A 39-year-old woman comes to the physician with a "pins and needles" sensation around her mouth for the last 2-3 weeks. She occasionally has similar sensations in her feet, along with muscle cramps, especially at the end of the day. Her past medical history is unremarkable, and she does not use tobacco, alcohol, or illicit drugs. Family history is not significant. Vital signs are normal, and examination is unremarkable. Laboratory findings results are as follows:

Complete blood count	
Hemoglobin	13.2 g/dL
Leukocytes	6,300/ µL
Serum chemistry	
Sodium	140 mEq/L
Potassium	4.0 mEq/L
Chloride	100 mEq/L

Bicarbonate	24 mEq/L
Blood urea nitrogen	10 mg/dL
Creatinine	0.8 mg/dL
Glucose	100 mg/dL
Calcium	6.5 mg/dL
Phosphorus	5.8 mg/dL
Total protein	7.0 g/dL
Albumin	4.0 g/dL

Which of the following is the most likely cause of this patient's condition?

A. Conversion of vitamin D to inactive metabolites

	mg/dL
Calcium	6.5 mg/dL
Phosphorus	5.8 mg/dL
Total protein	7.0 g/dL
Albumin	4.0 g/dL

Which of the following is the most likely cause of this patient's condition?

A. Conversion of vitamin D to inactive metabolites
B. Decreased secretion of parathyroid hormone
C. Impaired 1-hydroxylation of vitamin D
D. Inadequate availability of vitamin D
E. Inadequate calcium intake
F. Precipitation of calcium in soft tissues

	mg/dL
Calcium	6.5 mg/dL
Phosphorus	5.8 mg/dL
Total protein	7.0 g/dL
Albumin	4.0 g/dL

Which of the following is the most likely cause of this patient's condition?

- A. Conversion of vitamin D to inactive metabolites [0%]
- ✔ B. Decreased secretion of parathyroid hormone [73%]
- ✘ C. Impaired 1-hydroxylation of vitamin D [6%]
- D. Inadequate availability of vitamin D [10%]
- E. Inadequate calcium intake [7%]
- F. Precipitation of calcium in soft tissues [1%]

This patient's clinical features and laboratory findings are consistent with hypocalcemia caused by autoimmune primary hypoparathyroidism. Symptoms of hypocalcemia usually stem from neuromuscular irritability and manifest as perioral tingling and numbness, muscle cramps, tetany, carpopedal spasms, and seizures. Prolongation of the QT interval can also occur. If the hypocalcemia develops rapidly, as in surgical patients, the symptoms are typically more severe, even with modestly reduced serum calcium levels. However, chronic hypocalcemia may be asymptomatic even with markedly reduced serum calcium levels.

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

Post-surgical hypoparathyroidism can occur during thyroidectomy and sub-total parathyroidectomy (ie, removal of 3½ parathyroid glands for parathyroid hyperplasia). Autoimmune hypoparathyroidism is the most common nonsurgical syndrome.

(Choice A) Drugs such as phenytoin, carbamazepine, and rifampin cause vitamin D deficiency by inducing the P450 cytochrome system in the liver, which degrades vitamin D to inactive metabolites. This patient does not take any medications.

(Choice C) The kidneys are responsible for converting 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the enzyme 1-alpha-hydroxylase. Impaired 1-alpha-hydroxylation occurs with chronic kidney disease, which can lead to hyperphosphatemia, hypocalcemia, and secondary hyperparathyroidism. However, this patient's renal function appears normal.

(Choice D) Serum phosphorus is usually low in vitamin D deficiency.

(Choice E) Insufficient calcium intake induces the secretion of parathyroid hormone, causing secondary hyperparathyroidism. High parathyroid hormone levels have the following major effects on **calcium homeostasis:** increase in bone resorption with release of calcium into the circulation; increased conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in the kidneys, which stimulates gut calcium absorption; and increased renal phosphate loss resulting in **hypophosphatemia**.

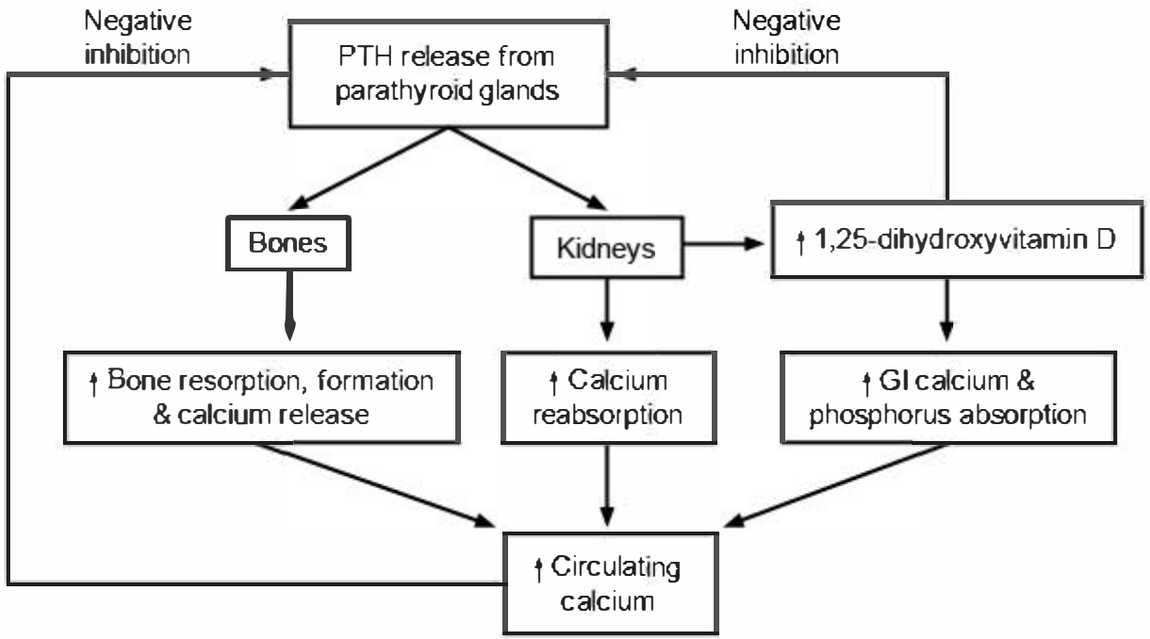
(Choice F) Precipitation of calcium with phosphate in the peripheral tissues can cause hypocalcemia, which can occur in renal failure, rhabdomyolysis, and phosphate administration. Hypocalcemia often also occurs in acute pancreatitis (due to precipitation of calcium soaps in the abdominal cavity) or in diffuse osteoblastic metastases (eg, prostate and breast cancer). This patient exhibits no signs or clinical features suggestive of these possible causes of hypocalcemia.

Educational objective:
Hypoparathyroidism (parathyroid hormone deficiency) is characterized by hypocalcemia and hyperphosphatemia in the presence of normal renal function. Causes of hypoparathyroidism include post-surgical, autoimmune and non-autoimmune parathyroid destruction, and defective calcium-sensing receptor.

2. Autoimmune

Exhibit Display

PTH, vitamin D & calcium axis



GI = gastrointestinal; **PTH** = parathyroid hormone.

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Zoom In | Zoom Out | Reset | Add To Flash Card

A 26-year-old woman comes to the office for a routine visit 6 months after the birth of her first child. Her pregnancy and vaginal delivery were uneventful and her infant is healthy; she breastfed for the first 5 months. The patient reports that during the first 2-3 months after childbirth she had excessive anxiety and worried frequently about her newborn daughter. She also felt unusually fatigued and irritable, which has worsened over the last several weeks. The patient has also experienced constipation, but her appetite is normal and she has gained 2.5 kg (5.5 lb) in the last 3 months. Blood pressure is 130/90 mm Hg and pulse is 60/min. Heart and lung sounds are normal. Mild bilateral lower extremity edema is present. Laboratory results are as follows:

Hemoglobin	12 g/dL
Serum chemistry	
Sodium	130 mEq/L
Potassium	4.2 mEq/L
Creatinine	1.1 mg/dL
Glucose	100 mg/dL
Total cholesterol	280 mg/dL

Which of the following is the best next step in management of this patient?

A. Cognitive-behavioral therapy

Hemoglobin	12 g/dL

Serum chemistry

Sodium	130 mEq/L
Potassium	4.2 mEq/L
Creatinine	1.1 mg/dL
Glucose	100 mg/dL
Total cholesterol	280 mg/dL

Which of the following is the best next step in management of this patient?

A. Cognitive-behavioral therapy
B. Echocardiography
C. Exercise and dietary modification
D. Morning serum cortisol
E. Thyroid function studies

Submit

Hemoglobin	12 g/dL

Serum chemistry

Sodium	130 mEq/L
Potassium	4.2 mEq/L
Creatinine	1.1 mg/dL
Glucose	100 mg/dL
Total cholesterol	280 mg/dL

Which of the following is the best next step in management of this patient?

- A. Cognitive-behavioral therapy [4%]
- B. Echocardiography [1%]
- C. Exercise and dietary modification [8%]
- D. Morning serum cortisol [9%]
- ✔ E. Thyroid function studies [74%]

Correct

74% Answered correctly

8 Seconds Time Spent

09/11/2018 Last Updated

Thyroiditis		
	Clinical features	**Diagnostic testing**
Chronic autoimmune thyroiditis (Hashimoto thyroiditis)	• Predominant **hypothyroid** features • Diffuse goiter	• Positive **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

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **TPO** = thyroid peroxidase.

Postpartum thyroiditis occurs in 7%-8% of women after childbirth, usually in the first 6 months. Patients can have a **brief hyperthyroid phase** due to release of preformed thyroid hormone but frequently have only mild, nonspecific symptoms (eg, anxiety [as seen in this patient], palpitations). The subsequent **hypothyroid phase** (eg, fatigue, weight gain despite normal appetite, constipation) often brings patients to medical attention.

Examination typically shows a nontender goiter, bradycardia, diastolic hypertension, lower extremity edema, and other findings (eg, coarse facies, delayed deep tendon reflex relaxation). In the hypothyroid phase, **TSH** will be elevated and **free T4** levels will be low. Other laboratory findings associated with hypothyroidism include hypercholesterolemia (due to thyroid effects on lipid metabolism) and hyponatremia.

Postpartum thyroiditis is similar to painless (silent) thyroiditis, but by convention the latter is not diagnosed within a year of childbirth. Both may be considered variants of chronic lymphocytic (Hashimoto) thyroiditis and are associated with elevated titers of **anti-thyroid peroxidase autoantibodies**. However, whereas Hashimoto thyroiditis frequently leads to permanent hypothyroidism, postpartum and painless thyroiditis are usually self-limited, and patients return to a euthyroid state over several months.

(Choice A) Postpartum thyroiditis and postpartum depression cause overlapping symptoms. Hypothyroidism should be excluded first as it is a reversible cause of depression. In general, postpartum depression is more often associated with weight loss and additional depressive symptoms (eg, anhedonia, feelings of inappropriate guilt). If thyroid function is normal, depression would be more likely.

(Choice B) Peripartum cardiomyopathy is characterized by systolic heart failure and occurs in the third trimester or first month after childbirth. It can lead to edema and hyponatremia but would not occur 6 months after pregnancy and would present with respiratory features (eg, dyspnea, orthopnea, lung crackles) and tachycardia (rather than borderline bradycardia). Hypothyroidism can cause lower extremity edema.

(Choice C) Weight gain and hypercholesterolemia in postpartum hypothyroidism usually resolve with restoration of the euthyroid state. Directed lifestyle and pharmacologic interventions are not usually needed.

thyroid function is normal, depression would be more likely.

(Choice B) Peripartum cardiomyopathy is characterized by systolic heart failure and occurs in the third trimester or first month after childbirth. It can lead to edema and hyponatremia but would not occur 6 months after pregnancy and would present with respiratory features (eg, dyspnea, orthopnea, lung crackles) and tachycardia (rather than borderline bradycardia). Hypothyroidism can cause lower extremity edema.

(Choice C) Weight gain and hypercholesterolemia in postpartum hypothyroidism usually resolve with restoration of the euthyroid state. Directed lifestyle and pharmacologic interventions are not usually needed.

(Choice D) Hypothyroidism and adrenal insufficiency can both cause hyponatremia. However, adrenal insufficiency is unlikely in this patient in light of the associated edema, weight gain, and normal blood pressure.

Educational objective:
Postpartum thyroiditis is an autoimmune disorder characterized by a possible brief hyperthyroid phase, a self-limited hypothyroid phase, and an ultimate return to a euthyroid state. It is associated with anti-thyroid peroxidase autoantibodies. Painless (silent) thyroiditis is a similar disorder, but by convention is not diagnosed within a year of childbirth.

References

- Approach to the patient with postpartum thyroiditis.

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A 66-year-old man is brought to the emergency department with dyspnea, tachypnea, crampy pain, and paresthesias in his extremities. He recently returned home after a long international flight. His temperature is 36.7 C (98.5 F), blood pressure is 120/80 mm Hg, pulse is 88/min, and respirations are 24/min. Physical examination is significant for carpopedal spasm and left calf swelling. CT scan reveals a segmental pulmonary embolus. Which of the following alterations in calcium metabolism is most likely present in this patient?

- A. Decrease in calcium bound to albumin
- B. Decrease in calcium bound to inorganic anions
- C. Decrease in total plasma calcium
- D. Increase in calcium bound to albumin
- E. Increase in calcium bound to inorganic anions
- F. Increase in total plasma calcium

Submit

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- A. Decrease in calcium bound to albumin [17%]
- B. Decrease in calcium bound to inorganic anions [9%]
- C. Decrease in total plasma calcium [16%]
- ✔ D. Increase in calcium bound to albumin [35%]
- ✘ E. Increase in calcium bound to inorganic anions [13%]
- F. Increase in total plasma calcium [7%]

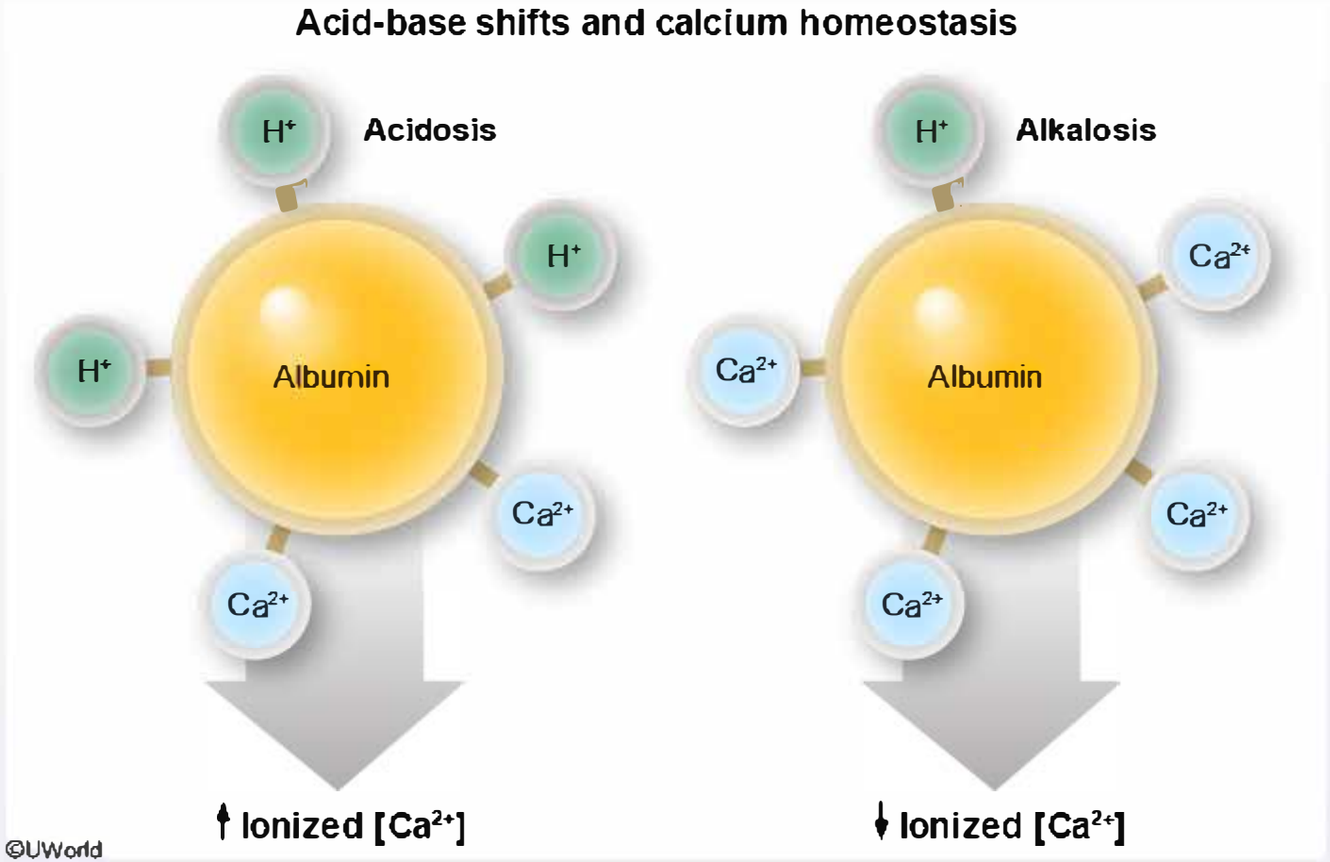
Incorrect
Correct answer
D

35%
Answered correctly

3 Seconds
TimeSpent

10/12/2018
Last Updated

Explanation



Plasma calcium exists in 3 forms: ionized calcium (45%), albumin-bound calcium (40%), and calcium bound to inorganic and organic anions (15%). Homeostasis of these forms is significantly influenced by the extracellular pH level. An increased extracellular pH (due to respiratory alkalosis in this patient) causes hydrogen ions to dissociate from albumin molecules, thereby freeing up the albumin to bind with calcium **(Choice A)**. This increase in the

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Ionized calcium is the only physiologically active form, which means that a decrease in ionized calcium can result in the clinical manifestations of hypocalcemia (eg, crampy pain, paresthesias, carpopedal spasm) even though total calcium is unchanged **(Choices C and F)**. Thus, patients can experience signs and symptoms of hypocalcemia due to respiratory alkalosis likely caused by hyperventilation, as may be seen in pulmonary embolism.

(Choices B and E) The amount of calcium bound to organic and inorganic anions remains unaltered in patients with acute respiratory alkalosis.

Educational objective:
Increased extracellular pH (eg, respiratory alkalosis) causes dissociation of hydrogen ions from albumin, allowing increased binding of calcium and a drop in unbound (ionized) calcium. Ionized calcium is the physiologically active form, and decreased levels can result in clinical manifestations of hypocalcemia.

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A 35-year-old man comes to the office with a year-long history of fatigue and weakness. He has had a significant decrease in appetite and interest in day-to-day activities due to lack of energy. He also reports cold intolerance, a dull constant headache, constipation, erectile dysfunction, and low libido. The patient has no fever, neck swelling, skin rash, head injury, or excessive urination. Temperature is 36.6 C (97.9 F), blood pressure is 98/72 mm Hg, pulse is 50/min, and respirations are 14/min. The skin is dry and pale. Neurologic examination shows delayed deep tendon reflexes. The testes are small and soft on palpation. Laboratory results are as follows:

Complete blood count	
Hemoglobin	10.2 g/dL
Leukocytes	5,000/mm^3
Neutrophils	45%
Eosinophils	10%
Lymphocytes	40%
Monocytes	5%
Serum chemistry	
Sodium	132 mEq/L
Potassium	4.0 mEq/L

Lymphocytes	40%
Monocytes	5%
Serum chemistry	
Sodium	132 mEq/L
Potassium	4.0 mEq/L
Glucose	56 mg/dL

Further evaluation in this patient would most likely show which of the following?

	Free T4	Serum cortisol	Aldosterone
A.	Low	Low	Normal
B.	Low	Low	Low
C.	Normal	Low	Low
D.	Normal	High	Low
E.	Normal	Normal	Low

Submit

Lymphocytes	40%
Monocytes	5%
Serum chemistry	
Sodium	132 mEq/L
Potassium	4.0 mEq/L
Glucose	56 mg/dL

Further evaluation in this patient would most likely show which of the following?

	Free T4	Serum cortisol	Aldosterone
A. [48%]	Low	Low	Normal
B. [40%]	Low	Low	Low
C. [8%]	Normal	Low	Low
D. [1%]	Normal	High	Low
E	Normal	Normal	Low

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

This patient's presentation suggests **panhypopituitarism** with inadequate production of multiple anterior pituitary hormones. Potential features include:

- **Central adrenal insufficiency** (**low cortisol** and ACTH) - fatigue, anorexia, hypoglycemia, eosinophilia. Skin may be pale due to decreased production of ACTH and melanocyte-stimulating hormone
- **Hypogonadotropic hypogonadism** (low FSH, LH, and testosterone) - low libido, erectile dysfunction, testicular atrophy
- **Central hypothyroidism** (low or inappropriately normal TSH, **low free T4**) - cold intolerance, constipation, bradycardia

Patients may have mild hyponatremia (due to antidiuretic hormone release) and mild hypotension (due to decreased peripheral arterial resistance). Unlike cortisol, adrenal **aldosterone** secretion is regulated primarily by the renin-angiotensin system and is **not affected** in hypopituitarism. In contrast, in primary adrenal insufficiency, aldosterone production is lost, leading to hyperkalemia and severe hypotension, and ACTH production is increased, with associated hyperpigmentation.

Hypopituitarism is often due to compression by pituitary or extrapituitary tumors and may be associated with mass-effect symptoms (eg, headache, visual field defects). Other causes include infiltrative diseases (eg, sarcoidosis, hemochromatosis), trauma, and vascular insults (apoplexy, Sheehan syndrome).

Educational objective:
Hypopituitarism is characterized by glucocorticoid deficiency, hypogonadism, and hypothyroidism. Typical features include fatigue, cold intolerance, hypoglycemia, anorexia, and low libido. In contrast to primary adrenal insufficiency, aldosterone is normal in central adrenal insufficiency due to hypopituitarism.

may be pale due to decreased production of ACTH and melanocyte-stimulating hormone

- **Hypogonadotropic hypogonadism** (low FSH, LH, and testosterone) - low libido, erectile dysfunction, testicular atrophy
- **Central hypothyroidism** (low or inappropriately normal TSH, **low free T4**) - cold intolerance, constipation, bradycardia

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Educational objective:

Hypopituitarism is characterized by glucocorticoid deficiency, hypogonadism, and hypothyroidism. Typical features include fatigue, cold intolerance, hypoglycemia, anorexia, and low libido. In contrast to primary adrenal insufficiency, aldosterone is normal in central adrenal insufficiency due to hypopituitarism.

References

- Neurology of the pituitary

A 46-year-old man comes to the office due to bilateral ankle and facial swelling, especially prominent in the periorbital area. He has no shortness of breath, fever, or changes in urine color. The patient does not use tobacco, alcohol, or illicit drugs. He has no significant medical history and takes no medications. His temperature is 37.1 C (99 F), blood pressure is 130/70 mm Hg, pulse is 78/min, and respirations are 14/min. Examination shows bilateral 1+ pitting ankle edema. Auscultation shows clear lungs, normal heart sounds, and no murmurs. Dipstick urinalysis is positive for protein. A 24-hour urine collection shows proteinuria of 4.6 g/day. Laboratory results are as follows:

Total serum calcium	7.5 mg/dL
Albumin	2.2 g/dL
Phosphorus	3.5 mg/dL
Magnesium	2.2 mg/dL
Creatinine	0.8 mg/dL

Which of the following is the most likely cause of this patient's low serum calcium level?

A. Decreased 1-alpha-hydroxylation of 25-OH vitamin D

B. Decreased 25-hydroxylation of vitamin D

C. Decreased levels of parathyroid hormone

Dipstick urinalysis is positive for protein. A 24-hour urine collection shows proteinuria of 4.6 g/day. Laboratory results are as follows:

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Albumin	2.2 g/dL
Phosphorus	3.5 mg/dL
Magnesium	2.2 mg/dL
Creatinine	0.8 mg/dL

Which of the following is the most likely cause of this patient's low serum calcium level?

- A. Decreased 1-alpha-hydroxylation of 25-OH vitamin D [20%]
- B. Decreased 25-hydroxylation of vitamin D [6%]
- ✗ C. Decreased levels of parathyroid hormone [2%]
- ✓ D. Decreased serum albumin [67%]
- E. Normal levels of parathyroid hormone with impaired action at target organs [3%]

Incorrect | 67% | 7 Seconds | 10/29/2018

Approximately 40%-45% of total blood calcium is bound to albumin and other plasma proteins; the remainder is transported in the blood as ionized calcium (40%-55%) or complexed with phosphate and other anions (5%-15%). As a result, patients with hypoalbuminemia may have a significant deficit in total blood calcium. However, the ionized plasma calcium (physiologically active form) is hormonally regulated and remains stable.

Assessing the clinical significance of hypocalcemia detected in a common serum metabolic panel requires **correction** for the serum albumin concentration. The serum calcium concentration decreases by **0.8 mg/dL for every 1 g/dL decrease in serum albumin**; the corrected calcium level can be calculated using the following formula:

$$\text{Corrected calcium} = (\text{measured total calcium}) + 0.8 \times (4.0\ \text{g/dL} - \text{serum albumin in g/dL})$$

This patient with nephrotic syndrome (heavy proteinuria, hypoalbuminemia, edema) has a corrected calcium of 8.94 mg/dL ([7.5 mg/dL] + 0.8 × [4 g/dL − 2.2 g/dL]). The hypocalcemia is most likely due to hypoalbuminemia (from nephrotic-range proteinuria) and is not clinically significant. Direct measurement of **ionized calcium** is performed in many clinical laboratories, but it requires special handling and may not be readily available.

(Choices A and B) Vitamin D is formed in the skin or absorbed from the intestine. It is then hydroxylated in the liver (25-hydroxylation) to produce physiologically inert 25-hydroxyvitamin D (25[OH]D). The second step (1-alpha-hydroxylation) occurs in the kidney to form the physiologically active form of vitamin D ($1,25[OH]_2D$), which plays an active role in calcium and phosphorus absorption from the small intestine. Patients with chronic renal failure are unable to form $1,25(OH)_2D$, leading to hypocalcemia secondary to decreased intestinal absorption. However, this patient's normal creatinine level makes this unlikely.

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(Choice C) Hypoparathyroidism can cause hypocalcemia, and is most commonly due to autoimmune destruction of the parathyroid gland or surgery (parathyroidectomy, thyroid, or radical head/neck surgery for cancer). In addition to hypocalcemia, these patients would be expected to have decreased parathyroid hormone (PTH) levels and elevated serum phosphorus. This patient's normal serum phosphorus makes this unlikely.

(Choice E) Pseudohypoparathyroidism is a rare disorder characterized by PTH resistance in target organs (kidney, bone). These patients have hypocalcemia, elevated phosphorus, and high PTH levels.

Educational objective:
Patients with hypoalbuminemia can have decreased total serum calcium. However, ionized calcium (physiologically active form) is hormonally regulated and remains stable.

References

A 24-year-old man comes to the office for follow-up of several enlarging thyroid nodules. The patient first noted the nodules 3 months ago and reports no associated pain or dysphagia. His medical history is unremarkable, and his family history is unknown as the patient is adopted. The patient is tall with a decreased upper-to-lower-body ratio. Detailed eye examination is unremarkable, but several nodules consistent with neuromas are noted on his lips and tongue. Musculoskeletal examination shows hypermobile joints and prominent kyphoscoliosis. A 3-cm, smooth, well-healed scar is noted on his right upper arm from a laceration sustained from in a bicycle injury in childhood. Laboratory tests show normal serum creatinine and calcium levels and an elevated serum calcitonin level. Histopathologic assessment from a biopsy of the thyroid nodules is consistent with medullary thyroid cancer.

Which of the following is the most likely diagnosis for this patient?

- A. Ehlers-Danlos syndrome
- B. Marfan syndrome
- C. Multiple endocrine neoplasia
- D. Neurofibromatosis type 1
- E. Von Hippel-Lindau disease

Submit

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Which of the following is the most likely diagnosis for this patient?

- A. Ehlers-Danlos syndrome [2%]
- B. Marfan syndrome [3%]
- ✔ C. Multiple endocrine neoplasia [88%]
- ✘ D. Neurofibromatosis type 1 [3%]
- E. Von Hippel-Lindau disease [1%]

Incorrect
Correct answer C

88% Answered correctly

35 Seconds Time Spent

07/30/2018 Last Updated

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

This patient has a **marfanoid habitus**, **mucosal neuromas**, and multifocal **medullary thyroid cancer (MTC)**, most likely due to **type 2B multiple endocrine neoplasia (MEN2B)**. MEN2A and MEN2B are caused by gain of function of mutations involving the ***RET* proto-oncogene** on chromosome 10.

In addition to MTC, MEN2A and MEN2B are also associated with **pheochromocytoma**, which may initially be asymptomatic but can cause severe hypertensive crisis during surgical resection of the thyroid masses. For this reason, patients with MTC should be tested for *RET* mutations and (if positive) pheochromocytoma with a plasma

reason, patients with MTC should be tested for *RET* mutations and (if positive) pheochromocytoma with a plasma fractionated metanephrine assay. Additional manifestations of MEN2B include intestinal neuromas (leading to gastrointestinal symptoms) and skeletal deformities (eg, kyphoscoliosis, lordosis). In contrast to MEN2A, primary hyperparathyroidism is not seen in MEN2B.

(Choices A and B) Ehlers-Danlos syndrome is characterized by joint hypermobility with recurrent joint dislocations, easy bruisability, and poor wound healing leading to wide scars (unlike the well-healed scar in this patient). Marfan syndrome is characterized by tall stature with disproportionately long extremities, joint hypermobility, and skeletal abnormalities (eg, kyphoscoliosis, pectus carinatum); however, ectopia lentis and aortic root dilation are cardinal manifestations. Mucosal neuromas and MTC are not associated with Ehlers-Danlos syndrome or Marfan syndrome.

(Choice D) Clinical features of neurofibromatosis type 1 (NF1) include café au lait spots, neurofibromas, axillary freckling, intracranial tumors, and skeletal anomalies. Although pheochromocytoma is associated with NF1, MTC and marfanoid habitus are not features.

(Choice E) Von Hippel-Lindau disease is linked to a wide variety of tumors, including hemangioblastoma, renal cell cancer, pheochromocytoma, and pancreatic neuroendocrine tumors. MTC, marfanoid habitus, and mucosal neuromas are not seen with this condition.

Educational objective:
Type 2B multiple endocrine neoplasia (MEN2B) is characterized by medullary thyroid cancer, pheochromocytoma, marfanoid habitus, and mucosal neuromas. Patients may also have other skeletal deformations (eg, kyphoscoliosis, lordosis). In contrast to MEN2A, primary hyperparathyroidism is not seen in MEN2B.

A 35-year-old man comes to the office after a year of weakness, fatigue, and weight loss. He has experienced reduced appetite and intermittent diarrhea. The patient had no improvement after several sessions with a clinical psychologist, who suggested evaluation for a physiological cause of his symptoms. His medical history is unremarkable, and he takes no regularly scheduled medications. The patient does not use tobacco, alcohol, or illicit drugs. Family history is notable for hypothyroidism (sister). Temperature is 37.2 C (99 F), blood pressure is 106/66 mm Hg, pulse is 94/min, and respirations are 14/min. On physical examination, the patient does not appear to be in acute distress. His neck shows no thyromegaly or lymphadenopathy. Cardiopulmonary examination is normal, and the abdomen is soft with normal bowel sounds and no organomegaly. Motor strength and deep tendon reflexes are normal and symmetric. Laboratory results are as follows:

Hemoglobin	12.3 g/dL
White blood cells	3000/mm^3
Serum sodium	130 mEq/L
Serum potassium	5.5 mEq/L
8 AM cortisol	7.2 µg/dL (normal: 5-23 µg/dL)
TSH	2.5 mIU/L

White blood cells	3000/mm³
Serum sodium	130 mEq/L
Serum potassium	5.5 mEq/L
8 AM cortisol	7.2 µg/dL (normal: 5-23 µg/dL)
TSH	2.5 mIU/L

Which of the following is the most appropriate next step in management of this patient?

A. 24-hour urine free cortisol
B. ACTH stimulation test
C. Insulin-induced hypoglycemia test
D. Intravenous hydrocortisone
E. Low-dose overnight dexamethasone suppression test

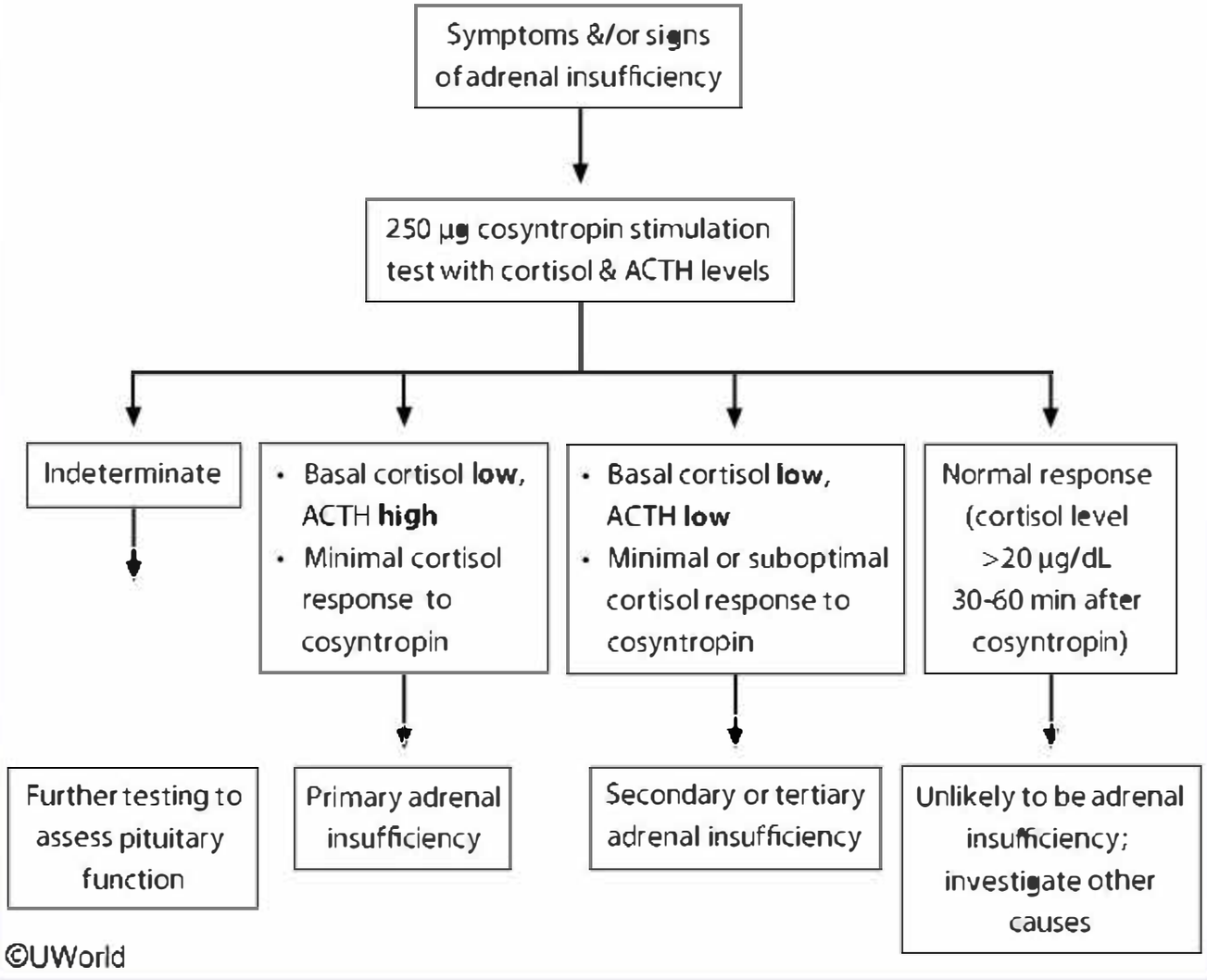
Submit

White blood cells	3000/mm³
Serum sodium	130 mEq/L
Serum potassium	5.5 mEq/L
8 AM cortisol	7.2 µg/dL (normal: 5-23 µg/dL)
TSH	2.5 mIU/L

Which of the following is the most appropriate next step in management of this patient?

- A. 24-hour urine free cortisol [21%]
- ✔ B. ACTH stimulation test [51%]
- ✘ C. Insulin-induced hypoglycemia test [4%]
- D. Intravenous hydrocortisone [5%]
- E. Low-dose overnight dexamethasone suppression test [16%]

Incorrect


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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This patient has chronic weakness, weight loss, hyponatremia, and hyperkalemia associated with a low-normal cortisol level. This is a typical presentation of **primary adrenal insufficiency** (PAI), also known as Addison disease. PAI can be due to autoimmune adrenalitis, infections (eg, tuberculosis), malignancy, or adrenal hemorrhage. The initial symptoms are nonspecific and include **fatigue**, weakness, and **weight loss**. **Gastrointestinal symptoms** occur in most patients. Aldosterone deficiency causes **volume depletion**, which can manifest as hypotension or syncope. Skin signs can include hyperpigmentation or vitiligo. Almost all patients have **hyponatremia** due to salt wasting, volume depletion, and increased antidiuretic hormone release. Most also have hyperkalemia due to aldosterone deficiency.

The initial evaluation should include an **8 AM serum cortisol** and **plasma ACTH**. A low cortisol level (<5 µg/dL) with high ACTH confirms PAI, a low cortisol level with low ACTH suggests central (pituitary or hypothalamic) adrenal insufficiency, and a high or high-normal cortisol level (>15 µg/dL) rules out PAI.

However, the ACTH assay can take several days, so an **ACTH stimulation test** (cosyntropin test) is usually performed concurrently to rapidly confirm the diagnosis. Cosyntropin is a synthetic ACTH analog. Infusion of a 250-µg bolus of cosyntropin normally triggers a rapid increase in serum cortisol, but patients with PAI will not have a significant rise. In addition, most patients with central adrenal insufficiency have a blunted response due to adrenal atrophy from chronically low ACTH. The ACTH stimulation test can clarify the diagnosis in patients with suspected PAI who have low-normal cortisol levels (5-15 µg/dL).

(Choice A) Urinary cortisol levels are decreased in severe PAI, but sensitivity is too low for use in the initial diagnosis.

(Choice A) Urinary cortisol levels are decreased in severe PAI, but sensitivity is too low for use in the initial diagnosis.

(Choice C) Cortisol is synthesized in response to hypoglycemia. In the insulin hypoglycemia test, insulin is given to induce hypoglycemia, and cortisol levels are measured. However, this test is technically cumbersome and can be hazardous in some patients.

(Choice D) Intravenous hydrocortisone is given for adrenal crisis (ie, abdominal pain, fever, hemodynamic instability). This patient has chronic, stable symptoms, and the diagnosis should be confirmed prior to treatment.

(Choice E) Dexamethasone suppresses release of ACTH from the pituitary, which subsequently reduces adrenal cortisol production. The dexamethasone suppression tests are used to evaluate hypercortisolism but are not used in PAI.

Educational objective:
The evaluation of adrenal insufficiency should include an 8 AM serum cortisol and plasma ACTH. In addition, an ACTH stimulation test (cosyntropin test) can identify patients with primary adrenal insufficiency (and most patients with central adrenal insufficiency) and should be performed in the initial evaluation.

References

- Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline

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A 56-year-old woman is found to have hypercalcemia during routine laboratory testing for a life insurance policy. She has a history of moderate asthma and has been evaluated for 2 episodes of acute bronchitis in the last 3 years. The patient has a 30-pack-year smoking history but does not use alcohol or illicit drugs. Her family history is negative for hypercalcemia. Current medications include inhaled budesonide and albuterol, and the patient takes a daily multivitamin tablet. Her temperature is 36.7 C (98 F), blood pressure is 120/70 mm Hg, pulse is 76/min, and respirations are 14/min. Neurologic examination shows no focal deficits and deep-tendon reflexes are normal. Laboratory results are as follows:

Hematocrit	43%
Leukocytes	6,300/mm^3
Platelets	200,000/mm^3
Serum calcium	11.2 mg/dL
Serum albumin	4.0 g/dL
Serum creatinine	1.0 mg/dL

Review of the patient's medical records reveals a serum calcium level of 10.9 mg/dL a year ago. Which of the following is the best next step to determine the cause of this patient's hypercalcemia?

A. Bone scan

Hematocrit	43%
Leukocytes	6,300/mm^3
Platelets	200,000/mm^3
Serum calcium	11.2 mg/dL
Serum albumin	4.0 g/dL
Serum creatinine	1.0 mg/dL

Review of the patient's medical records reveals a serum calcium level of 10.9 mg/dL a year ago. Which of the following is the best next step to determine the cause of this patient's hypercalcemia?

A. Bone scan
B. Chest x-ray
C. Serum alkaline phosphatase level
D. Serum parathyroid hormone level
E. Serum parathyroid hormone-related protein level
F. Serum protein electrophoresis

Platelets	200,000/mm³
Serum calcium	11.2 mg/dL
Serum albumin	4.0 g/dL
Serum creatinine	1.0 mg/dL

Review of the patient's medical records reveals a serum calcium level of 10.9 mg/dL a year ago. Which of the following is the best next step to determine the cause of this patient's hypercalcemia?

