Endocrine

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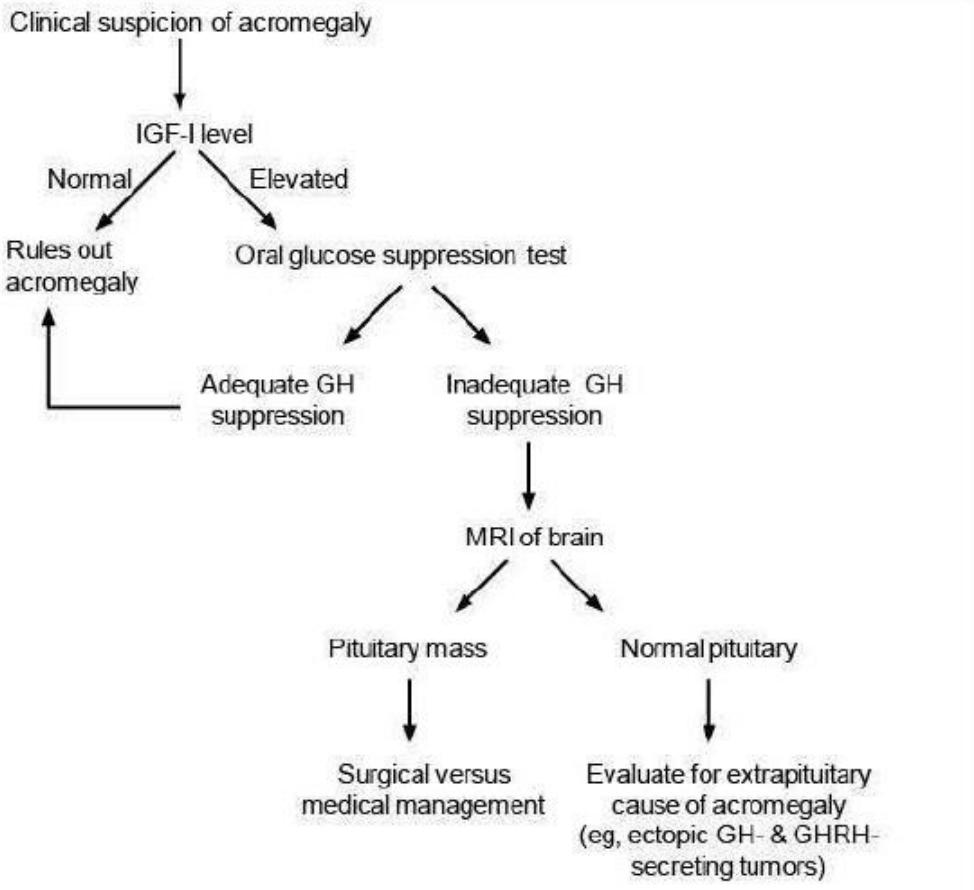

GH = growth hormone; GHRH = growth hormone-releasing hormone; IGF-1 = insulin-like growth factor 1.

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Common clinical features of untreated acromegaly	
Local tumor effect	Pituitary enlargement, visual field defects, headache, cranial nerve defects
Musculoskeletal/Skin	Gigantism, malocclusion jaw, arthralgias/arthritis, proximal myopathy, hyperhidrosis, skin tags, carpal tunnel syndrome
Cardiovascular	Cardiomyopathy, hypertension, heart failure, valvular disease (eg, mitral & aortic regurgitation)
Pulmonary / Gastrointestinal	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

Acute adrenal insufficiency (adrenal crisis)	
Etiology	• Adrenal hemorrhage or infarction • Acute illness/injury/surgery in patient with chronic adrenal insufficiency or long-term glucocorticoid use
Clinical features	• **Hypotension/shock** • Nausea, vomiting, abdominal pain • Weakness • Fever
Treatment	• **Hydrocortisone** or **dexamethasone** • High-flow intravenous fluids

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Primary versus central adrenal insufficiency		
	Primary	**Secondary**
Most common cause	Autoimmune	Chronic glucocorticoid therapy
Cortisol	↓	↓
ACTH	↑	↓
Aldosterone	↓	Normal
Clinical features	• Severe symptoms • Hyperpigmentation • Hyperkalemia • Hyponatremia • Hypotension	• Less severe symptoms • No hyperpigmentation • No hyperkalemia • Possible hyponatremia

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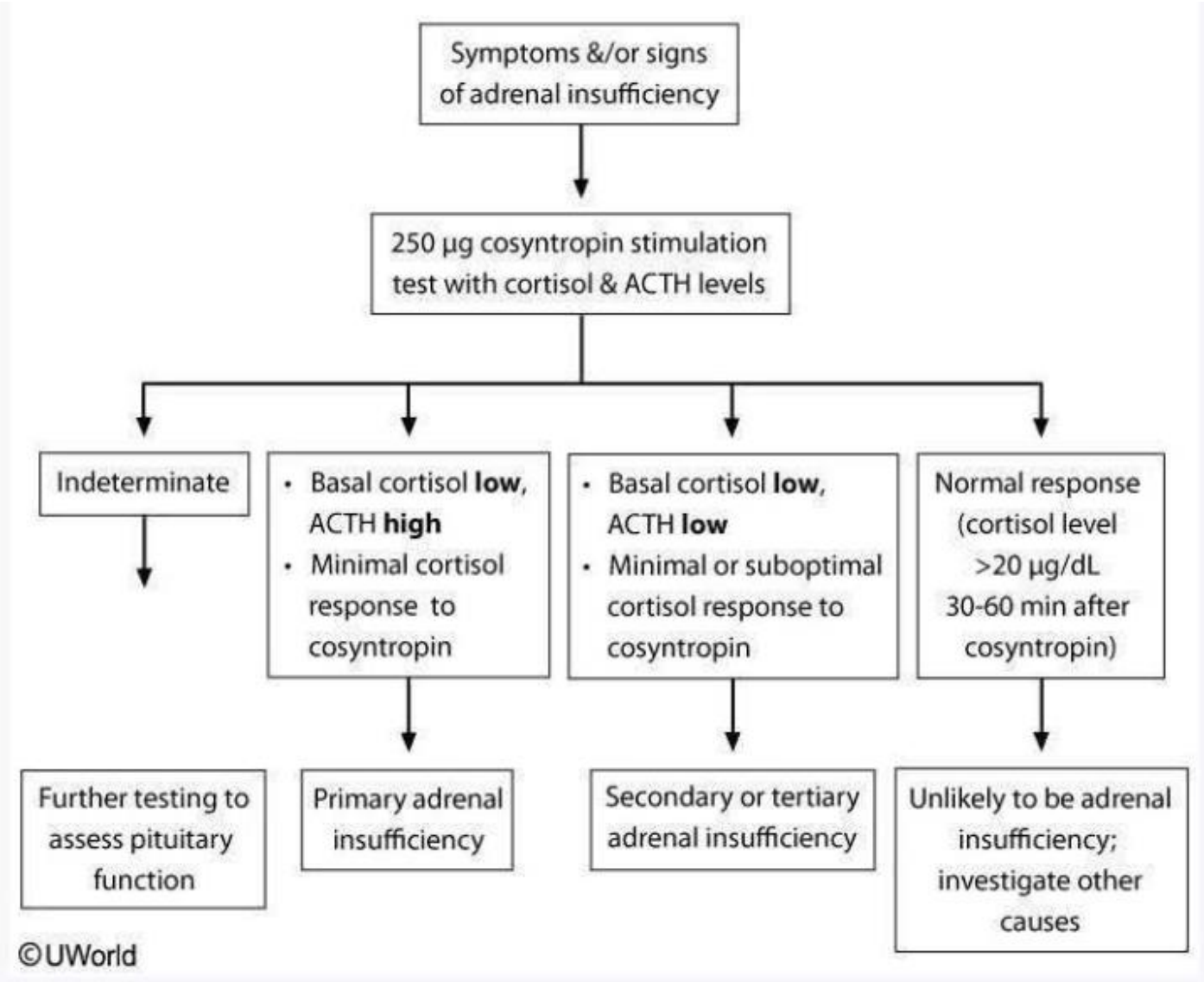
Chronic primary adrenal insufficiency	
Etiology	• **Autoimmune** • Infections (eg, tuberculosis, HIV, disseminated fungal) • Hemorrhagic infarction • Metastatic
Clinical features	• Fatigue, weakness, anorexia/weight loss, salt craving • Gastrointestinal symptoms • Postural hypotension • Hyperpigmentation or vitiligo • Hyponatremia, hyperkalemia • May lead to **acute adrenal crisis** (abdominal pain, shock, fever, altered mental status)
Diagnosis	• **ACTH**, serum **cortisol,** and high-dose (250 µg) **ACTH stimulation test** o Primary adrenal insufficiency: low cortisol, high ACTH o Secondary/tertiary adrenal insufficiency: low cortisol, low ACTH

- 
Symptoms &/or signs of adrenal insufficiency
250 µg cosyntropin stimulation test with cortisol & ACTH levels
Indeterminate
• Basal cortisol low, ACTH high
• Minimal cortisol response to cosyntropin
• Basal cortisol low, ACTH low
• Minimal or suboptimal cortisol response to cosyntropin
Normal response (cortisol level >20 µg/dL 30-60 min after cosyntropin)
Further testing to assess pituitary function
Primary adrenal insufficiency
Secondary or tertiary adrenal insufficiency
Unlikely to be adrenal insufficiency; investigate other causes
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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

- Serotonin is synthesized in carcinoid cells from tryptophan, which is also used in the production of niacin or nicotinic acid. Advanced disease results in increased tryptophan conversion to serotonin and its metabolite 5-hydroxyindoleacetic acid. This may result in tryptophan and niacin deficiency causing pellagra (with diarrhea, dermatitis, glossitis, angular stomatitis, and dementia).
- primary adrenal disease.

