational age/gender known, write below symbol. Key/legend used to define shading.
11. Termination of pregnancy (TOP)			Other abbreviations (e.g., TAB, VTOP) not used for sake of consistency.
12. Ectopic pregnancy (ECT)			Write ECT below symbol.

1. Definitions	Comments
	If possible, male partner should be to left of female partner on relationship line. Siblings should be listed from left to right in birth order (oldest to youngest).
2. Relationship line (horizontal)	
a. Relationships 	A break in a relationship line indicates the relationship no longer exists. Multiple previous partners do not need to be shown if they do not affect genetic assessment.
b. Consanguinity 	If degree of relationship not obvious from pedigree, it should be stated (e.g., third cousins) above relationship line.
3. Line of descent (vertical or diagonal)	
a. Genetic 	Biologic parents shown.
- Multiple gestation 	The horizontal line indicating monozygosity is placed between the individual's line and not between each symbol. An asterisk (*) can be used if zygosity proven.
- Family history not available/ known for individual 	
- No children by choice or reason unknown 	Indicate reason, if known.
- Infertility 	Indicate reason, if known.
b. Adoption 	Brackets used for all adoptions. Adoptive and biological parents denoted by dashed and solid lines of descent, respectively.

Instructions:
— D represents egg or sperm donor
— S represents surrogate (gestational carrier)
— If the woman is both the ovum donor and a surrogate, in the interest of genetic assessment, she will only be referred to as a donor (e.g., 4 and 5)); the pregnancy symbol and its line of descent are positioned below the woman who is carrying the pregnancy
— Available family history should be noted on the gamete donor and/or gestational carrier

Possible Reproductive Scenarios		Comments
1. Sperm donor		Couple in which woman is carrying pregnancy using donor sperm. No relationship line is shown between the woman carrying the pregnancy and the sperm donor.
2. Ovum donor		Couple in which woman is carrying pregnancy using a donor egg and partner's sperm. The line of descent from the birth mother is solid because there is a biologic relationship that may affect the fetus (e.g., teratogens).
3. Surrogate only		Couple whose gametes are used to impregnate a woman (surrogate) who carries the pregnancy. The line of descent from the surrogate is solid because there is a biological relationship that may affect the fetus (e.g., teratogens).
4. Surrogate ovum donor		Couple in which male partner's sperm is used to inseminate a) an unrelated woman or b) a sister who is carrying the pregnancy for the couple.
5. Planned adoption		Couple contracts with a woman to carry a pregnancy using ovum of the woman carrying the pregnancy and donor sperm.

Knudson's "Two-Hit" Theory of cancer causation



Hereditary Paraganglioma-Pheochromocytoma Syndromes

- **Hereditary paraganglioma-pheochromocytoma (PGL/PCC)** syndromes are characterized by **paragangliomas** (tumors that arise from neuroendocrine tissues symmetrically distributed along the paravertebral axis from the base of the skull to the pelvis) and by **pheochromocytomas** (paragangliomas that are confined to the adrenal medulla)
- Sympathetic paragangliomas hypersecrete catecholamines; parasympathetic paragangliomas are most often nonsecretory.

Extra-adrenal parasympathetic paragangliomas	**Sympathetic extra-adrenal paragangliomas**
Located predominantly in the skull base, neck, and upper mediastinum	Generally confined to the lower mediastinum, abdomen, and pelvis
About 95% are non-secretory	Typically secretory
Low risk for malignancy	High risk for malignancy

- *SDHA, SDHB, SDHC* and *SDHD* are four nuclear genes that encode

the four subunits of the mitochondrial enzyme succinate dehydrogenase (SDH).

Surveillance: Beginning at age ten years or at least ten years before the earliest age at diagnosis in the family, individuals at risk for hereditary PGL/PCC syndromes need to begin lifelong biochemical and clinical surveillance for signs and symptoms of PGL/PCC.

Agents/circumstances to avoid: Hypoxia, cigarette smoking.

Evaluation of relatives at risk: First-degree relatives (age ≥10 years) of an individual with a known *SDHA, SDHB, SDHC, SDHD, SDHAF2,* or *MAX* pathogenic variant should be offered molecular genetic testing to clarify their genetic status to improve diagnostic certainty and reduce the need for costly screening procedures in those who have not inherited the pathogenic variant.

Genetic counseling:

The hereditary PGL/PCC syndromes are inherited in an autosomal dominant manner. Pathogenic variants in *SDHD* (PGL1) demonstrate parent-of-origin effects and generally cause disease only when the pathogenic variant is inherited from the father.

Initial data suggest that pathogenic variants in *SDHAF2* (PGL2) and *MAX* exhibit parent-of-origin effects similar to those of pathogenic variants in *SDHD*. A proband with a hereditary PGL/PCC syndrome may have inherited the pathogenic variant from a parent or have a *de novo* pathogenic variant; the proportion of cases caused by *de novo* pathogenic variants is unknown.

Each child of an individual with a hereditary PGL/PCC syndrome has a 50% chance of inheriting the pathogenic variant. An individual who inherits a *SDHD* pathogenic variant from his/her mother is at a low but not negligible risk of developing disease; each of his/her offspring is at a 50% risk of inheriting the pathogenic variant. An individual who inherits an *SDHD* pathogenic variant from his/her father is at high risk of manifesting paragangliomas and, to a lesser extent, pheochromocytomas. If the pathogenic variant in the family is known, prenatal testing for pregnancies at increased risk is possible through laboratories offering either testing for the gene of interest or custom testing.

SDHB = "BAD" -- results in high risk of malignancy and extra-adrenal sympathetic paragangliomas

SDHD = "DAD" -- Exhibits parent of origin effects

Other causes of catecholamine secreting paragangliomas