A. Bone scan [1%]
B. Chest x-ray [17%]
C. Serum alkaline phosphatase level [1%]
✔ D. Serum parathyroid hormone level [67%]
E. Serum parathyroid hormone-related protein level [11%]
✘ F. Serum protein electrophoresis [0%]

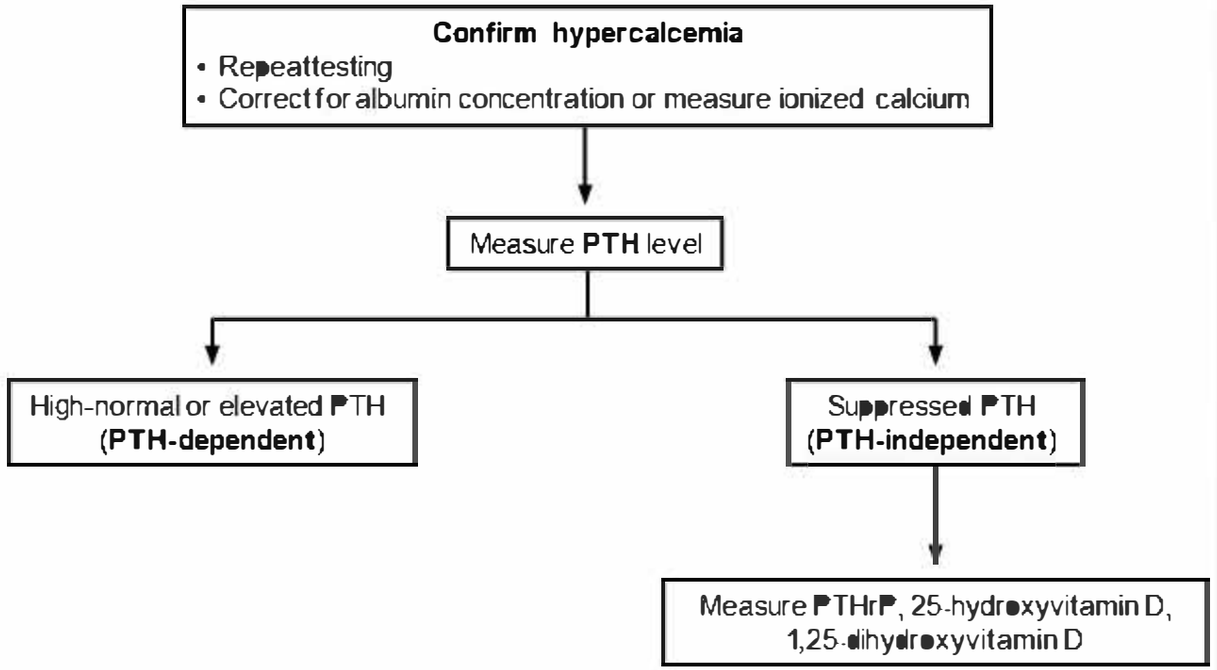
Incorrect
Correct answer

67%
Answered correctly

11 Seconds
Time Spent

06/03/2013
Last Updated

Diagnosis of hypercalcemia



Causes
- **Primary** (or tertiary) **hyperparathyroidism**
- Familial hypocalciuric hypercalcemia
- Lithium

Causes
- **Malignancy**
- Vitamin D toxicity
- Granulomatous diseases
- Drug-induced (eg, thiazides)
- Milk-alkali syndrome
- Thyrotoxicosis
- Vitamin A toxicity
- Immobilization

Causes of **hypercalcemia** can be categorized on the basis of parathyroid hormone (PTH) levels as PTH-dependent or PTH-independent:

- **PTH-independent** hypercalcemia (suppressed PTH) is usually due to malignancy, vitamin D toxicity, or extra-renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in granulomatous diseases (eg, sarcoidosis).
- **PTH-dependent** hypercalcemia (elevated or inappropriately normal PTH) is usually due to **primary hyperparathyroidism** (PHPT).

This patient has chronic, asymptomatic hypercalcemia, most likely due to PHPT. In normal individuals, elevated plasma calcium **suppresses PTH secretion**. However, in PHPT, PTH secretion from autonomously functioning parathyroid adenomas or parathyroid hyperplasia is not suppressed. Most patients with PHPT present with **mild, asymptomatic hypercalcemia**, although potential clinical features may include nephrolithiasis, osteoporosis, nausea, constipation, and neuropsychiatric symptoms ("stones, bones, abdominal moans, psychic groans"). In this patient with chronic, asymptomatic hypercalcemia and no family history of hypercalcemia, an elevated PTH level would be virtually diagnostic for PHPT.

(Choices A, B, E, and F) Most cases of PTH-independent hypercalcemia are due to malignancy. If the PTH is suppressed, diagnostic options may include chest imaging (primary or metastatic lung cancer), PTH-related protein (humoral hypercalcemia of malignancy), scintigraphic bone scan (bony metastasis), and serum protein electrophoresis (multiple myeloma). However, in hypercalcemia due to malignancy, serum calcium is typically much higher (often >14 mg/dL) than in this patient and more acute. In addition, patients are more likely to be symptomatic (eg, polyuria, dehydration, mental status changes).

would be virtually diagnostic for PHPT.

(Choices A, B, E, and F) Most cases of PTH-independent hypercalcemia are due to malignancy. If the PTH is suppressed, diagnostic options may include chest imaging (primary or metastatic lung cancer), PTH-related protein (humoral hypercalcemia of malignancy), scintigraphic bone scan (bony metastasis), and serum protein electrophoresis (multiple myeloma). However, in hypercalcemia due to malignancy, serum calcium is typically much higher (often >14 mg/dL) than in this patient and more acute. In addition, patients are more likely to be symptomatic (eg, polyuria, dehydration, mental status changes).

(Choice C) Although elevated alkaline phosphatase can suggest a possible bone disorder, it is not specific enough to detail the type of bone condition causing the hypercalcemia.

Educational objective:
Causes of hypercalcemia should be categorized on the basis of parathyroid hormone (PTH) levels. PTH-independent hypercalcemia (suppressed PTH) is usually due to malignancy. PTH-dependent hypercalcemia (elevated or inappropriately normal PTH) is usually due to primary hyperparathyroidism.

References

- Differential diagnosis of hypercalcemia.
- Hypercalcemia and parathyroid disorders.

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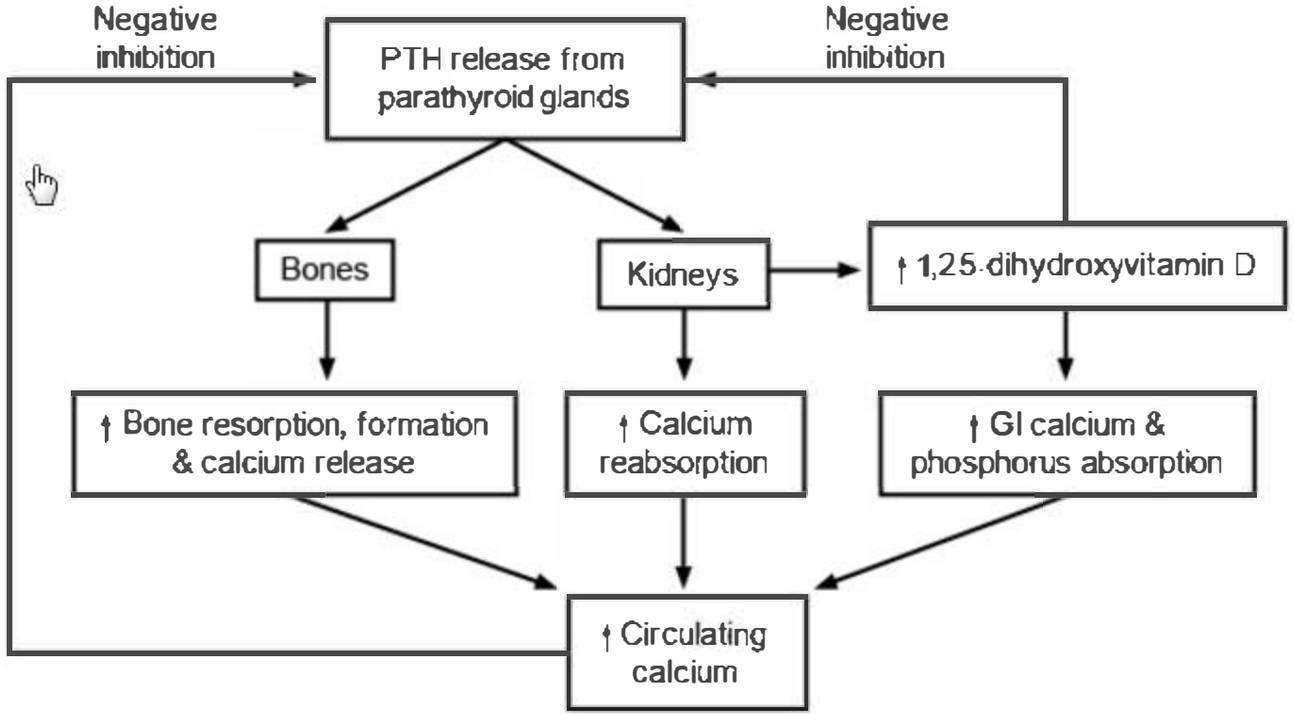
Exhibit Display

PTH, vitamin D & calcium axis



GI = gastrointestinal; PTH = parathyroid hormone.

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A 34-year-old woman, gravida 1 para 1, comes to the office for postpartum follow-up. She had a vaginal delivery 6 weeks ago that was complicated by severe postpartum bleeding requiring aggressive volume resuscitation and transfusion of 5 units of packed red blood cells. Since the delivery, the patient has been very fatigued with poor appetite. She is "very concerned" about having little energy to bond with her child; her family has been helping with the baby. The patient has been formula feeding her infant due to lack of milk production. Her prepregnancy weight was 63.5 kg (140 lb), weight at delivery was 82.5 kg (182 lb), and current weight is 56.2 kg (124 lb). Blood pressure is 90/69 mm Hg and pulse is 88/min. Examination shows a well-healed perineal laceration scar. Which of the following is the most likely cause of this patient's current symptoms?

- A. Adjustment disorder with depressed mood
- B. Pituitary ischemic necrosis
- C. Postpartum depression
- D. Postpartum thyroid inflammation
- E. Primary adrenal insufficiency
- F. Spontaneous pituitary hemorrhage

Submit

A 34-year-old woman, gravida 1 para 1, comes to the office for postpartum follow-up. She had a vaginal delivery 6 weeks ago that was complicated by severe postpartum bleeding requiring aggressive volume resuscitation and transfusion of 5 units of packed red blood cells. Since the delivery, the patient has been very fatigued with poor appetite. She is "very concerned" about having little energy to bond with her child; her family has been helping with the baby. The patient has been formula feeding her infant due to lack of milk production. Her prepregnancy weight was 63.5 kg (140 lb), weight at delivery was 82.5 kg (182 lb), and current weight is 56.2 kg (124 lb). Blood pressure is 90/69 mm Hg and pulse is 88/min. Examination shows a well-healed perineal laceration scar. Which of the following is the most likely cause of this patient's current symptoms?

- A. Adjustment disorder with depressed mood [1%]
- ✔ B. Pituitary ischemic necrosis [84%]
- ✘ C. Postpartum depression [6%]
- D. Postpartum thyroid inflammation [0%]
- E. Primary adrenal insufficiency [0%]
- F. Spontaneous pituitary hemorrhage [5%]

Incorrect
Correct answer

84%
Answered correctly

4 Seconds
Time Spent

05/29/2018
Last Updated

Sheehan syndrome	
Pathogenesis	• Obstetric hemorrhage complicated by hypotension • Postpartum pituitary infarction
Clinical features	• Lactation failure (↓ prolactin) • Amenorrhea, hot flashes, vaginal atrophy (↓ FSH, LH) • Fatigue, bradycardia (↓ TSH) • Anorexia, weight loss, hypotension (↓ ACTH) • Decreased lean body mass (↓ growth hormone)

This patient's **massive postpartum hemorrhage** with subsequent lactation failure, hypotension, and weight loss are concerning for **Sheehan syndrome** (**ischemic necrosis** of the pituitary gland). During pregnancy, the pituitary gland is physiologically enlarged and vulnerable to ischemia from hemorrhagic shock. This potentially life-threatening complication is characterized by anterior pituitary dysfunction; deficiencies in multiple hormone systems (ie, panhypopituitarism) are common.

Sheehan syndrome typically presents after delivery with **failure of postpartum lactation** due to prolactin deficiency and lactotroph cell necrosis. **Secondary adrenal insufficiency** (eg, persistent hypotension, weight loss, lethargy) is also a common complication due to impaired ACTH secretion. Amenorrhea (hypogonadotropic hypogonadism) and **central hypothyroidism** may also occur. Management involves replacing the deficient hormones, but there is no effective treatment to restore lactation.

(Choices A and C) Lactation failure is a risk factor for adjustment disorder with depressed mood ("postpartum blues") and postpartum depression. Although fatigue and poor appetite are common symptoms of mood disorders, hypotension and significant weight loss suggest an underlying medical disorder.

(Choice D) Postpartum thyroiditis is characterized by autoimmune inflammation and destruction of the thyroid within a year of delivery. It causes transient hyperthyroid symptoms (eg, weight loss, palpitations, tremor) followed by a self-limited hypothyroid state. However, it is not associated with hypotension or lactation failure.

(Choice E) Primary adrenal insufficiency manifests with similar symptoms such as fatigue, hypotension, and weight loss. However, most patients with primary adrenal insufficiency have hyperpigmentation (due to increased melanocyte-stimulating hormone) but not lactation failure.

(Choice F) Pituitary apoplexy generally refers to spontaneous hemorrhage into the pituitary gland and occurs most commonly in patients with a pituitary adenoma. Typical symptoms include acute headache, visual field defects, and decreased visual acuity. Symptomatic deficiencies of pituitary hormones are less common.

Educational objective:
Sheehan syndrome (postpartum ischemic necrosis of the anterior pituitary) is a potentially life-threatening complication of massive postpartum hemorrhage. It typically presents with lactation failure (prolactin deficiency) as well as hypotension and anorexia (secondary adrenal insufficiency).

References

- Sheehan's syndrome.

A 28-year-old woman develops tachycardia in the postoperative recovery room. She was admitted for a right femur fracture following a motor vehicle accident and had an open reduction and internal fixation of the fracture. While in the recovery area, she began experiencing nausea and vomiting, and became anxious and agitated. The patient has no known medical problems. She drinks 1 or 2 glasses of wine on weekends. Her temperature is 39.4 C (103 F), blood pressure is 160/90 mm Hg, pulse is 148/min, and respirations are 24/min. Pulse oximetry shows 98% on room air. On examination, the patient is delirious and has fine tremor. Mild lid lag is present. She has no muscle rigidity and deep-tendon reflexes are 2+ in the bilateral extremities. Laboratory results are as follows:

Hematocrit	30%
Sodium	132 mEq/L
Potassium	4.5 mEq/L
Bicarbonate	24 mEq/L
Blood urea nitrogen	32 mg/dL
Creatinine	1.2 mg/dL
Glucose	120 mg/dL

Blood urea nitrogen	32 mg/dL
Creatinine	1.2 mg/dL
Glucose	120 mg/dL
Creatine kinase, serum	176 U/L

Which of the following is the best next step in management of this patient?

- A. Echocardiogram
- B. Fluid bolus and intravenous dexamethasone
- C. Intravenous dantrolene
- D. Intravenous lorazepam
- E. Plasma free metanephrines
- F. Thyroid function tests and propranolol

Submit

Blood urea nitrogen	32 mg/dL
Creatinine	1.2 mg/dL
Glucose	120 mg/dL
Creatine kinase, serum	176 U/L

Which of the following is the best next step in management of this patient?

- A. Echocardiogram [1%]
- B. Fluid bolus and intravenous dexamethasone [11%]
- C. Intravenous dantrolene [35%]
- D. Intravenous lorazepam [9%]
- E. Plasma free metanephrines [1%]
- ✔ F. Thyroid function tests and propranolol [39%]

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.

This patient's presentation is concerning for **thyroid storm**, a life-threatening thyrotoxicosis usually triggered by a specific event (eg, thyroid or non-thyroid surgery, trauma, infection) in patients with undiagnosed or inadequately treated hyperthyroidism. Proposed mechanisms include a rapid increase in serum thyroid hormone levels or increased sensitivity to thyroid hormone. Characteristic features include tachycardia, hypertension, cardiac arrhythmias (eg, atrial fibrillation), and fever up to 40-41 C (104-106 F). Other findings include anxiety, altered mentation, seizure, severe nausea, vomiting, hepatic dysfunction, tremor, lid lag, and goiter.

Diagnosis is suspected clinically and confirmed by thyroid function studies documenting hyperthyroidism. Treatment includes beta blockers (eg, propranolol) for symptom control, thionamides (eg, propylthiouracil) to block new hormone synthesis, iodine solution to block thyroid hormone release (given at least an hour after propylthiouracil to prevent excess iodine incorporation into thyroid hormone), and glucocorticoids to decrease peripheral conversion of T4 to T3.

(Choice A) Echocardiography can identify causes of congestive heart failure or arrhythmias (eg, abnormal valves, ventricular dysfunction). However, this patient has no features of heart failure, and echocardiography is not needed.

(Choice B) Fluid resuscitation and intravenous dexamethasone should be given to patients with suspected acute adrenal insufficiency. These patients will have hypotension often associated with tachycardia, abdominal pain, vomiting, and weakness.

(Choice C) Intravenous dantrolene can treat malignant hyperthermia (MH), a hypermetabolic syndrome due to volatile anesthetics. MH typically presents with hypercarbia, sinus tachycardia, muscle rigidity, elevated creatine kinase, hyperkalemia, and hyperthermia. This patient's lid lag, normal potassium, and absence of muscle rigidity

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

vomiting, and weakness.

(Choice C) Intravenous dantrolene can treat malignant hyperthermia (MH), a hypermetabolic syndrome due to volatile anesthetics. MH typically presents with hypercarbia, sinus tachycardia, muscle rigidity, elevated creatine kinase, hyperkalemia, and hyperthermia. This patient's lid lag, normal potassium, and absence of muscle rigidity are more consistent with hyperthyroidism.

(Choice D) Intravenous lorazepam can treat alcohol withdrawal, which usually presents with tachycardia, hypertension, fever, and altered mental status. This patient's history of moderate alcohol use makes withdrawal less likely.

(Choice E) Free plasma metanephrines are elevated in pheochromocytoma, which usually presents with episodic hypertension and the classic triad (episodic headache, diaphoresis, and tachycardia). Pheochromocytoma is usually not associated with high fever.

Educational objective:
Thyroid storm is a life-threatening thyrotoxicosis often triggered by thyroid or non-thyroid surgery, trauma, infection, iodine contrast, or childbirth. It is characterized by tachycardia, hypertension, cardiac arrhythmias, high fever, tremor, altered mentation, and lid lag.

References

- Thyroid storm: an updated review.

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This patient's presentation is concerning for thyroid storm, a life-threatening thyrotoxicosis usually triggered by a

Exhibit Display

Risk factors	Adrenal hemorrhage/infarction Acute illness, injury, or surgery in patients with: • Chronic adrenal insufficiency • Chronic glucocorticoid use • Congenital adrenal hyperplasia
Clinical features	• **Hypotension/shock** • Nausea/vomiting, abdominal pain • Weakness • Fever • Acute kidney injury
Diagnostic testing	• Cortisol • Electrolytes, BUN, creatinine, glucose • ACTH • Renin • ACTH stimulation test when stable
Treatment	• **Hydrocortisone or dexamethasone** • High-flow intravenous fluids • Monitor serum electrolytes

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kinase, hyperkalemia, and hyperthermia. This patient's lid lag, normal potassium, and absence of muscle rigidity

A 62-year-old Caucasian woman complains of difficulty remembering important dates and appointments. She also describes poor concentration, daytime sleepiness and easy fatigability. She is concerned about her forgetfulness because her mother suffered from recurrent strokes and had severe memory loss. Her father died of chronic leukemia. Her daughter's recent job loss has caused her a lot of stress. She does not smoke or consume alcohol. Her appetite is decreased but she has gained 4 pounds over the last three months. She visited an otolaryngologist for hoarseness of recent onset. She takes over-the-counter laxatives for constipation and occasional aspirin for knee pain. She denies any other medication use. Which of the following is the most likely diagnosis in this patient?

- A. Alzheimer's dementia
- B. Dementia with Lewy bodies
- C. Multiinfarct dementia
- D. Hypothyroidism
- E. Normal pressure hydrocephalus
- F. Huntington's disease
- G. Chronic subdural hematoma
- H. Pseudodementia
- I. Vitamin B12 deficiency

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- B. Dementia with Lewy bodies
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- E. Normal pressure hydrocephalus
- F. Huntington's disease
- G. Chronic subdural hematoma
- H. Pseudodementia
- I. Vitamin B12 deficiency
- J. Thiamine deficiency
- K. Drug-induced dementia

Submit

for hoarseness of recent onset. She takes over-the-counter laxatives for constipation and occasional aspirin for knee pain. She denies any other medication use. Which of the following is the most likely diagnosis in this patient?

- A. Alzheimer's dementia [2%]
- B. Dementia with Lewy bodies [0%]
- C. Multiinfarct dementia [1%]
- ✔ D. Hypothyroidism [72%]
- E. Normal pressure hydrocephalus [0%]
- F. Huntington's disease [0%]
- G. Chronic subdural hematoma [0%]
- H. Pseudodementia [21%]
- ✘ I. Vitamin B12 deficiency [0%]
- J. Thiamine deficiency [0%]
- K. Drug-induced dementia [0%]

Incorrect
Correct answer

72%
Answered correctly

9 Seconds
Time Spent

03/09/2018
Last Updated

This woman suffers from hypothyroidism. This woman has several symptoms of hypothyroidism: weight gain, fatigue, constipation, hoarseness, and memory changes. Assuming she has Hashimoto's thyroiditis, laboratory studies will reveal an elevated TSH and decreased free T4. Administration of levothyroxine will quickly improve her symptoms.

(Choice A) Alzheimer's dementia presents with early problems in visuospatial abilities (e.g. getting lost in their neighborhood) and anterograde memory formation. Old memories tend to be preserved. Personality and behavioral changes (e.g. hypersexuality, agitation) may occur as the disease progresses. Hallucinations and changes in alertness are late findings.

(Choice B) Unlike Alzheimer's disease, dementia with Lewy bodies presents with alterations in alertness, visual hallucinations, and extrapyramidal symptoms. Memory deficits occur later in the course of disease than in Alzheimer's.

(Choice C) Patients often have a stepwise deterioration as damage from multiple strokes slowly adds up. It is characterized by risk factors for vascular disease, history of cerebrovascular disease, and imaging evidence of strokes. Psychiatric disturbances such as depression and agitation are common.

(Choice E) Normal pressure hydrocephalus (NPH) is a disease characterized by dementia, abnormal gait, and urinary incontinence. The gait is broad-based and shuffling and patients tend to be bradykinetic.

(Choice F) Huntington's disease is an autosomal dominant neurodegenerative disease affecting the caudate and putamen. The mean age of onset is between 35-44 years of age. Symptoms include choreathetoid movements, behavioral disturbances, and dementia. Treatment is supportive.

(Choice G) Chronic subdural hematomas are more common in elderly patients and alcoholics due to their decreased brain volume and propensity for falls. They present insidiously with decreased consciousness, headache, cognitive and memory deficits, balance problems, aphasia, or motor deficits. This patient does not have headache or other symptoms most consistent with chronic subdural hematomas.

(Choice H) Pseudodementia is a presentation of major depression in the elderly. Depressed patients may have memory changes and other symptoms concerning for dementia.

(Choice I) Vitamin B12 deficiency typically presents as dementia with megaloblastic anemia and posterior spinal column deficits. The most common cause is pernicious anemia.

(Choice J) Thiamine deficiency can lead to Wernicke-Korsakoff syndrome. This disease presents as ataxia, ophthalmoplegia, and confusion (Wernicke's) in addition to confabulation and amnesia (Korsakoff's). It is particularly common in alcoholics.

Educational objective:
Hypothyroidism is an important cause of reversible changes in memory and mentation. It will be accompanied by systemic changes such as weight gain, fatigue, and constipation.

A 38-year-old woman comes to the office with a 3-week history of weight loss, nausea, abdominal pain, and postural dizziness. She traveled to Thailand 6 months ago and has felt fatigued since then. Medical history is notable for moderate persistent asthma treated with an inhaled beta-2 agonist and inhaled corticosteroid. Over the last 2 years, the patient has had several asthma exacerbations requiring oral prednisone. She also has hypothyroidism treated with levothyroxine. The patient is married and is a stay-at-home mother. Blood pressure is 90/60 mm Hg and pulse is 96/min. Pharyngeal examination shows bilateral tonsillar enlargement. Skin examination shows increased pigmentation at the palmar creases and mucous membranes as well as a few patches of vitiligo. Initial laboratory testing shows mild hyponatremia and hyperkalemia with normal renal function. Complete blood count is normal, but differential shows moderate eosinophilia. Follow-up testing confirms a low 8 AM serum cortisol. Which of the following is the most likely cause of this patient's adrenal insufficiency?

- A. Adrenal hemorrhage
- B. Adrenal tumor
- C. Autoimmune adrenalitis
- D. Central adrenal insufficiency from glucocorticoid use
- E. HIV infection
- F. Tuberculosis

postural dizziness. She traveled to Thailand 6 months ago and has felt fatigued since then. Medical history is notable for moderate persistent asthma treated with an inhaled beta-2 agonist and inhaled corticosteroid. Over the last 2 years, the patient has had several asthma exacerbations requiring oral prednisone. She also has hypothyroidism treated with levothyroxine. The patient is married and is a stay-at-home mother. Blood pressure is 90/60 mm Hg and pulse is 96/min. Pharyngeal examination shows bilateral tonsillar enlargement. Skin examination shows increased pigmentation at the palmar creases and mucous membranes as well as a few patches of vitiligo. Initial laboratory testing shows mild hyponatremia and hyperkalemia with normal renal function. Complete blood count is normal, but differential shows moderate eosinophilia. Follow-up testing confirms a low 8 AM serum cortisol. Which of the following is the most likely cause of this patient's adrenal insufficiency?

- A. Adrenal hemorrhage [3%]
- B. Adrenal tumor [2%]
- ✔ C. Autoimmune adrenalitis [59%]
- ✘ D. Central adrenal insufficiency from glucocorticoid use [20%]
- E. HIV infection [1%]
- F. Tuberculosis [13%]

Incorrect
Correct answer

59%
Answered correctly

7 Seconds
Time Spent

07/26/2018
Last Updated

Clinical features of primary adrenal insufficiency	
Etiology	• **Autoimmune** • Infections (eg, tuberculosis, HIV, disseminated fungal) • Hemorrhagic infarction • Metastatic
Clinical presentation	• 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** & high-dose (250 µg) **ACTH stimulation test** • Primary adrenal insufficiency: Low cortisol, high ACTH • Secondary/tertiary adrenal insufficiency: Low cortisol, low ACTH

This patient has several features of chronic **primary adrenal insufficiency** (PAI), including weight loss, abdominal pain, and fatigue. **Hyperpigmentation** is a common finding and is due to cosecretion of melanocyte-stimulating hormone with ACTH (both are derived from proopiomelanocortin), which is increased in response to cortisol deficiency. In addition, loss of mineralocorticoid production can cause hypotension, hyponatremia, and

deficiency. In addition, loss of mineralocorticoid production can cause hypotension, hyponatremia, and **hyperkalemia**. Eosinophilia and hyperplasia of lymphoid tissue (eg, tonsils) are common but nonspecific findings.

Autoimmune adrenalitis is responsible for >90% of cases of PAI in developed countries. It is due to autoantibodies against adrenal enzymes that are responsible for corticosteroid synthesis. Autoimmune adrenalitis can occur as an isolated disorder or in association with other autoimmune syndromes (eg, hypothyroidism, vitiligo).

(Choice A) Bilateral adrenal hemorrhage due to sepsis (eg, *Neisseria meningitidis*) can lead to PAI; however, this is less common, and the onset of clinical features is typically acute and dramatic.

(Choice B) Hyperfunctioning adrenal tumors are a potential cause of hypercortisolism, not PAI. Bilateral adrenal metastasis can cause PAI but this is a rare occurrence.

(Choice D) Exogenous glucocorticoids can suppress pituitary secretion of ACTH and hypothalamic production of corticotropin-releasing hormone. However, in contrast to PAI, secretion of melanocyte-stimulating hormone is not increased so patients do not display hyperpigmentation. Also, mineralocorticoid production is controlled by the renin-angiotensin system; aldosterone levels are normal and hyperkalemia is not seen with exogenous glucocorticoid use.

(Choice E) PAI in HIV disease can be due to opportunistic infections (eg, cytomegalovirus, atypical mycobacteria, fungal infections) or inhibition of glucocorticoid synthesis by azole antifungal drugs. However, this patient has no apparent opportunistic infections, and her other autoimmune findings make autoimmune adrenalitis more likely.

(Choice F) PAI due to tuberculosis (TB) is uncommon in developed countries and typically seen in miliary disease. It is unlikely that the patient contracted TB and so rapidly developed manifestations of TB-induced PAI

metastasis can cause PAI but this is a rare occurrence.

(Choice D) Exogenous glucocorticoids can suppress pituitary secretion of ACTH and hypothalamic production of corticotropin-releasing hormone. However, in contrast to PAI, secretion of melanocyte-stimulating hormone is not increased so patients do not display hyperpigmentation. Also, mineralocorticoid production is controlled by the renin-angiotensin system; aldosterone levels are normal and hyperkalemia is not seen with exogenous glucocorticoid use.

(Choice E) PAI in HIV disease can be due to opportunistic infections (eg, cytomegalovirus, atypical mycobacteria, fungal infections) or inhibition of glucocorticoid synthesis by azole antifungal drugs. However, this patient has no apparent opportunistic infections, and her other autoimmune findings make autoimmune adrenalitis more likely.

(Choice F) PAI due to tuberculosis (TB) is uncommon in developed countries and typically seen in miliary disease. It is unlikely that the patient contracted TB and so rapidly developed manifestations of TB-induced PAI following her trip to Thailand 6 months ago.

Educational objective:
Autoimmune adrenalitis is the most common cause of primary adrenal insufficiency (PAI) in developed countries. The key differentiating features of PAI from central adrenal insufficiency are hyperpigmentation and hyperkalemia seen in PAI.

References

- Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society Clinical Practice Guideline.

A 38-year-old woman comes to the office with progressive muscle weakness over the last 6 months. She finds it difficult to climb stairs and comb her hair, and she is unable to walk even short distances without rest. There is no associated muscle pain. The patient was diagnosed with hypothyroidism a year ago when she started gaining weight and has been taking levothyroxine since then. Four months ago, she developed acute back pain. X-ray at that time revealed demineralization of the vertebral bones. Temperature is 37 C (98.6 F), blood pressure is 155/100 mm Hg, pulse is 76/min, and respirations are 15/min. BMI is 32 kg/m^2. Physical examination shows facial hirsutism and mild proximal muscle weakness in the extremities. The patient's muscles are not tender on palpation, and no fasciculations are noted. Deep tendon reflexes and sensory examination are normal. TSH is normal. Which of the following is most likely responsible for this patient's muscle weakness?

- A. Electrolyte abnormality
- B. Mitochondrial dysfunction
- C. Motor neuron disease
- D. Muscle atrophy
- E. Muscle inflammation
- F. Peripheral nerve demyelination

Submit

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- A. Electrolyte abnormality [31%]
- ✗ B. Mitochondrial dysfunction [4%]
- C. Motor neuron disease [8%]
- ✓ D. Muscle atrophy [30%]
- E. Muscle inflammation [21%]
- F. Peripheral nerve demyelination [4%]

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	↑

This patient has **painless muscle weakness** associated with weight gain, bone loss, hypertension, and **hirsutism**, which is consistent with hypercortisolism (**Cushing syndrome**). Although it is most commonly due to exogenous administration of glucocorticoids, Cushing syndrome can also be caused by an ACTH-producing pituitary tumor (Cushing disease), ectopic ACTH production (eg, small cell lung cancer), or primary adrenal disease. This patient requires further workup (eg, urinary or salivary cortisol, plasma ACTH, adrenal or brain imaging depending on results) to determine the etiology.

Regardless of etiology, myopathy in Cushing syndrome is typically characterized by weakness predominantly involving the proximal muscles and may be severe enough to interfere with daily activities. It is due to the direct **catabolic effects** of cortisol on skeletal muscle, which leads to **muscle atrophy**.

Glucocorticoid-induced muscle atrophy is thought to be mediated by the inhibition of Akt-1, an intracellular signaling molecule with serine/threonine kinase activity. Interference of insulin-like growth factor 1 signaling may also contribute. Furthermore, glucocorticoids may decrease muscle cell differentiation and protein synthesis.

(Choice A) Hypokalemia, hypomagnesemia, and hypercalcemia can cause muscle weakness, and hypocalcemia can cause tetany; however, none of these electrolyte abnormalities would be associated with hirsutism. In some patients with severe hypercortisolism (eg, due to ectopic ACTH syndrome), hypokalemia can develop (due to the partial mineralocorticoid effects of cortisol) and accentuate the muscle weakness; however, the weakness itself is due primarily to muscle atrophy caused by glucocorticoids.

(Choice B) Mitochondria generate ATP by oxidative phosphorylation. Mitochondrial dysfunction generally involves multiple organ systems (eg, nervous system involvement, eye abnormalities, gastrointestinal manifestations).

(Choice B) Mitochondria generate ATP by oxidative phosphorylation. Mitochondrial dysfunction generally involves multiple organ systems (eg, nervous system involvement, eye abnormalities, gastrointestinal manifestations). Isolated myopathy can occur but usually presents during childhood or adolescence with decreased exercise tolerance, muscle weakness, myalgias, and elevated creatine kinase.

(Choices C and E) Muscle weakness in motor neuron disease (eg, amyotrophic lateral sclerosis) may be characterized by features of upper motor neuron (hyperreflexia and spasticity) or lower motor neuron (atrophy and fasciculation) dysfunction. Inflammatory myopathies can cause progressive muscle weakness that is usually associated with myalgias and muscle tenderness. These disorders would not typically cause hypertension, hirsutism, or demineralization of bone.

(Choice F) Chronic inflammatory demyelinating polyradiculoneuropathy is an acquired inflammatory disorder characterized by demyelination of the peripheral nerves and nerve roots. It presents with progressive, symmetric muscle weakness and is usually associated with distal sensory loss and diminished deep tendon reflexes.

Educational objective:
Myopathy in Cushing syndrome is characterized by progressive painless muscle weakness predominantly involving the proximal muscles. It is due to the direct catabolic effects of cortisol on skeletal muscle, leading to muscle atrophy.

References

- Glucocorticoids differentially regulate degradation of MyoD and Id1 by N-terminal ubiquitination to promote

A 23-year-old woman comes to the office due to fatigue, anxiety, and difficulty sleeping over the last several months. The patient has used melatonin as a sleep aid but with no benefit. Medical history is remarkable only for menorrhagia, for which she takes a combination estrogen/progesterone contraceptive pill. Her mother has hypothyroidism and hypertension. The patient occasionally smokes marijuana but does not use tobacco or alcohol. Blood pressure is 120/78 mm Hg and pulse is 82/min. BMI is 18.8 kg/m^2. Examination of the neck shows a normal-size thyroid gland without nodules. Serum TSH is 1.5 μU/mL and total T4 is 15 μg/dL. Which of the following is the most likely explanation of this patient's laboratory findings?

- A. Displacement of thyroid hormones from binding proteins
- B. Immunoglobulin-induced hyperthyroidism
- C. Increased thyroid hormone-binding protein level
- D. Pituitary tumor
- E. Pregnancy
- F. Thyroid hormone resistance

Submit

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- A. Displacement of thyroid hormones from binding proteins [25%]
- B. Immunoglobulin-induced hyperthyroidism [16%]
- ✔ C. Increased thyroid hormone-binding protein level [45%]
- D. Pituitary tumor [3%]
- E. Pregnancy [2%]
- ✘ F. Thyroid hormone resistance [6%]

Incorrect
Correct answer
C

45%
Answered correctly

4 Seconds
Time Spent

11/08/2018
Last Updated

Conditions that alter TBG concentration	
Increased TBG	**Decreased TBG**
• **Estrogens** (eg, pregnancy, OCs, HRT) & estrogenic medications (eg, tamoxifen) • Acute hepatitis	• Androgenic hormones • High-dose glucocorticoids/hypercortisolism • Hypoproteinemia (eg, nephrotic syndrome, starvation) • Chronic liver disease

HRT = hormone replacement therapy; **OCs** = oral contraceptives; **TBG** = thyroxine-binding globulin.

This patient has an elevated total T4 concentration but her TSH is normal, suggesting a euthyroid state. Although she has nonspecific symptoms (eg, fatigue, anxiety), her vital signs and thyroid examination are normal. In light of her use of an oral contraceptive, this patient most likely has normal thyroid function with an **estrogen-induced** increase in **T4-binding globulin** (TBG).

More than 99% of the circulating thyroid hormone pool is bound to 3 major transport proteins: TBG, transthyretin, and albumin. Only the free (ie, unbound) thyroid hormones are biologically active. Changes in binding protein levels can affect the total circulating pool of thyroid hormones, but if the hypothalamic-pituitary-thyroid axis is intact, free hormone levels are unchanged.

High levels of estrogen (eg, pregnancy, oral contraceptive pills, hormone replacement therapy) increase the level of

High levels of estrogen (eg, pregnancy, oral contraceptive pills, hormone replacement therapy) increase the level of TBG by decreasing its catabolism and increasing its synthesis in the liver. As the additional TBG binds more thyroid hormone, thyroid hormone production increases to maintain a euthyroid state; this most likely explains this patient's slight elevation in **total** T4 level (her **free** T4 level would be expected to be normal).

(Choice A) In patients with normal hypothalamic-pituitary feedback, displacement of T4 from its binding proteins leads to decreased thyroid hormone production and lower total T4 levels (not higher, as seen in this patient) with normal free hormone levels. Medications with this effect include salicylates, furosemide, and heparin.

(Choice B) Graves disease causes hyperthyroidism due to stimulation of TSH receptors by thyrotropin-receptor antibodies. However, pituitary TSH secretion is suppressed and the thyroid gland is palpably enlarged.

(Choice D) In patients with a TSH-secreting pituitary adenoma, TSH is typically elevated, although a subset may have an inappropriately normal TSH. However, patients usually have a goiter and frequently have mass-effect symptoms (eg, headache).

(Choice E) Pregnancy can increase TBG levels but is less likely in a patient taking an oral contraceptive.

(Choice F) Resistance to thyroid hormone is a rare inherited disorder caused by defects in the thyroid hormone receptor. Patients can have elevated T4 levels with a normal or increased TSH, but most have a goiter, and this condition is usually apparent in childhood.

Educational objective:
Estrogen increases the level of T4-binding globulin. This effect is seen in pregnancy and in patients on oral contraceptives or menopausal estrogen replacement. Total thyroid hormone levels are elevated, but patients with

(Choice A) In patients with normal hypothalamic-pituitary feedback, displacement of T4 from its binding proteins leads to decreased thyroid hormone production and lower total T4 levels (not higher, as seen in this patient) with normal free hormone levels. Medications with this effect include salicylates, furosemide, and heparin.

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Educational objective:
Estrogen increases the level of T4-binding globulin. This effect is seen in pregnancy and in patients on oral contraceptives or menopausal estrogen replacement. Total thyroid hormone levels are elevated, but patients with normal hypothalamic-pituitary-thyroid function maintain a euthyroid state and normal TSH level.

References

- Drugs affecting thyroid function.

A 6-hour-old boy is in the newborn nursery with tachycardia. He was born at 40 weeks gestation to a 30-year-old woman with Graves' disease that was treated with surgical resection approximately 6 months before the pregnancy. Subsequently, the mother became mildly hypothyroid and was treated with levothyroxine during the pregnancy. The infant's weight is 2080 g (4 lb 9 oz) (<5th percentile), temperature is 37.2 C (99 F), and pulse is 190/min. Examination shows an irritable but consolable infant with warm, flushed skin. Which of the following is the most likely cause of this infant's condition?

- A. Ectopic thyroid tissue
- B. Inadequate maternal surgery
- C. Increased TSH production
- D. Transplacental levothyroxine
- E. Transplacental TSH-receptor antibody

Submit

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- A. Ectopic thyroid tissue [0%]
- B. Inadequate maternal surgery [0%]
- C. Increased TSH production [12%]
- D. Transplacental levothyroxine [37%]
- ✔ E. Transplacental TSH-receptor antibody [48%]

Correct

48% Answered correctly

4 Seconds TimeSpent

07/04/2018 Last Updated

Explanation

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

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This neonate's presentation (maternal history of **Graves' disease**, low birth weight, **tachycardia, warm skin, irritability**) is characteristic of neonatal **thyrotoxicosis** (neonatal Graves' disease). Thyrotoxicosis results from transplacental passage of **anti-TSH receptor antibodies** during the third trimester. Elevated anti-TSH receptor antibody levels can occur despite maternal treatment for Graves' disease and euthyroidism or hypothyroidism

transplacental passage of **anti-TSH receptor antibodies** during the third trimester. Elevated anti-TSH receptor antibody levels can occur despite maternal treatment for Graves' disease and euthyroidism or hypothyroidism during pregnancy. Neonates born to women with anti-TSH receptor antibodies >5 times the upper limit of normal are at greatest risk.

Most infants with thyrotoxicosis are born to mothers known to have Graves' disease. The most severe cases of thyrotoxicosis result in symptomatic fetuses (fetal tachycardia, hydrops, growth restriction.) Symptomatic patients require short-term treatment with **methimazole** plus a **β blocker** as neonatal hyperthyroidism has adverse effects on the developing nervous system (eg, growth retardation, developmental/behavioral problems). The condition generally **self-resolves** over the first few weeks to months of life as maternal antibody disappears from the infant's circulation.