  The initial step in the evaluation is to confirm **hypercortisolism** with a late-night **salivary cortisol** assay, 24-hour **urine free cortisol** measurement, and/or overnight **low-dose dexamethasone suppression test**. Two of these first-line tests should be abnormal to establish the diagnosis. If hypercortisolism is confirmed, ACTH levels are measured to differentiate ACTH-dependent (ie, Cushing disease, ectopic ACTH) from ACTH-independent (eg, adrenal adenoma) causes **(Choice C)**.
- This patient has several features suggesting **Cushing syndrome** (hypercortisolism). Weight gain, proximal muscle weakness, and hypertension are common presenting findings. Patients can experience easy **bruisability**, dermal atrophy, and wide purple striae due to the catabolic effects of cortisol on connective tissue; however, platelet function and coagulation proteins are normal. Dermatologic signs may include **hyperpigmentation** (in ACTH-dependent Cushing syndrome) and increased incidence of cutaneous fungal infections (eg, tinea versicolor, onychomycosis). Women can have features of **hyperandrogenism** (eg, menstrual irregularities, acne, hirsutism) due to co-secretion of adrenal androgens with cortisol.
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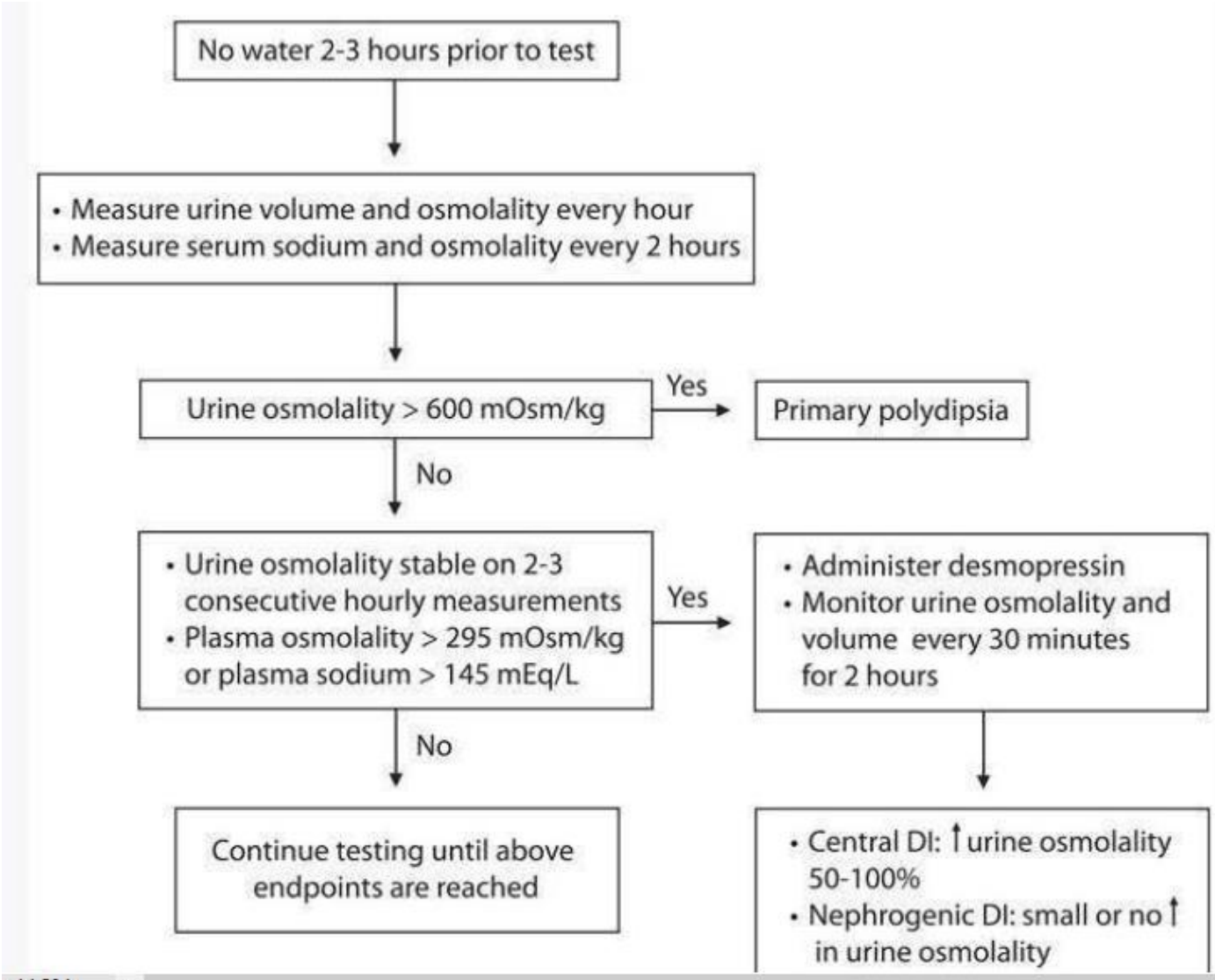
Glucocorticoid-induced myopathy	• Progressive proximal muscle **weakness** & atrophy **without pain** or tenderness • Lower-extremity muscles are more involved	Normal	Normal
Polymyalgia rheumatica	• Muscle **pain & stiffness** in the shoulder & pelvic girdle • Tenderness with decreased range of motion 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	Normal	↑



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DI can be central (decreased antidiuretic hormone [ADH] secretion from the pituitary) or nephrogenic (normal ADH levels with renal ADH resistance). Central DI patients usually do not have an intact thirst mechanism and can have serum sodium >150 mEq/L. Nephrogenic DI patients usually have an intact thirst mechanism with lower serum sodium (~145 mEq/L). However, some cases may not be clinically obvious. A water deprivation test can distinguish between central and nephrogenic DI and also definitively exclude primary polydipsia.

ADH-related causes of polyuria & polydipsia			
	Primary polydipsia	**Central DI**	**Nephrogenic DI**
Defect	↑ Water intake	↓ ADH release from pituitary	ADH resistance in kidney
Etiology	• Antipsychotics • Anxious, middle-age women	• Idiopathic • Trauma • Pituitary surgery • Ischemic encephalopathy	• Chronic lithium use • Hypercalcemia • Hereditary (*AVPR2* mutations)
Clinical features	Low serum Na	High serum Na	Normal serum Na

Diabetes mellitus increases the risk for cardiovascular events, renal disease, and blindness. The prevalence of diabetes in the United States is increasing. However, current guidelines differ regarding screening for diabetes in asymptomatic patients:

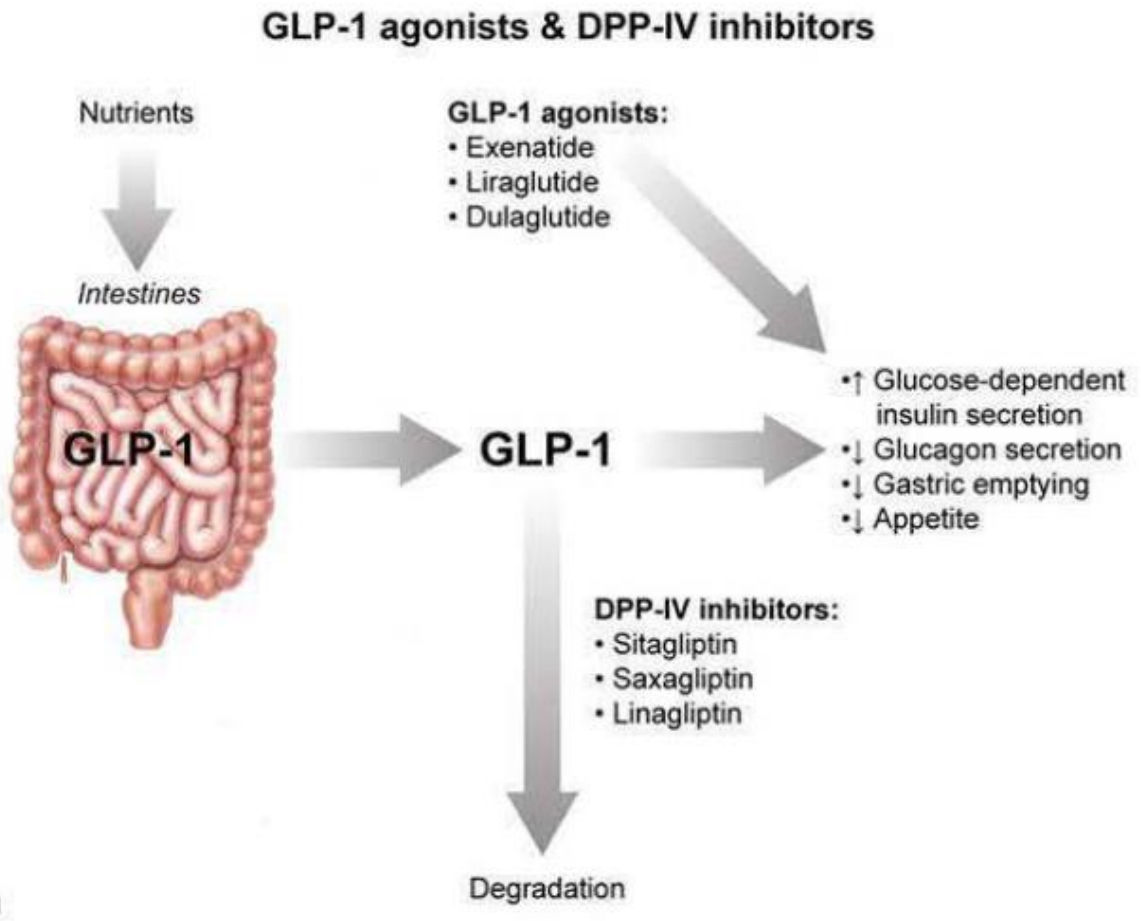
- The **US Preventive Services Task Force (USPSTF)** recommends screening in patients with sustained blood pressure (treated or untreated) >135/80 mm Hg. However, there is insufficient evidence to establish the benefits of screening patients with blood pressure ≤135/80 mm Hg.
- The **American Diabetes Association** recommends screening in all patients age ≥45 years, as well as those at any age with additional risk factors for diabetes.

(Choice E) The 13-valent pneumococcal conjugate vaccine (PCV13) is recommended for all adults age ≥65, followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV23) 6-12 months later. Sequential PCV13 and PPSV23 are also recommended for adults age <65 with certain very high-risk underlying conditions (eg, cerebrospinal fluid leaks, sickle cell disease, cochlear implants, congenital or acquired asplenia, immunocompromised status, chronic renal failure). PPSV23 alone is recommended for adults age <65 who are current smokers or have certain chronic medical conditions, including heart or lung disease, diabetes, and chronic liver disease.