(Choice A) Patients with ectopic thyroid tissue (ie, thyroglossal duct cysts) are usually euthyroid or hypothyroid, in contrast to this patient who is hyperthyroid.

(Choice B) This infant's mother has been mildly hypothyroid since her thyroidectomy. Excess hormone due to residual tissue is unlikely. In addition, maternal thyroid hormone does not cross the placenta in significant amounts.

(Choice C) TSH levels surge in healthy newborns immediately after delivery, leading to a rise in free T4 and T3. This increase in TSH and T4 is physiologic and the basis for neonatal screening for hypothyroidism. Infants with thyrotoxicosis can have suppression of the normal TSH surge.

(Choice D) Similar to endogenous thyroid hormone, levothyroxine does not cross the placenta to a significant

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(Choice C) TSH levels surge in healthy newborns immediately after delivery, leading to a rise in free T4 and T3. This increase in TSH and T4 is physiologic and the basis for neonatal screening for hypothyroidism. Infants with thyrotoxicosis can have suppression of the normal TSH surge.

(Choice D) Similar to endogenous thyroid hormone, levothyroxine does not cross the placenta to a significant degree. The fetus makes its own endogenous thyroid hormones.

Educational objective:
Infants born to women with Graves' disease are at risk for thyrotoxicosis due to passage of maternal TSH receptor antibodies across the placenta. Affected infants are irritable, tachycardic, and gain weight poorly. **Methimazole plus a β blocker** are given to symptomatic patients until the condition self-resolves over a few weeks to months.

References

- Fetal and neonatal thyrotoxicosis.
- Hyperthyroidism in pregnancy.

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A 45-year-old woman comes to the physician due to several months of progressively worsening watery diarrhea. She has cramps in her leg muscles and feels very dehydrated. She also has mild abdominal discomfort and describes her stools as tea colored. The patient has episodic flushing in her face. She follows a normal diet and has no fever or weight loss. There has been no recent travel to unusual places. The patient smokes 1-2 cigarettes a day and drinks socially. Her temperature is 36.8 C (98.1 F), blood pressure is 108/64 mm Hg, pulse is 118/min, and respirations are 18/min. Abdominal examination shows a nontender abdomen with normoactive bowel sounds. Laboratory results are as follows.

White blood cells	5600/µL
Hemoglobin	13.6 g/dL
Platelets	209,000/µL
Sodium	138 mEq/L
Potassium	2.1 mEq/L
Bicarbonate	20 mEq/L
Blood urea nitrogen	32 mg/dL
Creatinine	1.4 mg/dL
Glucose	116 mg/dL

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Bicarbonate	20 mEq/L
Blood urea nitrogen	32 mg/dL
Creatinine	1.4 mg/dL
Glucose	116 mg/dL

A CT scan of the abdomen shows a 3-cm mass in the pancreatic tail. Which of the following is the most likely diagnosis?

- A. Carcinoid syndrome
- B. Gastrinoma
- C. Pancreatic adenocarcinoma
- D. Systemic mastocytosis
- E. VIPoma

Submit

Potassium	2.1 mEq/L
Bicarbonate	20 mEq/L
Blood urea nitrogen	32 mg/dL
Creatinine	1.4 mg/dL
Glucose	116 mg/dL

A CT scan of the abdomen shows a 3-cm mass in the pancreatic tail. Which of the following is the most likely diagnosis?

- A. Carcinoid syndrome [38%]
- B. Gastrinoma [1%]
- C. Pancreatic adenocarcinoma [2%]
- D. Systemic mastocytosis [0%]
- ✔ E. VIPoma [57%]

Correct

57% Answered correctly

9 Seconds TimeSpent

08/15/2018 Last Updated

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)

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This patient's presentation suggests VIPoma, a rare tumor affecting the pancreatic cells that produce vasoactive intestinal peptide (VIP). Most affected adults are between ages 30-50. VIP binds to intestinal epithelial cells to increase fluid and electrolyte secretion in the intestinal lumen. Most patients develop **VIPoma syndrome** (pancreatic cholera) with **watery diarrhea** (can be tea colored and odorless), muscle weakness/cramps (due to hypokalemia), and hypo- or achlorhydria (due to decreased gastric acid secretion). The stool volume can be greater than 3L/day, leading to significant volume depletion. Other findings include facial flushing, lethargy, nausea, vomiting, abdominal pain, and weight loss. Patients can also have coexisting hyperparathyroidism as part

nausea, vomiting, abdominal pain, and weight loss. Patients can also have coexisting hyperparathyroidism as part of **multiple endocrine neoplasia (MEN)** syndrome.

Laboratory studies usually show **hypokalemia** due to increased intestinal potassium secretion. Other possible findings include hypercalcemia (due to increased bone resorption) and hyperglycemia (due to increased glycogenolysis). Stool studies are consistent with secretory diarrhea and show increased stool sodium and stool osmolal gap <50 mOsm/kg. A **VIP level** >75 pg/mL confirms VIPoma diagnosis. Abdominal imaging (cross-sectional triple-phase abdominal **CT or MRI**) can localize the tumor in the pancreas. Nearly 75% of VIPomas are in the pancreatic tail and 60%-80% have metastasized to the liver by the time of diagnosis. Treatment involves intravenous volume repletion, octreotide to decrease diarrhea, and possible hepatic resection in patients with metastasis to the liver.

(Choice A) Carcinoid syndrome can cause flushing, diarrhea, and bronchospasm. However, nearly 70%-80% of carcinoid tumors occur in the small intestine and do not usually involve the pancreas.

(Choice B) Gastrinomas can occur in the pancreas and cause diarrhea. However, they cause increased gastrin release with multiple gastric ulcers and dyspepsia (Zollinger-Ellison syndrome). In addition, they are not usually associated with facial flushing (seen in this patient).

(Choice C) Pancreatic adenocarcinoma involving the tail typically presents with abdominal and/or back pain, though it may occasionally cause steatorrhea, jaundice, or weight loss. The severe watery diarrhea with significant hypokalemia is more consistent with a neuroendocrine tumor like VIPoma.

(Choice D) Systemic mastocytosis involving the gastrointestinal tract can cause steatorrhea, hepatomegaly, and

carcinoid tumors occur in the small intestine and do not usually involve the pancreas.

(Choice B) Gastrinomas can occur in the pancreas and cause diarrhea. However, they cause increased gastrin release with multiple gastric ulcers and dyspepsia (Zollinger-Ellison syndrome). In addition, they are not usually associated with facial flushing (seen in this patient).

(Choice C) Pancreatic adenocarcinoma involving the tail typically presents with abdominal and/or back pain, though it may occasionally cause steatorrhea, jaundice, or weight loss. The severe watery diarrhea with significant hypokalemia is more consistent with a neuroendocrine tumor like VIPoma.

(Choice D) Systemic mastocytosis involving the gastrointestinal tract can cause steatorrhea, hepatomegaly, and peptic ulcer disease. Patients also usually develop skin symptoms including pruritus, facial flushing, and urticaria. However, mastocytosis would not cause the pancreatic mass seen in this patient.

Educational objective:

VIPoma is a rare tumor affecting the pancreatic cells that produce vasoactive intestinal peptide (VIP). Most patients develop VIPoma syndrome (pancreatic cholera) with watery diarrhea, muscle weakness/cramps (due to hypokalemia), and hypo- or achlorhydria (due to decreased gastric acid secretion). Stool studies are consistent with secretory diarrhea; a VIP level >75 pg/mL confirms VIPoma diagnosis.

References

- Pancreatic VIPomas: subject review and one institutional experience

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A 14-year-old boy comes to the office because he has been feeling a mass under his right nipple for the last three weeks. He has no medical problems and takes no medications. He does not use tobacco, alcohol, or ilicit drugs. The boy's stature and weight are average for his age and sex. Physical examination shows right gynecomastia with very mild tenderness. The left breast and the rest of the examination are unremarkable. He has normal Tanner 3 external genitalia and his testicular volume is 14 mL (normal 8 - 18 mL). What is the most appropriate next step in the management of this patient?

- A. Biopsy of right breast mass
- B. Karyotyping
- C. Magnetic resonance imaging of the brain
- D. Observation with reassurance
- E. Serum prolactin levels

Submit

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- ✗ A. Biopsy of right breast mass [8%]
- B. Karyotyping [0%]
- C. Magnetic resonance imaging of the brain [0%]
- ✓ D. Observation with reassurance [82%]
- E. Serum prolactin levels [7%]

Incorrect
Correct answer
D

82% Answered correctly
5 Seconds TimeSpent
08/02/2018 Last Updated

Explanation

A 14-year-old boy comes to the office because he has been feeling a mass under his right nipple for the last three weeks. He has no medical problems and takes no medications. He does not use tobacco, alcohol, or ilicit drugs. The boy's stature and weight are average for his age and sex. Physical examination shows right gynecomastia with very mild tenderness. The left breast and the rest of the examination are unremarkable. He has normal Tanner 3 external genitalia and his testicular volume is 14 mL (normal 8 - 18 mL). What is the most appropriate next step in the management of this patient?

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- C. Magnetic resonance imaging of the brain [0%]
- ✓ D. Observation with reassurance [82%]
- E. Serum prolactin levels [7%]

Incorrect
Correct answer
D

82%
Answered correctly

5 Seconds
TimeSpent

08/02/2018
Last Updated

Explanation

Common pathological causes of gynecomastia	
Increased estrogen production or peripheral conversion	• Testicular, adrenal, or human chorionic gonadotropin-secreting tumors • Cirrhosis or malnutrition • Thyrotoxicosis • Congenital excessive aromatase activity • Androgen use • Drugs (eg, spironolactone, cimetidine), herbal products (eg, tea tree oil, lavender oil)
Androgen deficiency	• Primary or secondary male hypogonadism (eg, Klinefelter syndrome, testicular damage) • Hyperprolactinemia • Renal failure

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Gynecomastia is enlarged benign glandular tissue of the male breast. It can occur in up to 2/3 of **pubertal boys** and present as unilateral or bilateral firm subareolar nodules (sometimes tender to the touch). The breast development is due to transiently increased testicular production of **estrogen** over testosterone and peripheral conversion of prohormones to estrogen. Pubertal gynecomastia resolves in most patients within a few months to 2 years without intervention. This patient's Tanner stage and testicular volume suggest mid to late puberty. The testicular volume in prepubertal boys is <3 mL (measured using a Prader orchidometer). This patient can be

conversion of prohormones to estrogen. Pubertal gynecomastia resolves in most patients within a few months to 2 years without intervention. This patient's Tanner stage and testicular volume suggest mid to late puberty. The testicular volume in prepubertal boys is <3 mL (measured using a Prader orchidometer). This patient can be observed clinically with **reassurance** as the gynecomastia will most likely resolve. Persistent gynecomastia after that time may require evaluation to exclude other causes (Table).

(Choice A) Biopsy of the breast mass is indicated in patients with suspected cancer. However, gynecomastia by itself carries a low cancer risk. One exception is **Klinefelter syndrome**, which does carry an increased risk of male breast cancer.

(Choice B) Karyotyping would be required in patients with suspected Klinefelter syndrome, which usually presents with small (<3 mL) and firm testes. However, this patient's appropriate testicular size for his stage of pubertal development makes this less likely.

(Choice C) Magnetic resonance imaging is indicated in patients with suspected pituitary tumor, which is less likely in this patient given his appropriate pubertal development.

(Choice E) Prolactin receptors are present in the male breast tissue. However, elevated prolactin causes breast enlargement indirectly by causing hypogonadism rather than direct stimulation of the male breast tissues.

Educational objective:
Pubertal gynecomastia is seen in up to 2/3 of adolescent boys during mid to late puberty. It can be unilateral, bilateral, or painful. No workup or treatment is necessary as it usually resolves within a few months to 2 years.

Gynecomastia is enlarged benign glandular tissue of the male breast. It can occur in up to 2/3 of pubertal boys

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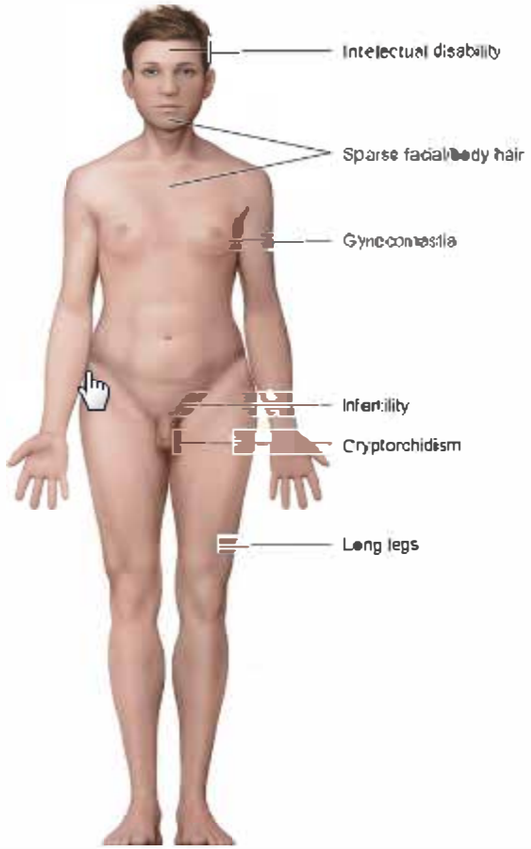
Klinefelter syndrome (47,XXY)



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Educational objective:

A 60-year-old man is hospitalized due to pneumonia. His other medical problems include hypertension, chronic obstructive pulmonary disease, and degenerative joint disease. The patient has a 60-pack-year smoking history and has consumed 2 12-oz cans of beer daily for the past 15 years. His medications include aspirin, metoprolol, enalapril, and albuterol and ipratropium inhalers. His temperature is 36.7 C (98 F), blood pressure is 140/80 mm Hg, pulse is 80/min, and respirations are 16/min. During his hospital stay, several blood tests were ordered and he was found to have hypothyroidism. Which of the following additional laboratory abnormalities would most likely be directly attributable to hypothyroidism?

- A. Hyperlipidemia
- B. Hypernatremia
- C. Hypocalcemia
- D. Neutropenia
- E. Thrombocytopenia

Submit

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- A. Hyperlipidemia [70%]
- B. Hypernatremia [4%]
- C. Hypocalcemia [17%]
- D. Neutropenia [4%]
- E. Thrombocytopenia [2%]

Incorrect
Correct answer
A

7●%
Answered correctly

5 Seconds
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Last Updated

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

adrenal insufficiency must be ruled out before diagnosing the syndrome of inappropriate antidiuretic hormone. However, hypothyroidism does not usually cause hypernatremia.

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(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.

Educational objective:

Hypothyroidism can cause additional metabolic abnormalities such as hyperlipidemia, hyponatremia and asymptomatic elevations of creatinine kinase and serum transaminases (aspartate aminotransferase and alanine aminotransferase). Most patients have hypercholesterolemia alone (due to decreased low-density lipoprotein [LDL] surface receptors and/or decreased LDL receptor activity) or combined with hypertriglyceridemia (due to decreased lipoprotein lipase activity).

References

Hyperlipidemia in patients with primary and secondary hypothyroidism

A week-old boy is brought to the emergency department due to vomiting and poor feeding. His mother received appropriate prenatal care, and the full-term infant was delivered at home. Temperature is 36.7 C (98 F), blood pressure is 40/24 mm Hg, pulse is 164/min, and respirations are 46/min. Physical examination is notable for sunken eyes, a depressed anterior fontanelle, and dry mucous membranes. Capillary refill is 3 seconds, and skin turgor is decreased. No abdominal masses are noted. Genital examination shows a normal uncircumcised penis with bilateral testes palpable in the scrotum. Laboratory results are as follows:

Serum chemistry

Sodium	128 mEq/L
Potassium	5.8 mEq/L
Blood urea nitrogen	25 mg/dL
Creatinine	0.7 mg/dL

Which of the following is most likely to be increased in this patient?

A. 11-deoxycorticosterone
B. 17-hydroxyprogesterone
C. Aldosterone
D. Cortisol

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A. 11-deoxycorticosterone
B. 17-hydroxyprogesterone
C. Aldosterone
D. Cortisol
E. Luteinizing hormone

Submit

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Serum chemistry

Sodium	128 mEq/L
Potassium	5.8 mEq/L
Blood urea nitrogen	25 mg/dL
Creatinine	0.7 mg/dL

Which of the following is most likely to be increased in this patient?

- A. 11-deoxycorticosterone [15%]
- ✔ B. 17-hydroxyprogesterone [62%]
- C. Aldosterone [15%]
- D. Cortisol [5%]
- E. Luteinizing hormone [0%]

Correct

62% Answered correctly

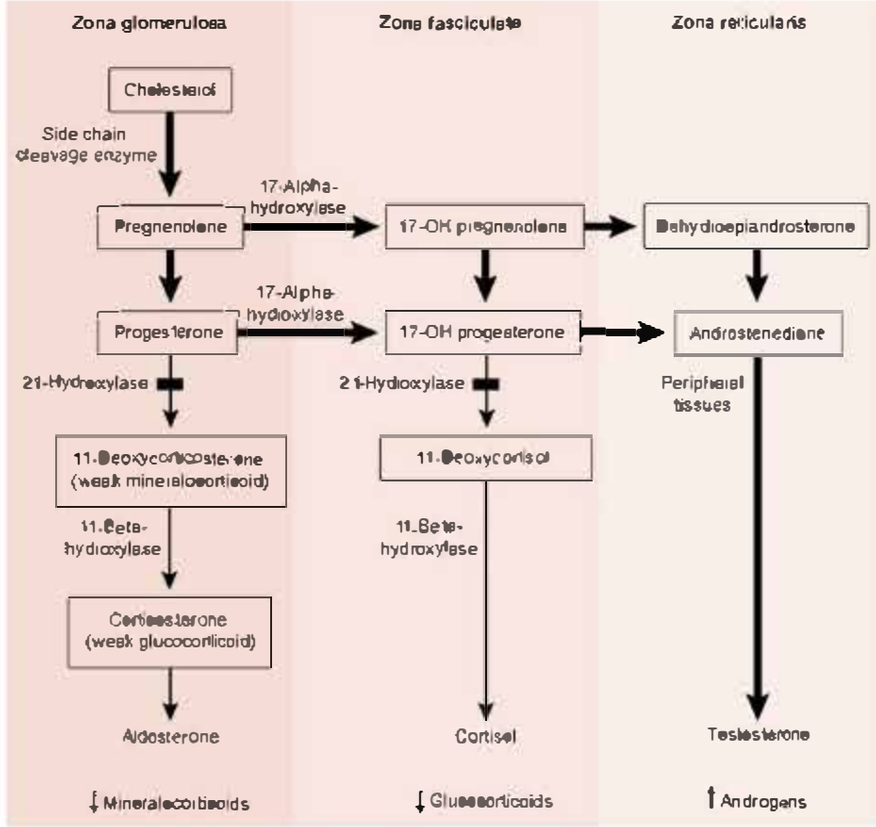
8 Seconds TimeSpent

07/24/2018 Last Updated

Cholesterol

Exhibit Display

21-Hydroxylase deficiency



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This infant has classic **congenital adrenal hyperplasia** (CAH) caused by **21-hydroxylase deficiency**, which results in:

- Inhibited conversion of progesterone to 11-deoxycorticosterone, a precursor to aldosterone: Decreased aldosterone causes **dehydration** (eg, sunken fontanelle, dry mucosa) and **salt-wasting** (eg, hypotension, hyponatremia, hyperkalemia) **(Choices A and C)**.
- Inhibited conversion of 17-hydroxyprogesterone to 11-deoxycortisol, a precursor to cortisol: Decreased cortisol results in fasting hypoglycemia **(Choice D)**.
- Increased conversion of 17-hydroxyprogesterone to androstenedione, a precursor to testosterone: Increased testosterone causes **virilization** and ambiguous genitalia in female infants. Male infants typically have no abnormal newborn genital findings, although they may have an enlarged penis or scrotal hyperpigmentation.

Newborn screening allows early detection of classic CAH, and a significantly **elevated 17-hydroxyprogesterone** level confirms the diagnosis. Treatment involves glucocorticoid and mineralocorticoid replacement.

(Choice E) LH is decreased in patients with classic CAH as elevated testosterone provides negative feedback to the hypothalamic-pituitary axis and inhibits LH secretion.

Educational objective:
Deficiency of 21-hydroxylase is the most common cause of congenital adrenal hyperplasia and classically presents with dehydration, salt-wasting, and virilization. Elevated 17-hydroxyprogesterone levels are diagnostic.

References

A 58-year-old man comes to the office due to a thyroid nodule that he first noticed a few weeks ago and which seems to have enlarged. There is no associated anxiety, heat or cold intolerance, or recent change in appetite or weight. Medical history is notable only for hypertension treated with lisinopril; the patient has no history of significant exposure to radiation. Family history is negative for thyroid disease. Blood pressure is 130/76 mm Hg and pulse is 79/min. Neck examination shows a hard, fixed, nontender nodule in the right thyroid lobe. Serum TSH level is normal. Ultrasonography of the thyroid gland shows a 4-cm right lobe nodule. Fine-needle aspiration biopsy shows a large number of follicular cells dispersed in clusters and microfollicles. Which of the following additional findings would be most consistent with a diagnosis of follicular thyroid cancer in this patient?

- A. Elevated serum calcitonin levels
- B. Invasion of the tumor capsule and/or blood vessels
- C. Lymph node involvement
- D. Presence of Hürthle cells
- E. Presence of psammoma bodies

Submit

A 58-year-old man comes to the office due to a thyroid nodule that he first noticed a few weeks ago and which seems to have enlarged. There is no associated anxiety, heat or cold intolerance, or recent change in appetite or weight. Medical history is notable only for hypertension treated with lisinopril; the patient has no history of significant exposure to radiation. Family history is negative for thyroid disease. Blood pressure is 130/76 mm Hg and pulse is 79/min. Neck examination shows a hard, fixed, nontender nodule in the right thyroid lobe. Serum TSH level is normal. Ultrasonography of the thyroid gland shows a 4-cm right lobe nodule. Fine-needle aspiration biopsy shows a large number of follicular cells dispersed in clusters and microfollicles. Which of the following additional findings would be most consistent with a diagnosis of follicular thyroid cancer in this patient?

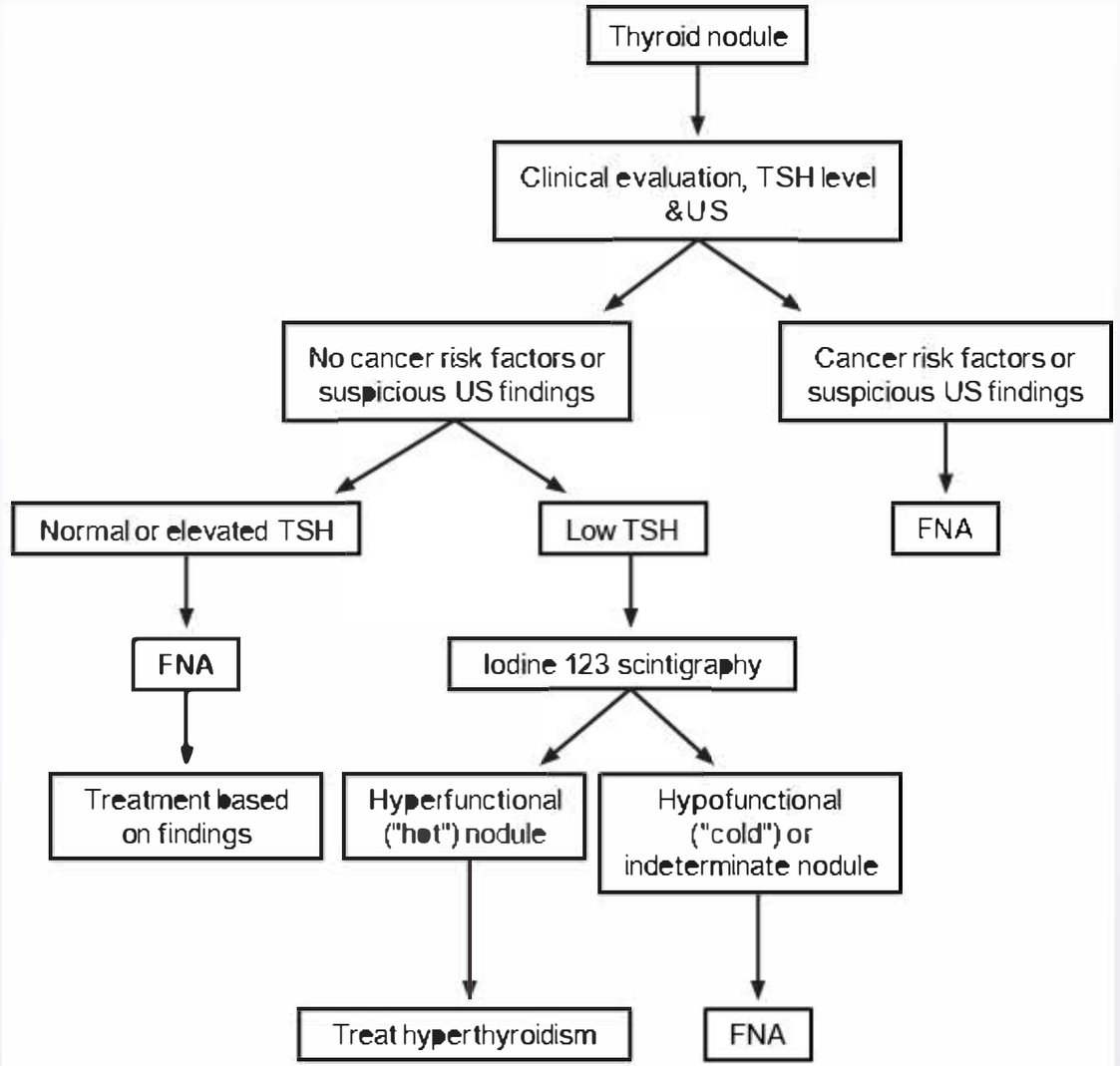
- A. Elevated serum calcitonin levels [7%]
- ✔ B. Invasion of the tumor capsule and/or blood vessels [55%]
- C. Lymph node involvement [4%]
- D. Presence of Hürthle cells [17%]
- E. Presence of psammoma bodies [15%]

Correct

55% Answered correctly

4 Seconds TimeSpent

09/08/2018 Last Updated



FNA = fine needle aspiration; **US** = ultrasound.

Follicular thyroid cancer (FTC) is the second most common thyroid epithelial malignancy (after papillary cancer) and has a peak incidence at age 40-60. It typically presents with a firm thyroid **nodule** and is often discovered incidentally on examination or imaging for other purposes. Thyroid scintigraphy usually shows a nonmetabolically active ("cold") nodule.

Diagnosis of FTC based on a limited tissue sample (eg, fine-needle biopsy) is not possible as the cytologic findings (large numbers of follicular cells arranged in microfollicles, clusters, and clumps, often categorized as "follicular neoplasm") are similar in both FTC and benign follicular adenomas. However, in contrast to benign adenomas, FTC is characterized by **invasion of the tumor capsule** and/or blood vessels, a finding that is typically made on examination of a surgically excised nodule. This invasion pattern accounts for the tendency of FTC to metastasize via **hematogenous spread** to distant tissues (eg, bone, lung).

(Choice A) Calcitonin is secreted by the parafollicular cells of the thyroid. Serum calcitonin levels are used in the diagnosis and follow-up of medullary thyroid carcinoma as well as in the diagnosis of multiple endocrine neoplasia type 2.

(Choices C and E) Papillary thyroid cancer is characterized by slow spread into local tissues and regional lymph nodes. Pathologic findings include large cells with ground glass cytoplasm; pale nuclei with inclusion bodies and central grooving; and grainy, lamellated calcifications known as **psammoma bodies**. In contrast to papillary thyroid cancer, lymph node involvement is not common in follicular cancer.

(Choice D) **Hürthle cells** are large, polygonal cells with eosinophilic cytoplasm containing large quantities of mitochondria. They are seen in FTC, but are a nonspecific finding, and are also seen in benign adenomas and chronic lymphocytic (Hashimoto) thyroiditis.

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(Choice D) **Hürthle cells** are large, polygonal cells with eosinophilic cytoplasm containing large quantities of mitochondria. They are seen in FTC, but are a nonspecific finding, and are also seen in benign adenomas and chronic lymphocytic (Hashimoto) thyroiditis.

Educational objective:
Diagnosis of follicular thyroid cancer (FTC) based on a limited tissue sample is not possible as the cytologic findings are similar to benign follicular adenomas. However, examination of a surgically excised nodule will show invasion of the tumor capsule and/or blood vessels. FTC can metastasize via hematogenous spread to distant tissues.

References

- How to interpret thyroid fine-needle aspiration biopsy reports: a guide for the busy radiologist in the era of the Bethesda Classification System.

Item 20 of 40
Question Id: 3499

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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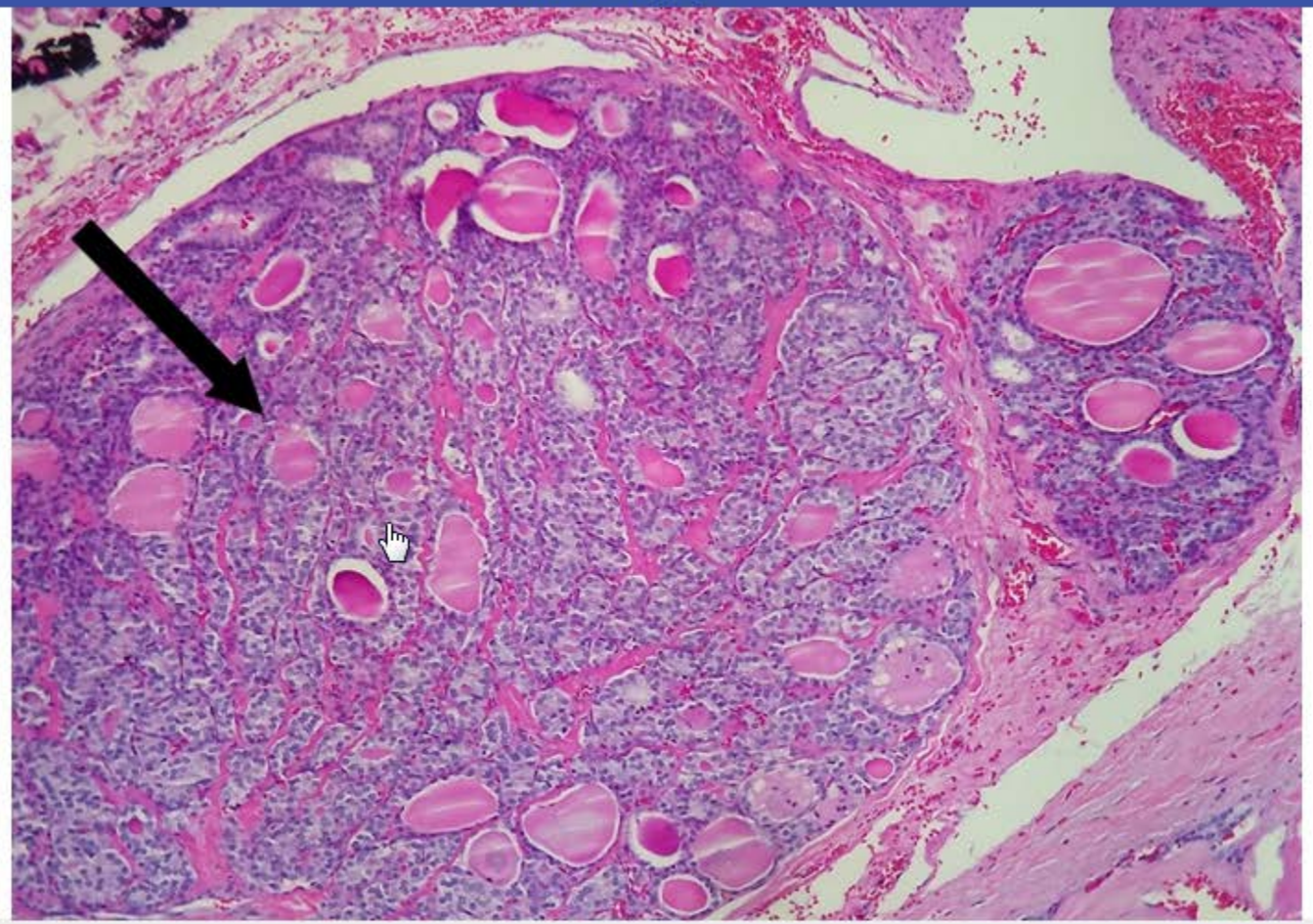

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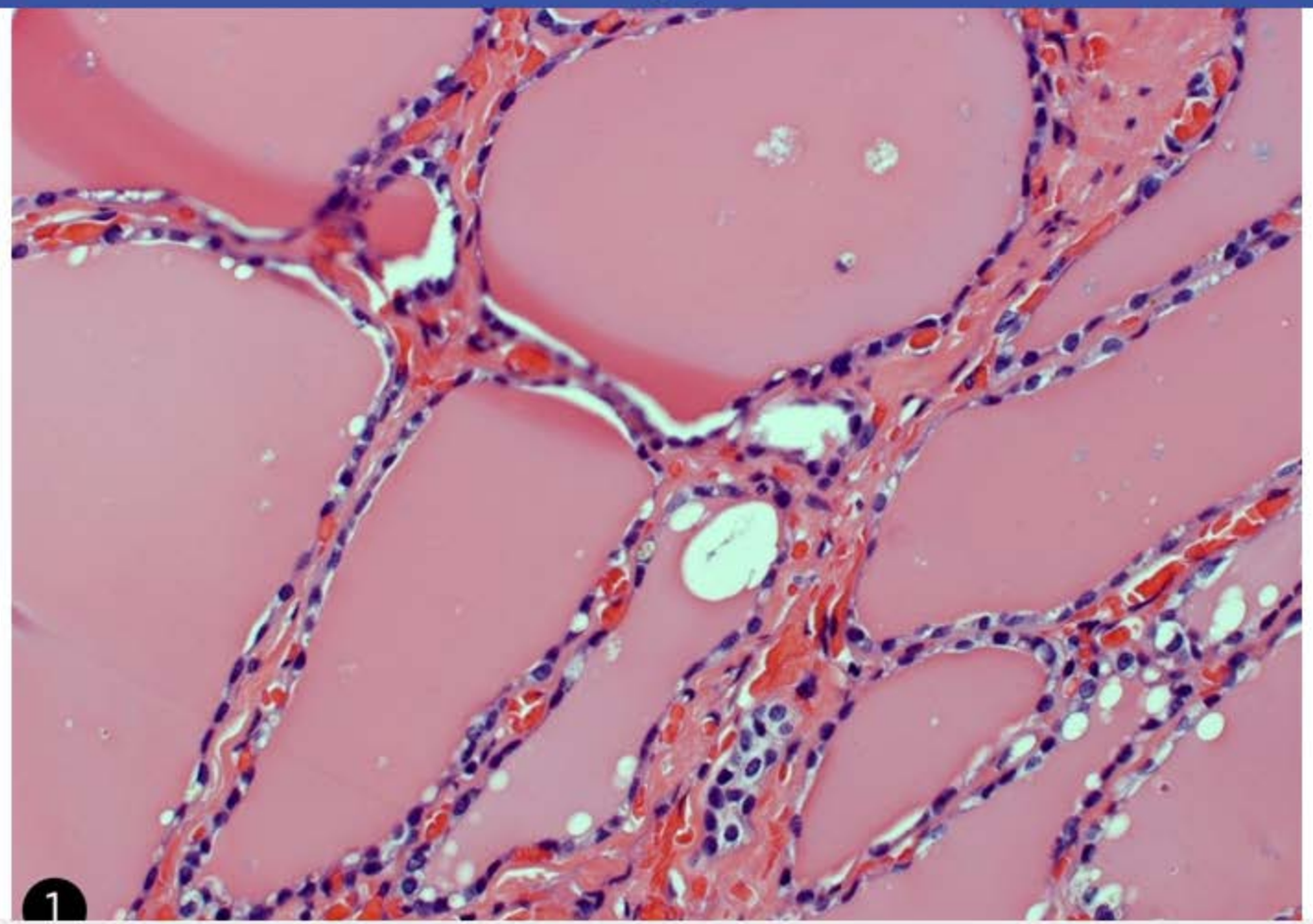

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A 65-year-old woman comes to the emergency department due to a 2-week history of constipation and abdominal pain. The patient also has urinary frequency and constant thirst. Her medical history is significant for persistent atrial fibrillation treated with diltiazem and rivaroxaban, hypertension treated with hydrochlorothiazide, and hypothyroidism treated with levothyroxine. In addition, the patient was diagnosed with osteoporosis 3 months ago; she declined treatment with bisphosphonates and instead opted to treat only with over-the-counter vitamin and mineral supplements. She does not use tobacco or alcohol. On physical examination, temperature is 36.8 C (98.2 F), blood pressure is 120/70 mm Hg, pulse is 90/min and irregular, and respirations are 12/min. Mucous membranes are dry, and the abdomen is soft and nontender without rebound tenderness or rigidity. Bowel sounds are decreased but present. Bedside dipstick urinalysis is within normal limits. Which of the following is the most likely cause of this patient's current symptoms?

- A. Adverse effect of diltiazem
- B. Diabetic ketoacidosis
- C. Hypothyroidism
- D. Milk-alkali syndrome
- E. Thiazide-induced hypercalcemia
- F. Vitamin A toxicity

pain. The patient also has urinary frequency and constant thirst. Her medical history is significant for persistent atrial fibrillation treated with diltiazem and rivaroxaban, hypertension treated with hydrochlorothiazide, and hypothyroidism treated with levothyroxine. In addition, the patient was diagnosed with osteoporosis 3 months ago; she declined treatment with bisphosphonates and instead opted to treat only with over-the-counter vitamin and mineral supplements. She does not use tobacco or alcohol. On physical examination, temperature is 36.8 C (98.2 F), blood pressure is 120/70 mm Hg, pulse is 90/min and irregular, and respirations are 12/min. Mucous membranes are dry, and the abdomen is soft and nontender without rebound tenderness or rigidity. Bowel sounds are decreased but present. Bedside dipstick urinalysis is within normal limits. Which of the following is the most likely cause of this patient's current symptoms?

- A. Adverse effect of diltiazem [7%]
- B. Diabetic ketoacidosis [2%]
- C. Hypothyroidism [6%]
- ✔ D. Milk-alkali syndrome [33%]
- E. Thiazide-induced hypercalcemia [43%]
- F. Vitamin A toxicity [6%]

Correct

33% Answered correctly

21 Seconds TimeSpent

06/16/2018 Last Updated

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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This patient has typical symptoms of **hypercalcemia**, including abdominal pain, constipation, and polydipsia. In light of initiation of over-the-counter supplements for osteoporosis 3 months ago, her symptoms are likely due to **milk-alkali syndrome** (MAS). MAS is caused by excessive intake of **calcium and absorbable alkali** (eg, calcium carbonate preparations used in patients with osteoporosis). The resulting hypercalcemia causes **renal**

milk-alkali syndrome (MAS). MAS is caused by excessive intake of **calcium and absorbable alkali** (eg, calcium carbonate preparations used in patients with osteoporosis). The resulting hypercalcemia causes **renal vasoconstriction** and decreased glomerular blood flow. In addition, inhibition of the Na-K-2Cl cotransporter (due to activation of calcium-sensing receptors in the thick ascending loop) and impaired antidiuretic hormone activity lead to loss of sodium and free water. This results in hypovolemia and increased reabsorption of bicarbonate (augmented by the increased intake of alkali).

Medications that raise the risk of MAS include thiazide diuretics, ACE inhibitors/angiotensin II receptor blockers, and nonsteroidal anti-inflammatory drugs. In addition to hypercalcemia, metabolic findings in MAS include hypophosphatemia, hypomagnesemia, **metabolic alkalosis**, and **acute kidney injury**. Parathyroid hormone levels are suppressed.

(Choice A) Diltiazem is a calcium channel blocker that can cause constipation, but it does not cause other symptoms of hypercalcemia (ie, polyuria and polydipsia).

(Choice B) Diabetic ketoacidosis can be the initial presentation of type 1 diabetes mellitus and presents with polyuria, polydipsia, and weight loss. However, new onset of type 1 diabetes is uncommon in older individuals, and urinalysis would show glucose and ketones.

(Choice C) Hypothyroidism can cause constipation but is unlikely to lead to hypercalcemia and would be accompanied by other findings (eg, weight gain, cold intolerance, fatigue). Hyperthyroidism (and excessive replacement of levothyroxine in hypothyroidism) can cause mild hypercalcemia due to increased bone turnover but is unlikely to cause constipation.

polyuria, polydipsia, and weight loss. However, new onset of type 1 diabetes is uncommon in older individuals, and urinalysis would show glucose and ketones.

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(Choices E) Thiazides can be associated with mild hypercalcemia due to increased calcium reabsorption in the distal tubule. However, symptomatic calcemia as seen in this patient would be extremely unlikely due to thiazide therapy alone, especially as there is no indication that her thiazide dose has changed.

(Choice F) Excessive doses of vitamin A can increase bone turnover and lead to abdominal pain and hypercalcemia; however, hypercalcemia is usually mild, and vitamin A toxicity would also manifest as dry skin, headache, and blurry vision.

Educational objective:

Milk-alkali syndrome is caused by excessive intake of calcium and absorbable alkali. It can be seen in patients taking calcium bicarbonate for osteoporosis. Clinical findings include symptomatic hypercalcemia, metabolic alkalosis, and acute kidney injury.

References

- Antacids, altered mental status, and milk-alkali syndrome.

A 7-year-old boy is brought to the office for severe facial acne that has developed over the past few months. His mother tried treating it with topical benzoyl peroxide and a salicylic acid face wash with no improvement. She also noticed a significant increase in her son's growth, and he is now much taller than his fraternal twin brother. The patient is otherwise healthy with no chronic medical conditions and takes no medications. Height is at the 98th percentile and weight is at the 85th percentile for age and sex. Neurologic examination is normal. Skin examination shows severe cystic acne involving the face and shoulders. Examination reveals coarse pubic and axillary hair. Testicular volume is 2 mL. Bone age is 2 standard deviations higher than chronological age. Baseline LH levels are low and do not increase after stimulation with a GnRH agonist. Which of the following is the most likely diagnosis in this patient?

- A. Hypothyroidism
- B. Idiopathic precocious puberty
- C. Klinefelter syndrome
- D. McCune-Albright syndrome
- E. Nonclassic congenital adrenal hyperplasia
- F. Pituitary microadenoma

Submit

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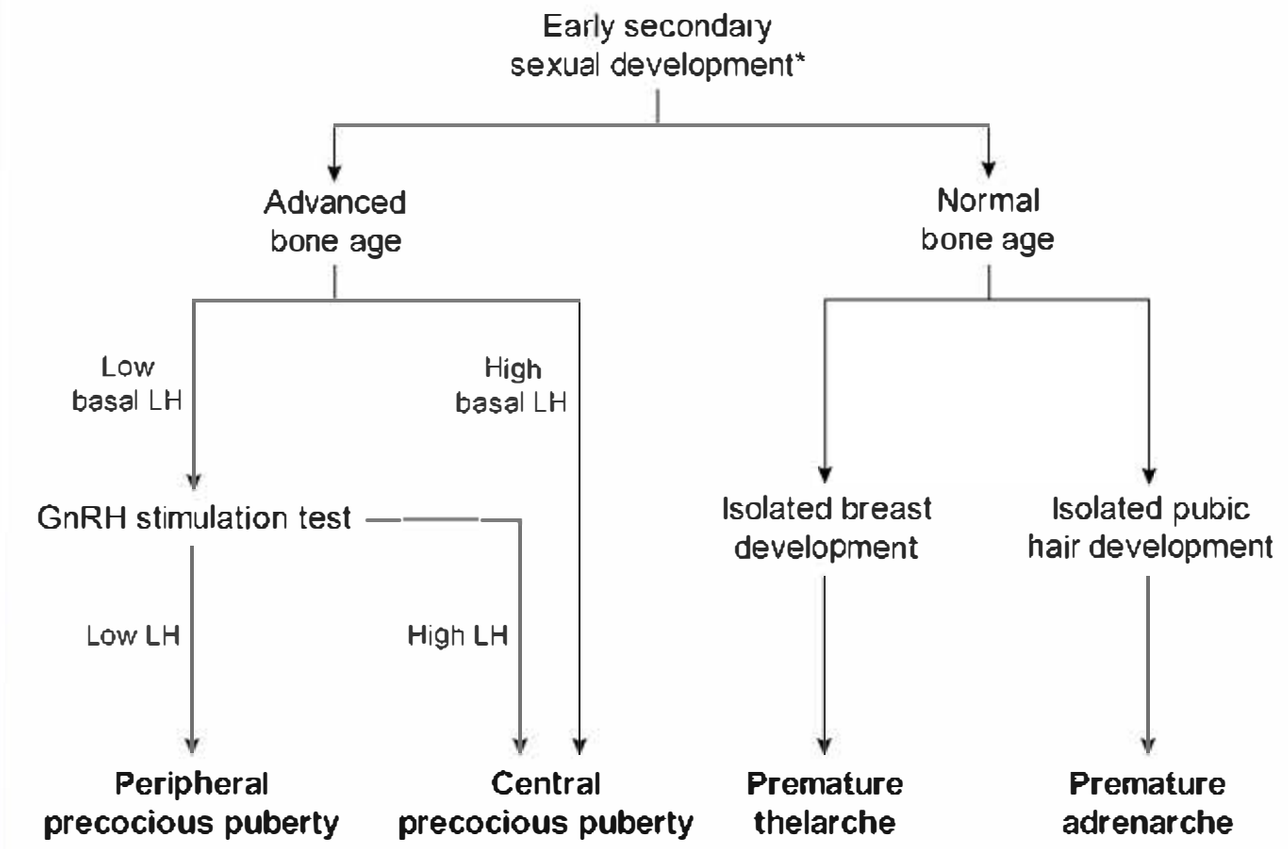
- A. Hypothyroidism [0%]
- B. Idiopathic precocious puberty [29%]
- C. Klinefelter syndrome [7%]
- D. McCune-Albright syndrome [6%]
- ✔ E. Nonclassic congenital adrenal hyperplasia [40%]
- F. Pituitary microadenoma [15%]

Evaluation of precocious puberty



*Secondary sexual development in girls age <8 or boys age <9.

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Precocious puberty is the onset of secondary sexual characteristics (eg, **pubic/axillary hair**, **cystic acne**, accelerated growth) in girls age <8 and **boys age <9**. Patients with precocious puberty are initially assessed by obtaining a bone age, which differentiates true precocious puberty (advanced bone age) from an isolated premature thelarche/adrenarche (normal bone age). In patients with **advanced bone age** (>2 standard deviations above chronological age), LH levels differentiate between peripheral and central precocious puberty. Patients with peripheral (gonadotropin-independent) precocious puberty have a **low/normal LH level** due to inhibition of the hypothalamus by high circulating androgen levels from the adrenal glands or testes.

This patient's early onset of secondary sexual characteristics, advanced bone age, and low LH level are suggestive of peripheral precocious puberty, likely **nonclassic congenital adrenal hyperplasia** (CAH) secondary to **21-hydroxylase (*CYP21A2*) deficiency**. Similar to classic CAH, the 21-hydroxylase deficiency impairs the conversion of 17-hydroxyprogesterone to 11-deoxycortisol; 17-hydroxyprogesterone is shunted toward adrenal androgen overproduction (ie, precocious puberty). However, in patients with nonclassic CAH, sufficient glucocorticoid and mineralocorticoid levels are maintained; therefore, patients have normal electrolytes (no salt wasting).

(Choice A) Severe, untreated primary hypothyroidism can cause gonadotropin-dependent precocious puberty; however, boys typically have premature testicular enlargement and short stature, not accelerated linear growth.

(Choices B and F) Idiopathic precocious puberty (premature activation of the hypothalamic-pituitary-gonadal axis) and pituitary microadenomas cause gonadotropin-dependent (central) precocious puberty. Due to continuous activation of the hypothalamus, patients with central precocious puberty have either a high basal LH or an LH level that increases with GnRH stimulation.

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(Choices B and F) Idiopathic precocious puberty (premature activation of the hypothalamic-pituitary-gonadal axis) and pituitary microadenomas cause gonadotropin-dependent (central) precocious puberty. Due to continuous activation of the hypothalamus, patients with central precocious puberty have either a high basal LH or an LH level that increases with GnRH stimulation.

(Choice C) Klinefelter syndrome (47,XXY) causes primary hypogonadism, which is characterized by low testosterone and elevated LH levels. Patients have a tall stature; however, puberty is typically delayed.

(Choice D) McCune-Albright syndrome is a rare cause of gonadotropin-independent precocious puberty that presents with irregular café-au-lait macules and fibrous dysplasia of bone, which are not seen in this patient.

Educational objective:
Nonclassic congenital adrenal hyperplasia is a cause of gonadotropin-independent precocious puberty. Patients can have premature secondary sexual characteristics (eg, pubic hair, cystic acne), accelerated growth and bone age, and low/normal LH levels.

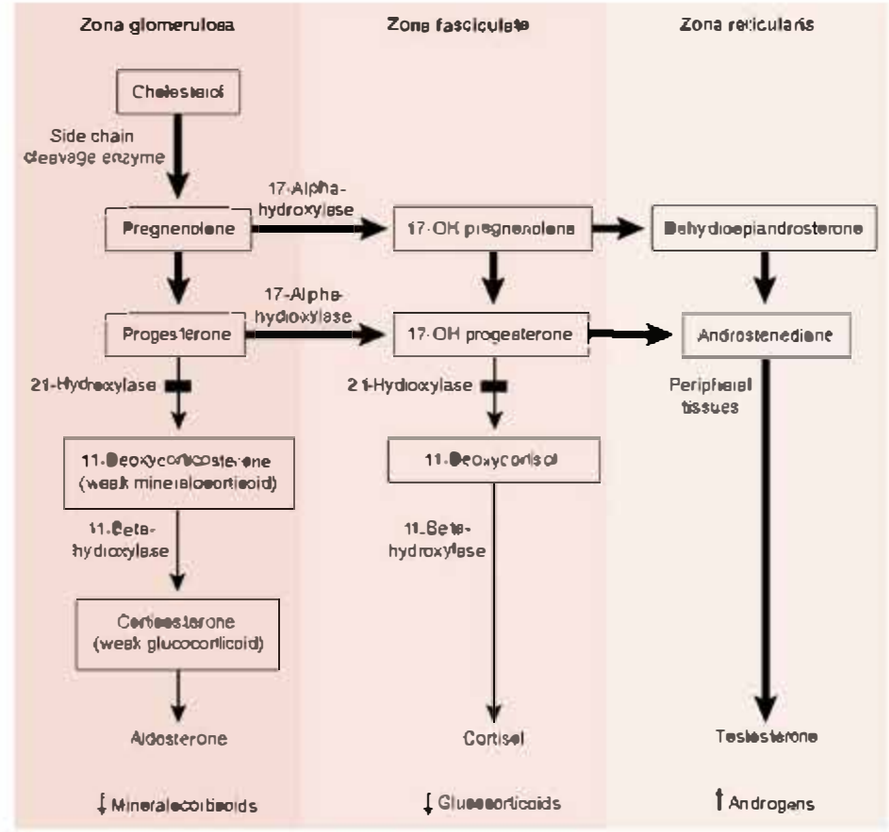
References

- Nonclassic congenital adrenal hyperplasia due to 21-hydroxylase deficiency: clinical presentation, diagnosis,

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

Exhibit Display

21-Hydroxylase deficiency



Zoom In | Zoom Out | Reset | Add To Flash Card

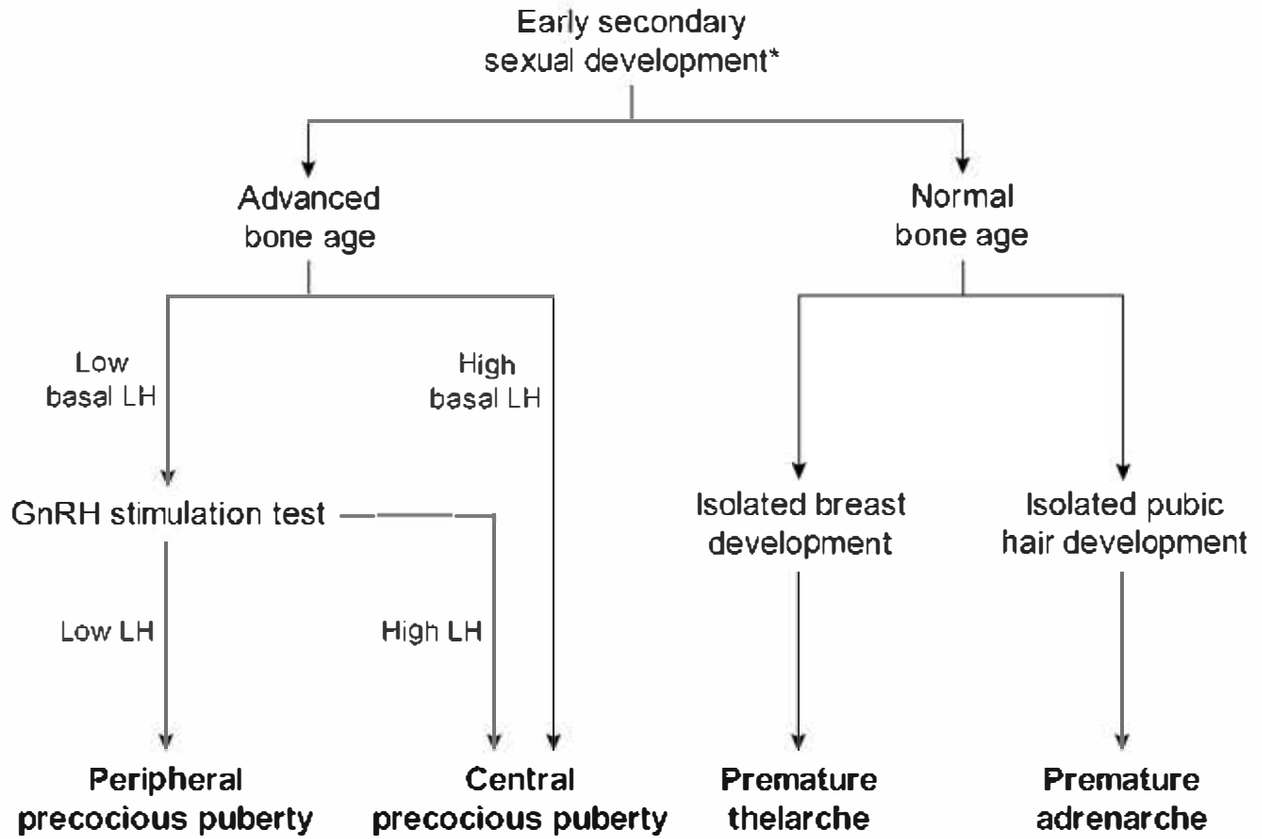
A 5-year-old girl is brought to the office for evaluation of pubic hair. Her mother noticed dark hair under the girl's arms and in her pubic area several days ago when helping her bathe. The patient has no headaches, visual changes, abdominal pain, or behavioral changes. She is obese and currently on a diet and exercise program. Several maternal relatives have type 2 diabetes mellitus. The patient's height has been tracking along the 50th percentile and weight at the 97th percentile. Physical examination shows a cooperative girl with mild facial acne. No breast buds are palpable. She has dark, coarse hair across the pubis and under both axillae. External genitalia appear normal. Bone age is normal. Which of the following is the most likely diagnosis for this patient?

- A. Congenital adrenal hyperplasia
- B. Granulosa cell tumor
- C. Hepatoblastoma
- D. Hypothalamic glioma
- E. Idiopathic precocious puberty
- F. McCune-Albright syndrome
- G. Pituitary hamartoma
- H. Premature adrenarche

A 5-year-old girl is brought to the office for evaluation of pubic hair. Her mother noticed dark hair under the girl's arms and in her pubic area several days ago when helping her bathe. The patient has no headaches, visual changes, abdominal pain, or behavioral changes. She is obese and currently on a diet and exercise program. Several maternal relatives have type 2 diabetes mellitus. The patient's height has been tracking along the 50th percentile and weight at the 97th percentile. Physical examination shows a cooperative girl with mild facial acne. No breast buds are palpable. She has dark, coarse hair across the pubis and under both axillae. External genitalia appear normal. Bone age is normal. Which of the following is the most likely diagnosis for this patient?

- A. Congenital adrenal hyperplasia [17%]
- B. Granulosa cell tumor [7%]
- C. Hepatoblastoma [0%]
- D. Hypothalamic glioma [0%]
- E. Idiopathic precocious puberty [14%]
- ✗ F. McCune-Albright syndrome [4%]
- G. Pituitary hamartoma [0%]
- ✓ H. Premature adrenarche [54%]

Evaluation of precocious puberty



*Secondary sexual development in girls age <8 or boys age <9.

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Development of secondary sexual characteristics is premature (ie, precocious) in girls age <8 and boys age <9. **Obese** children are at high risk for precocious development as adiposity can trigger excess insulin production, which then stimulates the adrenal glands to produce sex hormones.

Isolated **premature adrenarche** is caused by early activation of **adrenal androgens**. Typical manifestations include body odor, oily skin, **acne**, and **pubic and axillary hair**. However, estrogen and testosterone levels remain normal; therefore, there are no other signs of premature puberty (eg, breast development, testicular enlargement) or virilization (eg, clitoromegaly). Mildly elevated dehydroepiandrosterone sulfate present in children with premature adrenarche is not sufficient to affect skeletal growth; therefore, **bone age is normal** in these patients.

Isolated premature adrenarche is generally benign but a risk factor for developing polycystic ovary syndrome, type 2 diabetes mellitus, and metabolic syndrome, especially in obese patients.

(Choice A) Girls with classic congenital adrenal hyperplasia (CAH) present in infancy with salt-wasting and virilization. Due to partial 21-hydroxylase deficiency, nonclassic (late-onset) CAH manifests in childhood with premature pubarche/adrenarche (without virilization). However, significant elevations in androgen levels associated with CAH accelerate skeletal maturity, and an advanced bone age is expected.

(Choice B) Granulosa cell estrogen/progesterone-secreting tumors typically present in middle-aged women with an ovarian mass and menstrual abnormalities. In rare cases, children with this tumor may have premature breast development and menses due to hyperestrogenism, but not isolated acne and pubic hair.

(Choice C) Malignant testosterone-secreting hepatoblastomas are a rare cause of premature adrenarche and

virilization. Due to partial 21-hydroxylase deficiency, nonclassic (late-onset) CAH manifests in childhood with premature pubarche/adrenarche (without virilization). However, significant elevations in androgen levels associated with CAH accelerate skeletal maturity, and an advanced bone age is expected.

(Choice B) Granulosa cell estrogen/progesterone-secreting tumors typically present in middle-aged women with an ovarian mass and menstrual abnormalities. In rare cases, children with this tumor may have premature breast development and menses due to hyperestrogenism, but not isolated acne and pubic hair.

(Choice C) Malignant testosterone-secreting hepatoblastomas are a rare cause of premature adrenarche and occur almost exclusively in boys.

(Choices D, E, and G) Hypothalamic glioma, pituitary hamartoma, and idiopathic precocious puberty are causes of central precocious puberty, which is characterized by advanced bone age, elevated FSH and LH, and true precocious development (eg, breast development).

(Choice F) McCune-Albright syndrome is characterized by peripheral precocious puberty, irregular café-au-lait macules, and fibrous dysplasia of the bone. Girls typically have premature vaginal bleeding and breast development, which are not seen in this child.

Educational objective:
Premature adrenarche is caused by early activation of adrenal androgens and is more common in obese children. Typical presentation includes precocious development of pubic and axillary hair, acne, and body odor in a child with a normal bone age.

A 53-year-old man comes to the physician complaining of increased urinary frequency for the past 4 weeks. He has no burning with urination, urgency, or difficulty initiating urination. He wakes up several times at night to urinate. His mouth feels dry all the time and he drinks fluids almost every hour to alleviate his thirst. The patient's medications include hydrochlorothiazide and amlodipine for hypertension. His sister was diagnosed with diabetes mellitus at a young age. His blood pressure is 120/76 mm Hg, pulse is 85/min, and respirations are 15/min. He is afebrile. His body mass index is 32 kg/m^2. Laboratory results are as follows:

Blood glucose	93 mg/dL
Serum sodium	150 mEq/L
Serum potassium	4.1 mEq/L
Bicarbonate	24 mEq/L
Blood urea nitrogen	21 mg/dL
Serum creatinine	1.1 mg/dL
Serum uric acid	10.1 mg/dL
Serum osmolality	314 mOsm/kg
Urine osmolality	124 mOsm/kg

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Which of the following is most consistent with this patient's findings?

A. Benign prostatic hyperplasia
B. Diabetes insipidus
C. Glucose diuresis
D. Hydrochlorothiazide side effect
E. Primary polydipsia
F. Renal tubular acidosis
G. Syndrome of inappropriate antidiuretic hormone
H. Urea diuresis

Serum uric acid	10.1 mg/dL
Serum osmolality	314 mOsm/kg
Urine osmolality	124 mOsm/kg

Which of the following is most consistent with this patient's findings?

- A. Benign prostatic hyperplasia [0%]
- ✔ B. Diabetes insipidus [74%]
- C. Glucose diuresis [1%]
- ✘ D. Hydrochlorothiazide side effect [10%]
- E. Primary polydipsia [3%]
- F. Renal tubular acidosis [1%]
- G. Syndrome of inappropriate antidiuretic hormone [4%]
- H. Urea diuresis [3%]

Incorrect
Correct answer

74%
Answered Correctly

10 Seconds
Time Spent

05/28/2018
Last Updated

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

ADH = antidiuretic hormone; DI = diabetes insipidus.

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This patient has polyuria with dilute urine and increased water intake. Polyuria in the nonhospitalized patient is most commonly due to diabetes mellitus, primary polydipsia (previously known as psychogenic polydipsia), and central or nephrogenic diabetes insipidus (DI). This patient's normal glucose makes diabetes mellitus less likely. Primary polydipsia is due to increased water intake that leads to a dilute urine (urine osmolality < 1/2 plasma osmolality) and hyponatremia (sodium <137 mEq/L). Serum Na >145 mEq/L with dilute urine excludes primary

Primary polydipsia is due to increased water intake that leads to a dilute urine (urine osmolality < 1/2 plasma osmolality) and hyponatremia (sodium <137 mEq/L). Serum Na >145 mEq/L with dilute urine excludes primary polydipsia and suggests DI in this patient **(Choice E)**.

DI can be central or nephrogenic. Central DI is due to decreased antidiuretic hormone (ADH) secretion from the pituitary. Nephrogenic DI has normal ADH levels with varying degrees of renal ADH resistance. The decreased ADH action in both types of DI leads to decreased renal water reabsorption and water loss with polyuria. This results in dilute urine and hypernatremia. Central DI usually has significant hypernatremia (>150 mEq/L) due to an impaired thirst mechanism. Patients with nephrogenic DI usually have an intact thirst mechanism and adequate water intake; they usually compensate for renal water loss and may have a normal sodium level.

(Choice A) Benign prostatic hyperplasia can present with urinary hesitancy, weak urinary stream, nocturia, and incomplete voiding with overflow incontinence. However, it does not usually cause this degree of dilute urine or hypernatremia.

(Choices C and H) Osmotic diuresis is usually due to solutes (eg, glucose, mannitol, urea) that are not well reabsorbed in the kidney. Patients develop polyuria with a high serum osmolality. However, this patient's normal serum glucose and relatively normal blood urea nitrogen make this less likely.

(Choice D) Hydrochlorothiazide (HCTZ) acts in the distal kidney and can cause hypokalemia, hyperglycemia, and hyperuricemia. Although this patient's polyuria could be due to HCTZ, diuretics more commonly cause hyponatremia instead of hypernatremia. In addition, diuretic use usually stimulates ADH release to result in concentrated urine rather than the very dilute urine seen in this patient.

serum glucose and relatively normal blood urea nitrogen make this less likely.

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(Choice F) Renal tubular acidosis (RTA) usually presents with a normal anion gap metabolic acidosis. The serum bicarbonate is typically <20 mEq/L, which is not present in this patient. In addition, RTA does not typically cause the degree of hypernatremia or dilute urine seen in this patient.

(Choice G) Syndrome of inappropriate antidiuretic hormone (SIADH) leads to inappropriately high ADH concentration and concentrated urine with urine osmolality > serum osmolality. The excess water reabsorption in the kidney leads to hyponatremia and a lower serum uric acid level. However, polyuria is not commonly associated with SIADH. This patient's dilute urine, elevated uric acid, and hypernatremia also make this unlikely.

Educational objective:

Polyuria in nonhospitalized patients can be due to primary polydipsia or diabetes insipidus (DI). Primary polydipsia is due to increased water intake that leads to a dilute urine (urine osmolality < 1/2 plasma osmolality) and hyponatremia (sodium <137 mEq/L). Serum Na >145 mEq/L with dilute urine excludes primary polydipsia and favors DI. DI can be central (decreased antidiuretic hormone [ADH] release from pituitary) or nephrogenic (normal ADH level but with renal ADH resistance).

A 6-year-old girl is brought to the office by her parents after they noticed the development of axillary and pubic hair. She has also had a significant growth spurt over the past year. There has been no change in her behavior or school performance. The patient has no headaches, vomiting, or visual disturbances. She has no chronic medical conditions and takes no medications. Family history is unremarkable. BMI is at the 97th percentile for age and sex. The abdomen is soft, nontender, and nondistended. Axillary hair is present and pubic hair is Tanner stage 3; external genitalia are normal. The breasts are Tanner stage 3. Neurologic examination is normal. Bone age is advanced. Serum FSH and LH levels are elevated. Which of the following is the most likely etiology of this patient's symptoms?

- A. Early activation of the hypothalamic-pituitary-ovarian axis
- B. Estrogen-producing ovarian cysts
- C. Excess peripheral conversion of testosterone to estrogen
- D. Excess production of 17-hydroxyprogesterone
- E. Exogenous estrogen exposure
- F. Increased adrenal production of dehydroepiandrosterone sulfate

Submit

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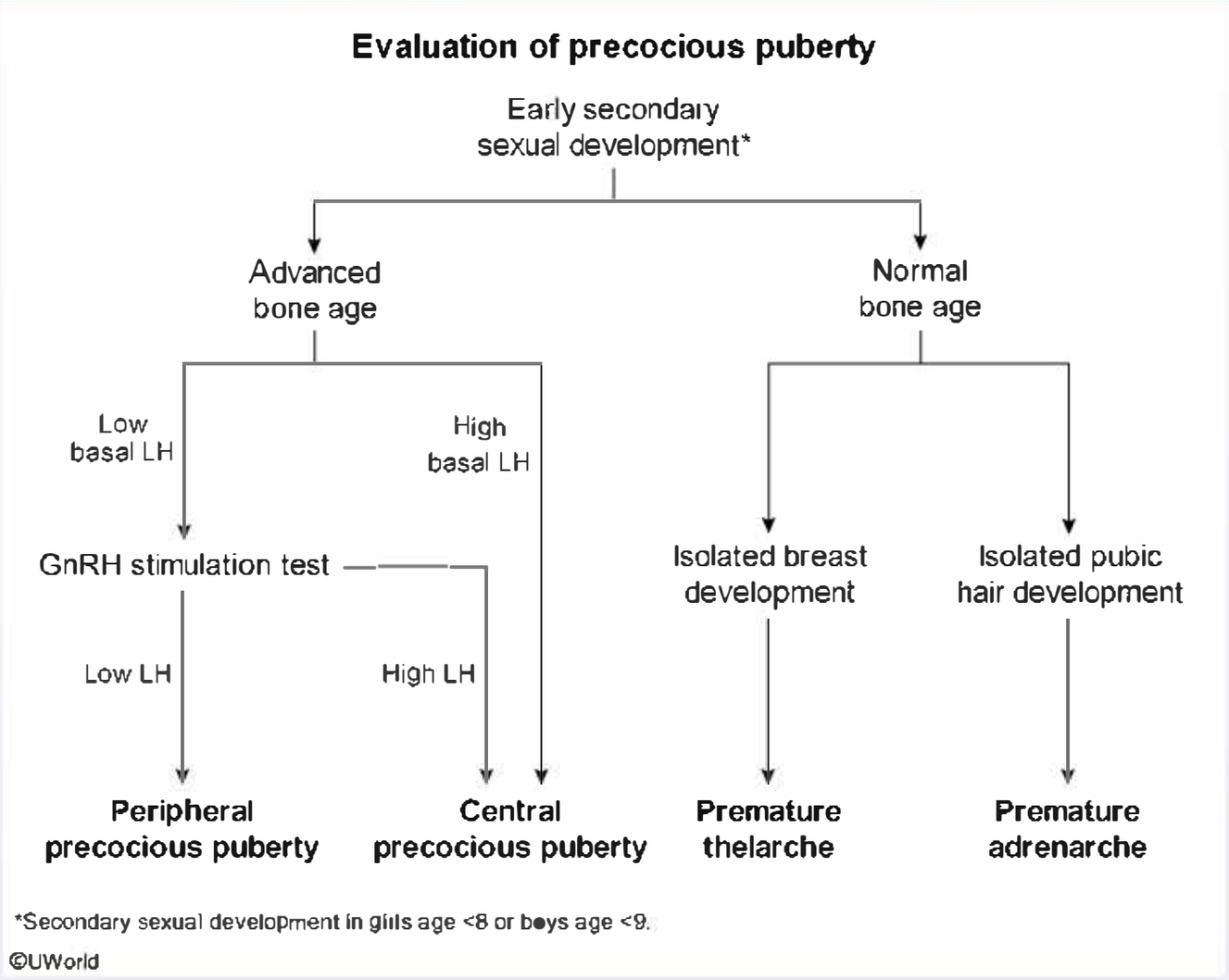
- ✔ A. Early activation of the hypothalamic-pituitary-ovarian axis [82%]
- B. Estrogen-producing ovarian cysts [2%]
- C. Excess peripheral conversion of testosterone to estrogen [5%]
- D. Excess production of 17-hydroxyprogesterone [5%]
- ✘ E. Exogenous estrogen exposure [1%]
- F. Increased adrenal production of dehydroepiandrosterone sulfate [3%]

Incorrect
Correct answer

82%
Answered correctly

4 Seconds
Time Spent

07/22/2018
Last Updated



This patient has **breast** and **pubic/axillary hair** development consistent with **precocious puberty**, the onset of

This patient has **breast** and **pubic/axillary hair** development consistent with **precocious puberty**, the onset of secondary sexual characteristics in girls age <8 and boys age <9. The initial evaluation of patients with precocious puberty is a bone age radiograph, which helps differentiate true precocious puberty from other causes of early pubic/axillary hair development (eg, premature adrenarche). Patients with true precocious puberty have increased estrogen/testosterone levels that accelerate skeletal maturation, resulting in **advanced bone age** and increased growth velocity (as seen in this patient).

The etiology of precocious puberty is categorized as either central (gonadotropin-dependent) or peripheral (gonadotropin-independent).

- **Central precocious puberty** (CPP) results from **early activation** of the **hypothalamic-pituitary-gonadal (HPG) axis**. Pulsatile GnRH secretion stimulates **elevated FSH and LH levels**, as seen in this patient.
- Peripheral precocious puberty (PPP) is caused by gonadal or adrenal release of excess sex hormones. Basal levels of FSH and LH are typically low due to negative feedback and remain low following GnRH agonist stimulation.

Patients with CPP require MRI of the brain to evaluate for a hypothalamic or pituitary tumor activating the HPG axis. If MRI is negative, the cause is most likely idiopathic precocious puberty, and GnRH therapy can be initiated. GnRH desensitizes the pituitary and suppresses FSH and LH secretion to slow pubertal progression and maximize height potential.

(Choices B and E) Estrogen-producing ovarian cysts and exogenous estrogen exposure result in PPP. Although girls may demonstrate premature development of secondary sexual characteristics and may also have advanced

height potential.

(Choices B and E) Estrogen-producing ovarian cysts and exogenous estrogen exposure result in PPP. Although girls may demonstrate premature development of secondary sexual characteristics and may also have advanced bone age, they have low FSH and LH levels.

(Choice C) Excess peripheral conversion of testosterone to estrogen, as seen with aromatase excess, results in precocious puberty in girls but low FSH and LH due to feedback inhibition.

(Choices D and F) Elevated 17-hydroxyprogesterone is found in patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. Significant increases in dehydroepiandrosterone sulfate occur in patients with an adrenal tumor. CAH and adrenal tumors can cause PPP; affected patients have low FSH and LH levels.

Educational objective:
Precocious puberty, the onset of secondary sexual characteristics in girls age <8 and boys age <9, has both central and peripheral causes. Central precocious puberty is due to early activation of the hypothalamic-pituitary-gonadal axis and presents with increased levels of FSH and LH.

References

- Central precocious puberty: revisiting the diagnosis and therapeutic management.
- Gonadotropin-releasing hormone stimulation test for precocious puberty.

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A 36-year-old man comes to the office with a 6-month history of fatigue, mild headache, and decreased libido. His past medical history is notable for type 2 diabetes and bipolar disorder. His medications include metformin and risperidone. The patient smokes a pack of cigarettes a day and drinks 2 or 3 cans of beer daily. Blood pressure is 126/73 mm Hg and pulse is 86/min. His BMI is 31 kg/m^2. Physical examination shows decreased testicular volume but is otherwise normal. Laboratory results are as follows:

LH	0.5 mIU/mL
Testosterone, total	100 ng/dL (normal: 240-950 ng/dL)
TSH	0.05 µU/mL
Thyroxine (T_4), free	0.45 ng/dL (normal: 0.9-1.7 ng/dL)
Prolactin	35 ng/mL

Which of the following is the most likely diagnosis?

A. Alcohol-related testicular atrophy
B. Chromosomal abnormality
C. Chronic autoimmune thyroiditis
D. Medication side effect

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D. Medication side effect
E. Pituitary adenoma

Submit

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Prolactin	35 ng/mL

Which of the following is the most likely diagnosis?

- ✗ A. Alcohol-related testicular atrophy [1%]
- B. Chromosomal abnormality [0%]
- C. Chronic autoimmune thyroiditis [1%]
- D. Medication side effect [42%]
- ✓ E. Pituitary adenoma [54%]

Incorrect

Common causes of hypogonadism in men	
Primary (testicular)	• Congenital (eg, Klinefelter syndrome, cryptorchidism) • Drugs (eg, alkylating agents, ketoconazole) • Orchitis (eg, mumps), trauma, torsion • Chronic kidney disease
Secondary (pituitary/hypothalamic)	• **Gonadotroph damage**: Tumor, cranial trauma, infiltrative diseases (eg, hemochromatosis), apoplexy • **Gonadotropin suppression**: Exogenous androgens, hyperprolactinemia, diabetes mellitus, morbid obesity
Combined (primary & secondary)	• Hypercortisolism • Cirrhosis

This patient has **hypopituitarism** featuring central hypogonadism (low LH and testosterone) and central hypothyroidism (low TSH and thyroxine) along with mildly elevated prolactin. This is strongly suggestive of a **nonfunctioning pituitary adenoma**, which usually arises from the gonadotropin-secreting cells (**gonadotrophs**) in the pituitary gland. Normal gonadotrophs secrete LH and FSH (which are dimeric hormones consisting of a common α-subunit and a different β-subunit), but the dysfunctional cells in most gonadotroph adenomas secrete primarily the common **α-subunit**.

The clinical symptoms of α-subunit overproduction are usually minimal ("nonfunctioning" adenoma), and the

The clinical symptoms of α-subunit overproduction are usually minimal ("nonfunctioning" adenoma), and the diagnosis is not usually apparent until the adenoma is large enough to cause features of **mass effect** on local tissues (eg, headache, visual field defects, disruption of the surrounding pituitary function). Production of most **pituitary hormones** (eg, TSH, LH) will be **decreased** due to compression of the neighboring normal pituitary cells. By contrast, **prolactin** levels are often **mildly to moderately elevated** due to anatomic disruption of the dopaminergic neural pathways that normally suppress prolactin secretion. (A more significant elevation of prolactin [eg, >200 ng/mL] would suggest a prolactin-secreting adenoma (prolactinoma) rather than a nonfunctioning adenoma.)

(Choice A) Excessive alcohol intake can cause hypogonadism by suppressing LH release by the pituitary or by directly inhibiting testosterone production in the testes. However, pituitary TSH production is usually unaffected by alcohol, and this patient's moderate intake is unlikely to have significant endocrine effects.

(Choice B) Klinefelter syndrome (47,XXY) is a chromosomal disorder associated with hypogonadism, small testes, and decreased virilization. The hypothalamic-pituitary axis is usually intact, however, and LH is increased. This patient's late onset of symptoms makes a chromosomal abnormality unlikely.

(Choice C) Chronic autoimmune thyroiditis (Hashimoto thyroiditis) is characterized by immune-mediated destruction of thyroid follicles and is the most common cause of hypothyroidism in the general population. Patients will have low free T_4 and elevated TSH.

(Choice D) Many commonly used antipsychotic medications (eg, risperidone) can cause hyperprolactinemia due to blockade of the normal dopamine-dependent regulation of prolactin secretion. However, TSH is usually

directly inhibiting testosterone production in the testes. However, pituitary TSH production is usually unaffected by alcohol, and this patient's moderate intake is unlikely to have significant endocrine effects.

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(Choice D) Many commonly used antipsychotic medications (eg, risperidone) can cause hyperprolactinemia due to blockade of the normal dopamine-dependent regulation of prolactin secretion. However, TSH is usually unaffected.

Educational objective:
Hypopituitarism with a mild to moderate increase in prolactin suggests a nonfunctioning (gonadotroph) adenoma. Patients may develop symptomatic hypogonadism or hypothyroidism but are frequently asymptomatic until the adenoma becomes very large and causes a mass effect on surrounding tissues.

References

- Pituitary adenomas: an overview.

A 65-year-old man comes to the office due to recurrent falls. For the last several months, he has had a sensation of imbalance that is worse at night, but with no associated pain or motor weakness. Medical history is notable for type 2 diabetes mellitus diagnosed 20 years ago and hypertension diagnosed 10 years ago. The patient was found to have nonproliferative diabetic retinopathy at his last ophthalmologic visit. Current medications include insulin, metformin, rosuvastatin, and ramipril. He does not smoke, but drinks 1 or 2 beers daily and often more on weekends. Physical examination shows decreased proprioception and vibration sense in the feet. Ankle jerk reflexes are absent. Finger-to-nose and heel-to-shin tests are normal, but the patient sways and tends to fall when his eyes are closed. Bilateral hammer toe deformities are present in the feet. The remainder of the examination is unremarkable. Which of the following processes is predominantly responsible for this patient's neurologic symptoms?

- A. Axonopathy of large nerve fibers
- B. Axonopathy of small nerve fibers
- C. Degeneration of cerebellar hemispheres
- D. Degeneration of lateral spinothalamic tract
- E. Diffuse demyelination of lower extremity nerve fibers

Submit

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- ✔ A. Axonopathy of large nerve fibers [30%]
- B. Axonopathy of small nerve fibers [34%]
- ✘ C. Degeneration of cerebellar hemispheres [10%]
- D. Degeneration of lateral spinothalamic tract [7%]
- E. Diffuse demyelination of lower extremity nerve fibers [15%]

Incorrect

30%

5 Seconds

10/05/2018

Diabetes mellitus is the most common cause of peripheral neuropathy, with the risk related to the duration of disease and glycemic status. Neuronal injury in diabetes is due to a number of factors, including microvascular injury, demyelination, oxidative stress, and deposition of glycosylation end products. This leads to a length-dependent axonopathy, with clinical features occurring first in the longest nerves (eg, feet).

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).

This patient primarily has features of large fiber involvement, with loss of position sense causing gait imbalance (worsened with eye closure as there is no visual compensation for the loss of proprioception) and weakness of the intrinsic muscles of the feet leading to foot deformities (eg, hammer toe deformity).

(Choice C) Degeneration of the cerebellar hemispheres (eg, due to alcohol use) can cause gait disturbances due to incoordination of the limbs. However, most patients will have additional abnormalities, including dysmetria (eg, finger-to-nose), dysarthric speech, and intention tremor.

(Choice D) Proprioception and vibration sense are carried by the posterior column of the spinal cord, and lesions here may resemble large fiber neuropathy. By contrast, the anterolateral system (eg, lateral spinothalamic tract) carries primarily pain and temperature sensation.

This patient primarily has features of large fiber involvement, with loss of position sense causing gait imbalance (worsened with eye closure as there is no visual compensation for the loss of proprioception) and weakness of the intrinsic muscles of the feet leading to foot deformities (eg, hammer toe deformity).

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(Choice D) Proprioception and vibration sense are carried by the posterior column of the spinal cord, and lesions here may resemble large fiber neuropathy. By contrast, the anterolateral system (eg, lateral spinothalamic tract) carries primarily pain and temperature sensation.

(Choice E) Patchy demyelination may occur in diabetic neuropathy. Diffuse demyelination is seen in Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy, and is usually associated with more severe motor weakness.

Educational objective:
Sensorimotor polyneuropathy in diabetes is characterized by length-dependent axonopathy. Small fiber involvement causes pain and paresthesias, whereas large fiber injury causes numbness, loss of proprioception and vibration sense, and diminished ankle reflexes.

References

- Physiology in medicine: neuromuscular consequences of diabetic neuropathy.

A 70-year-old man is brought to the emergency department after his daughter found him lethargic and confused in his home. He was sick with a "cold" for the past 2 days. The patient lives alone and ambulates with a walker after suffering a stroke 5 years ago. His daughter lives nearby and helps him with his activities. On arrival, his temperature is 38 C (100.4 F), blood pressure is 90/65 mm Hg, pulse is 112/min, and respirations are 24/min. Mucous membranes are dry. His airway is maintained, and oxygen is administered. Intravenous access is secured, and blood and urine samples are drawn. Laboratory results are as follows:

Sodium	134 mEq/L
Potassium	5.9 mEq/L
Chloride	101 mEq/L
Bicarbonate	22 mEq/L
Blood urea nitrogen	110 mg/dL
Glucose	1000 mg/dL
Serum calcium	9.2 mg/dL
Amylase	100 U/L
Aspartate aminotransferase	15 U/L
Alanine	

aminotransferase	15 U/L
Alanine aminotransferase	17 U/L

Arterial blood gases:

pH	7.40
PaCO2	38 mm Hg
PaO2	90 mm Hg

Which of the following is the best initial treatment for this patient?

- A. 0.45% saline
- B. Long-acting insulin analogue
- C. Normal saline
- D. Potassium chloride
- E. Sodium bicarbonate
- F. Subcutaneous insulin

aminotransferase

Arterial blood gases:

pH	7.40
PaCO2	38 mm Hg
PaO2	90 mm Hg

Which of the following is the best initial treatment for this patient?