Diabetes risk factors in adults with BMI >25 kg/m^2
• Physical inactivity • First-degree relative with diabetes • High-risk race/ethnicity (eg, African American, Latino, Native American, Asian, Pacific Islander) • Women whose children's birth weight ≥9 lb • History of gestational diabetes mellitus • Hypertension or prior cardiovascular disease • Dyslipidemia (low HDL & high triglyceride level) • History of polycystic ovarian syndrome • History of glucose intolerance

A_{1c}	• Preferred test in nonfasting state • ≥6.5% = Diabetes mellitus • 5.7-6.4% = Increased risk for diabetes • <5.7% = Normal
Fasting blood glucose	• No caloric intake for >8 hours • **≥126 mg/dL** = Diabetes mellitus • 100-125 mg/dL = Increased risk for diabetes • <100 mg/dL = Normal
Random glucose levels	• **≥200 mg/dL** with symptoms of hyperglycemia = Diabetes mellitus • 140-199 mg/dL = Increased risk for diabetes • <140 mg/dL = Normal
Oral glucose tolerance test	• Most sensitive test • 75 g glucose load with glucose testing for 2 hours • **≥200 mg/dL** = Diabetes mellitus • 140-199 mg/dL= Increased risk for diabetes • <140 mg/dL = Normal
• Testing may be repeated in cases of discordant or equivocal results • If a patient is asymptomatic, a positive test should be reconfirmed with the same test on a different day	

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



- Intensive blood pressure (BP) control is the primary intervention proven to slow the decline in GFR once azotemia develops. Most patients with diabetes mellitus should be treated toward a target BP of 140/90 mm Hg, and patients with diabetic nephropathy may benefit from more intensive BP control. Most guidelines now recommend a target BP of 130/80 mm Hg for patients who are diabetic with signs of nephropathy. Angiotensin-converting enzyme (ACE) inhibitors, and perhaps angiotensin receptor blockers (ARBs), are the preferred antihypertensive drugs for patients with diabetes mellitus. These drugs may have actions in addition to BP control, such as reducing intraglomerular pressure, which may be renoprotective. However, ACE inhibitors or ARBs in patients with diabetic nephropathy must be initiated carefully as they may induce an acute decline in GFR and hyperkalemia.

- **(Choice D)** Intensive glycemic management (Hb_{A1c} <7.0%) has been shown to reduce the occurrence and progression of microalbuminuria. However, a more aggressive reduction of glycemic control beyond this target is associated with an increased risk for hypoglycemia and may actually increase the risk for cardiac events.

  (Choice E) Animal studies have found that dietary restriction of protein results in a decrease in protein excretion, as well preservation of GFR; however, studies in humans are conflicting. Generally, a diet consisting of 0.8 g/kg/day of protein is recommended for patients with diabetic nephropathy and azotemia.

JNC 8 recommendations for treating hypertension		
	Initiate Rx	**Goal blood pressure**
Age ≥60	≥150 mm Hg systolic BP **or** >90 mm Hg diastolic BP	<150/90 mm Hg
Age <60, chronic kidney disease, diabetes	≥140 mm Hg systolic BP **or** >90 mm Hg diastolic BP	<140/90 mm Hg
Initial treatment choice	Black	Thiazide diuretic or CCB, alone or in combination (ACE/ARB not first-line)
	Other ethnicities	Thiazide diuretic, ACEI, ARB, or CCB alone or in combination
	All ethnicities with chronic kidney disease or diabetes	ACEI or ARB, alone or in combination with other drug classes

- ACEI

Drugs for neuropathic pain	
Drug	**Mechanism of action**
Tricyclic antidepressants (eg, amitriptyline, nortriptyline)	• ↓ Reuptake of serotonin & norepinephrine • Inhibition of pain signals
Anticonvulsants (eg, gabapentin, pregabalin)	• Decreased depolarization of neurons in CNS
Opioids	• Activation of central opioid receptors
Capsaicin (topical)	• Loss of membrane potential in nociceptive fibers
Lidocaine (topical)	• Decreased depolarization of neurons in peripheral nerves

Symmetric distal **sensorimotor polyneuropathy** is the most common neuropathy in patients with diabetes, and clinical features depend on the type of nerve fibers involved.

- **Small fiber** injury is characterized by predominance of **positive symptoms** (eg, pain, paresthesias, allodynia) **(Choice B)**.
- **Large fiber** involvement is characterized by predominance of **negative symptoms** (eg, numbness, loss of proprioception and vibration sense, diminished ankle reflexes).

Effect of intensive glycemic control in type 2 diabetes	
Macrovascular complications (eg, acute myocardial infarction, stroke)	No change (possible long-term ↓)
Microvascular complications (eg, nephropathy, retinopathy)	↓
Mortality	No change (A1c 6%-7%) ↑ (A1c <6%)

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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;

- The best markers indicating resolution of **ketonemia** are the **serum anion gap** and direct assay of **beta-hydroxybutyrate (BH)**, which is the predominant ketone in DKA. The anion gap estimates the unmeasured anion concentration in the blood and returns to normal with the elimination of ketoacid anions. BH is converted to acetoacetate and acetone, which can be measured by the commonly used nitroprusside test, but this test does not detect BH itself. Therefore, either calculation of the anion gap or direct assay of serum BH is recommended to follow ketonemia **(Choice A)**. A rise in serum bicarbonate and arterial pH provides further confirmation of the improvement in acidosis.

- This patient's symptoms are suggestive of diabetic autonomic neuropathy of the gastrointestinal tract, with predominant symptoms of delayed gastric emptying, or gastroparesis. Diabetic autonomic neuropathy occurs in >50% of patients with longstanding type 1 or 2 diabetes mellitus and can manifest as disorders of esophageal motility (eg, dysphagia), gastric emptying (eg, gastroparesis), or intestinal function (eg, diarrhea, constipation, incontinence). Gastroparesis presents with symptoms of anorexia, nausea, vomiting, early satiety, or postprandial fullness. Hypoglycemic episodes can occur with insulin administration prior to meals in patients with impaired gastric emptying or delayed absorption.

  Treatment of patients with diabetic gastroparesis includes a combination of optimizing diabetes control; dietary modifications with increased fiber intake and **small, frequent meals**; and medications to improve gastric emptying. **Metoclopramide** has both prokinetic and antiemetic properties and is useful for symptomatic relief of nausea, bloating, and postprandial fullness in patients with diabetic gastroparesis. The use of metoclopramide can be associated with a small (<1%) risk of extrapyramidal side effects (eg, tardive dyskinesia). Other alternate therapeutic options include **erythromycin** (more useful when used intravenously for acute exacerbations) and cisapride (restricted use in the United States due to the risk of cardiac arrhythmias and death).

- **(Choice D)** Progesterone analogs (eg, megestrol acetate, medroxyprogesterone acetate) are useful in the palliation of anorexia and in improving appetite and weight gain in patients with cancer-related anorexia/cachexia syndrome. They have no role in the treatment of patients with diabetic gastroparesis.

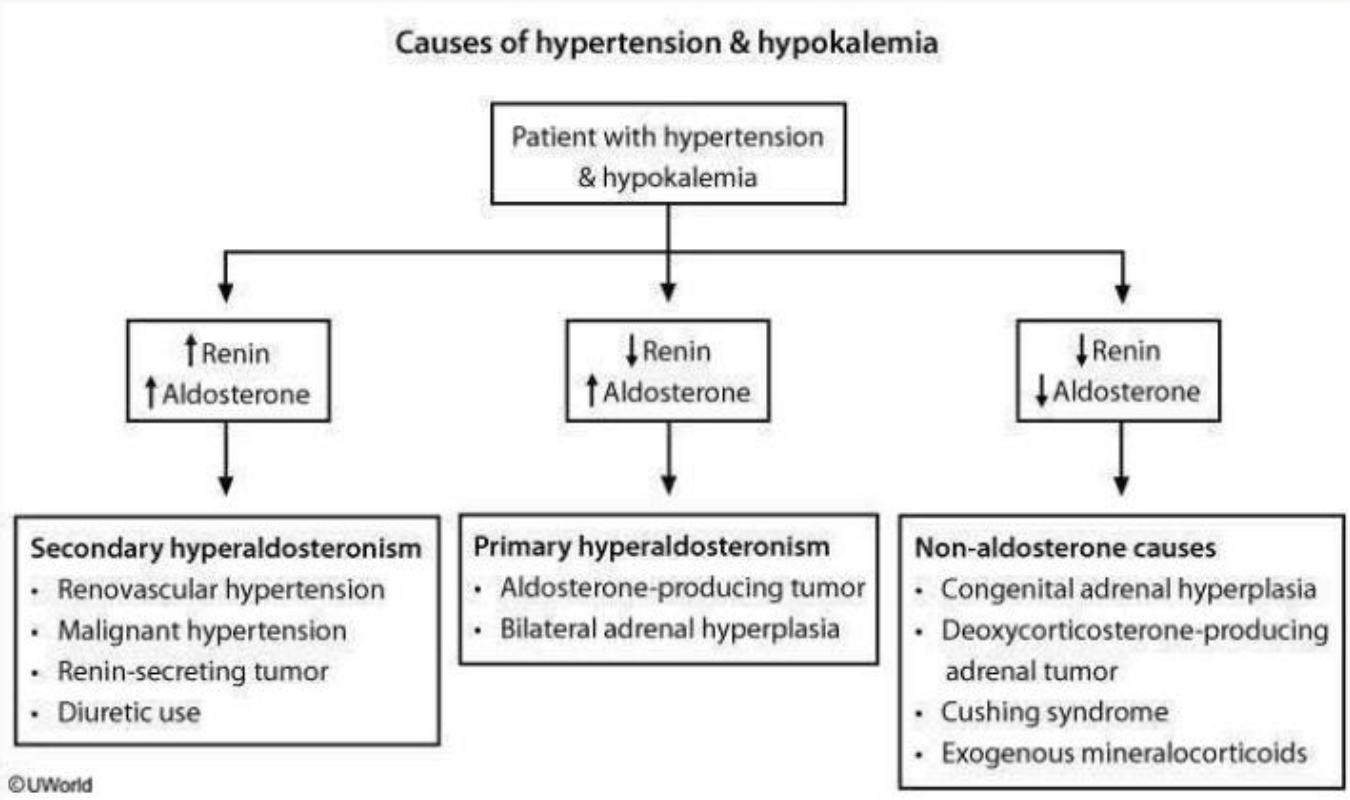
Clinical features of glucagonoma	
Clinical presentation	**Necrolytic migratory erythema** • Erythematous papules/plaques on face, perineum, extremities • Lesions enlarge & coalesce over next 7-14 days with central clearing & blistering, crusting & scaling at borders **Diabetes mellitus** • Mild hyperglycemia easily controlled with oral agents & diet • Usually does not require insulin **Gastrointestinal symptoms** • Diarrhea, anorexia, abdominal pain, or occasional constipation **Other findings** • Weight loss • Neuropsychiatric (eg, ataxia, dementia, proximal muscle weakness) • Association with venous thrombosis
Diagnosis	• Hyperglycemia with elevated glucagon >500 pg/mL • Normocytic, normochromic anemia due to likely anemia of chronic disease or glucagon directly affecting erythropoiesis • Abdominal imaging (computed tomography or magnetic resonance imaging) to localize tumor &/or metastases

- The liver maintains glucose levels in the blood via **glycogenolysis** and **gluconeogenesis**. During fasting states, glycogen reserves drop dramatically in the firs 12 hours, by which time gluconeogenesis starts to play an important role. After 24 hours, gluconeogenesis represents the sole source of glucose production. The main substrates for gluconeogenesis are **gluconeogenic amino acids** (from breakdown of muscle protein), **lactate** (from anaerobic glycolysis), and **glycerol 3-phosphate** (from triacylglycerol in adipose). Alanine is the major gluconeogenic amino acid in the liver, and it is converted into pyruvate by alanine aminotransferase. Pyruvate is eventually converted to glucose through a series of reactions, and free glucose is then released into the bloodstream.