- A. 0.45% saline [1%]
- B. Long-acting insulin analogue [2%]
- ✔ C. Normal saline [80%]
- D. Potassium chloride [1%]
- E. Sodium bicarbonate [1%]
- F. Subcutaneous insulin [12%]

Correct

80%
Answered correctly

13 Seconds
Time Spent

10/05/2018
Last Updated

Hyperosmolar hyperglycemic state	
Patient characteristics	• Type 2 diabetes • Older age
Clinical symptoms	• Gradual hyperglycemic symptoms (eg, polyuria, polydipsia) • Altered mentation
Laboratory studies	• Glucose >1000 mg/dL • Normal pH & bicarbonate • Normal anion gap • Negative or small serum ketones • Serum osmolality >320 mOsm/kg
Initial management	• Aggressive hydration with **normal saline** • **Intravenous insulin** • Careful monitoring & supplementation of **potassium**

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This patient has severe hyperglycemia associated with acute mental status changes consistent with **hyperosmolar hyperglycemic state** (HHS). Unlike diabetic ketoacidosis (DKA), HHS is caused by a relative rather than absolute insulin deficiency, and accumulation of ketoacids will be minimal (arterial pH and anion gap are typically normal). However, the plasma glucose is often >1000 mg/dL (compared to 300-500 mg/dL in DKA) and the effective plasma osmolality, which is approximately equal to (2 x plasma sodium in mEq/L + plasma

are typically normal). However, the plasma glucose is often >1000 mg/dL (compared to 300-500 mg/dL in DKA) and the effective plasma osmolality, which is approximately equal to (2 x plasma sodium in mEq/L + plasma glucose in mg/dL ÷ 18), can be severely elevated (often >320 mOsm/kg).

Severe hyperglycemia induces an **osmotic diuresis**, which can lead to a deficit of 8-10 liters in total body water. In light of this, **fluid replacement** is the most important initial step in management of HHS, and aggressive hydration will improve tissue perfusion and responsiveness to insulin therapy. This patient has prominent evidence of dehydration with hypotension, tachycardia, and dry mucous membranes. **Normal saline** (NS) is recommended for volume resuscitation in the first few hours of treatment (regardless of sodium levels), with a subsequent change to 0.45% NS if the corrected sodium (measured sodium in mEq/L + [2 mEq/L sodium for each 100 mg/dL that glucose is above 100 mg/dL]) is normal or high on repeat laboratory testing **(Choice A)**.

(Choices B and F) Glucose can be lowered with careful insulin therapy; **intravenous regular or short-acting insulin** is preferred to subcutaneous insulin, as hypovolemia and systemic vasoconstriction in HHS can lead to erratic absorption of insulin from subcutaneous tissues. Subcutaneous insulin can sometimes be administered in patients with mild DKA but would not be appropriate for this patient with HHS and marked hypovolemia.

(Choice D) Most patients, including those with normal initial serum potassium levels, will have a total body potassium deficit, and insulin therapy can rapidly cause hypokalemia as it drives potassium into cells. Therefore, potassium should be monitored frequently, with supplemental potassium added to intravenous fluids if levels are between 3.3 and 5.3 mEq/L.

(Choice E) Infusion of sodium bicarbonate is sometimes used in patients with DKA and severe acidosis (pH <6.9). It is not needed in HHS.

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(Choices B and F) Glucose can be lowered with careful insulin therapy; **intravenous regular or short-acting insulin** is preferred to subcutaneous insulin, as hypovolemia and systemic vasoconstriction in HHS can lead to erratic absorption of insulin from subcutaneous tissues. Subcutaneous insulin can sometimes be administered in patients with mild DKA but would not be appropriate for this patient with HHS and marked hypovolemia.

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(Choice E) Infusion of sodium bicarbonate is sometimes used in patients with DKA and severe acidosis (pH <6.9). It is not needed in HHS.

Educational objective:
Hyperosmolar hyperglycemic state is characterized by severe hyperglycemia with mental status changes. Severe hyperglycemia induces an osmotic diuresis, which can lead to a deficit of 8-10 liters in total body water. Fluid replacement with normal saline is the most important initial step in management of hyperosmolar hyperglycemic state.

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A 56-year-old man is admitted to the hospital with severe nausea and vomiting. He has also had fatigue, poor appetite, polyuria, polydipsia, and constipation for several weeks. The patient has a history of hypertension and type 2 diabetes mellitus. His home medications include metformin, lisinopril, and hydrochlorothiazide. He has a 40-pack-year smoking history and drinks alcohol occasionally. Temperature is 36.7 C (98 F), blood pressure is 110/70 mm Hg, pulse is 102/min, and respirations are 16/min. His mucous membranes are dry. The rest of the physical examination is unremarkable. Laboratory results are as follows:

Calcium	14.8 mg/dL
Albumin	4.0 g/dL
Parathyroid hormone, intact	5 pg/mL
Creatinine	1.9 mg/dL
Urea nitrogen	54 mg/dL
Glucose	180 mg/dL
25-hydroxyvitamin D	50 ng/mL (normal, 20-60 ng/mL)
1,25-dihydroxyvitamin D	17 pg/mL (normal, 15-65 pg/mL)

Urea nitrogen	54 mg/dL
Glucose	180 mg/dL
25-hydroxyvitamin D	50 ng/mL (normal, 20-60 ng/mL)
1,25-dihydroxyvitamin D	17 pg/mL (normal, 15-65 pg/mL)

Which of the following is the most likely cause of this patient's hypercalcemia?

- A. Chronic kidney disease
- B. Hydrochlorothiazide-induced hypercalcemia
- C. Hypercalcemia of malignancy
- D. Osteoporosis
- E. Primary hyperparathyroidism
- F. Sarcoidosis

Submit

Urea nitrogen	54 mg/dL
Glucose	180 mg/dL
25-hydroxyvitamin D	50 ng/mL (normal, 20-60 ng/mL)
1,25-dihydroxyvitamin D	17 pg/mL (normal, 15-65 pg/mL)

Which of the following is the most likely cause of this patient's hypercalcemia?

- A. Chronic kidney disease [14%]
- B. Hydrochlorothiazide-induced hypercalcemia [24%]
- ✔ C. Hypercalcemia of malignancy [58%]
- D. Osteoporosis [0%]
- E. Primary hyperparathyroidism [1%]
- F. Sarcoidosis [0%]

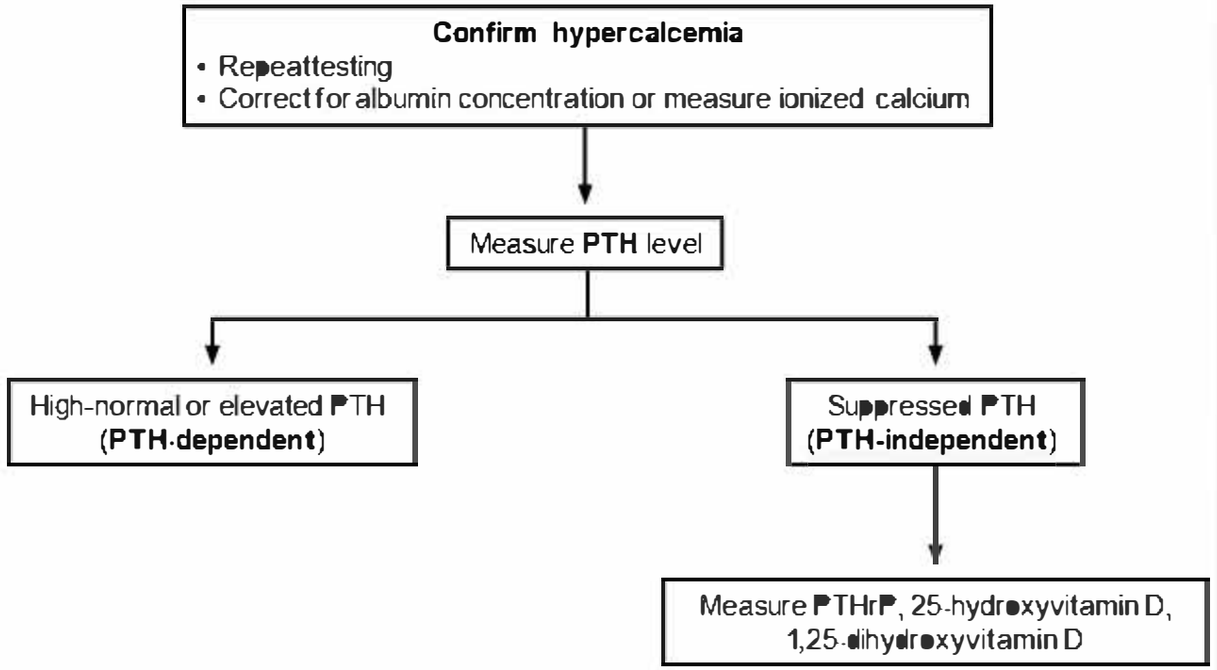
Correct

58% Answered correctly

8 Seconds TimeSpent

06/09/2018 Last Updated

Diagnosis of hypercalcemia



Causes
- **Primary** (or tertiary) **hyperparathyroidism**
- Familial hypocalciuric hypercalcemia
- Lithium

Causes
- **Malignancy**
- Vitamin D toxicity
- Granulomatous diseases
- Drug-induced (eg, thiazides)
- Milk-alkali syndrome
- Thyrotoxicosis
- Vitamin A toxicity
- Immobilization

Hypercalcemia can be categorized as either **parathyroid hormone (PTH) dependent** (high-normal or increased PTH [eg, hyperparathyroidism]) or **independent** (low/suppressed PTH). **Humoral hypercalcemia of malignancy** (HHM) is the most common cause of PTH-independent hypercalcemia and frequently presents with very high (eg, >14 mg/dL), symptomatic (eg, polyuria, constipation, nausea) calcium levels. HHM should be strongly suspected in this patient in light of his smoking history, systemic symptoms (eg, fatigue, poor appetite), and **markedly elevated calcium** with **low PTH**.

HHM is due to secretion of **PTH-related protein** (PTHrP) by malignant cells and is associated with squamous cell (eg, lung, head and neck), renal, bladder, breast, or ovarian carcinomas. PTHrP causes increased bone resorption and increased reabsorption of calcium in the distal renal tubule. However, PTHrP does not induce the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D to the same extent as PTH does, and so 1,25-dihydroxyvitamin D levels will be low or low-normal.

Other causes of PTH-independent hypercalcemia in malignancy include bony destruction by osteolytic metastasis (eg, breast, non-small cell lung cancer, non-Hodgkin lymphoma, multiple myeloma), increased production of 1,25-dihydroxyvitamin D (eg, lymphoma), and increased interleukin-6 levels (eg, multiple myeloma).

(Choice A) Chronic kidney disease causes decreased renal production of vitamin D, leading to hypocalcemia, hyperphosphatemia, and a compensatory rise in PTH (secondary hyperparathyroidism).

(Choice B) Hydrochlorothiazide increases urinary calcium reabsorption, which can mildly increase serum calcium levels (usually <12 mg/dL). Severe hypercalcemia does not occur.

(Choice D) Rapid bony destruction due to skeletal metastasis may cause hypercalcemia, but the gradual bone

hyperphosphatemia, and a compensatory rise in PTH (secondary hyperparathyroidism).

(Choice B) Hydrochlorothiazide increases urinary calcium reabsorption, which can mildly increase serum calcium levels (usually <12 mg/dL). Severe hypercalcemia does not occur.

(Choice D) Rapid bony destruction due to skeletal metastasis may cause hypercalcemia, but the gradual bone loss seen in osteoporosis does not affect serum calcium levels.

(Choice E) Primary hyperparathyroidism rarely causes severe hypercalcemia (calcium is usually <12 mg/dL), and this patient's suppressed PTH level rules out this diagnosis.

(Choice F) Sarcoidosis and certain hematologic malignancies (eg, lymphoma) can cause hypercalcemia due to increased conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. However, this patient's low-normal 1,25-dihydroxyvitamin D level makes this less likely.

Educational objective:
Humoral hypercalcemia of malignancy is the most common cause of parathyroid hormone (PTH)-independent hypercalcemia and frequently presents with very high, symptomatic calcium levels. It is due to secretion of PTH-related protein by malignant cells. Other mechanisms of tumor-related hypercalcemia include osteolytic bone metastasis, increased production of 1,25-dihydroxyvitamin D, and increased interleukin-6 levels.

References

- Mechanisms and treatment of hypercalcemia of malignancy.
- Approach to diagnosis and treatment of hypercalcemia in a patient with malignancy

A 28-year-old man with type 1 diabetes mellitus comes to the emergency department with a 2-day history of abdominal pain, nausea, and vomiting. He has a history of medical noncompliance and has not used insulin for the past 5 days. His temperature is 36.7 C (98 F), blood pressure is 96/62 mm Hg, pulse is 112/min, and respirations are 26/min. Examination shows dry mucous membranes. The abdomen is soft with mild diffuse tenderness. Laboratory studies are as follows.

Serum chemistry

Sodium	134 mEq/L
Potassium	5.2 mEq/L
Chloride	97 mEq/L
Bicarbonate	12 mEq/L
Glucose	400 mg/dL

Arterial blood gases

pH	7.19
PaO_2	84 mm Hg
$PaCO_2$	25 mm Hg

Glucose	400 mg/dL

Arterial blood gases

pH	7.19
PaO_2	84 mm Hg
$PaCO_2$	25 mm Hg

Serum and urine ketones are positive. Which of the following is the best index to monitor the response to the treatment of this patient's current condition?

- A. Serum acetoacetate
- B. Serum anion gap
- C. Serum osmolality
- D. Urine glucose
- E. Urine ketones

Submit

Glucose	400 mg/dL

Arterial blood gases

pH	7.19
PaO_2	84 mm Hg
$PaCO_2$	25 mm Hg

Serum and urine ketones are positive. Which of the following is the best index to monitor the response to the treatment of this patient's current condition?

- A. Serum acetoacetate [5%]
- ✔ B. Serum anion gap [80%]
- ✘ C. Serum osmolality [5%]
- D. Urine glucose [1%]
- E. Urine ketones [7%]

Incorrect

7 Seconds

10/04/2018

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.

This patient's presentation (hyperglycemia with an anion gap metabolic acidosis) is consistent with diabetic

This patient's presentation (hyperglycemia with an anion gap metabolic acidosis) is consistent with diabetic ketoacidosis (DKA). Treatment of DKA includes insulin to lower serum glucose and ketones, intravenous fluids to correct dehydration, and replacement of electrolytes. Patients should have serum glucose measured every hour and electrolytes and anion gap measured every 2-4 hours. Intravenous insulin therapy can lower serum glucose by 50-75 mg/dL per hour but ketosis and acidosis resolve more slowly.

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.

(Choice C) Serum osmolality does not need to be measured as it can be estimated accurately from the serum sodium and glucose concentrations ([2 x Na in mEq/L] + [glucose in mg/dL ÷ 18]). Although serum osmolality may be elevated in DKA, it is not as sensitive for monitoring response to treatment.

(Choice D) Glucosuria typically resolves once serum glucose is corrected below 200-250 mg/dL. However, at this level, there is often still significant ketonemia and acidemia.

(Choice E) Urine ketone detection uses the nitroprusside test, which detects acetoacetate and acetone only. In addition, urine ketone levels are delayed with respect to serum ketones.

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.

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(Choice D) Glucosuria typically resolves once serum glucose is corrected below 200-250 mg/dL. However, at this level, there is often still significant ketonemia and acidemia.

(Choice E) Urine ketone detection uses the nitroprusside test, which detects acetoacetate and acetone only. In addition, urine ketone levels are delayed with respect to serum ketones.

Educational objective:

The best markers indicating resolution of DKA are the serum anion gap and beta-hydroxybutyrate levels. The serum anion gap estimates the unmeasured anion concentration in the blood and returns to normal with disappearance of ketoacid anions.

References

- Management of adult diabetic ketoacidosis

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A 30-year-old Hispanic male presents to the office with complaints of palpitations, tremor, nervousness and headache. His past history is insignificant. His mother has type 2 diabetes, which is well-controlled with medications. His temperature is 37.0° C (98.6° F), pulse is 100/min, blood pressure is 150/80 mm Hg, and respirations are 16/min. He appears anxious, sweaty and shaky. His neurological examination is non-focal, and examination of other systems is unremarkable. His fingerstick blood glucose level is 38 mg/dL. Intravenous administration of a bolus of 50% dextrose leads to the improvement of his symptoms. He is then subjected to supervised prolonged fasting. After an overnight fast, laboratory studies reveal:

Blood glucose	40 mg/dL
Serum insulin	15 microU/L (normal value is < 6 microU/L with hypoglycemia)
Serum pro-insulin	9 microU/L (normal value is < 20% of total immunoreactive insulin)
C-peptide level	0.8 nmol/L (normal value is less than 0.2 nmol/L)
Sulfonylurea	Negative
IGF-II	Negative

Based on the above information, what is the most likely cause of this patient's hypoglycemia?

Serum insulin	15 microU/L (normal value is < 6 microU/L with hypoglycemia)
Serum pro-insulin	9 microU/L (normal value is < 20% of total immunoreactive insulin)
C-peptide level	0.8 nmol/L (normal value is less than 0.2 nmol/L)
Sulfonylurea	Negative
IGF-II	Negative

Based on the above information, what is the most likely cause of this patient's hypoglycemia?

- A. Beta cell tumor
- B. Non-beta cell tumor
- C. Sulfonylurea agents
- D. Exogenous insulin
- E. Glucagonoma

Submit

Serum insulin	15 microU/L (normal value is < 6 microU/L with hypoglycemia)
Serum pro-insulin	9 microU/L (normal value is < 20% of total immunoreactive insulin)
C-peptide level	0.8 nmol/L (normal value is less than 0.2 nmol/L)
Sulfonylurea	Negative
IGF-II	Negative

Based on the above information, what is the most likely cause of this patient's hypoglycemia?

- ✔ A. Beta cell tumor [85%]
- B. Non-beta cell tumor [2%]
- C. Sulfonylurea agents [1%]
- ✘ D. Exogenous insulin [7%]
- E. Glucagonoma [1%]

Incorrect

85%

7 Seconds

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.

(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.

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(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.

(Choice E) Glucagonoma produces a characteristic skin rash (necrotic migratory erythema) with elevated blood glucose levels (not hypoglycemia).

Educational Objective:
Hypoglycemia is associated with multiple differential diagnoses. Helpful tests used in the evaluation of hypoglycemic patients are measurements of c-peptide, proinsulin and sulfonylurea levels. Hypoglycemia secondary to insulinoma is associated with elevated insulin, c-peptide and proinsulin levels.

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A 55-year-old man comes to the physician for a routine follow-up visit. He has had type 2 diabetes mellitus and hypertension for the last 5 years. He had an acute myocardial infarction 2 years ago. The patient's current medications include metformin, lisinopril, atorvastatin, and low-dose aspirin. He is very compliant with his diet and medications. His glycemic control was very good until a few months ago, when he noticed that his blood sugar levels were running high. The patient's body mass index is 32 kg/m^2. His physical examination is otherwise unremarkable. Laboratory results are as follows:

Blood urea nitrogen	14 mg/dL
Serum creatinine	1.0 mg/dL
Fasting blood glucose	156 mg/dL
HBA1c	8.0%

The patient strongly desires to lose at least 5 kg (11 lb) in the next 6 months. In addition to lifestyle changes, which of the following anti-diabetic medications is most appropriate for reducing weight and controlling blood sugars?

A. Dipeptidyl dipeptidase-4 (DPP4) inhibitor
B. Glucagon-like peptide-1 (GLP-1) agonist
C. Insulin

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B. Glucagon-like peptide-1 (GLP-1) agonist
C. Insulin
D. Sulfonylurea
E. Thiazolidinedione

Submit

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Serum creatinine	1.0 mg/dL
Fasting blood glucose	156 mg/dL
HBA1c	8.0%

The patient strongly desires to lose at least 5 kg (11 lb) in the next 6 months. In addition to lifestyle changes, which of the following anti-diabetic medications is most appropriate for reducing weight and controlling blood sugars?

- A. Dipeptidyl dipeptidase-4 (DPP4) inhibitor [19%]
- ✔ B. Glucagon-like peptide-1 (GLP-1) agonist [47%]
- C. Insulin [6%]
- D. Sulfonylurea [17%]
- E. Thiazolidinedione [9%]

Correct

47% Answered correctly

10 Seconds TimeSpent

09/13/2018 Last Updated

Exhibit Display

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.

Zoom In | Zoom Out | Reset | Add To Flash Card

Type 2 diabetes mellitus is usually due to increased insulin resistance combined with eventual pancreatic beta cell failure. Most type 2 diabetics require >1 medication for maintaining optimal glycemic control, and many eventually require insulin. Metformin is the preferred initial drug in patients without contraindications (eg, renal insufficiency). Patients with suboptimal control on metformin require a second drug, with the choice depending on several factors (eg, patient preference, efficacy, risk of hypoglycemia, cost, weight gain or desired weight loss, presence of comorbidities, side effects).

This patient is overweight and requires ~1% reduction of his HBA1c. Sulfonylureas are typically added to metformin in suboptimally controlled patients, but they would likely cause weight gain and possible hypoglycemia **(Choice D)**. Thiazolidinediones (eg, pioglitazone) are an option in metformin-failure patients unable to take sulfonylureas, but they also cause weight gain and could possibly induce congestive heart failure in this patient with heart disease **(Choice E)**. A **GLP-1 agonist** (eg, exenatide or liraglutide) would be the most appropriate choice in this patient as it can induce weight loss with lower hypoglycemia risk. However, these agents are associated with acute pancreatitis.

(Choice A) DPP-4 inhibitors increase endogenous incretins to improve glycemic control. Although they have a low risk of hypoglycemia and can be used in patients with chronic kidney disease, they do not affect weight. GLP-1 analogues are significantly more efficacious for inducing weight loss and improving glycemic control in overweight individuals such as this patient.

(Choice C) Adding insulin to metformin would improve glycemic control, but it is generally associated with significant weight gain and the risk of hypoglycemia. In addition, most guidelines recommend adding insulin to metformin in patients with HBA1c >8.5%.

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(Choice C) Adding insulin to metformin would improve glycemic control, but it is generally associated with significant weight gain and the risk of hypoglycemia. In addition, most guidelines recommend adding insulin to metformin in patients with HBA1c >8.5%.

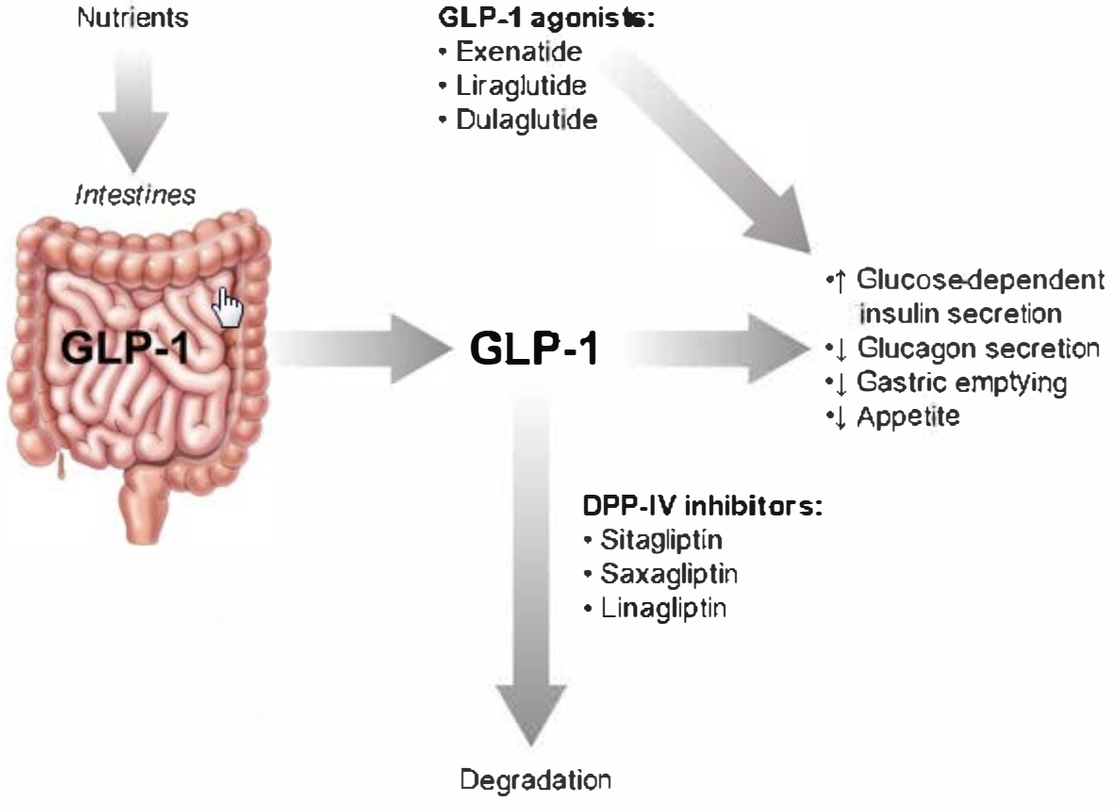
Educational objective:
Current guidelines recommend initial metformin in type 2 diabetics without contraindications (eg, renal insufficiency). Patients with suboptimal control on metformin require a second drug, with the choice depending on factors such as patient preference, efficacy, risk of hypoglycemia, cost, weight gain or desired weight loss, presence of comorbidities, and side effects. GLP-1 agonists (eg, exenatide, liraglutide) induce weight loss and have lower hypoglycemia risk.

References

require insulin. Metformin is the preferred initial drug in patients without contraindications (eg, renal insufficiency)

Exhibit Display

GLP-1 agonists & DPP-IV inhibitors



Zoom In | Zoom Out | Reset | Add To Flash Card

A 62-year-old woman comes to the office for follow-up of diabetes treatment. She has had type 2 diabetes mellitus for the last 10 years and is managed with oral metformin twice daily and insulin glargine at bedtime. The patient has no chest pain, dizziness, sweating, polyuria, or palpitations. She checks her blood glucose level every morning and has had values of 75-132 mg/dL over the last month. Medical history is notable for hypertension and mild intermittent asthma, for which she takes lisinopril, amlodipine, and albuterol as needed. Blood pressure is 128/72 mm Hg and pulse is 79/min. BMI is 41 kg/m^2. Laboratory results show a random glucose level of 298 mg/dL and hemoglobin A1c of 8.1%. Which of the following best explains the suboptimal glycemic control in this patient?

- A. Autoimmune pancreatitis
- B. Dawn phenomenon
- C. Inadequate basal insulin coverage
- D. Insulin-neutralizing antibodies
- E. Postprandial hyperglycemia

Submit

A 62-year-old woman comes to the office for follow-up of diabetes treatment. She has had type 2 diabetes mellitus for the last 10 years and is managed with oral metformin twice daily and insulin glargine at bedtime. The patient has no chest pain, dizziness, sweating, polyuria, or palpitations. She checks her blood glucose level every morning and has had values of 75-132 mg/dL over the last month. Medical history is notable for hypertension and mild intermittent asthma, for which she takes lisinopril, amlodipine, and albuterol as needed. Blood pressure is 128/72 mm Hg and pulse is 79/min. BMI is 41 kg/m². Laboratory results show a random glucose level of 298 mg/dL and hemoglobin A1c of 8.1%. Which of the following best explains the suboptimal glycemic control in this patient?

- A. Autoimmune pancreatitis [0%]
- B. Dawn phenomenon [18%]
- C. Inadequate basal insulin coverage [41%]
- ✗ D. Insulin-neutralizing antibodies [3%]
- ✓ E. Postprandial hyperglycemia [35%]

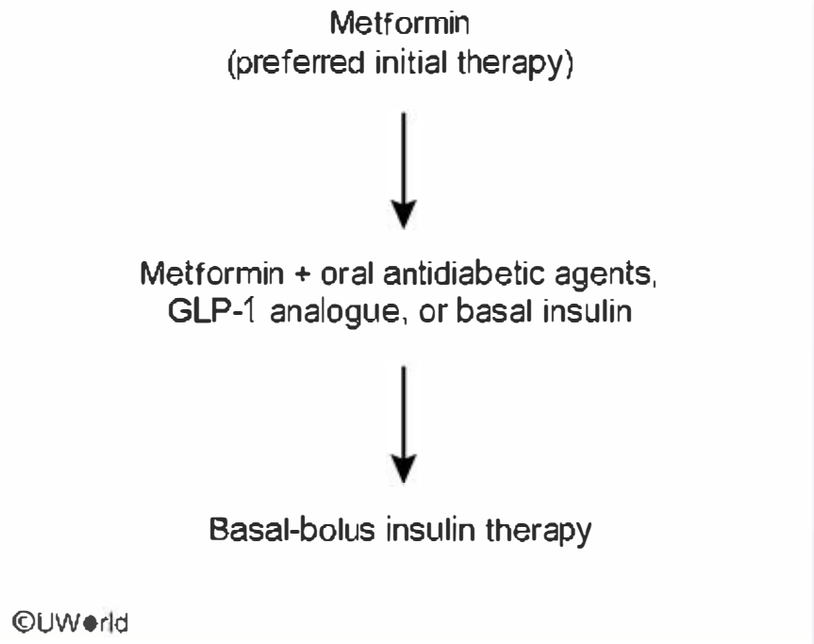
Incorrect
Correct answer
E

35%
Answered correctly

4 Seconds
TimeSpent

06/22/2018
Last Updated

Progressive therapeutic intensification in type 2 diabetes mellitus



This patient's morning (fasting) glucose readings are within her target range (usual suggested target is 80-130 mg/dL) to only minimally elevated. However, her random glucose level (298 mg/dL) is very high, and her hemoglobin A1c is above goal (target ≤7% in most patients). As both fasting/premeal and postprandial glucose levels contribute to hemoglobin A1c, it is likely that this patient is experiencing frequent **postprandial hyperglycemia** leading to impaired overall glycemic control.

The goal of therapy in such patients is to control postprandial glucose excursions without causing fasting hypoglycemia. A combined regimen—including a **long-acting basal insulin** (eg, insulin glargine) to control baseline fasting glucose and a **rapid-acting mealtime insulin** (eg, insulin aspart) to control postprandial glucose excursions—may be needed to provide optimal overall control.

(Choice A) Autoimmune pancreatitis can cause diabetes mellitus due to destruction of beta cells. However, this patient does not have other features of autoimmune pancreatitis, such as intermittent/chronic abdominal pain, obstructive jaundice, or extrabiliary manifestations (eg, Sjögren syndrome).

(Choice B) The dawn phenomenon is a hyperglycemic surge in the early morning hours due to the diurnal increase in counter regulatory hormones (eg, growth hormone, cortisol). The dawn phenomenon causes elevated fasting, rather than postprandial, hyperglycemia.

(Choice C) Basal insulin therapy with glargine should provide ~24-hour peakless coverage; therefore, inadequate basal insulin would cause fasting hyperglycemia. This patient's fasting glucose readings are within her target range.

(Choice D) Insulin-neutralizing antibodies can cause significant insulin resistance requiring very high doses of insulin to control blood glucose. However, these antibodies were more commonly seen with bovine and porcine insulin, and incidence has declined as non-human insulins have been replaced with purified human insulin and insulin analogues.

Educational objective:
Patients with diabetes mellitus who have an elevated hemoglobin A1c despite good control of fasting glucose may

(Choice B) The dawn phenomenon is a hyperglycemic surge in the early morning hours due to the diurnal increase in counter regulatory hormones (eg, growth hormone, cortisol). The dawn phenomenon causes elevated fasting, rather than postprandial, hyperglycemia.

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(Choice D) Insulin-neutralizing antibodies can cause significant insulin resistance requiring very high doses of insulin to control blood glucose. However, these antibodies were more commonly seen with bovine and porcine insulin, and incidence has declined as non-human insulins have been replaced with purified human insulin and insulin analogues.

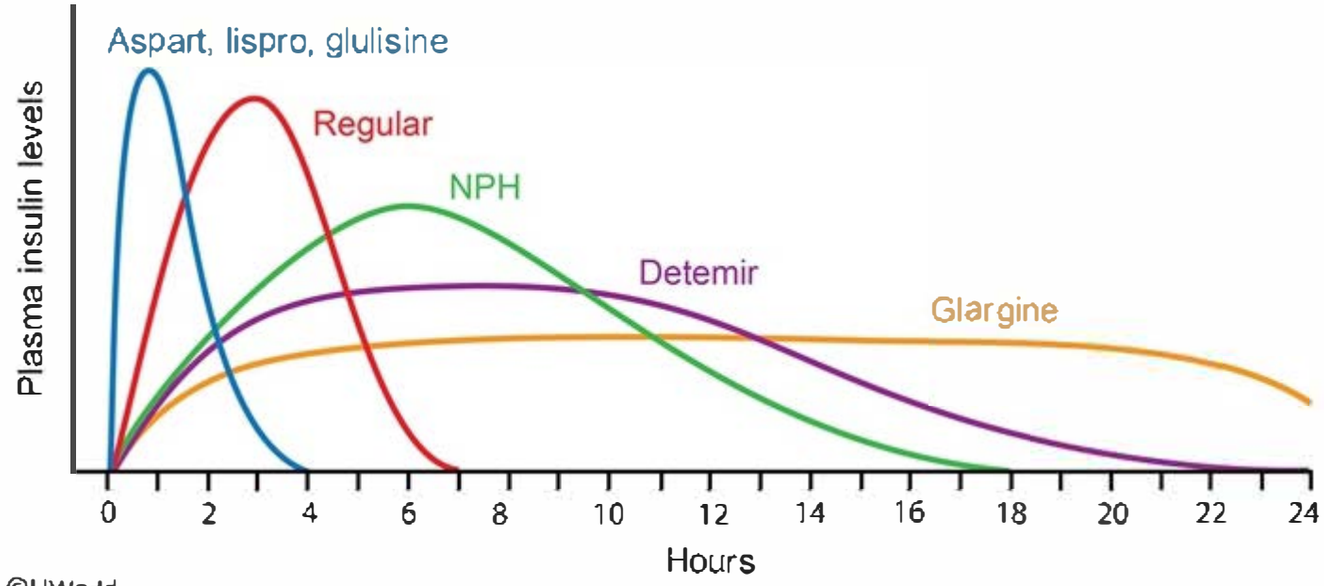
Educational objective:
Patients with diabetes mellitus who have an elevated hemoglobin A1c despite good control of fasting glucose may have postprandial hyperglycemia. A combined regimen including a long-acting basal insulin (to control baseline/fasting glucose) and a rapid-acting mealtime insulin (to control postprandial glucose) may be needed to provide optimal control.

References

- Diagnosis and management of diabetes: synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes.

Exhibit Display

Pharmacokinetic profiles of common insulin preparations



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Medical Care in Diabetes.

A 22-year-old female presents with complaints of heat intolerance, sweating and palpitations. She also reports menstrual irregularities, increased appetite and diarrhea. Her pulse is 102/min and regular, blood pressure is 116/80 mm Hg, temperature is 37.2° C (99° F), and respirations are 14/min. Physical examination reveals a diffusely enlarged, nontender thyroid gland. TSH level is 0.05 mU/L. Free T4 and T3 levels are elevated. Radioactive iodine uptake at 24 hours is 50 percent. Thyroid stimulating immunoglobulins are present. She is started on propylthiouracil 300 mg daily in three divided doses. After two weeks, she returns and complains of a sore throat. Her pulse is 98/min and regular, temperature is 38.6° C (101.5° F), blood pressure is 115/76 mm Hg, and respirations are 15/min. The soft palate, pharynx, and tonsils are red and swollen. **What is the most appropriate next step in the management of this patient?**

- A. Add propranolol
- B. Increase propylthiouracil dose
- C. Stop propylthiouracil
- D. Throat culture
- E. Oral penicillin
- F. Acetaminophen

Submit

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- A. Add propranolol [3%]
- ✗ B. Increase propylthiouracil dose [1%]
- ✓ C. Stop propylthiouracil [60%]
- D. Throat culture [21%]
- E. Oral penicillin [7%]
- F. Acetaminophen [4%]

Incorrect

The antithyroid drugs propylthiouracil (PTU) and methimazole (MMI) are associated with a number of minor, as well as potentially life-threatening, side effects. Agranulocytosis is the most feared side effect, and is seen in approximately 0.3% of patients treated with antithyroid drugs. It is caused by immune destruction of granulocytes, and most cases occur within 90 days of treatment. Routine monitoring of the granulocyte count is not cost effective and not advocated. 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 less 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.

(Choice A) Propranolol can be used for symptomatic relief of thyrotoxic symptoms; however, the most important next step is to discontinue PTU and check the WBC count.

(Choice B) Increasing the propylthiouracil dosage would be lethal in this case.

(Choice D, E and F) The treatment of antithyroid drug-induced agranulocytosis includes discontinuation of the offending drug and intravenous administration of broad spectrum antibiotics (especially for *Pseudomonas*). Granulocyte colony stimulating factors may be useful in increasing the WBC count. Throat culture, oral penicillin and acetaminophen can be done/given as part of the evaluation/management (along with CBC with differential count) of this patient; however, these steps are not going to reverse this patient's underlying problem, and are therefore not the appropriate next steps.

Educational Objective:

Fever and sore throat in any patient taking antithyroid drugs suggests agranulocytosis. Antithyroid drugs should be

and not advocated. 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 less 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.

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Educational Objective:
Fever and sore throat in any patient taking antithyroid drugs suggests agranulocytosis. Antithyroid drugs should be stopped and WBC count checked. Routine WBC count measurement in patients taking antithyroid drugs is not cost effective.

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A 36-year-old woman comes to the physician for evaluation of several weeks of fatigue and weakness. She has had no appetite or weight changes, heat or cold intolerance, nausea or vomiting, or constipation. Her past medical and family histories are unremarkable. Temperature is 36.7 C (98 F), blood pressure is 120/70 mm Hg, pulse is 76/min, and respirations are 14/min. The neurologic examination is nonfocal, and deep-tendon reflexes are normal. Laboratory results are as follows:

Hematocrit	43%
Leukocytes	6,000/μL
Platelets	200,000/μL
Serum calcium	7.8 mg/dL
Serum albumin	4.0 g/dL
Serum creatinine	1.0 mg/dL
Serum parathyroid hormone level	110 pg/mL

Which of the following is the best next step in management of this patient?

A. Bone scan

Leukocytes	6,000/μL
Platelets	200,000/μL
Serum calcium	7.8 mg/dL
Serum albumin	4.0 g/dL
Serum creatinine	1.0 mg/dL
Serum parathyroid hormone level	110 pg/mL

Which of the following is the best next step in management of this patient?

A. Bone scan
B. Serum 25-hydroxy vitamin D level
C. Serum alkaline phosphatase level
D. Serum parathyroid hormone-related protein level
E. Serum protein electrophoresis

Platelets	200,000/ µL
Serum calcium	7.8 mg/dL
Serum albumin	4.0 g/dL
Serum creatinine	1.0 mg/dL
Serum parathyroid hormone level	110 pg/mL

Which of the following is the best next step in management of this patient?

- A. Bone scan [4%]
- ✔ B. Serum 25-hydroxy vitamin D level [83%]
- C. Serum alkaline phosphatase level [6%]
- D. Serum parathyroid hormone-related protein level [4%]
- E. Serum protein electrophoresis [1%]

Correct

83%
Answered correctly

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Diagnostic approach to hypocalcemia

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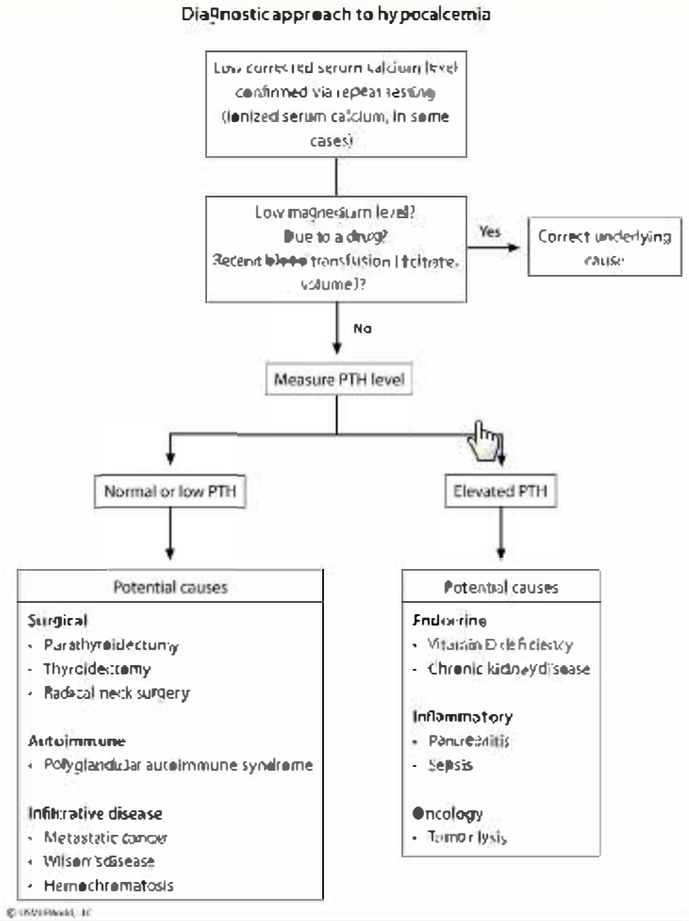

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Potential causes | Potential causes

Patients with hypocalcemia can be asymptomatic at initial presentation (found incidentally) or may complain only of nonspecific symptoms (eg, fatigue, anxiety, depression). Involuntary contractions (tetany) involving the lips, face, and extremities are seen in severe hypocalcemia.

In asymptomatic patients, a single low serum calcium level must always be confirmed by a second serum calcium value. Hypoalbuminemia, hypomagnesemia, and certain drugs (eg, calcium chelators, bisphosphonates, phenytoin) can also cause hypocalcemia and should be considered.

After hypocalcemia has been confirmed, the next step is to check parathyroid hormone (PTH) level. The most common cause of hypoparathyroidism seen in hypocalcemia is due to a recent parathyroid surgery or surgeries involving the surrounding area (eg, thyroidectomy). An elevated PTH level is commonly seen in vitamin D deficiency and chronic kidney disease. This patient has normal serum creatinine, and the next step is to check the 25-hydroxy vitamin D level to diagnose vitamin D deficiency.

(Choice A) A bone scan can be used to identify a metastatic bone tumor. Most tumors produce hypercalcemia with bone metastasis; some tumors with osteoblastic metastasis (eg, breast, prostate) can cause hypocalcemia due to the use of calcium in new bone formation. However, this is very rare and vitamin D deficiency is a much more common cause. Metastatic malignancy also produces systemic symptoms such as weight loss and bone pain.

(Choice C) Although an elevated alkaline phosphatase can suggest a possible bone etiology, it is not specific enough to detail the type of bone condition causing the hypocalcemia (eg, osteomalacia from vitamin D deficiency).

(Choice D) Production of parathyroid-related protein from malignant tumor cells causes **hypercalcemia**.

(Choice A) A bone scan can be used to identify a metastatic bone tumor. Most tumors produce hypercalcemia with bone metastasis; some tumors with osteoblastic metastasis (eg, breast, prostate) can cause hypocalcemia due to the use of calcium in new bone formation. However, this is very rare and vitamin D deficiency is a much more common cause. Metastatic malignancy also produces systemic symptoms such as weight loss and bone pain.

(Choice C) Although an elevated alkaline phosphatase can suggest a possible bone etiology, it is not specific enough to detail the type of bone condition causing the hypocalcemia (eg, osteomalacia from vitamin D deficiency).

(Choice D) Production of parathyroid-related protein from malignant tumor cells causes **hypercalcemia**.

(Choice E) Serum protein electrophoresis (SPEP) is used to detect an elevated M-protein level seen in multiple myeloma. Checking SPEP would be an appropriate step had this patient presented with **hypercalcemia** and an elevated total protein level.

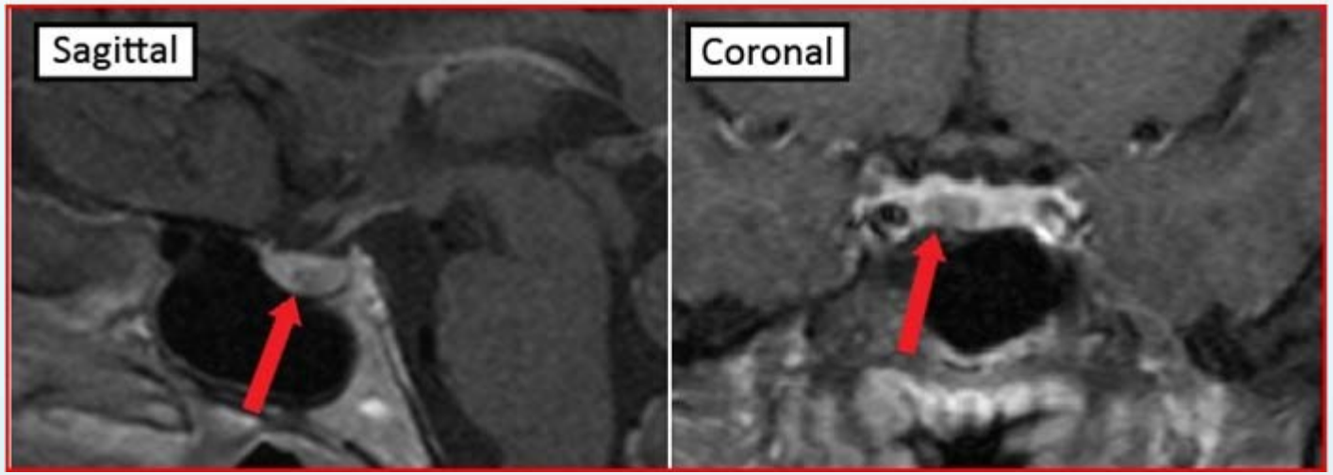
Educational objective:

Patients with hypocalcemia may be asymptomatic at initial presentation or may complain only of nonspecific symptoms (eg, fatigue, anxiety). After confirmation of hypocalcemia, the next step is to check parathyroid hormone (PTH) level to distinguish between low PTH-associated conditions (eg, parathyroid surgery, polyglandular autoimmune) and elevated PTH-associated conditions (eg, vitamin D deficiency, chronic kidney disease).

References

- Assessment and management of patients with abnormal calcium.

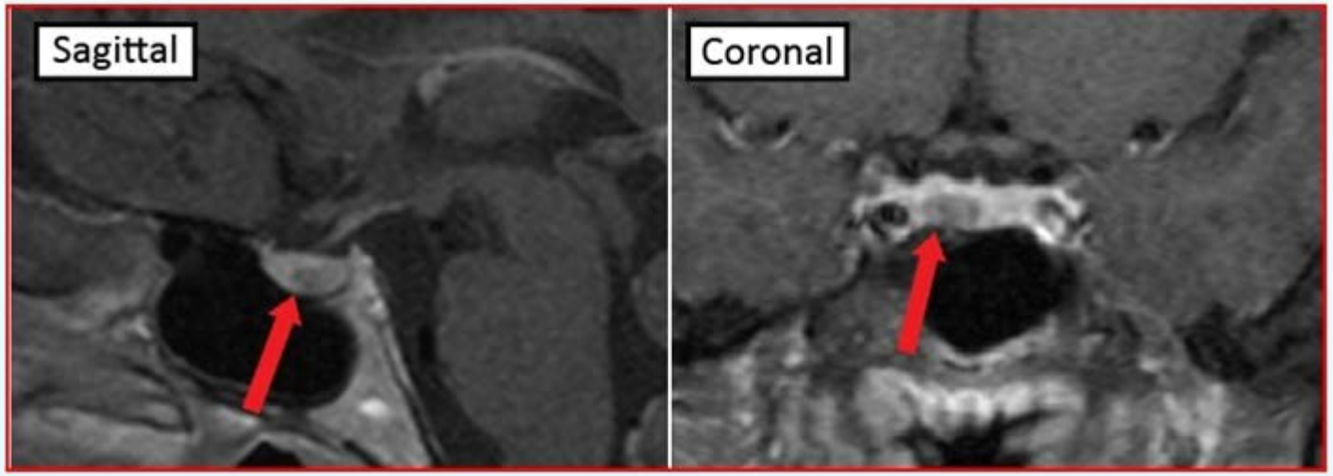
A 37-year-old woman comes to the office with a 7-month history of galactorrhea and amenorrhea. She has also had worsening vaginal dryness, but no headaches or visual symptoms. The patient's medical history is unremarkable, and she does not use tobacco, alcohol, or illicit drugs. She is married, has 2 children, and remarks that her family is "complete." The patient's husband has undergone vasectomy. Her temperature is 36.7 C (98 F), blood pressure is 120/80 mm Hg, pulse is 72/min, and respirations are 14/min. Visual field testing is normal. Pregnancy test is negative, serum prolactin level is 150 ng/mL (154 ng/mL on repeat measurement), and thyrotropin (TSH) and serum creatinine are normal. MRI of the pituitary gland reveals a 6-mm hypointense lesion, as shown in the image below, which is consistent with a pituitary adenoma.



Which of the following is the most appropriate next step in management of this patient?

A. Monitoring by periodic serum prolactin and MRI

as shown in the image below, which is consistent with a pituitary adenoma.



Which of the following is the most appropriate next step in management of this patient?

- A. Monitoring by periodic serum prolactin and MRI
- B. Radiotherapy
- C. Transsphenoidal surgery
- D. Treatment with cabergoline
- E. Treatment with estrogen

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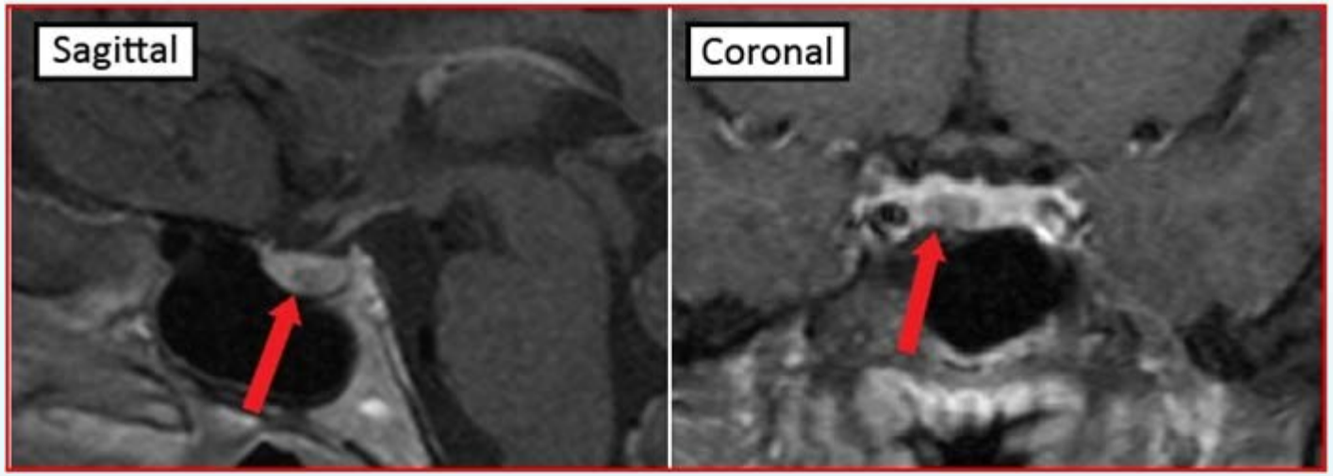


Which of the following is the most appropriate next step in management of this patient?

A. Monitoring by periodic serum prolactin and MRI [6%]

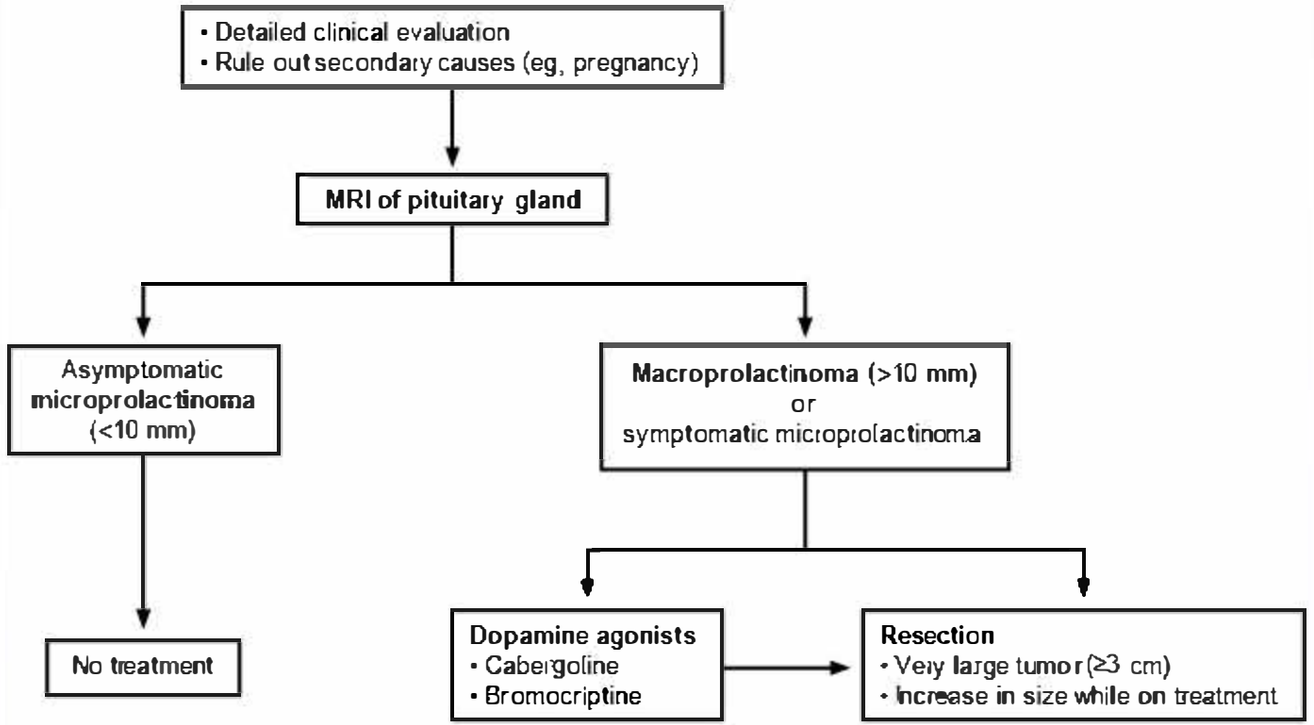
B. Radiotherapy [1%]

✗ C. Transsphenoidal surgery [26%]

✓ D. Treatment with cabergoline [64%]

E. Treatment with estrogen [1%]

Management of hyperprolactinemia in premenopausal women



This patient has a **pituitary microadenoma** (<10 mm) associated with **galactorrhea** and symptoms of low estrogen (eg, amenorrhea, vaginal dryness). Any mass lesion in the pituitary gland can cause a mild elevation in prolactin due to disruption of the normal inhibitory dopaminergic regulation of prolactin secretion. However, significant elevations in the prolactin level (eg, serum prolactin level >200 ng/mL or repeat level >100 ng/mL) suggest a prolactin-secreting tumor (**prolactinoma**). Elevated prolactin levels suppress gonadotropin-releasing

prolactin due to disruption of the normal inhibitory dopaminergic regulation of prolactin secretion. However, significant elevations in the prolactin level (eg, serum prolactin level >200 ng/mL or repeat level >100 ng/mL) suggest a prolactin-secreting tumor (**prolactinoma**). Elevated prolactin levels suppress gonadotropin-releasing hormone, LH, and estradiol, leading to oligo-amenorrhea in premenopausal females. Men and postmenopausal women often have minimal early symptoms and are more likely to seek evaluation when a large tumor (>1 cm, macroadenoma) causes mass-effect symptoms (eg, headache, visual field defects).

Asymptomatic patients with an incidental finding of a microprolactinoma may be observed over time **(Choice A)**. Patients with **macroprolactinomas** or **symptomatic tumors** of any size (as with this patient) should be treated with **dopaminergic agonists** (eg, cabergoline, bromocriptine), which can **normalize prolactin levels** and **reduce tumor size**. Patients who fail to respond or who have very large tumors (>3 cm) should be referred for transsphenoidal resection **(Choice C)**.

(Choice B) Patients with residual prolactinoma tissue following resection can be considered for radiotherapy. However, the response to radiotherapy is generally delayed, and radiotherapy may lead to panhypopituitarism.

(Choice E) Estrogen replacement therapy may be given to reduce the risk of osteoporosis in hypoestrogenic women with microprolactinoma who do not tolerate dopamine agonists. However, estrogen does not reduce tumor size.

Educational objective:
Patients with a macroprolactinoma (>1 cm) or a symptomatic prolactinoma should be treated with dopaminergic agonists (eg, cabergoline, bromocriptine), which can lower prolactin levels and reduce tumor size.

A 27-year-old man comes to the physician for follow-up of hypertension. He feels healthy and has no complaints. Two weeks ago, he was found to have high blood pressure during an emergency department visit for a sports injury. The patient has a strong family history of hypertension and stroke. His blood pressure is 155/97 mm Hg and pulse is 78/min. Physical examination and basic laboratory workup are unremarkable. He is instructed to follow a low-salt diet and started on low-dose (12.5 mg daily) hydrochlorothiazide. Two weeks later, the patient comes to the emergency department complaining of muscle cramps, weakness, and palpitations. His blood pressure is 150/93 mm Hg and pulse is 82/min. Mucous membranes are moist. Laboratory results are as follows:

Potassium	2.5 mEq/L
Glucose	78 mg/dL
Serum creatinine	1.0 mg/dL

Which of the following is the best next step in management of this patient?

A. Computed tomography angiography of the abdomen
B. Dexamethasone suppression test
C. Plasma renin activity and aldosterone concentration
D. Serum thiazide level
E. Urine potassium excretion by 24-hour collection

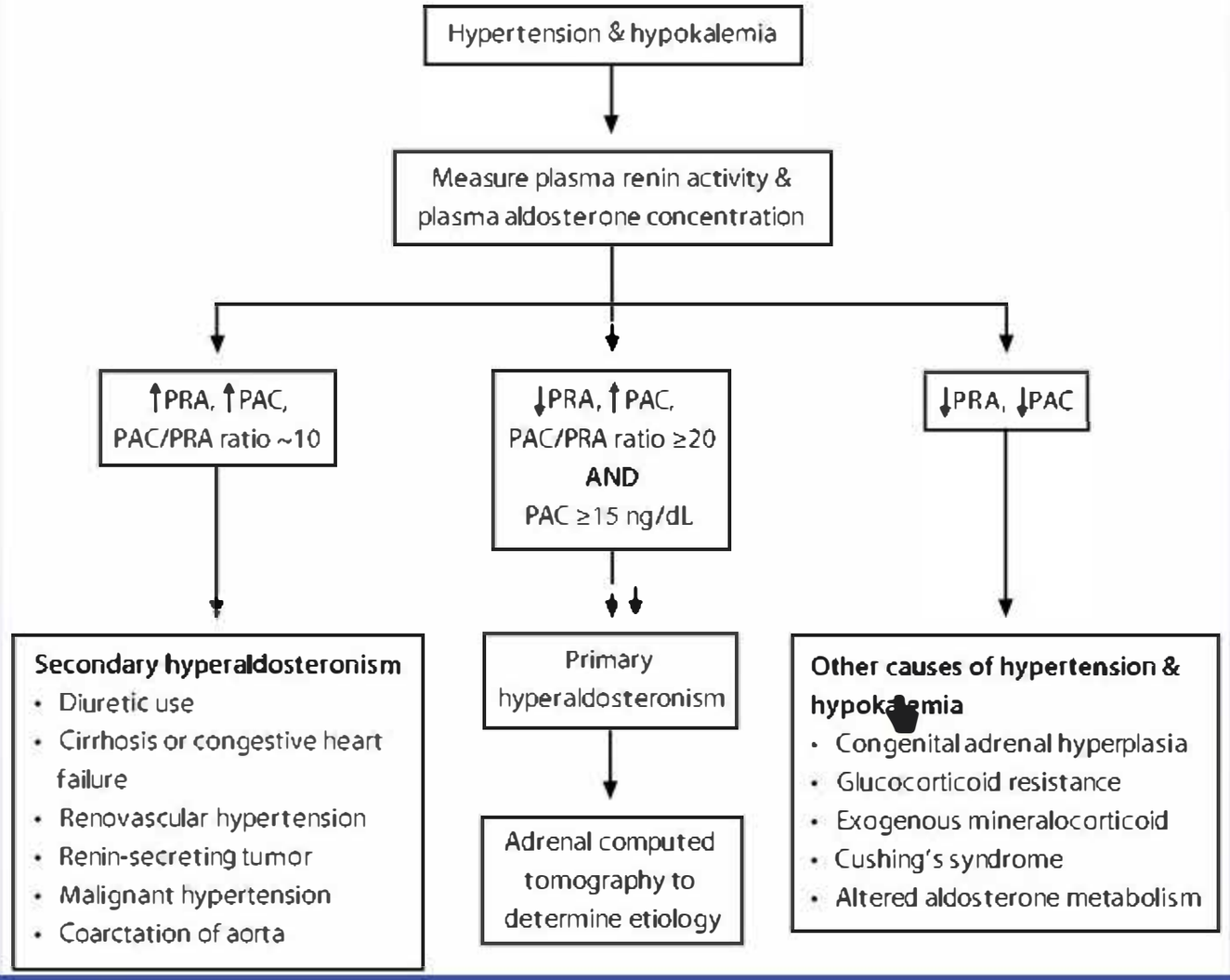
injury. The patient has a strong family history of hypertension and stroke. His blood pressure is 155/97 mm Hg and pulse is 78/min. Physical examination and basic laboratory workup are unremarkable. He is instructed to follow a low-salt diet and started on low-dose (12.5 mg daily) hydrochlorothiazide. Two weeks later, the patient comes to the emergency department complaining of muscle cramps, weakness, and palpitations. His blood pressure is 150/93 mm Hg and pulse is 82/min. Mucous membranes are moist. Laboratory results are as follows:

Potassium	2.5 mEq/L
Glucose	78 mg/dL
Serum creatinine	1.0 mg/dL

Which of the following is the best next step in management of this patient?

- A. Computed tomography angiography of the abdomen [3%]
- B. Dexamethasone suppression test [2%]
- ✔ C. Plasma renin activity and aldosterone concentration [67%]
- D. Serum thiazide level [22%]
- E. Urine potassium excretion by 24-hour collection [4%]

Evaluation of suspected hyperaldosteronism



This younger hypertensive patient with significant family history raises suspicion for a secondary cause of hypertension. The easily induced hypokalemia after starting a thiazide diuretic suggests primary hyperaldosteronism. Patients with mild primary hyperaldosteronism may not have spontaneous hypokalemia, but they are prone to developing diuretic-induced hypokalemia. Other findings include metabolic alkalosis and mild hypernatremia (143-147 mEq/L). The best screening test is early-morning plasma aldosterone concentration (PAC) to plasma renin activity (PRA) ratio. A PAC/PRA ratio >20 with plasma aldosterone >15 ng/dL suggests primary hyperaldosteronism.

(Choice A) Computed tomography angiography of the abdomen is a screening test for renovascular hypertension due to renal artery stenosis or fibromuscular dysplasia. These conditions cause secondary hyperaldosteronism. A PAC/PRA ratio <10 will be present in these patients. Computed tomography angiogram is not required in this patient at this time.

(Choice B) Dexamethasone suppression test can diagnose Cushing's syndrome. Patients typically develop findings such as central obesity, purple striae, proximal muscle wasting, glucose intolerance, and hypertension. This patient's normal glucose makes this unlikely.

(Choice D) Thiazide diuretics can cause hypokalemia. However, low-dose thiazide is usually not associated with the degree of hypokalemia seen in this patient.

(Choice E) Urine potassium excretion by collecting 24-hour urine has been used to document inappropriate potassium excretion. A 24-hour urinary potassium level >30 mEq in the presence of hypokalemia suggests hyperaldosteronism. However, this test is no longer commonly used.

(PAC) to plasma renin activity (PRA) ratio. A PAC/PRA ratio >20 with plasma aldosterone >15 ng/dL suggests primary hyperaldosteronism.

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Educational objective:

Patients with mild primary hyperaldosteronism may not have spontaneous hypokalemia, but they are prone to developing diuretic-induced hypokalemia.

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A 50-year-old man comes to the office with a 2-day history of malaise, fever, fatigue, and pain in the front of his neck. He recovered from an upper respiratory illness a week prior to the onset of his current symptoms, but he previously had felt well. The patient was seen in the clinic occasionally in the remote past for sexually transmitted infections, but his medical history is otherwise unremarkable. He lives alone and is sexually active with both men and women. Temperature is 38.5 C (101.3 F), blood pressure is 150/70 mm Hg, and pulse is 110/min. The thyroid gland is diffusely enlarged and tender. Laboratory results are as follows:

Complete blood count	
Hemoglobin	13.9 g/dL
Hematocrit	44%
Platelets	200,000/mm^3
Leukocytes	10,500/mm^3
TSH	<0.001 μU/mL
Free T4	4.6 ng/dL (0.9-2.4 ng/dL)
Erythrocyte sedimentation rate	100 mm/hr

Which of the following is the most likely diagnosis in this patient?

A. Acute retroviral syndrome

Platelets	200,000/mm^3
Leukocytes	10,500/mm^3
TSH	<0.001 µU/mL
Free T4	4.6 ng/dL (0.9-2.4 ng/dL)
Erythrocyte sedimentation rate	100 mm/hr

Which of the following is the most likely diagnosis in this patient?

A. Acute retroviral syndrome
B. Disseminated gonococcal infection
C. Graves disease
D. Hashimoto thyroiditis
E. Infectious mononucleosis
F. Subacute thyroiditis
G. Suppurative thyroiditis

Submit

Platelets	200,000/mm³
Leukocytes	10,500/mm³
TSH	<0.001 µU/mL
Free T4	4.6 ng/dL (0.9-2.4 ng/dL)
Erythrocyte sedimentation rate	100 mm/hr

Which of the following is the most likely diagnosis in this patient?

- A. Acute retroviral syndrome [1%]
- B. Disseminated gonococcal infection [0%]
- C. Graves disease [3%]
- D. Hashimoto thyroiditis [4%]
- E. Infectious mononucleosis [0%]
- ✔ F. Subacute thyroiditis [71%]
- G. Suppurative thyroiditis [18%]

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

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; TPO = thyroid peroxidase.

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This patient has primary **hyperthyroidism** (elevated free T4, suppressed TSH). In light of his associated fever, neck pain, **tender goiter**, and elevated erythrocyte sedimentation rate, this is most likely due to **subacute thyroiditis**. Subacute (de Quervain, subacute granulomatous) thyroiditis is thought to be due to a **postviral** inflammatory process and is often preceded by an upper respiratory illness.

Thyrotoxicosis in subacute thyroiditis resolves spontaneously within a few weeks and may be followed by a hypothyroid phase lasting a few months. Most patients eventually recover to a euthyroid state. Treatment is symptomatic with **beta blockers** to control thyrotoxic symptoms and **nonsteroidal anti-inflammatory drugs** (NSAIDs) for pain relief. Glucocorticoids are used for severe thyroid pain not responding to NSAIDs.

(Choices A, B, and E) Infectious mononucleosis is characterized by pharyngitis, fever and other systemic symptoms, lymphadenopathy, and splenomegaly. Acute HIV infection can cause a mononucleosis-like illness with fever, pharyngitis, and lymphadenopathy, often with a generalized macular rash and gastrointestinal symptoms. Disseminated gonococcal infection typically presents with fever, chills, vesiculopustular rash, and polyarthralgias or purulent monoarthritis. None of these disorders is associated with a goiter or hyperthyroid state.

(Choices C and D) Chronic lymphocytic (Hashimoto) thyroiditis typically presents with hypothyroidism, although patients may develop a brief hyperthyroid phase. However, the goiter seen in both Hashimoto thyroiditis and Graves disease is nontender, and fever is not common.

(Choice G) Suppurative infection of the thyroid gland (infectious thyroiditis) is a rare condition causing high-grade fever and pain at the thyroid gland. The thyroid gland may be palpably enlarged due to abscess formation. However, patients are usually euthyroid as the involvement of the thyroid gland is focal.

(NSAIDs) for pain relief. Glucocorticoids are used for severe thyroid pain not responding to NSAIDs.

(Choices A, B, and E) Infectious mononucleosis is characterized by pharyngitis, fever and other systemic symptoms, lymphadenopathy, and splenomegaly. Acute HIV infection can cause a mononucleosis-like illness with fever, pharyngitis, and lymphadenopathy, often with a generalized macular rash and gastrointestinal symptoms. Disseminated gonococcal infection typically presents with fever, chills, vesiculopustular rash, and polyarthralgias or purulent monoarthritis. None of these disorders is associated with a goiter or hyperthyroid state.

(Choices C and D) Chronic lymphocytic (Hashimoto) thyroiditis typically presents with hypothyroidism, although patients may develop a brief hyperthyroid phase. However, the goiter seen in both Hashimoto thyroiditis and Graves disease is nontender, and fever is not common.

(Choice G) Suppurative infection of the thyroid gland (infectious thyroiditis) is a rare condition causing high-grade fever and pain at the thyroid gland. The thyroid gland may be palpably enlarged due to abscess formation. However, patients are usually euthyroid as the involvement of the thyroid gland is focal.

Educational objective:
Subacute (de Quervain) thyroiditis is characterized by fever, neck pain, and a tender goiter following an upper respiratory illness. Patients have a self-limited thyrotoxic phase followed by hypothyroidism and eventual recovery of thyroid function. Treatment is symptomatic with beta blockers and nonsteroidal anti-inflammatory drugs.

References

- Subacute, silent, and postpartum thyroiditis.

A 36-year-old woman, gravida 0 para 0, comes to the office with frequent headaches and amenorrhea for the last 2 months. The patient has also had weight loss, intermittent palpitations, and vague visual disturbances. Her medical history is unremarkable, and she takes no medications. The patient experienced menarche at age 12 and has had normal menstrual cycles all her life. She does not smoke cigarettes or drink alcohol. Blood pressure is 130/60 mm Hg, and pulse is 103/min and regular. Weight is 69 kg (152 lb); a year ago it was 76 kg (168 lb). Examination shows a symmetrically enlarged, nontender thyroid gland. Auscultation of the chest shows tachycardia with regular heart rhythm. A fine hand tremor is noted. The remainder of the physical examination is unremarkable. Laboratory results are as follows:

Serum T3	222 ng/dL
Serum T4	13.9 µg/dL
Serum TSH	6 µU/mL

Which of the following is the most likely diagnosis for this patient?

A. Generalized resistance to thyroid hormone
B. Graves disease
C. Hashimoto thyroiditis
D. Normal pregnancy

Examination shows a symmetrically enlarged, nontender thyroid gland. Auscultation of the chest shows tachycardia with regular heart rhythm. A fine hand tremor is noted. The remainder of the physical examination is unremarkable. Laboratory results are as follows:

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- C. Hashimoto thyroiditis
- D. Normal pregnancy
- E. Surreptitious thyroid hormone intake
- F. TSH-secreting pituitary adenoma

Submit

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Serum T3	222 ng/dL
Serum T4	13.9 µg/dL
Serum TSH	6 µU/mL

Which of the following is the most likely diagnosis for this patient?

- A. Generalized resistance to thyroid hormone [3%]
- B. Graves disease [14%]
- C. Hashimoto thyroiditis [2%]
- D. Normal pregnancy [2%]
- ✗ E. Surreptitious thyroid hormone intake [4%]
- ✓ F. TSH-secreting pituitary adenoma [72%]

Incorrect
Correct answer

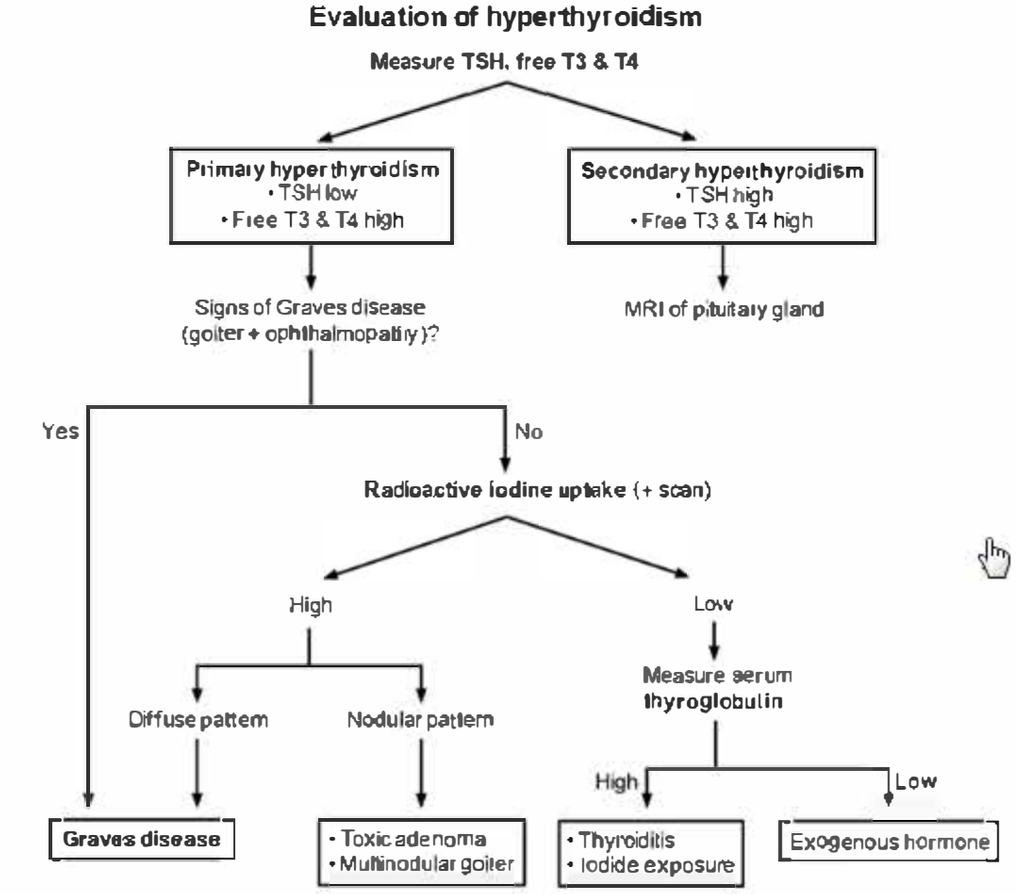
72%
Answered correctly

10 Seconds
Time Spent

10/08/2018
Last Updated

Evaluation of hyperthyroidism

Exhibit Display



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This patient has clinical features of **central hyperthyroidism** (elevation of both TSH and thyroid hormones) associated **with tumor mass effects** (ie, headache, visual symptoms, impaired production of other pituitary hormones). Although uncommon, a TSH-producing **pituitary adenoma** is the likely cause of this patient's hyperthyroid state.

Most TSH-secreting pituitary adenomas are macroadenomas. Patients with this condition typically have a goiter due to the effect of TSH on growth of the thyroid follicles. However, they do not have the extrathyroidal manifestations of Graves disease such as infiltrative ophthalmopathy or pretibial myxedema. Laboratory testing shows a high concentration of circulating thyroid hormone with an elevated or inappropriately normal TSH. By contrast, patients with non-TSH-dependent hyperthyroidism (much more common) will have a suppressed TSH.

(Choice A) Resistance to thyroid hormone is an autosomal dominant condition due to mutations in the thyroid hormone receptor. Patients have elevated T3 and T4 and normal to elevated TSH levels, often with an associated goiter. However, these patients are clinically hypo-, not hyperthyroid.

(Choices B and C) Graves disease is an autoimmune disorder associated with antibodies to the TSH receptor that stimulate release of thyroid hormone. Chronic lymphocytic (Hashimoto) thyroiditis is associated with thyroid peroxidase antibodies and can cause transient hyperthyroidism due to inflammatory destruction of thyroid follicles and release of thyroid hormone. The hyperthyroidism in both of these common disorders is TSH-independent, and TSH is suppressed.

(Choice D) Normal pregnancy is associated with upregulation of thyroid hormone production due to increased thyroid-binding globulin and stimulation of TSH receptors by hCG. However, feedback inhibition of TSH secretion

that stimulate release of thyroid hormone. Chronic lymphocytic (Hashimoto) thyroiditis is associated with thyroid peroxidase antibodies and can cause transient hyperthyroidism due to inflammatory destruction of thyroid follicles and release of thyroid hormone. The hyperthyroidism in both of these common disorders is TSH-independent, and TSH is suppressed.

(Choice D) Normal pregnancy is associated with upregulation of thyroid hormone production due to increased thyroid-binding globulin and stimulation of TSH receptors by hCG. However, feedback inhibition of TSH secretion is intact, and pregnant women with clinical hyperthyroidism will have suppressed TSH.

(Choice E) Surreptitious intake of thyroid hormone is occasionally seen in patients who are attempting to lose weight. In such cases, TSH is suppressed and the thyroid would not be enlarged.

Educational objective:
TSH-secreting pituitary adenomas cause hyperthyroidism with elevated thyroid hormone and elevated or inappropriately normal TSH levels. Most TSH-secreting tumors are macroadenomas and can be associated with mass effect symptoms including headache, visual field defects, and impaired function of surrounding pituitary tissue.

References

- Thyrotropin-secreting pituitary adenomas: epidemiology, diagnosis, and management.

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A 53-year-old woman comes to the office due to severe insomnia, hot flashes, and mood swings for the past several months. Her last menstrual period was a year ago. The patient had a recent wrist fracture that did not require surgery. She has a history of hypothyroidism diagnosed 7 years ago for which she takes levothyroxine, and the dose has been stable for several years. The patient's last TSH level was 3.5 μU/mL. She has no other chronic medical problems. She does not use tobacco, alcohol, or illicit drugs. Blood pressure is 120/70 mm Hg and pulse is 75/min. BMI is 24 kg/m². Physical examination shows a non-enlarged thyroid without nodules. Pelvic examination reveals an erythematous, atrophic vulva and vagina without discharge or bleeding. The uterus is small, and the ovaries are not palpable. Initiation of oral estrogen replacement therapy in this patient would most likely result in which of the following?

A. Circulating level of total T4 would decrease
B. Conversion from T4 to T3 would decrease
C. Level of TSH would decrease
D. Liver metabolism of thyroid hormones would increase
E. Requirement for L-thyroxine would increase

Submit

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- A. Circulating level of total T4 would decrease [19%]
- ✗ B. Conversion from T4 to T3 would decrease [6%]
- C. Level of TSH would decrease [17%]
- D. Liver metabolism of thyroid hormones would increase [10%]
- ✓ E. Requirement for L-thyroxine would increase [46%]

Incorrect
Correct answer

46%
Answered correctly

5 Seconds
TimeSpent

06/17/2018
Last Updated

Major drug interactions of levothyroxine	
↓ **Levothyroxine absorption**	• Bile acid binding agents (eg, 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

TBG = thyroxine-binding globulin.

Most patients with hypothyroidism have an increased requirement for levothyroxine after starting oral estrogen (estrogen replacement therapy or oral contraceptives). **Oral estrogen** formulations decrease clearance of thyroxine-binding globulin (TBG), leading to **elevated TBG levels**. TBG is synthesized and sialylated in the liver. Transdermal estrogen bypasses the liver and does not affect TBG levels.

Patients with normal thyroid function can readily increase thyroxine production to saturate the increased number of

Patients with normal thyroid function can readily increase thyroxine production to saturate the increased number of TBG binding sites, but hypothyroid patients are dependent on exogenous thyroid replacement and cannot compensate. This results in decreased free thyroxine and increased TSH **(Choice C)**. As a result, **higher dosing of levothyroxine** may be required. A rise in estrogen levels is also one of the main reasons for higher levothyroxine requirements during pregnancy.

(Choice A) Due to the increased TBG following the initiation of oral estrogen, free T4 levels in hypothyroid patients can decline. However, total circulating thyroid hormone levels would be unchanged or increase slightly.

(Choice B) Estrogen has no effect on the conversion of T4 to T3. Drugs that inhibit conversion of T4 to T3 include glucocorticoids, beta blockers, iopanoic acid (oral cholecystography contrast agent), and propylthiouracil.

(Choice D) T4 and T3 are metabolized by deiodination (major method), glucuronidation, and sulfation in the liver. Phenobarbital, rifampin, phenytoin, and carbamazepine increase hepatic clearance of thyroid hormone by increasing the activity of these enzymes (mainly deiodination).

Educational objective:
Oral estrogen preparations increase levels of thyroxine-binding globulin (TBG). Patients on thyroid replacement may need a higher dose to saturate the increased number of TBG binding sites.

References

- Interaction of estrogen therapy and thyroid hormone replacement in postmenopausal women.

A 45-year-old man comes to the emergency department with a 2-week history of progressively worsening shortness of breath. The patient has no history of cardiopulmonary disease, although his wife, who has accompanied him, states that he snores heavily at night. In addition, over the last several months his hands and feet have become enlarged; he is not able to take his wedding ring off and his shoes no longer fit. The patient has no significant medical history and takes no medications. He does not use tobacco or alcohol. On examination, he has coarse facial features with prominent frontal bones and jaw and crowding of the pharyngeal space. Extremities show enlarged, swollen hands and feet. There are fine crackles at the lung bases. Which of the following is most likely to be found on echocardiogram?

- A. Apical left ventricular aneurysm
- B. Asymmetric thickening of the interventricular septum
- C. Concentric left ventricular hypertrophy
- D. Flail posterior mitral valve leaflet
- E. Moderate pericardial effusion

Submit

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- A. Apical left ventricular aneurysm [2%]
- B. Asymmetric thickening of the interventricular septum [14%]
- ✔ C. Concentric left ventricular hypertrophy [68%]
- ✘ D. Flail posterior mitral valve leaflet [9%]
- E. Moderate pericardial effusion [4%]

Incorrect
Correct answer
C

68%
Answered correctly

8 Seconds
TimeSpent

11/09/2018
Last Updated

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

This patient has several typical manifestations of **acromegaly**, including coarsening of facial features, pharyngeal crowding, and enlargement of hands and feet. Acromegaly is caused by excessive secretion of growth hormone, usually from a pituitary somatotroph adenoma. Growth hormone increases hepatic production of insulin-like growth factor-I (IGF-I), which causes excessive growth of bone and soft tissues, leading to the clinical manifestations of the disease.

In the heart, acromegaly causes **concentric myocardial hypertrophy** leading to diastolic dysfunction, along with left ventricular dilation and global hypokinesis. This cardiomyopathy is worsened by concurrent hypertension,

In the heart, acromegaly causes **concentric myocardial hypertrophy** leading to diastolic dysfunction, along with left ventricular dilation and global hypokinesis. This cardiomyopathy is worsened by concurrent hypertension, obstructive sleep apnea (seen in this patient), and valvular heart disease, which are common in acromegaly. Complications include **heart failure** (eg, dyspnea, crackles at bases) and **arrhythmias**. Cardiovascular disease is the leading cause of death in patients with acromegaly, but normalization of growth hormone levels following successful treatment markedly reduces cardiovascular mortality.