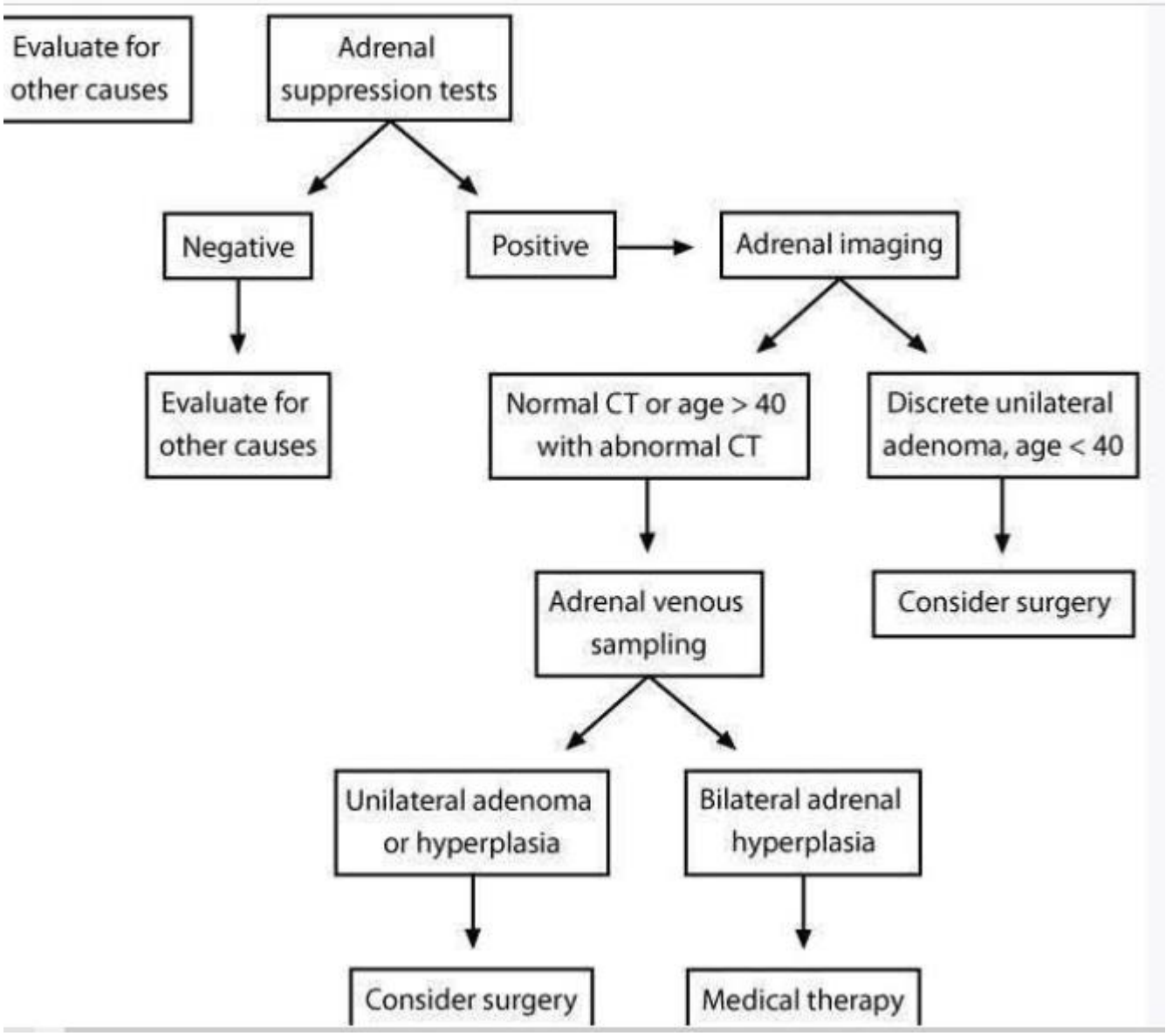
Major drug interactions of levothyroxine	
↓ levothyroxine absorption	• Bile acid binding agents (e.g., cholestyramine) • Iron, calcium, aluminum hydroxide • Proton pump inhibitors, sucralfate
↑ TBG concentration	• Estrogen (oral), tamoxifen, raloxifene • Heroin, methadone
↓ TBG concentration	• Androgens,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

- Transdermal estrogen bypasses the liver and does not affect TBG levels.

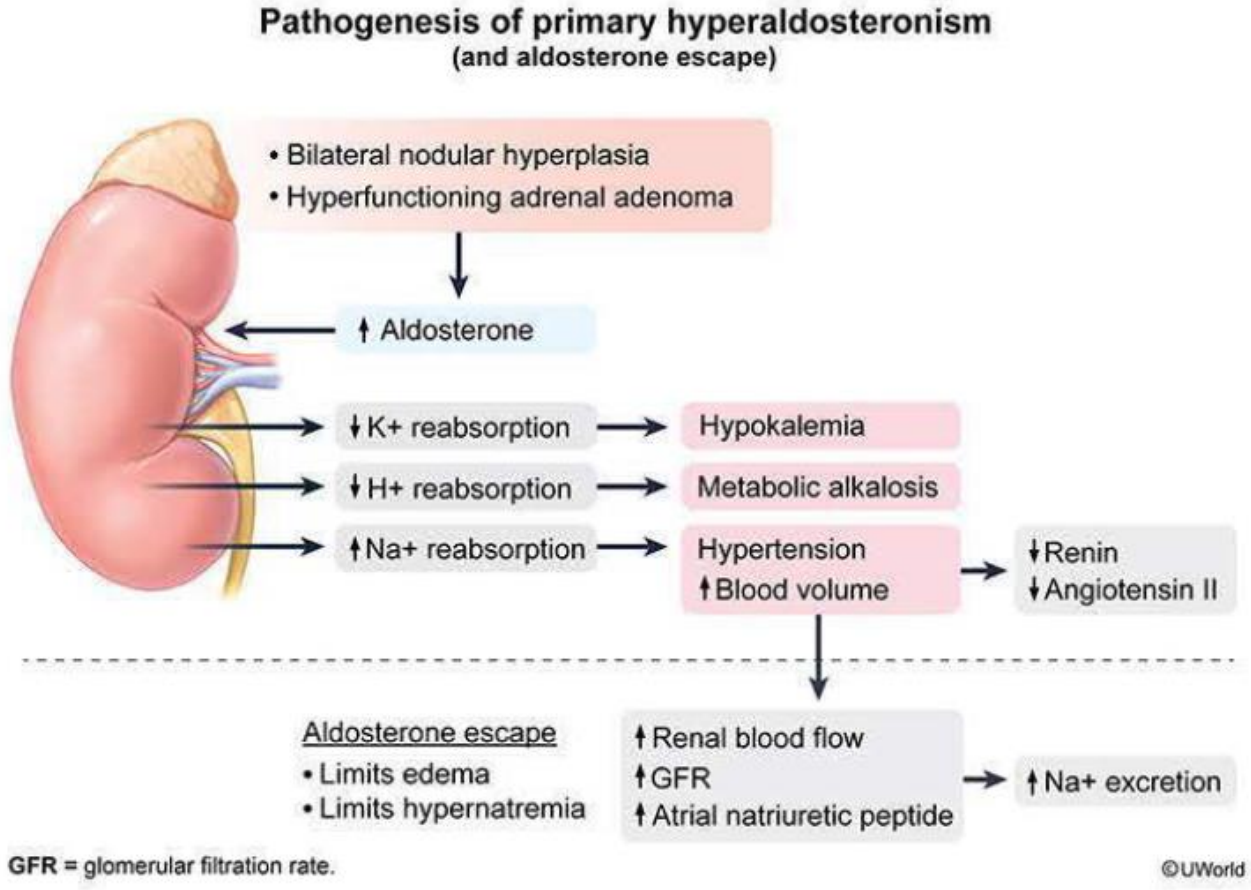
Clinical features of primary hyperaldosteronism	
Clinical presentation	• Hypertension, metabolic alkalosis, hypokalemia, mild hypernatremia • No significant peripheral edema due to aldosterone escape
Diagnosis	• Elevated plasma aldosterone, low plasma renin • Plasma aldosterone to plasma renin activity 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



- **(Choices A and D)** Aldosterone increases sodium reabsorption (saves sodium), potassium secretion, and hydrogen secretion in the distal renal tubules. The sodium reabsorption also leads to water absorption. However, this is countered in a few days by a spontaneous diuresis that lowers the water and sodium (aldosterone escape). This returns the volume status to slightly above normal and results in mild hypernatremia (143-147 mEq/L) without significant peripheral edema. The hypokalemia directly increases renal bicarbonate resorption, which, combined with increased hydrogen secretion, results in metabolic alkalosis.

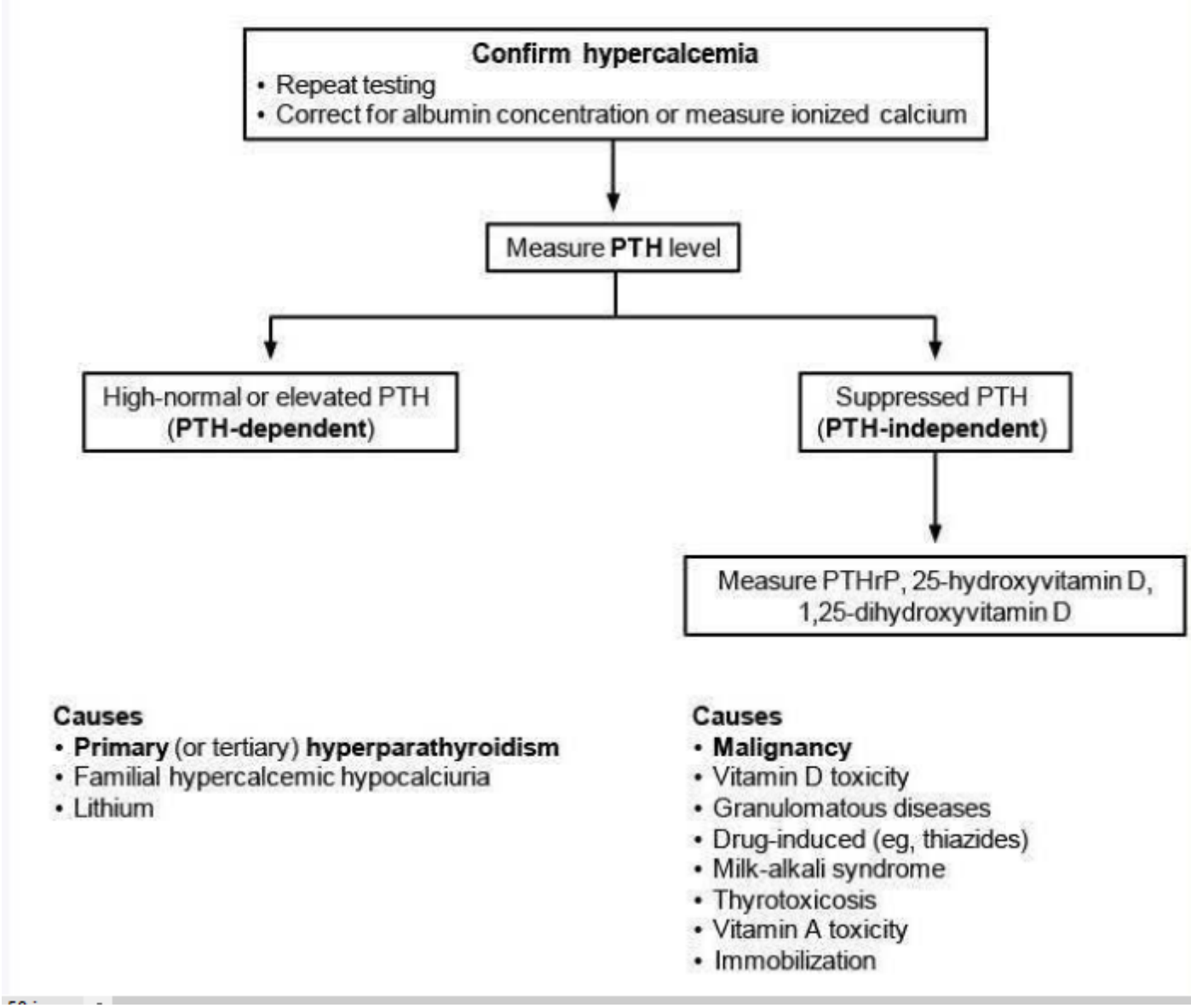
- 
Evaluate for other causes
Adrenal suppression tests
Negative
Positive
Adrenal imaging
Evaluate for other causes
Normal CT or age > 40 with abnormal CT
Discrete unilateral adenoma, age < 40
Adrenal venous sampling
Consider surgery
Unilateral adenoma or hyperplasia
Bilateral adrenal hyperplasia
Consider surgery
Medical therapy

Multiple endocrine neoplasia type 1	
Organ/System	**Clinical features**
Pituitary adenomas (10%-20%)	Pituitary tumors that are prolactin secreting, growth hormone secreting, ACTH secreting, or non-hormone secreting
Primary **hyperparathyroidism** (>90%)	• Multiple parathyroid adenomas or parathyroid hyperplasia • Hypercalcemia (asymptomatic or associated with polyuria, kidney stones, or decreased bone density)
Pancreas/GI tract (60%-70%)	• **Gastrinoma** - recurrent peptic ulcers • Insulinoma - hypoglycemia • VIPoma - secretory diarrhea, hypokalemia, hypochlorhydria • Glucagonoma - weight loss, necrolytic migratory erythema, hyperglycemia



Milk-alkali syndrome	
Pathophysiology	• Excessive intake of **calcium & absorbable alkali** • Renal vasoconstriction & decreased GFR • Renal loss of sodium & water, reabsorption of bicarbonate
Symptoms	• Nausea, vomiting, constipation • Polyuria, polydipsia • Neuropsychiatric symptoms
Laboratory findings	• Hypercalcemia • Metabolic alkalosis • Acute kidney injury • Suppressed PTH
Treatment	• Discontinuation of causative agent • Isotonic saline followed by furosemide

GFR = glomerular filtration rate; PTH = parathyroid hormone.



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- Corrected Ca = Serum Ca+ (0.8*(4-Serum Albumin))

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

	Diabetic ketoacidosis	**Hyperosmolar hyperglycemic state**
Patient characteristics	• Type 1 diabetics usually • Younger age	• Type 2 diabetics usually • Older age
Clinical symptoms	• Less pronounced altered mentation • More rapid onset of hyperglycemic symptoms • Hyperventilation & abdominal pain common	• More pronounced altered mentation • Gradual onset of hyperglycemic symptoms • Hyperventilation & abdominal pain less common
Laboratory studies	• Glucose 250-500 mg/dL • Bicarbonate <18 mEq/L • Elevated anion gap • Positive serum ketones • Serum osmolality <320 mOsm/kg	• Glucose >600 mg/dL • Bicarbonate >18 mEq/L • Normal anion gap • Negative or small serum ketones • Serum osmolality >320 mOsm/kg

space. Despite normal serum levels, patients with HHS or DKA have a total body potassium deficit (3–5 mg/kg) due to excessive urinary loss caused by osmotic diuresis induced by hyperglycemia. The clinical implication of potassium depletion is that insulin therapy for HHS can abruptly lower serum potassium levels and cause severe hypokalemia.

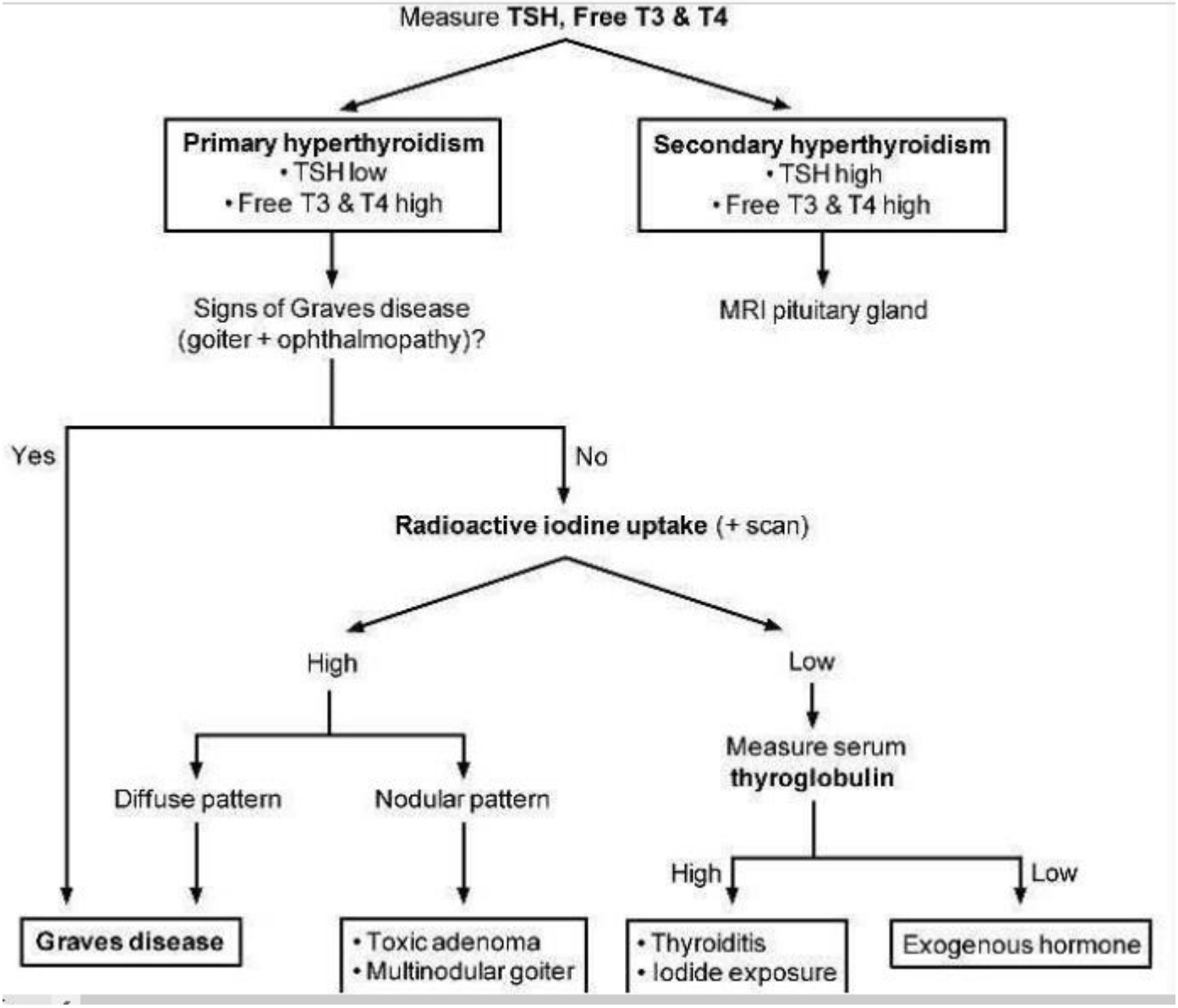
Primary hyperparathyroidism	
Etiology	• **Parathyroid adenoma** (most common), hyperplasia, carcinoma • Increased risk in MEN types 1 & 2A
Symptoms	• **Asymptomatic** (most common) • Mild, nonspecific symptoms (eg, fatigue, constipation) • Abdominal pain, renal stones, bone pain, neuropsychiatric symptoms
Diagnostic findings	• **Hypercalcemia** • **Elevated or inappropriately normal PTH** • Elevated 24-hour urinary calcium excretion
Parathyroidectomy indications	• Age <50 • **Symptomatic hypercalcemia** • **Complications:** Osteoporosis, nephrolithiasis/calcinosis, CKD • **Elevated risk of complications:** Calcium ≥1 mg/dL above normal, urinary calcium excretion >400 mg/day