(Choice A) Left ventricular aneurysm is most often a result of anterior Q-wave myocardial infarction due to occlusion of the left anterior descending artery, which would present with chest pain. Less common causes include hypertrophic cardiomyopathy and Chagas disease.

(Choice B) Hypertrophic cardiomyopathy - a congenital cardiomyopathy that should be distinguished from myocardial hypertrophy due to other cardiovascular diseases (eg, hypertensive, valvular, ischemic) - is characterized by asymmetric thickening of the interventricular septum, leading to left ventricular outflow tract obstruction, diastolic dysfunction, and mitral regurgitation. It would not explain the features of acromegaly seen in this patient.

(Choice D) Flail mitral leaflet is caused by rupture of the chordae tendineae due to mitral valve prolapse, endocarditis, or myxomatous degeneration or by rupture of the papillary muscles in acute myocardial infarction. Acute mitral regurgitation due to a flail leaflet is characterized by severe pulmonary edema and hypotension with a hyperdynamic precordium.

(Choice E) A mild to moderate pericardial effusion, by itself, may not produce any specific symptoms or signs

hypertrophic cardiomyopathy and Chagas disease.

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(Choice E) A mild to moderate pericardial effusion, by itself, may not produce any specific symptoms or signs unless cardiac tamponade occurs. Signs of tamponade include tachycardia, elevated jugular pressure, pulsus paradoxus, and edema.

Educational objective:
Acromegaly causes concentric myocardial hypertrophy, diastolic dysfunction, left ventricular dilation, and global hypokinesis. This cardiomyopathy is often worsened by concurrent hypertension, obstructive sleep apnea, and valvular heart disease. Complications include heart failure and arrhythmias.

References

Enlarged organs | Tongue, thyroid, salivary glands, liver, spleen, kidney, prostate

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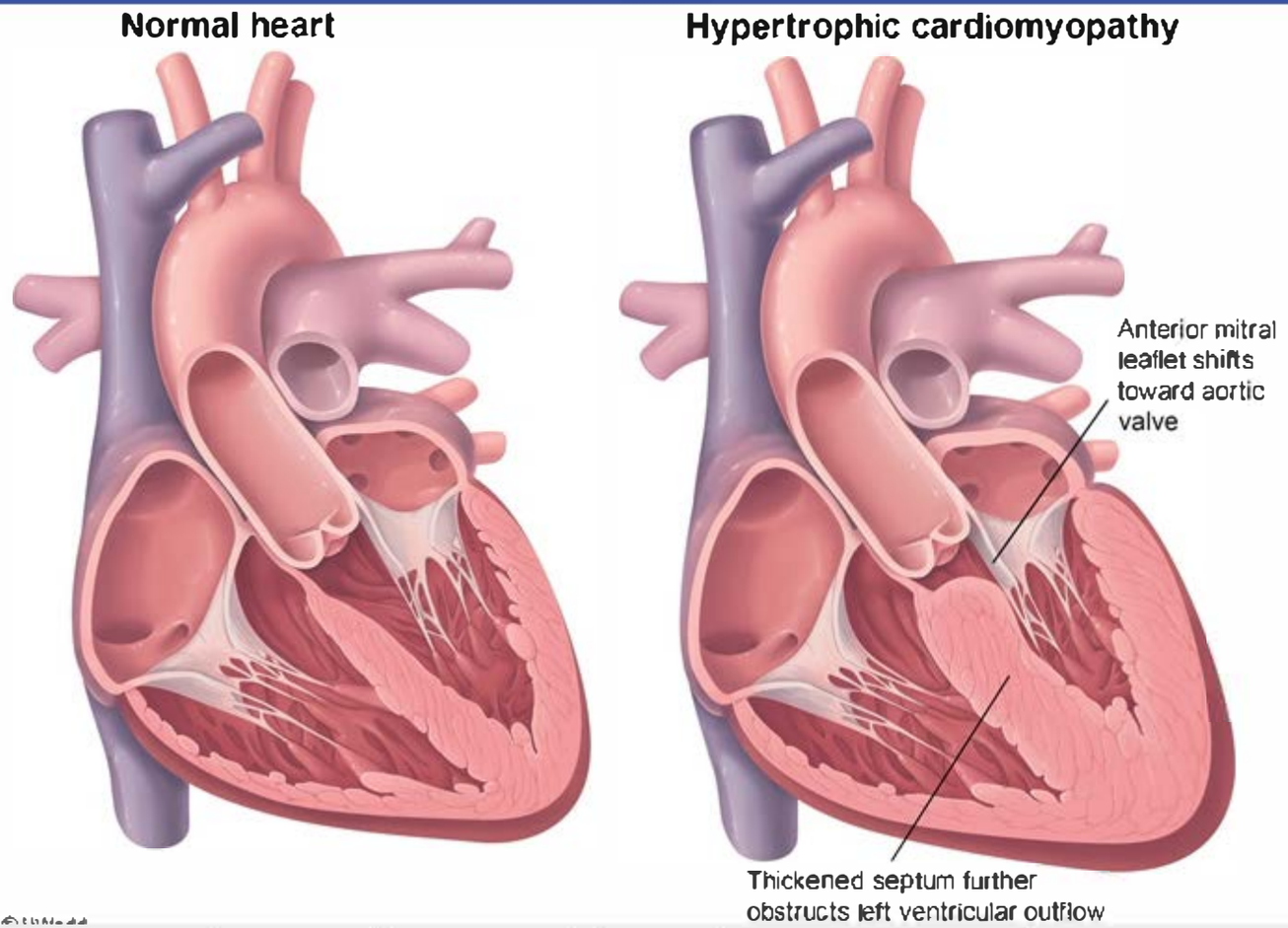

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myocardial hypertrophy due to other cardiovascular diseases (eg, hypertensive, valvular, ischemic) - is

A 65-year-old man comes to the office with a 1-year history of erectile dysfunction and decreased libido. He has hypertension that was diagnosed 5 years ago and is controlled with diet. The patient has no history of cardiac problems, unexpected weight loss, visual changes, or symptoms of neuropathy. Family history is unremarkable. On examination, there is minimal bilateral gynecomastia without galactorrhea. Genitourinary examination shows decreased testicular size. The remainder of the physical examination, including visual fields on confrontation, is unremarkable. Laboratory results are as follows:

Serum chemistry	
Creatinine	1.1 mg/dL
Alanine aminotransferase	21 U/L
Endocrine	
Hemoglobin A1c	5.8%
FSH, serum	5 mU/mL
LH, serum	3 mU/mL
Testosterone, serum	174 ng/dL (normal, 300-800 ng/dL)
TSH	1.3 μU/mL

Repeat early morning testosterone level is 162 ng/dL. Which of the following is the best next step in management

Endocrine

Hemoglobin A1c	5.8%
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Testosterone, serum	174 ng/dL (normal, 300-800 ng/dL)
TSH	1.3 µU/mL

Repeat early-morning testosterone level is 162 ng/dL. Which of the following is the best next step in management of this patient?

A. Angiography of the deep arteries of the penis
B. Measurement of serum prolactin level
C. Measurement of transferrin saturation
D. Sildenafil treatment
E. Testosterone therapy

Submit

Endocrine

Hemoglobin A1c	5.8%
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TSH	1.3 µU/mL

Repeat early-morning testosterone level is 162 ng/dL. Which of the following is the best next step in management of this patient?

- A. Angiography of the deep arteries of the penis [0%]
- ✔ B. Measurement of serum prolactin level [69%]
- ✘ C. Measurement of transferrin saturation [0%]
- D. Sildenafil treatment [3%]
- E. Testosterone therapy [24%]

Incorrect
Correct answer

69%
8 Seconds
03/06/2018

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Male hypogonadism

	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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This patient has gynecomastia and testicular atrophy. His laboratory results show low testosterone levels and inappropriately normal gonadotropin (ie, LH, FSH) levels, indicating **secondary (central) hypogonadism**. Low levels of testosterone normally increase LH and FSH levels due to loss of feedback inhibition. Therefore, low or even normal LH and FSH levels suggest an inappropriate hypothalamic-pituitary response.

Secondary hypogonadism can be due to mass lesions in the hypothalamus or pituitary, hyperprolactinemia (due to **suppression of gonadotropin-releasing hormone**), long-term use of glucocorticoids or opiates, or severe systemic illness. Secondary hypogonadism is also more common in individuals with obesity or type 2 diabetes mellitus. Patients with secondary hypogonadism should have measurement of **serum prolactin**. In men with prolactinoma, gynecomastia is present only in approximately one third of patients, and galactorrhea is uncommon. Visual field defects are present only when the tumor impinges on the optic chiasm. Patients should also have screening for other pituitary hormone deficiencies (eg, TSH). **Pituitary imaging** with MRI is indicated for patients with elevated prolactin, mass-effect symptoms (eg, visual field defects), very low (<150 ng/dL) testosterone levels, or disruptions in other pituitary hormones.

(Choice A) Angiography of the penile deep arteries may be indicated when a vascular etiology of erectile impotence is suspected. However, this test is invasive and not routinely performed.

(Choice C) Hemochromatosis should be suspected when hypogonadism is associated with abnormal skin pigmentation, diabetes mellitus, elevated liver enzymes, and arthropathy. It is unlikely that this patient has hemachromatosis considering his absence of family history, age at presentation, and lack of other clinical features.

(Choice D) Phosphodiesterase type 5 inhibitors (eg, sildenafil) are useful in patients with erectile dysfunction due

(Choice A) Angiography of the penile deep arteries may be indicated when a vascular etiology of erectile impotence is suspected. However, this test is invasive and not routinely performed.

(Choice C) Hemochromatosis should be suspected when hypogonadism is associated with abnormal skin pigmentation, diabetes mellitus, elevated liver enzymes, and arthropathy. It is unlikely that this patient has hemachromatosis considering his absence of family history, age at presentation, and lack of other clinical features.

(Choice D) Phosphodiesterase type 5 inhibitors (eg, sildenafil) are useful in patients with erectile dysfunction due to a variety of causes. However, symptomatic treatment may not be needed if a correctable cause is found.

(Choice E) Testosterone therapy may be required if serum prolactin and MRI of the pituitary are normal. Dopaminergic agonists are the preferred therapy for prolactinoma.

Educational objective:
Secondary hypogonadism can be due to mass lesions in the hypothalamus or pituitary, hyperprolactinemia, long-term use of glucocorticoids or opiates, or severe systemic illness. Patients should have measurement of serum prolactin and screening for other pituitary hormone deficiencies. Pituitary imaging is indicated for patients with elevated prolactin, mass-effect symptoms, very low testosterone levels, or disruptions in other pituitary hormones.

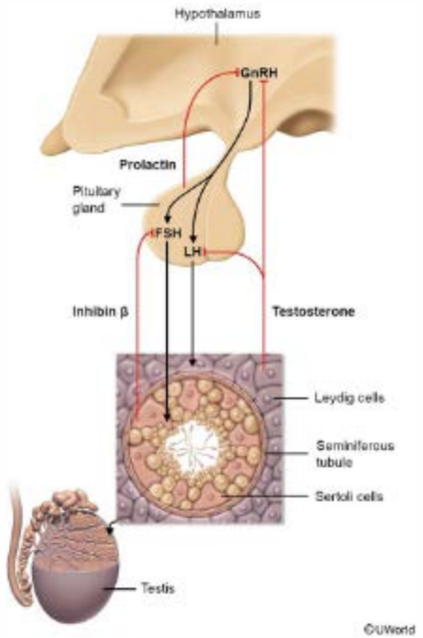
References

- Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline.

Notes

FRONT

Prolactin and gonadotropin production



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BACK

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(Choice C) Hemochrom

A 16-year-old girl comes to the office for evaluation of excessive facial hair. The patient has used multiple creams and makeup over the last year but is still embarrassed by the facial hair. She also has had irregular menstrual cycles since menarche at age 12; her last menstrual period was 6 weeks ago. She is an avid runner. Blood pressure is 122/70 mm Hg and pulse is 87/min. BMI is 20 kg/m². Physical examination shows hirsutism. The patient has normal external female genitalia; the rest of the examination is unremarkable. Urine pregnancy test is negative. Laboratory results are as follows:

17-hydroxyprogesterone	350 ng/mL (normal: <15)
Serum testosterone	80 ng/mL (normal: 20-75)
Serum dehydroepiandrosterone sulfate	390 µg/dL (normal: 37-307)

Serum glucose and electrolytes are normal. Which of the following is the most likely diagnosis in this patient?

A. Adrenal carcinoma
B. Cushing syndrome
C. Germ cell tumor
D. Idiopathic hirsutism
E. Nonclassic congenital adrenal hyperplasia
F. Polycystic ovary syndrome

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- E. Nonclassic congenital adrenal hyperplasia
- F. Polycystic ovary syndrome
- G. Use of performance-enhancing agents

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Serum glucose and electrolytes are normal. Which of the following is the most likely diagnosis in this patient?

- A. Adrenal carcinoma [3%]
- B. Cushing syndrome [0%]
- C. Germ cell tumor [3%]
- D. Idiopathic hirsutism [0%]
- ✔ E. Nonclassic congenital adrenal hyperplasia [74%]
- F. Polycystic ovary syndrome [11%]
- ✘ G. Use of performance-enhancing agents [6%]

Incorrect
Correct answer

74%
Answered correctly

12 Seconds
Time Spent

07/29/2018
Last Updated

Nonclassic congenital adrenal hyperplasia	
Pathophysiology	• Autosomal recessive • ↓ 21-hydroxylase activity • Normal gluco- & mineralocorticoids • ↑ Androgens
Clinical features	• Early pubic/axillary hair growth • Severe acne • Hirsutism & oligomenorrhea in girls • ↑ Growth velocity & bone age • ↑ 17-hydroxyprogesterone level
Treatment	• Hydrocortisone

This patient has **nonclassic** (late-onset) **congenital adrenal hyperplasia** (CAH) based on hyperandrogenism and an **elevated 17-hydroxyprogresterone** (17-OHP) level. The majority of nonclassic CAH is due to a partial deficiency in **21-hydroxylase**, which results in impaired conversion of 17-OHP to 11-deoxycortisol. Buildup of 17-OHP is then diverted toward adrenal androgen synthesis, resulting in **hyperandrogenism**.

Girls with nonclassic CAH typically present in **adolescence** or early adulthood with **irregular menses**, severe acne, and **hirsutism**; virilization (eg, clitoromegaly, deepening of the voice) is rare. Since the enzyme deficiency in nonclassic CAH is relatively mild, sufficient glucocorticoids and mineralocorticoids are produced; therefore, patients do not have the salt-wasting seen in classic CAH, and electrolytes and blood pressure remain normal. Diagnosis

Girls with nonclassic CAH typically present in **adolescence** or early adulthood with **irregular menses**, severe acne, and **hirsutism**; virilization (eg, clitoromegaly, deepening of the voice) is rare. Since the enzyme deficiency in nonclassic CAH is relatively mild, sufficient glucocorticoids and mineralocorticoids are produced; therefore, patients do not have the salt-wasting seen in classic CAH, and electrolytes and blood pressure remain normal. Diagnosis is confirmed by an exaggerated 17-OHP response on ACTH stimulation test.

(Choice A) Androgen-producing adrenal tumors typically present in adulthood with rapidly progressive hirsutism and virilization. Serum DHEAS is markedly elevated with concentrations >700 µg/dL.

(Choice B) Cushing syndrome can cause hirsutism due to elevated adrenal androgens. However, this patient has no Cushingoid features such as moon facies, buffalo hump, central obesity, hypertension, or electrolyte abnormalities. 17-OHP levels are usually normal in Cushing syndrome.

(Choice C) Ovarian germ cell tumors (eg, embryonal carcinoma, choriocarcinoma) typically present with abdominal ascites, pelvic mass, and pregnancy symptoms (eg, breast tenderness). However, they do not usually cause hirsutism. In addition, these tumors often secrete β-hCG, creating a false-positive pregnancy test.

(Choice D) Idiopathic hirsutism is due to excessive conversion of testosterone to dihydrotestosterone in the hair follicles. There is usually a positive family history and normal 17-OHP and androgen levels.

(Choice F) Patients with polycystic ovary syndrome have menstrual irregularities and hyperandrogenism; however, 17-OHP is not elevated.

(Choice G) Anabolic steroid use for performance enhancement presents with hirsutism, voice deepening, increased muscle bulk, and virilization. However, exogenous androgens would not cause elevated 17-OHP.

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Educational objective:
Nonclassic congenital adrenal hyperplasia is caused by a partial deficiency of 21-hydroxylase and typically presents with hyperandrogenism (eg, irregular menses, hirsutism) and elevated 17-hydroxyprogesterone level.

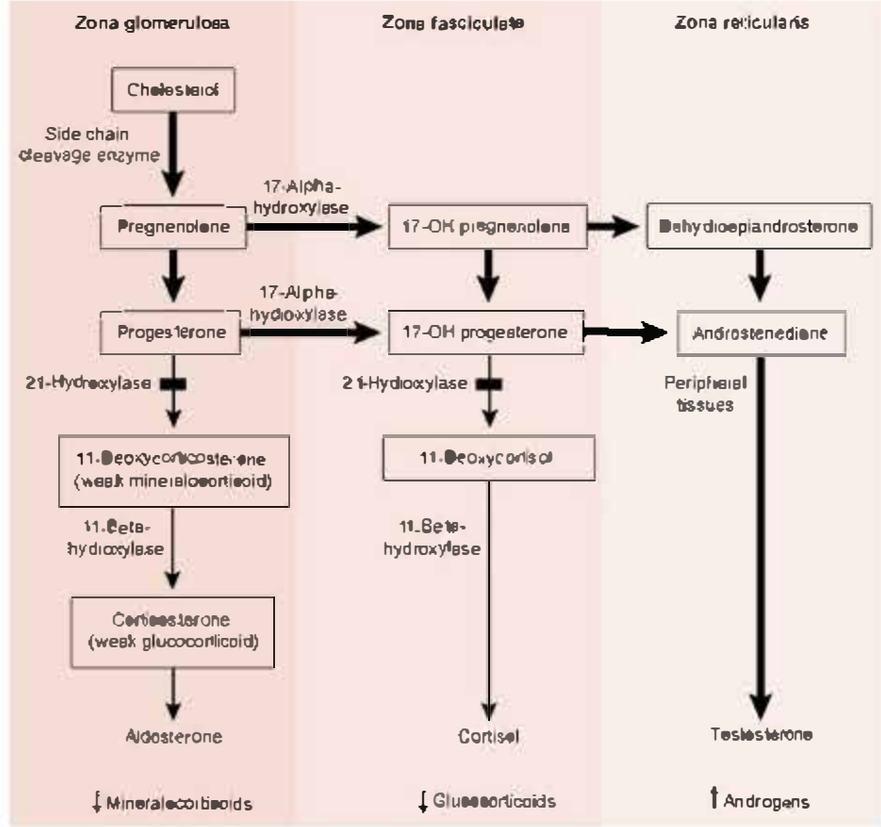
References

- Non-classic congenital adrenal hyperplasia.

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

Exhibit Display

21-Hydroxylase deficiency



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A 25-year-old woman comes to the office due to hair loss. For the past 6 months, she has noticed thinning hair on her head and an increased amount of hair in the shower drain. The patient is not currently sexually active but has had 5 lifetime partners. Menarche was at age 11. She has light periods every 35-50 days. She takes an over-the-counter sleep aid, but does not use tobacco, alcohol, or illicit drugs. The patient's mother is age 56 and has endometrial carcinoma; her paternal grandmother died from metastatic breast cancer diagnosed at age 72. Review of systems is negative except for extensive facial and back acne. BMI is 33 kg/m^2. Physical examination shows thinning hair at the forehead with a receding hairline. The thyroid is nonenlarged with no nodules. Cardiac examination shows a regular rate and rhythm; there are no murmurs. The abdomen is obese with no palpable masses. A urine pregnancy test is negative. Serum prolactin and thyroid function tests are normal. Which of the following additional tests is indicated in this patient?

- A. *BRCA* mutation testing
- B. Diagnostic laparoscopy
- C. Iron studies
- D. Oral glucose tolerance test
- E. Rapid plasma reagin serology

Submit

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- A. *BRCA* mutation testing [12%]
- B. Diagnostic laparoscopy [4%]
- C. Iron studies [7%]
- ✔ D. Oral glucose tolerance test [70%]
- E. Rapid plasma reagin serology [3%]

70% 5 Seconds 10/21/2018

Polycystic ovary syndrome	
Clinical features	• **Androgen excess** (eg, acne, male pattern baldness, hirsutism) • Oligoovulation or anovulation (eg, **menstrual irregularities**) • Obesity • **Polycystic ovaries** on ultrasound
Pathophysiology	• ↑ Testosterone levels • ↑ Estrogen levels • LH/FSH imbalance
Comorbidities	• Metabolic syndrome (eg, diabetes, hypertension) • Obstructive sleep apnea • Nonalcoholic steatohepatitis • Endometrial hyperplasia/cancer
Treatment options	• Weight loss (first-line) • Oral contraceptives for menstrual regulation • Clomiphene citrate for ovulation induction

This patient has clinical evidence of hyperandrogenism, **irregular menses**, and obesity typical of **polycystic ovary syndrome (PCOS)**. Hyperandrogenism is manifested by **male pattern hair loss** (eg, androgenic alopecia), hirsutism, and **severe acne** (eg, nodulocystic, acne on the back). These findings alone are sufficient to make a

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Patients with PCOS are at increased risk for multiple comorbidities, including dyslipidemia, hypertension, and type 2 diabetes mellitus (eg, metabolic syndrome) and should undergo screening for these conditions. An **oral glucose tolerance test** is the gold standard for diagnosing **type 2 diabetes mellitus** in patients with PCOS as it is more sensitive in detecting glucose intolerance than standard screening tests (eg, fasting glucose, HbA1c). Due to obesity and metabolic syndrome, patients are at risk for developing obstructive sleep apnea, nonalcoholic fatty liver disease, and endometrial cancer.

(Choice A) *BRCA* mutation testing is indicated for patients with a family history of ovarian cancer at any age or personal/family history of breast cancer at age ≤50 in a first-degree relative. It is not indicated for a family history of endometrial cancer or breast cancer at an advanced age.

(Choice B) A diagnostic laparoscopy would demonstrate enlarged polycystic ovaries in a patient with PCOS, but it is not required for this diagnosis. Polycystic ovaries can also be incidental findings in some patients without hyperandrogenism or menstrual irregularities (eg, no PCOS).

(Choice C) Excessive menstrual bleeding can cause iron deficiency, which in severe cases may lead to diffuse hair loss (eg, telogen effluvium). However, this patient has oligomenorrhea with minimal vaginal bleeding, making anemia unlikely.

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(Choice E) Rapid plasma reagin serology is used to detect syphilis, a sexually transmitted infection. Secondary syphilis may present with patchy or "moth-eaten" alopecia, but typical presentation also includes constitutional symptoms (eg, malaise, fever, weight loss) and a maculopapular rash.

Educational objective:
Polycystic ovary syndrome (PCOS) may present with androgenic alopecia (male-pattern hair loss), irregular menses, and obesity. Patients with PCOS are at increased risk of developing type 2 diabetes mellitus and should be screened with an oral glucose tolerance test.

References

- Pathophysiology, risk factors, and screening methods for prediabetes in women with polycystic ovary

A 28-year-old woman, gravida 2 para 0 aborta 2, comes to the office following a miscarriage. She had a previous first-trimester miscarriage 9 months ago. The patient has no other known medical problems. She has not experienced any recent change in appetite or weight, diarrhea, constipation, heat or cold intolerance, dyspnea, or hoarseness. The patient's mother has hypothyroidism treated with levothyroxine and hypertension treated with hydrochlorothiazide. The patient does not use tobacco or alcohol. Examination shows a symmetrically enlarged, nontender, firm thyroid gland. There is no cervical lymphadenopathy, and the rest of the physical examination is normal. Her TSH level is 7.2 μU/mL and free T4 is normal. Pelvic ultrasonography is normal. Which of the following autoantibodies is most likely associated with this patient's medical condition?

- A. Anticardiolipin antibody
- B. Antimitochondrial antibody
- C. Antithyroid peroxidase antibody
- D. Thyroid-stimulating immunoglobulin
- E. TSH-receptor-blocking antibody

Submit

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- A. Anticardiolipin antibody [39%]
- ✗ B. Antimitochondrial antibody [2%]
- ✓ C. Antithyroid peroxidase antibody [39%]
- D. Thyroid-stimulating immunoglobulin [4%]
- E. TSH-receptor-blocking antibody [14%]

Incorrect
Correct answer
C

39%
Answered correctly

4 Seconds
TimeSpent

11/09/2018
Last Updated

Causes of recurrent pregnancy loss	
Structural	• Uterine: fibroids, adhesions, polyps • Cervical insufficiency
Chromosomal	• Aneuploidy • Translocations/rearrangements • Mosaicism
Immunologic/ Hematologic	• Hypercoagulable disorders (eg, antiphospholipid syndrome) • Alloimmune intolerance
Endocrine	• Thyroid disease • Polycystic ovary syndrome • Diabetes mellitus • Hyperprolactinemia
Other	• Advancing maternal age • Defective endometrial receptivity • Decreased ovarian reserve • Celiac disease

This patient has subclinical hypothyroidism (normal thyroxine level with a mild elevation in TSH) and a symmetrically enlarged nontender thyroid, consistent with **chronic lymphocytic (Hashimoto) thyroiditis**.

This patient has subclinical hypothyroidism (normal thyroxine level with a mild elevation in TSH) and a symmetrically enlarged nontender thyroid, consistent with **chronic lymphocytic (Hashimoto) thyroiditis**. **Antithyroid peroxidase** (anti-TPO) and antithyroglobulin antibodies are present in >90% of patients with Hashimoto thyroiditis, and high titers of anti-TPO antibodies are associated with an increased risk of progression from subclinical to overt hypothyroidism. High titers of anti-TPO are also associated with increased risk of **miscarriage** in both euthyroid and hypothyroid women (possibly due to disruptions in thyroid metabolism, to which the body is particularly sensitive in pregnancy).

Treatment with levothyroxine is recommended in patients with subclinical hypothyroidism who have elevated anti-TPO antibodies even if they do not have symptoms. Treatment likely reduces the risk of future miscarriage. The titers of anti-TPO antibodies are often highest early in the course of Hashimoto thyroiditis but decrease with time and thyroid hormone treatment.

(Choice A) The risk of recurrent pregnancy loss is also increased in patients with antiphospholipid antibody syndrome (APS). Anticardiolipin antibodies and lupus anticoagulant are typically checked in women with recurrent pregnancy loss. However, APS is not associated with thyroid dysfunction or goiter.

(Choice B) Antimitochondrial antibodies are present in primary biliary cholangitis, which characteristically presents with fatigue and pruritus associated with elevated alkaline phosphatase levels, and may progress to cirrhosis.

(Choice D) Thyroid-stimulating immunoglobulins (TSIs) are present in patients with Graves disease. TSIs stimulate TSH receptors on the thyroid follicular cells, resulting in thyroid hormone overproduction rather than hypothyroidism.

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(Choice E) Antibodies against TSH receptors can block the interaction of TSH with its receptors on thyroid follicular cells and are a less common cause of hypothyroidism. Hypothyroid individuals with TSH-blocking antibodies would have thyroid atrophy rather than enlargement. Anti-TPO antibodies are more likely associated with miscarriage.

Educational objective:
Antithyroid peroxidase (anti-TPO) antibodies are present in >90% of patients with Hashimoto thyroiditis, and high titers of anti-TPO are associated with an increased risk of progression to overt hypothyroidism. High titers of anti-TPO are also associated with increased risk of miscarriage in both euthyroid and hypothyroid women.

References

- Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence.

A 12-year-old girl is brought to the emergency department by her parents for assessment of confusion and rapid breathing. Three days ago the patient developed rhinorrhea, cough, and fever, which have since resolved. The parents say that over the past 48 hours the patient has had increased urination, abdominal pain, and fatigue progressing to somnolence. On arrival, the patient's temperature is 36.7 C (98 F), blood pressure is 110/70 mm Hg, pulse is 138/min, respirations are 36/min, and pulse oximetry is 99% on room air. On physical examination, she is ill-appearing with tachypnea, subcostal retractions, and dry mucous membranes. There is diffuse abdominal tenderness without rebound. Laboratory results are as follows:

Complete blood count	
Hematocrit	42%
Leukocytes	13,000/mm^3
Serum chemistry	
Sodium	129 mEq/L
Potassium	4.8 mEq/L
Chloride	98 mEq/L
Bicarbonate	9 mEq/L
Blood urea nitrogen	24 mg/dL

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Bicarbonate	9 mEq/L
Blood urea nitrogen	24 mg/dL
Creatinine	1.2 mg/dL
Glucose	450 mg/dL

Which of the following is most likely decreased in this patient?

A. Blood renin activity
B. Circulating free fatty acids
C. Hypothalamic vasopressin production
D. Liver glucose production
E. Total body potassium
F. Urine solute excretion

Submit

Chloride	98 mEq/L
Bicarbonate	9 mEq/L
Blood urea nitrogen	24 mg/dL
Creatinine	1.2 mg/dL
Glucose	450 mg/dL

Which of the following is most likely decreased in this patient?

- A. Blood renin activity [3%]
- B. Circulating free fatty acids [5%]
- ✗ C. Hypothalamic vasopressin production [4%]
- D. Liver glucose production [8%]
- ✓ E. Total body potassium [73%]
- F. Urine solute excretion [5%]

Incorrect
Correct answer

73%
Answered Correctly

8 Seconds
Time Spent

09/24/2018
Last Updated

Diabetic ketoacidosis in children	
Clinical features	• Polyuria/nocturia • Polydipsia, polyphagia • Vomiting, abdominal pain • Weight loss, fatigue • Kussmaul respirations (deep, rapid breathing) • Dehydration
Laboratory findings	• Glucose >200 mg/dL • Bicarbonate <15 mEq/L • pH <7.3 • Anion gap >14 • Serum/urine ketones
Management	• 10 mL/kg isotonic fluid bolus over 1 hour • Insulin infusion + isotonic fluids with potassium
Complications	• Cerebral edema

This patient with **hyperglycemia** and an **anion gap metabolic acidosis** has **diabetic ketoacidosis** (DKA), likely due to undiagnosed type 1 diabetes mellitus. **Infection** (eg, upper respiratory infection with fever, cough, and

This patient with **hyperglycemia** and an **anion gap metabolic acidosis** has **diabetic ketoacidosis** (DKA), likely due to undiagnosed type 1 diabetes mellitus. **Infection** (eg, upper respiratory infection with fever, cough, and rhinorrhea in this patient) frequently precipitates DKA due to increased catecholamine, cortisol, and glucagon release. Presenting symptoms typically include **polyuria**, polydipsia, **abdominal pain**, and fatigue. On examination, patients are often **dehydrated** and breathing rapidly (ie, Kussmaul respirations) to compensate for the metabolic acidosis.

During DKA, serum glucose exceeds the threshold for reabsorption by the kidneys, resulting in glucosuria and an osmotic diuresis. This diuresis is accompanied by a net renal loss of potassium with **depletion of total body potassium stores**. However, serum potassium levels may be normal (as seen in this patient) or elevated because acidemia and decreased insulin activity cause a potassium shift to the extracellular fluid compartment.

Treatment involves gradual fluid repletion and insulin administration. Insulin promotes potassium redistribution to the intracellular fluid compartment. Therefore, intravenous fluids are supplemented with potassium to prevent hypokalemia.

(Choice A) Osmotic diuresis associated with DKA causes a reduction in effective circulating blood volume, which activates the renin-angiotensin-aldosterone system. Blood urea nitrogen and creatinine are often acutely elevated due to hypovolemia, as seen in this patient.

(Choice B) DKA is characterized by an increase in circulating free fatty acids due to an underlying relative excess of glucagon to insulin and consequent increase in lipolysis.

(Choice C) Hyperglycemia in DKA contributes not only to osmotic diuresis and hypovolemia but also to serum

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(Choice C) Hyperglycemia in DKA contributes not only to osmotic diuresis and hypovolemia but also to serum hyperosmolality. These effects generally promote pituitary vasopressin release.

(Choice D) Hepatic gluconeogenesis increases in DKA due to increased circulating glucagon, catecholamines, and cortisol.

(Choice F) Hyperglycemia in DKA causes an osmotic diuresis with increased urinary excretion of glucose, ketones, sodium, potassium, and phosphate.

Educational objective:
Diabetic ketoacidosis (DKA) presents with polyuria, abdominal pain, and fatigue and is often precipitated by infection. Laboratory results demonstrate hyperglycemia and an anion gap metabolic acidosis. DKA is characterized by an osmotic diuresis that reduces total body potassium even though serum potassium may be normal or elevated.

References

- Improving care for pediatric diabetic ketoacidosis.

- Glucose >200 mg/dl

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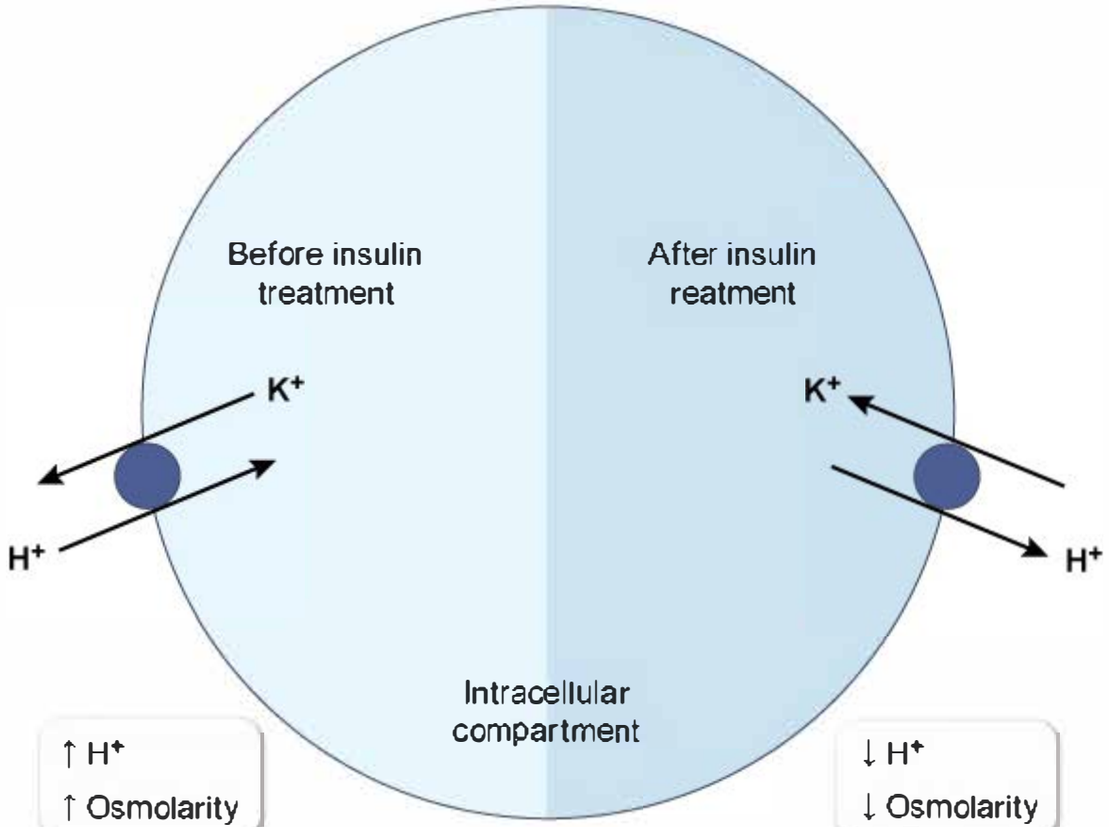

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Treatment involves gradual fluid repletion and insulin administration. Insulin promotes potassium redistribution to

A 60-year-old man is brought to the emergency department by his daughter due to a 2-day history of confusion and lethargy. According to the daughter, he has had a constant dry cough, fatigue, anorexia, polyuria, and constipation for several weeks. In addition, the patient has lost 9.1 kg (20 lb) over the past 3 months. He has no associated pain. The patient's medical history is significant for hypertension treated with chlorthalidone and for gastroesophageal reflux disease treated with over-the-counter antacids. He smokes 2 packs of cigarettes daily and consumes alcohol occasionally. Blood pressure is 130/90 mm Hg and pulse is 90/min. Temporal wasting is noted. Chest and abdominal examinations are normal. Mental status examination shows somnolence and disorientation to time. Neurologic examination shows decreased deep tendon reflexes. Laboratory results are as follows:

Serum chemistry

Sodium	140 mEq/L
Potassium	4 mEq/L
Chloride	104 mEq/L
Bicarbonate	24 mEq/L
Creatinine	1.6 mg/dL
	14.4

Calcium	14.4 mg/dL
Glucose	100 mg/dL
Alkaline phosphatase, serum	130 U/L
Phosphorus (inorganic), serum	2.2 mg/dL

Which of the following is the most likely cause of this patient's symptoms?

A. Elevated parathyroid hormone
B. Elevated parathyroid hormone-related protein
C. Increased 1,25-dihydroxyvitamin D production
D. Local cytokine production
E. Metastatic osteolysis
F. Milk-alkali syndrome

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G. Thiazide-induced hypercalcemia

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Phosphorus (inorganic), serum	2.2 mg/dL

Which of the following is the most likely cause of this patient's symptoms?

- ✗ A. Elevated parathyroid hormone [7%]
- ✓ B. Elevated parathyroid hormone-related protein [78%]
- C. Increased 1,25-dihydroxyvitamin D production [1%]
- D. Local cytokine production [0%]
- E. Metastatic osteolysis [8%]
- F. Milk-alkali syndrome [2%]
- G. Thiazide-induced hypercalcemia [2%]

Incorrect
Correct answer

78%
Answered correctly

17 Seconds
Time Spent

09/15/2018
Last Updated

Hypercalcemia of malignancy			
Cause	**Tumor type**	**Mechanism**	**Diagnostic**
PTHrP*	• **Squamous cell** • Renal & bladder • Breast & ovarian	• PTH mimic	• ↓ PTH • ↑ PTHrP
Bone metastases	• **Breast** • Multiple myeloma	• ↑ **Osteolysis**	• ↓ PTH & PTHrP • ↓ Vitamin D
1,25-dihydroxyvitamin D	• Lymphoma	• ↑ Calcium absorption	• ↓ PTH • ↑ Vitamin D

*PTHrP causes approximately 80% of malignancy-associated hypercalcemia.

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

This patient has polyuria and neuropsychiatric symptoms consistent with hypercalcemia. Severe hypercalcemia can also cause impaired neuromuscular excitability, leading to weakness, diminished reflexes, and decreased gastrointestinal motility. In light of this patient's weight loss, temporal wasting, dry cough, and smoking history, he most likely has **humoral hypercalcemia of malignancy (HHM)** due to squamous cell carcinoma of the lung. HHM is a paraneoplastic syndrome due to the release of **parathyroid hormone-related protein** (PTHrP) by malignant cells, which is structurally similar to parathyroid hormone (PTH) and acts on the PTH-1 receptor. PTHrP causes increased bone resorption and reabsorption of calcium in the distal renal tubule. Increased phosphate excretion

cells, which is structurally similar to parathyroid hormone (PTH) and acts on the PTH-1 receptor. PTHrP causes increased bone resorption and reabsorption of calcium in the distal renal tubule. Increased phosphate excretion leads to hypophosphatemia.

HHM is characterized by **severe** (eg, >14 mg/dL) **and rapid-onset hypercalcemia**. The diagnosis is often suspected on clinical grounds and can be confirmed by an elevated PTHrP level and suppressed PTH level. HHM is usually seen in advanced malignancy and confers a poor prognosis.

(Choice A) Primary hyperparathyroidism causes gradual-onset, mild-to-moderate hypercalcemia (usually <14 mg/dL). Symptoms (eg, renal stones, osteoporosis, constipation), if present, are typically chronic and nonspecific.

(Choice C) Granulomatous diseases (eg, sarcoidosis) and lymphoma can cause hypercalcemia due to extrarenal production of 1,25-dihydroxyvitamin D. However, hypercalcemia due to excess 1,25-dihydroxyvitamin D would be associated with hyperphosphatemia rather than hypophosphatemia. Also, sarcoidosis is more common at age <40.

(Choices D and E) Osteolytic malignancies (eg, breast cancer, multiple myeloma) cause hypercalcemia due to stimulation of osteoclasts by local production of cytokines. This is significantly less common than HHM, and serum phosphorus levels are usually normal. In addition, most patients have significant associated bone pain.

(Choice F) Milk-alkali syndrome is caused by excessive intake of calcium and absorbable alkali. It is characterized by hypercalcemia, metabolic alkalosis, and acute kidney injury. Bicarbonate levels are elevated due to increased intake and decreased renal excretion of bicarbonate.

(Choice G) Thiazide diuretics cause increased reabsorption of calcium in the distal tubule. The resulting

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(Choice F) Milk-alkali syndrome is caused by excessive intake of calcium and absorbable alkali. It is characterized by hypercalcemia, metabolic alkalosis, and acute kidney injury. Bicarbonate levels are elevated due to increased intake and decreased renal excretion of bicarbonate.

(Choice G) Thiazide diuretics cause increased reabsorption of calcium in the distal tubule. The resulting hypercalcemia is mild (usually <12 mg/dL) and rarely symptomatic.