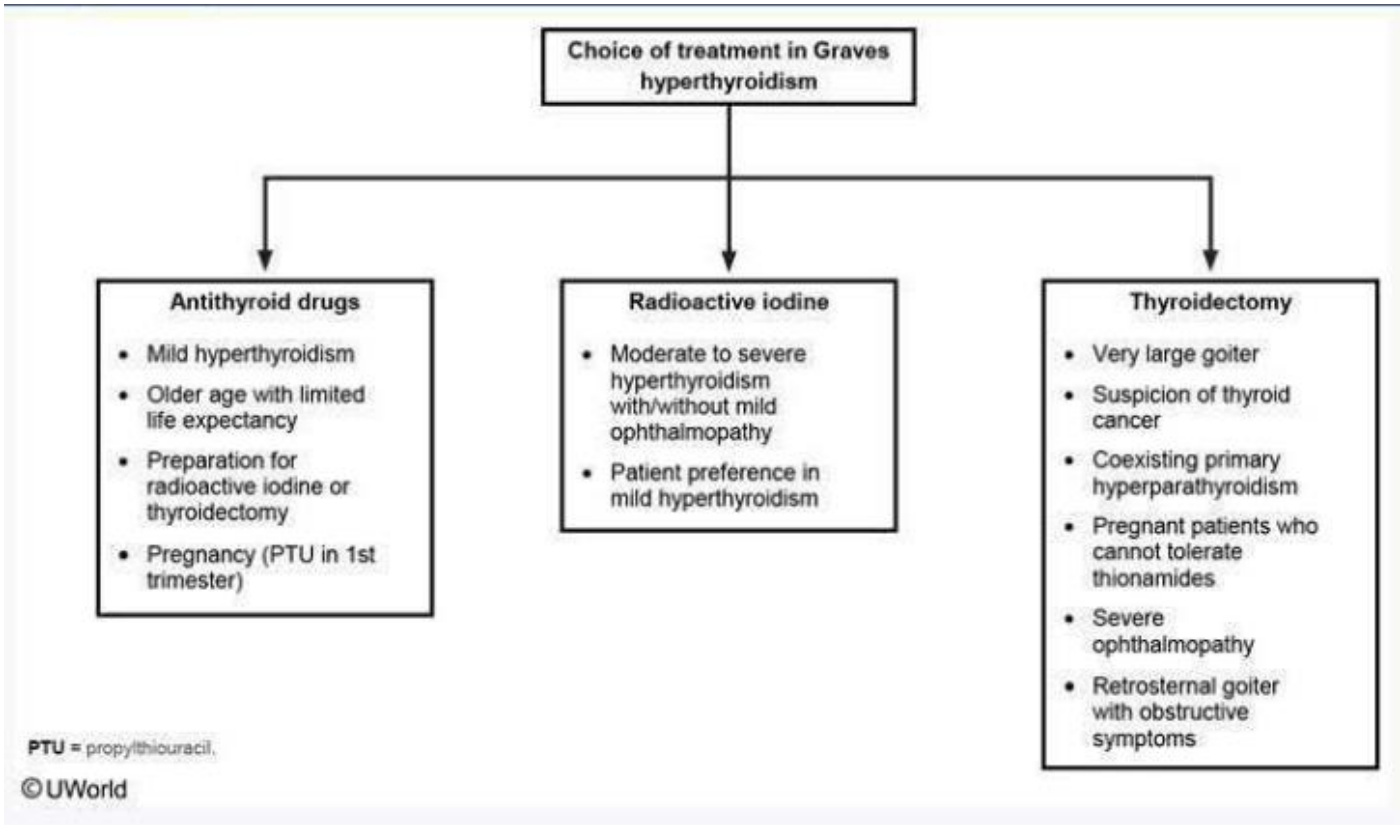
Neonatal thyrotoxicosis	
Pathophysiology	• Transplacental passage of maternal anti-TSH receptor antibodies • Antibodies bind to infant's TSH receptors & cause excessive thyroid hormone release
Clinical features	• Warm, moist skin • Tachycardia • Poor feeding, irritability, poor weight gain • Low birth weight or preterm birth
Diagnosis	• Maternal anti-TSH receptor antibodies ≥500% normal
Treatment	• Self-resolves within 3 months (disappearance of maternal antibody) • Methimazole PLUS β blocker

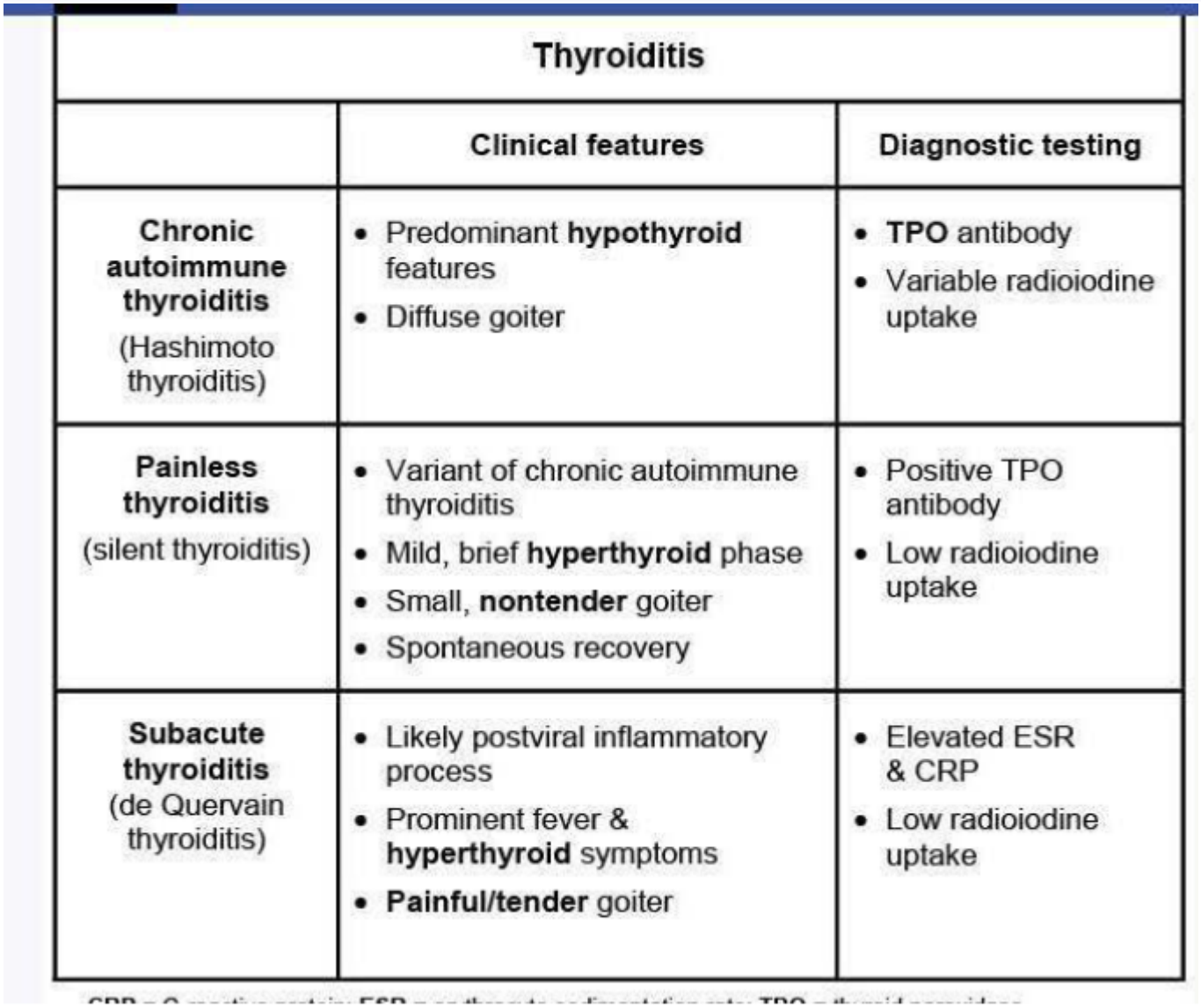
- Maternal anti-TSH measured at 22 wks of gestation
- Current recommendations state that once the patient complains of fever and sore throat, the antithyroid drug .should be discontinued promptly and the WBC count measured. A total WBC count Jess than 1 ,000/cubic mm warrants permanent discontinuation of the drug. If the total WBC count is more than 1 ,500 per cubic mm, antithyroid drug toxicity is unlikely to be the cause of the sore throat and fever.

Treatment of Graves disease	
Treatment	**Adverse effects**
Antithyroid drugs (thionamides)	• **Agranulocytosis** • Methimazole: 1st-trimester teratogen, cholestasis • Propylthiouracil: **Hepatic failure**, ANCA-associated vasculitis
Radioiodine ablation	• Permanent hypothyroidism • Worsening of ophthalmopathy • Possible radiation side effects
Surgery	• Permanent hypothyroidism • Risk of recurrent laryngeal nerve damage • Risk of hypoparathyroidism

ANCA = antineutrophilic cytoplasmic antibodies.

- The most common side effect of ATDs is allergic reaction (2% of patients). The most serious side effect is agranulocytosis (0.3% of patients), and all patients must be informed about it.
- 

- 

- 

Thyroiditis

	Clinical features	Diagnostic testing
Chronic autoimmune thyroiditis (Hashimoto thyroiditis)	• Predominant **hypothyroid** features • Diffuse goiter	• **TPO** antibody • Variable radioiodine uptake
Painless thyroiditis (silent thyroiditis)	• Variant of chronic autoimmune thyroiditis • Mild, brief **hyperthyroid** phase • Small, **nontender** goiter • Spontaneous recovery	• Positive TPO antibody • Low radioiodine uptake
Subacute thyroiditis (de Quervain thyroiditis)	• Likely postviral inflammatory process • Prominent fever & **hyperthyroid** symptoms • **Painful/tender** goiter	• Elevated ESR & CRP • Low radioiodine uptake

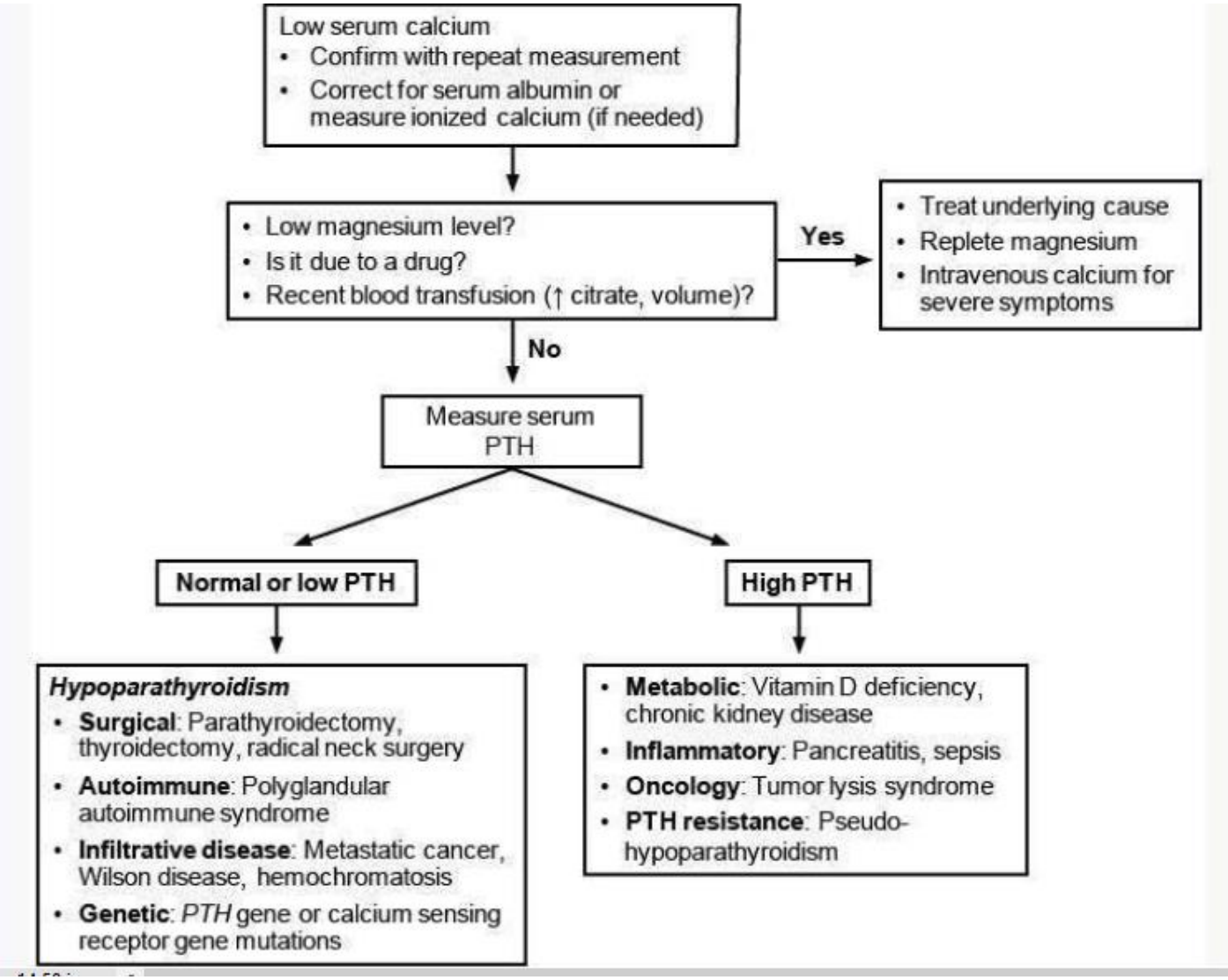
- Many TSH-secreting pituitary adenomas overproduce the alpha-subunit. and an elevated ratio of alpha-subunit to TSH suggests a pituitary adenoma.

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

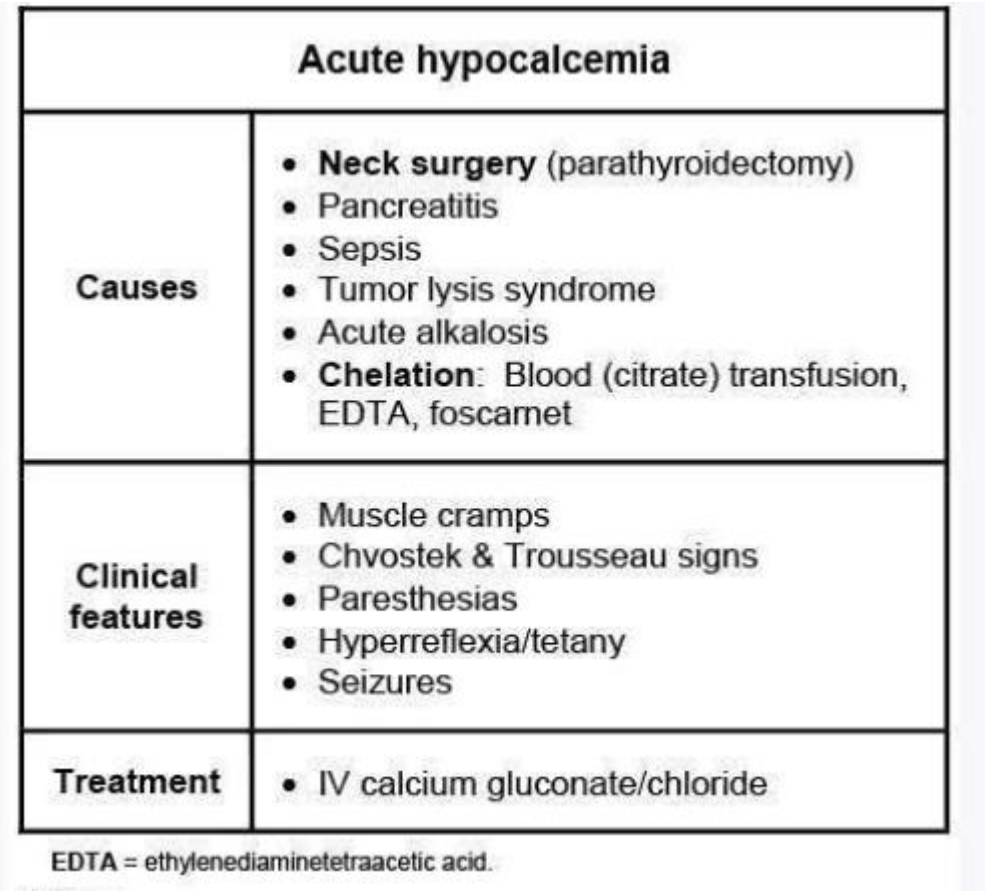
Thyrotoxicosis with normal or ↑ RAIU	Thyrotoxicosis with ↓ RAIU
• **Graves disease** • Toxic multinodular goiter • Toxic nodule	• **Painless (silent) thyroiditis** • **Subacute (de Quervain) thyroiditis** • Amiodarone-induced thyroiditis • Excessive dose (or surreptitious intake) of levothyroxine • Struma ovarii • Iodine-induced • Extensive thyroid cancer metastasis
RAIU = radioactive iodine uptake.	

Clinical manifestations of Graves disease	
General	Heat intolerance, weight loss, sweating
Eyes	Lid lag, **proptosis**, diplopia
Skin	Hair loss, **infiltrative dermopathy** (pretibial myxedema)
Cardiovascular	Tachycardia, hypertension, atrial fibrillation
Nails	Onycholysis, clubbing (acropachy)
Endocrine	Hyperglycemia, hypercalcemia, bone loss, menstrual irregularities
Gastrointestinal	Diarrhea
Neurology	Tremors, hyperreflexia, proximal muscle weakness

Cardiovascular effects of thyrotoxicosis	
Rhythm	• Sinus tachycardia • Premature atrial & ventricular complexes • **Atrial fibrillation**/flutter
Hemodynamic effects	• **Systolic hypertension** & ↑pulse pressure • ↑Contractility & cardiac output • ↓Systemic vascular resistance • ↑**Myocardial oxygen demand**
Heart failure	• High-output failure • Exacerbation of pre-existing low-output failure
Angina symptoms	• Coronary vasospasm • Pre-existing coronary atherosclerosis



- Hypomagnesemia is very common in hospitalized alcoholics and can cause hypocalcemia by inducing resistance to parathyroid hormone (PTH) as well as by decreasing PTH secretion. The cause of hypomagnesemia in alcoholics is multifactorial, and may include urinary losses, malnutrition, acute pancreatitis, and diarrhea.



Acute hypocalcemia	
Causes	• **Neck surgery** (parathyroidectomy) • Pancreatitis • Sepsis • Tumor lysis syndrome • Acute alkalosis • **Chelation**: Blood (citrate) transfusion, EDTA, foscarnet
Clinical features	• Muscle cramps • Chvostek & Trousseau signs • Paresthesias • Hyperreflexia/tetany • Seizures
Treatment	• IV calcium gluconate/chloride

EDTA = ethylenediaminetetraacetic acid.

- Hypocalcemia is uncommon following blood transfusion in patients with normal liver function as citrate is rapidly metabolized by the liver; however, this patient likely has hepatic dysfunction due to the liver laceration as well as ischemic liver injury due to hypotension. Other infused substances that can chelate calcium in the blood include lactate, foscarnet, and sodium ethylenediaminetetraacetic acid (EDTA).

(Choice D) Hypomagnesemia (not hypermagnesemia) can present similarly to hypocalcemia. Severe hypermagnesemia causes hyporeflexia, paralysis, apnea, and cardiac arrest. Rarely, very severe hypermagnesemia can cause hypocalcemia by inhibiting parathyroid hormone release, but this would typically be seen with infusions of magnesium, such as in the treatment of severe preeclampsia and eclampsia.

The causes of primary hypoparathyroidism include:

1. Post-surgical (most common cause)
2. Autoimmune
3. Congenital absence or maldevelopment of the parathyroid glands (eg, DiGeorge syndrome)
4. Defective calcium-sensing receptor on the parathyroid glands
5. Non-autoimmune destruction of the parathyroid gland due to infiltrative diseases such as hemochromatosis, Wilson disease, and neck irradiation

In normal individuals, a blood glucose level below 60 mg/dL results in near-complete suppression of insulin secretion. The patient in this vignette thus presents with hypoglycemia and inappropriately elevated serum insulin levels.

There are two important causes of hypoglycemia in non-diabetic patients with elevated insulin levels:

1. insulinoma (beta cell tumor)
2. surreptitious use of insulin or sulfonylurea

Elevated C-peptide levels and proinsulin levels greater than 5 pmol/L are seen in patients with beta cell tumors; therefore, this is the most likely diagnosis.

- **(Choice B)** Non-beta cell tumors, typically large mesenchymal tumors, can lead to hypoglycemia independent of insulin. Such tumors produce insulin-like growth factor II (IGF II), which has an insulinomimetic action after binding to insulin receptors. In patients with suspected non-beta cell tumors, the serum IGF II level can be measured. Patients with this condition characteristically have suppressed insulin and c-peptide levels.

  (Choice C) Sulfonylurea causes an increased output of endogenous insulin from the beta cells. Patients with sulfonylurea-induced hypoglycemia are sometimes difficult to differentiate from those with insulinoma because increased insulin and c-peptide levels are seen in both groups. Nonetheless, the proinsulin level is sometimes lower than 20% of the total insulin immunoreactivity. The diagnosis is confirmed by measuring the plasma sulfonylurea level.

  (Choice D) Exogenous insulin-induced hypoglycemia is associated with very high serum insulin levels combined with low c-peptide levels. The low c-peptide levels result from the suppression of endogenous insulin production.

	Primary (testicular disease)	Secondary (pituitary/hypothalamic disease)
Findings	• ↓ Energy/libido, ↓ body hair • Gynecomastia more likely • ↑ LH/FSH • ↓↓ Testosterone/sperm count	• ↓ Energy/libido, ↓ body hair • Gynecomastia less likely • ↓/Normal LH/FSH • ↓ Testosterone/sperm count

Causes	• Congenital
	  ○ Klinefelter syndrome
	  ○ Varicocele
	• Acquired
	  ○ Radiation
	  ○ Infection (eg, mumps)
	  ○ Trauma
	  ○ Medications (eg, alkylating agents, glucocorticoids)
	  ○ Chronic disease
		• Congenital
		  ○ Kallman syndrome
		• Gonadotropin suppression
		  ○ Hyperprolactinemia
		  ○ Glucocorticoids/opiates
		• Gonadotroph cell damage
		  ○ Benign/malignant tumors
		  ○ Pituitary apoplexy
		  ○ Infiltration (eg, hemochromatosis)
		  ○ Systemic disease

Evaluation	• Karyotype • Others based on clinical suspicion	• Prolactin • Transferrin • +/- MRI

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Clinical features of hypopituitarism	
Etiology	**Pituitary causes** • Primary (eg, adenoma) or metastatic mass • Infiltration (eg, hemochromatosis, lymphocytic hypophysitis) • Hemorrhage (pituitary apoplexy) or infarction (Sheehan syndrome) **Hypothalamic causes** • Mass lesions • Radiation therapy • Infiltration (sarcoidosis) • Trauma to skull base • Infections (tuberculosis meningitis)
Clinical presentation	**ACTH deficiency (secondary adrenal insufficiency)** • Postural hypotension, tachycardia, fatigue, weight loss, hypoglycemia, eosinophilia **Hypothyroidism (central)** • Fatigue, cold intolerance, constipation, dry skin, bradycardia, slowed deep-tendon reflexes **Gonadotropins** • Women: Amenorrhea, infertility • Men: Infertility, loss of libido

- Hypothyroidism can cause additional metabolic abnormalities such as hyperlipidemia, hyponatremia and asymptomatic elevations of creatinine kinase (usually <10x normal) and serum transaminases (aspartate aminotransferase and alanine aminotransferase). Hypercholesteremia with high low-density lipoprotein (LDL) is due primarily to decreased surface LDL receptors (type 2a hyperlipidemia) and/or decreased LDL receptor activity. Hypothyroidism can also decrease lipoprotein lipase activity to cause hypertriglyceridemia.

  Most hypothyroid patients have either hypercholesterolemia alone or combined hypertriglyceridemia and hypercholesterolemia. Isolated hypertriglyceridemia due to hypothyroidism is rare. The lipid abnormalities may take months to resolve despite adequate treatment of hypothyroidism. Statins can increase the risk of myopathy in poorly controlled hypothyroidism and should be given with caution in these patients.

(Choice B) Hypothyroidism can cause hyponatremia due to decreased free water clearance. Hypothyroidism and adrenal insufficiency must be ruled out before diagnosing the syndrome of inappropriate antidiuretic hormone. However, hypothyroidism does not usually cause hypernatremia.

(Choice C) Serum calcium is usually normal in hypothyroidism unless a patient has coexisting hypoparathyroidism (eg, polyglandular autoimmune failure or surgical complication during thyroid surgery). However, thyrotoxicosis can cause hypercalcemia and is due to increased bone resorption.

(Choices D and E) Hypothyroid patients most commonly develop normocytic, normochromic anemia due to decreased red blood cell mass. Chronic autoimmune thyroiditis may cause pernicious anemia, but some patients can have macrocytosis without megaloblastic anemia. Some hypothyroid patients may develop acquired von Willebrand syndrome with increased bleeding risk; resultant menorrhagia can sometimes cause iron deficiency anemia in women of reproductive age. However, hypothyroidism is less commonly associated with thrombocytopenia and neutropenia.

myopathy. Myopathy occurs in over one third of patients with hypothyroidism, and can range from an asymptomatic elevation in CK to myalgias, muscle hypertrophy, proximal myopathy, and rhabdomyolysis. Serum CK can be elevated for years before a patient develops clinical symptoms of hypothyroidism, and there is no clear correlation between the degree of CK elevation and severity of muscle disease. Inflammatory markers (eg, erythrocyte sedimentation rate, C-reactive protein) may be normal or mildly elevated.

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Euthyroid sick syndrome		
	Early/mild	**Prolonged/severe**
T3	↓	↓
T4	Normal	↓
TSH	Normal	↓
Reverse T3	↑	↑

This patient with low serum (total) T3, normal serum (total) T4, and normal TSH in the setting of acute illness (eg, ulcerative colitis flare treated with glucocorticoids) has **euthyroid sick syndrome** (ESS).

T4 is produced exclusively in the thyroid gland, whereas T3 is produced mainly by peripheral conversion of T4 by deiodination. ESS encompasses a variety of alterations in thyroid physiology, the most common of which is termed "**low T3 syndrome**" and is thought to be the result of **decreased conversion** of T4 to T3. Factors in acute illness that inhibit peripheral deiodination include high endogenous cortisol levels, inflammatory cytokines (eg, tumor necrosis factor), starvation, and certain medications (eg, **glucocorticoids**, amiodarone).

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(Choices A and C) Hospitalized patients, particularly those in intensive care units, can have reduced levels of plasma binding proteins (eg, thyroxine-binding protein, transthyretin, albumin). Because most T4 circulates in bound form, this leads to a significant drop in total T4 levels, although free hormone levels are unaffected. The serum (total) T4 level is normal in this patient.

(Choice D) Thyroid hormones undergo significant enterohepatic circulation, with reabsorption in the jejunum and upper ileum. Excessive fecal loss of thyroid hormone can occur in small intestinal disease (eg, Crohn disease, celiac disease). Ulcerative colitis does not directly involve the small intestine and is unlikely to affect reabsorption.

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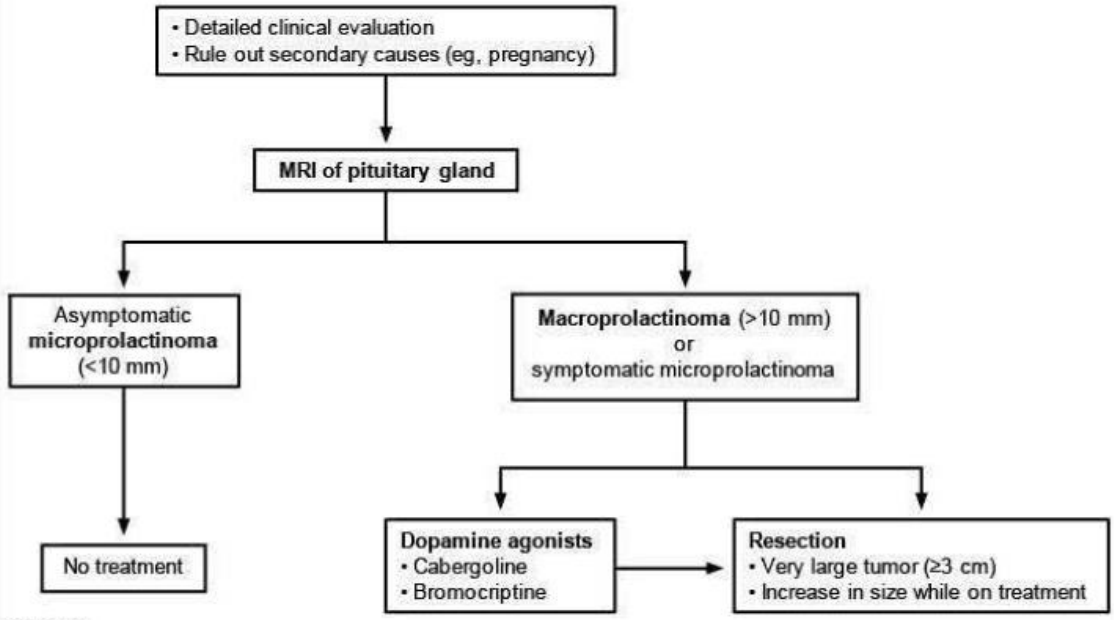
Management of hyperprolactinemia in premenopausal women



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Prolactinoma overview	
Clinical features	• **Premenopausal women**: Oligo/amenorrhea, infertility, galactorrhea, hot flashes, decreased bone density • **Postmenopausal women**: Mass effect symptoms (headache, visual field defects) • **Men**: Infertility, decreased libido, impotence, gynecomastia
Laboratory/ imaging	• Serum prolactin (often >200 ng/mL) • Rule out renal insufficiency (creatinine) & hypothyroidism (thyroid-stimulating hormone, thyroxine) • Magnetic resonance imaging of the brain/pituitary
Treatment	• Dopamine agonist (cabergoline) • Trans-sphenoidal surgery

Clinical features of VIPoma	
Clinical presentation	• **Watery diarrhea** • Hypo- or achlorhydria due to ↓ gastric acid secretion • Associated flushing, lethargy, nausea, vomiting, muscle weakness/cramps
Laboratory findings	• **Hypokalemia** (↑intestinal potassium secretion) • Hypercalcemia (increased bone resorption) • Hyperglycemia due to increased glycogenolysis • Stool studies show secretory diarrhea with ↑ sodium & osmolal gap <50 mOsm/kg
Diagnosis	• Watery diarrhea with VIP level >75 pg/mL • **Abdominal CT** or MRI to localize tumor in pancreas (usually in pancreatic tail)

Clinical features of osteomalacia	
Causes	• Malabsorption • Intestinal bypass surgery • Celiac sprue • Chronic liver disease • Chronic kidney disease
Symptoms/ signs	• May be asymptomatic • Bone pain and muscle weakness • Muscle cramps • Difficulty walking, waddling gait
Diagnosis	• ↑ Alkaline phosphatase, ↑ PTH • ↓ serum calcium and phosphorus, ↓ urinary calcium • ↓ 25 OH-D levels • X-rays may show thinning of cortex with reduced bone density • Bilateral and symmetric **pseudofractures** (Looser zones) are characteristic radiologic finding