Educational objective:
Humoral hypercalcemia of malignancy is characterized by severe, symptomatic hypercalcemia. It is due to the release of parathyroid hormone-related protein by tumor cells, leading to increased bone resorption and reabsorption of calcium in the distal renal tubule.

References

- Cancer-related hypercalcemia.

A 5-year-old girl is brought to the office for evaluation of pubic hair. Her mother first noticed dark hair in the genital area while helping her daughter bathe several weeks ago. The patient has also developed axillary hair and adult-type body odor over the last 2 weeks. She has no known medical conditions and takes no daily medications. She started kindergarten 3 months ago. The girl's mother underwent menarche at age 12. Weight is at the 75th percentile, height is at the 90th percentile, and BMI is at the 25th percentile. Fundoscopic examination and pupillary reaction are normal bilaterally. Cardiopulmonary examination is normal. The abdomen is soft and nontender; no masses are palpable. Breasts are prepubertal. Sparse, dark, coarse hair is noted in both axillae and over the mons pubis and labia majora. There is no clitoromegaly. Mild comedonal acne is present on the forehead, nose, and chin. Which of the following is the best next step in evaluation of this patient?

- A. Bone age evaluation
- B. Karyotype analysis
- C. Pelvic ultrasound
- D. Serum prolactin level
- E. Serum TSH level

Submit

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- ✔ A. Bone age evaluation [76%]
- B. Karyotype analysis [1%]
- C. Pelvic ultrasound [16%]
- D. Serum prolactin level [2%]
- E. Serum TSH level [2%]

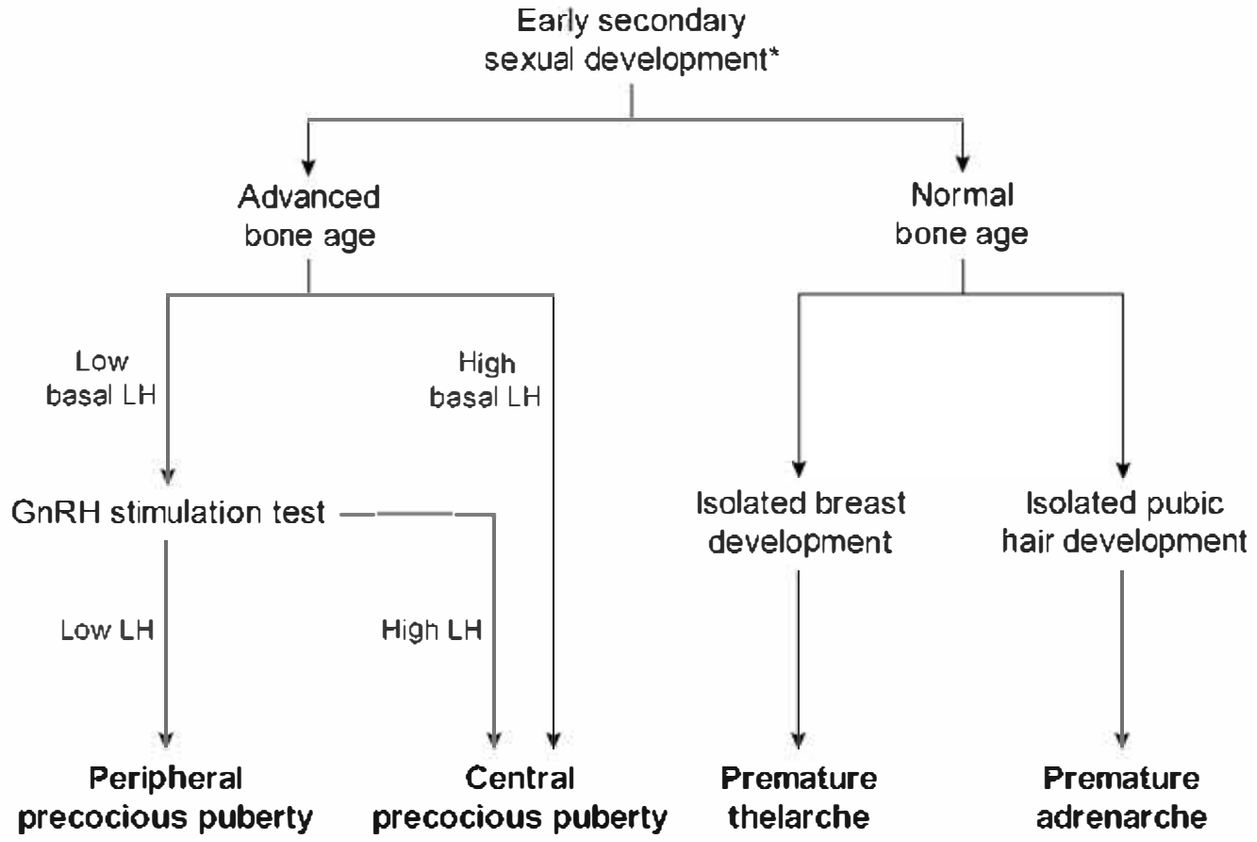
Correct

76% Answered correctly

5 Seconds TimeSpent

07/13/2018 Last Updated

Evaluation of precocious puberty



*Secondary sexual development in girls age <8 or boys age <9.

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This child has **precocious puberty**, the premature development of secondary sexual characteristics in **girls age <8** or in **boys age <9**. Secondary sexual characteristics include breast tissue (stimulated by estrogens), as well as acne, adult-type body odor, and pubic and axillary hair (stimulated by androgens). By history and examination, the patient in this vignette has signs of excess androgens (ie, acne, body odor, axillary and pubic hair) but normal estrogen levels (no evidence of breast development).

Initial management typically includes a **bone age** evaluation, which is a radiographic assessment of the hand and wrist to assess **skeletal maturation**. Normal ossification of bone occurs in a predictable, age-specific sequence. This ossification can be affected by genetics and nutrition in addition to pathologic hormonal causes (eg, excessive estrogen). For example, premature elevated estrogen in cases of precocious puberty can lead to premature epiphyseal fusion and, in turn, an advanced bone age compared to chronologic age. Conversely, if a patient's bone age correlates with chronologic age, the clinical findings are often attributed to a benign pubertal variant.

(Choice B) Karyotype analysis, which identifies chromosomal abnormalities, is not routinely performed in the evaluation of precocious puberty. Karyotyping is most useful postnatally when a specific chromosomal disorder is suspected (eg, Klinefelter syndrome, Turner syndrome).

(Choice C) An abdominal or pelvic ultrasound may be indicated in the evaluation of precocious puberty if there is concern for a peripheral production of endogenous hormones (eg, ovarian or adrenal tumor). Supportive findings would include an advanced bone age with suppressed LH and FSH levels. This patient's presentation first warrants a bone age evaluation.

(Choice D) Prolactinomas are typically benign pituitary tumors that produce elevated prolactin levels causing

suspected (eg, Klinefelter syndrome, Turner syndrome).

(Choice C) An abdominal or pelvic ultrasound may be indicated in the evaluation of precocious puberty if there is concern for a peripheral production of endogenous hormones (eg, ovarian or adrenal tumor). Supportive findings would include an advanced bone age with suppressed LH and FSH levels. This patient's presentation first warrants a bone age evaluation.

(Choice D) Prolactinomas are typically benign pituitary tumors that produce elevated prolactin levels causing secondary amenorrhea and/or galactorrhea. An elevated prolactin level does not cause precocious puberty.

(Choice E) Rarely, chronic hypothyroidism can present with precocious puberty in addition to classic signs of hypothyroidism (eg, constipation, short stature). TSH is thought to inappropriately activate the FSH receptor. However, the increased estrogens produce breast development or vaginal bleeding, which this patient does not have.

Educational objective:

Precocious puberty is the onset of secondary sexual characteristics before age 8 in girls and age 9 in boys. Initial evaluation includes obtaining a bone age evaluation to assess skeletal maturation.

References

- Premature adrenarche.

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A 26-year-old woman calls the office with a question about management of hypothyroidism during pregnancy. The patient is not pregnant but wishes to become pregnant soon. She has a history of hypothyroidism for several years and has been on a stable dose of levothyroxine. TSH checked 3 months ago was 2.0 μU/mL. The patient currently has mild fatigue but is otherwise asymptomatic. Family history is notable for primary hypothyroidism in her mother, who is doing well on a regimen of liothyronine (T_3) and levothyroxine (T_4). Which of the following is the most appropriate recommendation for this patient?

A. Continue the current levothyroxine dose through pregnancy
B. Decrease the levothyroxine dose when the patient becomes pregnant
C. Increase the levothyroxine dose prior to pregnancy
D. Increase the levothyroxine dose when the patient becomes pregnant
E. Switch to combination treatment with liothyronine and levothyroxine

Submit

A 26-year-old woman calls the office with a question about management of hypothyroidism during pregnancy. The patient is not pregnant but wishes to become pregnant soon. She has a history of hypothyroidism for several years and has been on a stable dose of levothyroxine. TSH checked 3 months ago was 2.0 μU/mL. The patient currently has mild fatigue but is otherwise asymptomatic. Family history is notable for primary hypothyroidism in her mother, who is doing well on a regimen of liothyronine (T_3) and levothyroxine (T_4). Which of the following is the most appropriate recommendation for this patient?

- ✗ A. Continue the current levothyroxine dose through pregnancy [16%]
- B. Decrease the levothyroxine dose when the patient becomes pregnant [9%]
- C. Increase the levothyroxine dose prior to pregnancy [5%]
- ✓ D. Increase the levothyroxine dose when the patient becomes pregnant [67%]
- E. Switch to combination treatment with liothyronine and levothyroxine [0%]

Incorrect
Correct answer
D

67%
Answered correctly

4 Seconds
TimeSpent

11/09/2018
Last Updated

Explanation

Maternal thyroid testing in pregnancy, first trimester		
Hormone	**Change**	**Mechanism**
Total T4	Increased	• β-hCG stimulates thyroid hormone production in first trimester • Estrogen stimulates TBG; thyroid increases hormone production to maintain steady free T4 levels
Free T4	Unchanged or mildly increased	
TSH	Decreased	• Increased β-hCG & thyroid hormone suppress TSH secretion

β-hCG = β-human chorionic gonadotropin; TBG = thyroxine-binding globulin.

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During pregnancy, estrogen induces an increase in serum **thyroxine-binding globulin** levels, requiring an increase in the amount of thyroid hormone needed to saturate the binding sites. Thyroxine production is also increased due to the stimulatory effects of hCG on TSH receptors (as hCG and TSH have a similar alpha subunit). These changes lead to an increase in **total thyroid hormone** levels, with a minimal increase in free hormone levels and a decrease in TSH. However, patients with pre-existing hypothyroidism are unable to increase thyroxine production appropriately and are at risk for a worsening hypothyroid state and adverse fetal and maternal effects (eg, gestational hypertension, preeclampsia, premature delivery, postpartum hemorrhage).

Individuals such as this patient on a stable dose of thyroid replacement should have their dose **increased** by

production appropriately and are at risk for worsening hypothyroid state and adverse fetal and maternal effects (eg, gestational hypertension, preeclampsia, premature delivery, postpartum hemorrhage).

Individuals such as this patient on a stable dose of thyroid replacement should have their dose **increased** by approximately 30% at the time the pregnancy is detected **(Choices A and B)**. The dose should be adjusted subsequently (typically in 4-week increments) based on TSH using **pregnancy-specific norms**. Total T_4 should also be followed and maintained within pregnancy-specific norms.

(Choice C) This patient has been on a stable dose of levothyroxine and has a TSH in the low-normal range (<2.5 µU/mL). She does not require dosing adjustments at this time.

(Choice E) T_3 is the active form of thyroid hormone and is produced predominantly by conversion from T_4 in peripheral tissues. However, T_3 has a short half-life, and supplementation with liothyronine (oral T_3) is associated with wide fluctuations in blood levels. T_3 supplementation is not recommended for most patients with primary hypothyroidism, and those who are taking T_3 should be changed to levothyroxine alone if considering pregnancy.

Educational objective:
Levothyroxine requirements increase during pregnancy. Patients with hypothyroidism should increase their levothyroxine dose at the time pregnancy is detected, with subsequent dose adjustments based on TSH and total T_4 using pregnancy-specific norms.

References

- Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice

A 34-year-old woman comes to the office with an uncomfortable sensation of rapid heartbeat for the last few weeks. She has had no associated chest pain or shortness of breath. The patient reports that her anxiety level has been high recently due to stress at work, and she has lost close to 2 kg (4.4 lb) during this time. Her last menstrual period was 5 days ago. Medical history is unremarkable, and she takes no medications. On examination, the thyroid gland is diffusely enlarged and nontender. Laboratory results are as follows:

Complete blood count

Hemoglobin	12.9 g/dL
Hematocrit	39%
Platelets	200,000/mm^3
Leukocytes	8500/mm^3

Serum chemistries

Sodium	139 mEq/L
Potassium	4.2 mEq/L
Chloride	100 mEq/L
Bicarbonate	25 mEq/L
Urea nitrogen	[illegible]

Urea nitrogen	10 mg/dL
Creatinine	1.0 mg/dL
Calcium	9.1 mg/dL
Glucose	102 mg/dL
TSH	<0.001 µU/mL
Free T4	4.6 ng/dL (0.9-2.4 ng/dL)

ECG shows sinus tachycardia at 120/min. Radioactive iodine uptake is <5%, and anti-thyroid peroxidase antibodies are present in high titers. Which of the following is the most appropriate next step in management of this patient?

A. Alprazolam
B. Levothyroxine
C. Methimazole
D. Prednisone
E. Propranolol
F. Radioactive iodine

Calcium	9.1 mg/dL
Glucose	102 mg/dL
TSH	<0.001 μU/mL
Free T4	4.6 ng/dL (0.9-2.4 ng/dL)

ECG shows sinus tachycardia at 120/min. Radioactive iodine uptake is <5%, and anti-thyroid peroxidase antibodies are present in high titers. Which of the following is the most appropriate next step in management of this patient?

- A. Alprazolam [0%]
- B. Levothyroxine [2%]
- C. Methimazole [23%]
- D. Prednisone [4%]
- ✔ E. Propranolol [64%]
- ✘ F. Radioactive iodine [4%]

Incorrect
Correct answer

64%
Answered correctly

42 Seconds
Time Spent

11/09/2018
Last Updated

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.	

This patient has **primary hyperthyroidism** (elevated free T4, suppressed TSH), with signs of thyrotoxicosis including tachycardia, anxiety, and weight loss. Primary hyperthyroidism can result from:

- Overproduction of thyroid hormone (eg, Graves disease, toxic nodular goiter)
- Release of preformed hormone (eg, painless thyroiditis, subacute thyroiditis)

These etiologies can be distinguished with **radioactive iodine uptake** (RAIU) scintigraphy, which will be increased in cases of hormone overproduction and low or undetectable in cases of release of preformed hormone. In this patient, the low RAIU and nontender goiter are most consistent with **painless (silent) thyroiditis**.

Painless thyroiditis is associated with **thyroid peroxidase autoantibodies** and is considered a variant of chronic lymphocytic (Hashimoto) thyroiditis. It is similar to postpartum thyroiditis but by definition excludes patients within a

Painless thyroiditis is associated with **thyroid peroxidase autoantibodies** and is considered a variant of chronic lymphocytic (Hashimoto) thyroiditis. It is similar to postpartum thyroiditis but by definition excludes patients within a year of pregnancy. Following a **self-limited** hyperthyroid phase, patients often develop a hypothyroid phase, which may persist or return to a euthyroid state. Painless thyroiditis does not require specific therapy. However, as hyperthyroidism causes adrenergic overstimulation, a **beta blocker** (eg, propranolol) may be prescribed to control symptoms, especially palpitations or tremulousness.

(Choice A) Alprazolam is a benzodiazepine used primarily in the short-term treatment of anxiety. In this patient, blocking the effects of adrenergic hyperstimulation will likely relieve her symptoms, and additional symptomatic therapy may not be needed.

(Choice B) Levothyroxine is required for the subset of patients who develop significant hypothyroidism.

(Choices C and F) Methimazole works primarily by decreasing thyroid hormone production; RAI causes radiation-induced destruction of thyroid follicular cells. As a result, these treatments are used for thyrotoxicosis due to thyroid hormone overproduction but are not helpful for patients with excess release of preformed hormone.

(Choice D) Prednisone is used to treat thyroid pain in patients with subacute (de Quervain) thyroiditis who do not respond to nonsteroidal anti-inflammatory drugs. Although subacute thyroiditis would also be associated with low RAIU, it presents with a painful, tender goiter and is typically preceded by an upper respiratory tract infection. Prednisone is also used in some patients with amiodarone-induced thyrotoxicosis.

Educational objective:

Painless thyroiditis is a variant of chronic lymphocytic (Hashimoto) thyroiditis. It is characterized by a self-limited

(Choice A) Alprazolam is a benzodiazepine used primarily in the short-term treatment of anxiety. In this patient, blocking the effects of adrenergic hyperstimulation will likely relieve her symptoms, and additional symptomatic therapy may not be needed.

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Educational objective:
Painless thyroiditis is a variant of chronic lymphocytic (Hashimoto) thyroiditis. It is characterized by a self-limited hyperthyroid phase due to release of preformed thyroid hormone, followed by a hypothyroid phase or return to a euthyroid state. It does not require specific therapy, but a beta blocker may be prescribed to control symptoms due to hyperthyroidism (eg, palpitations, tremulousness).

References

- Subacute, silent, and postpartum thyroiditis.

A 55-year-old man comes to the clinic for follow-up of hypertension. The patient was diagnosed with hypertension 3 months ago after an episode of transient vision loss in his right eye. He has occasional headaches and general fatigue but otherwise feels well. His current medications include aspirin, lisinopril, and low-dose hydrochlorothiazide. His blood pressure is 157/95 mm Hg and pulse is 69/min. BMI is 26 kg/m^2. Cardiac examination shows a fourth heart sound on auscultation. There are no bruits in the carotids or abdomen. Pulses are 2+ in all extremities. Laboratory results are as follows:

Potassium	3.1 mEq/L
Creatinine	0.9 mg/dL
Plasma renin activity	undetectable

Which of the following best explains this patient's laboratory findings?

A. Lisinopril side effect
B. Malignant hypertension
C. Primary hyperaldosteronism
D. Thiazide side effect
E. Unilateral renal artery stenosis

hydrochlorothiazide. His blood pressure is 157/95 mm Hg and pulse is 69/min. BMI is 26 kg/m². Cardiac examination shows a fourth heart sound on auscultation. There are no bruits in the carotids or abdomen. Pulses are 2+ in all extremities. Laboratory results are as follows:

Potassium	3.1 mEq/L
Creatinine	0.9 mg/dL
Plasma renin activity	undetectable

Which of the following best explains this patient's laboratory findings?

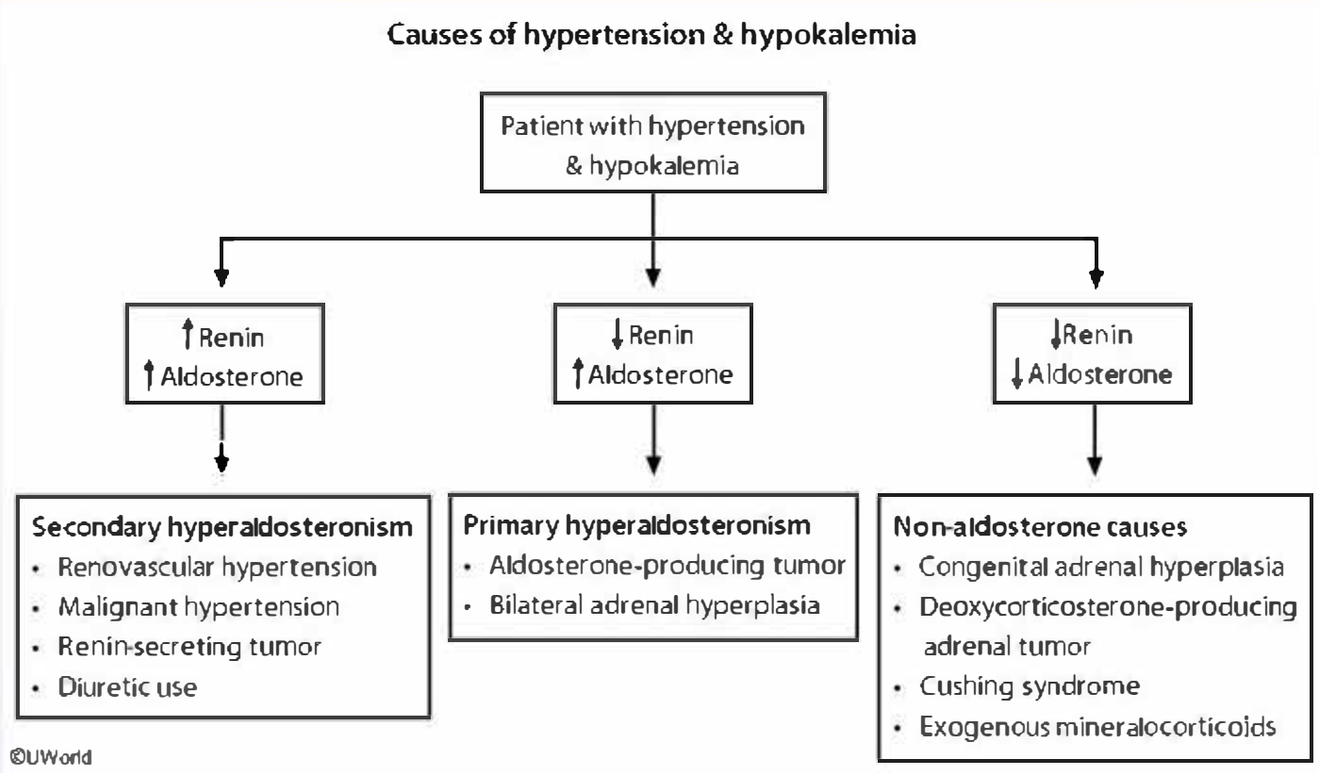
- ✗ A. Lisinopril side effect [6%]
- B. Malignant hypertension [2%]
- ✓ C. Primary hyperaldosteronism [72%]
- D. Thiazide side effect [15%]
- E. Unilateral renal artery stenosis [2%]

Incorrect
Correct answer

72%
Answered correctly

9 Seconds
Time Spent

08/10/2018
Last Updated



This patient with hypertension and undetectable plasma renin activity most likely has **primary hyperaldosteronism** (PH). PH is the most common cause of **secondary hypertension** and is usually due to an adrenal adenoma or bilateral adrenal hyperplasia. Patients typically develop **hypertension**, mild hypernatremia, **hypokalemia**, and **metabolic alkalosis**. Plasma renin activity (PRA) is low in PH due to feedback inhibition. Hypokalemia and hypertension with suppressed PRA may also be seen in congenital adrenal hyperplasia, Cushing's syndrome, or exogenous mineralocorticoid intake.

Serum potassium may be normal initially in patients with PH, but treatment with diuretics may trigger severe, symptomatic hypokalemia. Although aldosterone causes increased renal reabsorption of sodium, most patients with PH do not have edema or clinically significant hypernatremia due to **aldosterone escape**.

(Choice A) ACE inhibitors decrease conversion of angiotensin I to angiotensin II. Aldosterone levels are decreased and PRA is reflexively increased. ACE inhibitors are associated with hyperkalemia and a rise in creatinine due to reduced glomerular filtration rate.

(Choice B) Malignant hypertension is characterized by markedly elevated blood pressure with end-organ damage to the eye (eg, retinal hemorrhages, papilledema), kidney (eg, nephrosclerosis), and central nervous system (eg, hemorrhage, encephalopathy). It also causes secondary hyperaldosteronism with elevated PRA. This patient's normal creatinine and undetectable PRA make malignant hypertension less likely.

(Choice D) Diuretic use in the absence of PH may also cause hypokalemia, but it is associated with a compensatory rise in PRA.

(Choice E) Unilateral renal artery stenosis is characterized by hypertension, abdominal bruits, and episodes of flash pulmonary edema. Renovascular hypertension also causes a rise in PRA, leading to secondary hyperaldosteronism.

Educational objective:
Primary hyperaldosteronism is characterized by hypertension, mild hypernatremia, metabolic alkalosis, and suppressed plasma renin activity. Hypokalemia is not always present at baseline but can be severe with diuretic use. Clinically significant hypernatremia and edema are not seen due to aldosterone escape.

- Renovascular hypertension
- Maligna
- Renin-s
- Diuretic

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Exhibit Display

Secondary causes of hypertension

Condition	Clinical clues/features
Renal parenchymal disease	• Elevated serum creatinine • Abnormal urinalysis (proteinuria, red blood cell casts)
Renovascular disease	• Severe hypertension (≥180 mm Hg systolic &/or 120 mm Hg diastolic) after age 55 • Possible recurrent flash pulmonary edema or resistant heart failure • Unexplained rise in serum creatinine • Abdominal bruit
Primary aldosteronism	• Easily provoked hypokalemia • Slight hypernatremia • Hypertension with adrenal incidentaloma
Pheochromocytoma	• Paroxysmal elevated blood pressure with tachycardia • Pounding headaches, palpitations, diaphoresis • Hypertension with an adrenal incidentaloma

Add To Flash Card

- Renovascular hypertension
- Maligna
- Renin-s
- Diuretic

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Exhibit Display

	• Hypertension with adrenal incidentaloma
Pheochromocytoma	• Paroxysmal elevated blood pressure with tachycardia • Pounding headaches, palpitations, diaphoresis • Hypertension with an adrenal incidentaloma
Cushing syndrome	• Central obesity, facial plethora • Proximal muscle weakness, abdominal striae • Ecchymosis, amenorrhea/erectile dysfunction • Hypertension with adrenal incidentaloma
Hypothyroidism	• Fatigue, dry skin, cold intolerance • Constipation, weight gain, bradycardia
Primary hyperparathyroidism	• Hypercalcemia (polyuria, polydipsia) • Kidney stones • Neuropsychiatric presentations (confusion, depression, psychosis)
Coarctation of the aorta	• Differential hypertension with brachial-femoral pulse delay

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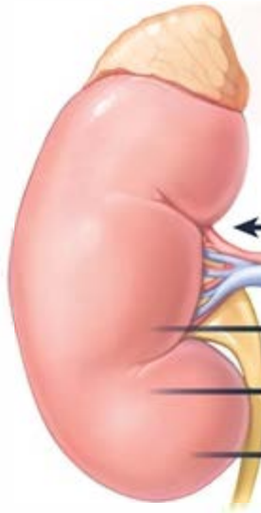
Exhibit Display

Pathogenesis of primary hyperaldosteronism
(and aldosterone escape)



- Bilateral nodular hyperplasia
- Hyperfunctioning adrenal adenoma

↑ Aldosterone

↑ K+ reabsorption → Hypokalemia

↑ H+ reabsorption → Metabolic alkalosis

↑ Na+ reabsorption → Hypertension, ↑ Blood volume → ↑ Renin, ↑ Angiotensin II

Aldosterone escape
- Limits edema
- Limits hypernatremia

↑ Renal blood flow, ↑ GFR, ↑ Atrial natriuretic peptide → ↑ Na+ excretion

GFR = glomerular filtration rate.

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normal creatinine and undetectable PRA make malignant hypertension less likely

A 56-year-old woman with recently diagnosed diabetes comes to the physician complaining of weight loss. She has lost 20 pounds (9 kg) over the last 6 months. She initially attributed her weight loss to diabetes, but it has been well controlled with sitagliptin. The patient has no palpitations, abdominal pain, or vomiting, but she does have occasional watery stools. She has no history of hypertension or hyperlipidemia. She is treated with a steroid cream for an eczematous perioral rash that recently has affected her right thigh. The patient's temperature is 37° C (98.6° F), blood pressure is 110/70 mm Hg, pulse is 78/min, and respirations are 14/min. Her body mass index is 18 kg/m^2. There is no thyromegaly. The lungs are clear to auscultation. Abdominal examination is unremarkable. Skin examination shows erythematous plaques with central clearing and eroded borders on her right thigh and in the perioral region. Laboratory results are as follows:

White blood cells	6,400/mm^3
Hemoglobin	8.7 g/dL
Hematocrit	29%
Platelets	193,000/mm^3
Sodium	144 mEq/L
Potassium	3.8 mEq/L
Bicarbonate	23 mEq/L
Blood urea nitrogen	16 mg/dL

Platelets	193,000/mm³
Sodium	144 mEq/L
Potassium	3.8 mEq/L
Bicarbonate	23 mEq/L
Blood urea nitrogen	16 mg/dL
Creatinine	0.6 mg/dL
Glucose	112 mg/dL

Hemoglobin A1c is 6.2%.

Which of the following is most likely to yield the diagnosis in this patient?

A. Gastrin levels

B. Glucagon levels

C. Insulin levels and anti-glutamic acid decarboxylase antibodies

D. Thyroid function tests

E. Urinary 5-hydroxyindoleacetic acid excretion

Sodium	144 mEq/L
Potassium	3.8 mEq/L
Bicarbonate	23 mEq/L
Blood urea nitrogen	16 mg/dL
Creatinine	0.6 mg/dL
Glucose	112 mg/dL

Hemoglobin A1c is 6.2%.

Which of the following is most likely to yield the diagnosis in this patient?

- A. Gastrin levels [11%]
- ✔ B. Glucagon levels [45%]
- C. Insulin levels and anti-glutamic acid decarboxylase antibodies [17%]
- D. Thyroid function tests [7%]
- ✘ E. Urinary 5-hydroxyindoleacetic acid excretion [19%]

Incorrect

Windows Media Player

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

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This patient's presentation suggests glucagonoma. Glucagonoma is a rare pancreatic neuroendocrine tumor that usually presents with diabetes mellitus, necrolytic migratory erythema (NME), weight loss, diarrhea, and anemia. NME usually presents as erythematous papules or plaques that coalesce to form a large, painful, and inflammatory blister and/or crusting with central clearing. NME commonly occurs in the perineum, extremities, and face.

Glucagonoma is often diagnosed late due to early nonspecific clinical features. The diabetes is usually mild in these patients, with normal to slightly high insulin levels, and is controlled with lifestyle changes and oral medications (rarely requiring insulin). The normocytic and normochromic anemia may be due to anemia of chronic disease or glucagon's direct effect on erythropoiesis.

The serum glucagon level >500 pg/mL usually confirms the diagnosis in suspected patients. Glucagon can be elevated in other conditions (eg, hypoglycemia, sepsis, Cushing syndrome, pancreatitis) but is typically <500 pg/mL. Abdominal imaging (computed tomography or magnetic resonance imaging) can localize the tumor and evaluate for metastases.

(Choice A) Gastrinoma is a gastrin-producing neuroendocrine tumor that typically presents with abdominal pain (upper gastrointestinal ulceration), diarrhea, anemia, and weight loss. Diabetes mellitus and NME do not usually occur with gastrinoma.

(Choice C) Indolent late-onset autoimmune type 1 diabetes occurs in older patients and may initially present similar to type 2 diabetes mellitus. These patients have anti-glutamic acid decarboxylase antibodies and low insulin levels. They are difficult to control with oral anti-diabetic agents and progress relatively quickly to insulin dependency compared to typical patients with type 2 diabetes.

(upper gastrointestinal ulceration), diarrhea, anemia, and weight loss. Diabetes mellitus and NME do not usually occur with gastrinoma.

(Choice C) Indolent late-onset autoimmune type 1 diabetes occurs in older patients and may initially present similar to type 2 diabetes mellitus. These patients have anti-glutamic acid decarboxylase antibodies and low insulin levels. They are difficult to control with oral anti-diabetic agents and progress relatively quickly to insulin dependency compared to typical patients with type 2 diabetes.

(Choice D) Although weight loss and diarrhea can be caused by thyrotoxicosis, this patient does not have other features (eg, tremor, goiter, tachycardia, lid lag) suggesting thyrotoxicosis.

(Choice E) Diarrhea and weight loss may occur in patients with carcinoid syndrome, but episodic flushing (not seen in this patient) is the most characteristic feature.

Educational objective:
Glucagonoma often presents with nonspecific symptoms and requires a high index of suspicion to make the diagnosis. Glucagonoma should be suspected in patients presenting with mild diabetes mellitus or hyperglycemia with necrotic migratory erythema, diarrhea, anemia, and weight loss. Glucagon >500 pg/mL usually confirms the diagnosis.

References

- Clinical spectrum of hyperglucagonemia associated with malignant neuroendocrine tumors.
- Endocrine pancreatic tumors with glucagon hypersecretion: a retrospective study of 23 cases during 20 years.

A 35-year-old man is evaluated for poor exercise tolerance and muscle weakness. He has no past medical history. His blood pressure is 175-185 mm Hg systolic and 105-115 mm Hg diastolic on repeat measurements. His pulse is 78-95/min. Laboratory results are as follows:

Sodium	146 mEq/L
Potassium	2.4 mEq/L
Glucose	95 mg/dL
Creatinine	0.7 mg/dL

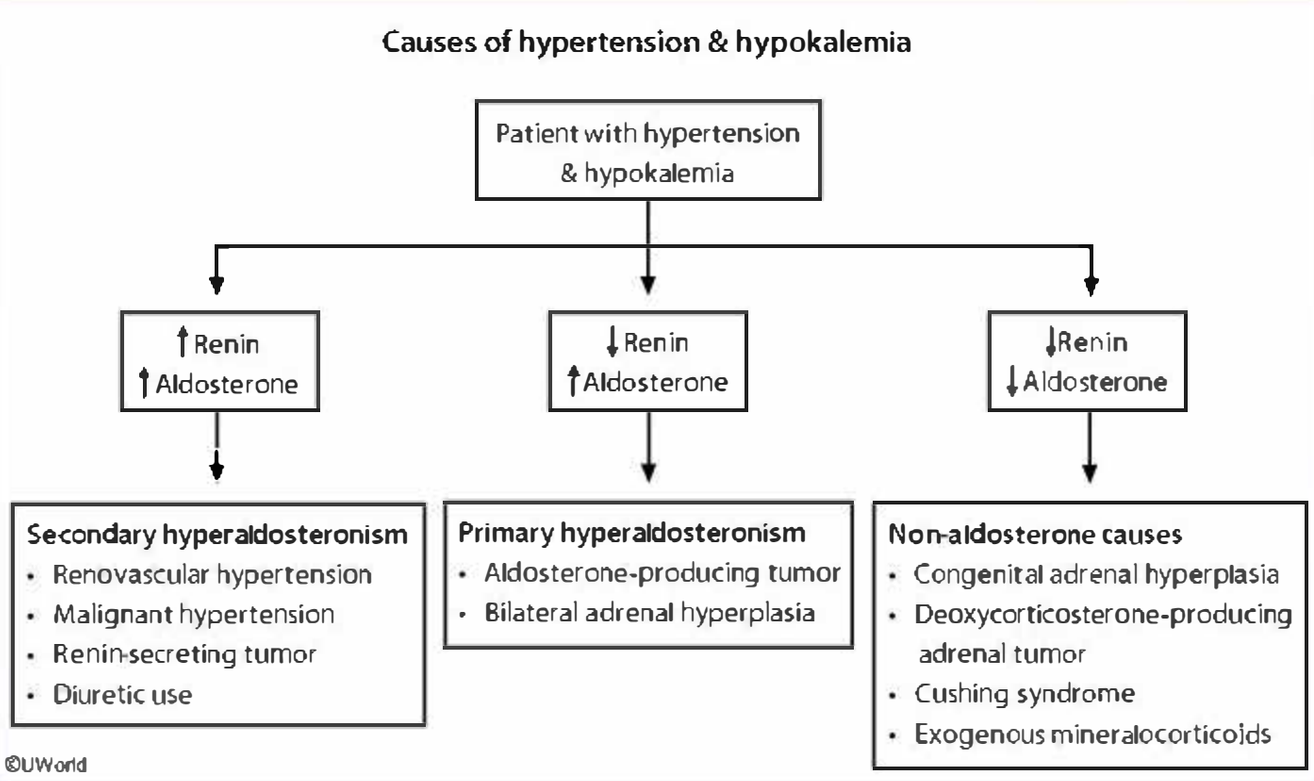
Computed tomography scan of the abdomen reveals a 3-cm mass in the left adrenal gland. Which of the following additional findings would be expected in this patient?

	Plasma renin activity	Serum aldosterone	Serum bicarbonate
A.	High	High	Low
B.	High	High	High
C.	Low	High	High
D.	Low	High	Low
E.	High	Low	High

Sodium	146 mEq/L
Potassium	2.4 mEq/L
Glucose	95 mg/dL
Creatinine	0.7 mg/dL

Computed tomography scan of the abdomen reveals a 3-cm mass in the left adrenal gland. Which of the following additional findings would be expected in this patient?

	Plasma renin activity	Serum aldosterone	Serum bicarbonate
A. [7%]	High	High	Low
B. [4%]	High	High	High
✔ C. [65%]	Low	High	High
D. [21%]	Low	High	Low
✘ E.	High	Low	High



This younger patient with significant hypertension raises suspicion for secondary causes of hypertension. The hypokalemia, combined with computed tomography scan showing a 3-cm adrenal mass, suggests primary hyperaldosteronism (Conn's syndrome). Conn's syndrome is usually due to an adrenal adenoma or bilateral adrenal hyperplasia. Patients typically develop hypertension, mild hypernatremia, hypokalemia, and metabolic alkalosis. The elevated aldosterone leads directly to decreased renin through a feedback inhibition **(Choice E)**. The hypokalemia can cause muscle weakness and decreased exercise tolerance in some patients.

The hypokalemia can cause muscle weakness and decreased exercise tolerance in some patients.

(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.

(Choice B) Secondary hyperaldosteronism causes elevated renin, elevated aldosterone, and metabolic alkalosis. Typical causes include renovascular hypertension, malignant hypertension, diuretics, and renin-secreting tumor. This patient's 3-cm adrenal mass makes the first 3 causes less likely. A renin-secreting tumor is very rare and much less likely than an aldosterone-secreting adenoma in this patient.

Educational objective:
Primary hyperaldosteronism (Conn's syndrome) causes hypertension, mild hypernatremia, hypokalemia, and metabolic alkalosis. The diagnosis of Conn's syndrome is suggested by low renin and elevated aldosterone levels.

References

- Primary aldosteronism.

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A 17-year-old girl comes to the office for evaluation of irregular menses. The patient reports irregular menses since menarche at age 13, and her menstrual cycle has become increasingly unpredictable. Over the past year, she has had 5 menstrual periods. Her most recent period was 6 weeks ago and it lasted 10 days, with heavy bleeding and large clots. The patient has also gained 10 kg (22 lb) over the last year and has been unable to lose weight despite changes in her diet. She has no medical problems and has had no surgeries. She does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/80 mm Hg and pulse is 76/min. BMI is 28 kg/m^2. Physical examination shows coarse hair along the chin. There is no thyromegaly or palpable neck masses. The abdomen is soft and nontender, with no striae or palpable masses. Deep tendon reflexes of the extremities are normal, and no pedal edema is present. Hemoglobin is 10.2 g/dL. TSH and prolactin levels are normal. A urine pregnancy test is negative. Which of the following is the best next step for addressing this patient's irregular menses?

- A. Order CT scan of the adrenal gland
- B. Prescribe clomiphene citrate
- C. Prescribe combined oral contraceptives
- D. Prescribe leuprolide
- E. Prescribe levothyroxine
- F. Prescribe spironolactone

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- A. Order CT scan of the adrenal gland [4%]
- B. Prescribe clomiphene citrate [3%]
- ✔ C. Prescribe combined oral contraceptives [88%]
- D. Prescribe leuprolide [1%]
- E. Prescribe levothyroxine [0%]
- ✘ F. Prescribe spironolactone [1%]

Incorrect
Correct answer

88%
Answered correctly

8 Seconds
Time Spent

05/15/2018
Last Updated

Polycystic ovary syndrome	
Clinical features	• **Androgen excess** (eg, acne, male pattern baldness, hirsutism) • Oligoovulation or anovulation (eg, **menstrual irregularities**) • Obesity • **Polycystic ovaries** on ultrasound
Pathophysiology	• ↑ Testosterone levels • ↑ Estrogen levels • LH/FSH imbalance
Comorbidities	• Metabolic syndrome (eg, diabetes, hypertension) • Obstructive sleep apnea • Nonalcoholic steatohepatitis • Endometrial hyperplasia/cancer
Treatment options	• Weight loss (first-line) • Oral contraceptives for menstrual regulation • Clomiphene citrate for ovulation induction

This patient's **irregular menses**, **hirsutism** (eg, coarse hair along chin), and weight gain are consistent with **polycystic ovary syndrome (PCOS)**. Patients with PCOS often have hyperandrogenism, diagnosed either clinically (eg, hirsutism, severe acne, androgenic alopecia) or biochemically (eg, elevated testosterone levels).

polycystic ovary syndrome (PCOS). Patients with PCOS often have hyperandrogenism, diagnosed either clinically (eg, hirsutism, severe acne, androgenic alopecia) or biochemically (eg, elevated testosterone levels). Hyperandrogenism, and the subsequent hyperestrogenism (due to peripheral androgen conversion), results in chronic anovulation. Anovulatory cycles cause irregular menses, decreased progesterone secretion, and **uncontrolled endometrial proliferation** from unopposed estrogen. When menstrual periods do occur, they are often associated with heavy bleeding that may result in anemia.

The first-line therapy for menstrual regulation is a combination of weight loss and **combined estrogen/progestin oral contraceptives**. Combined oral contraceptives contain progesterone to stimulate endometrial differentiation (ie, limit continued proliferation) and estrogen to stabilize the uterine lining, which restores normal cycles. In addition, combined oral contraceptives reduce hirsutism by blocking adrenal androgen secretion and increasing production of sex hormone-binding globulin, which binds and decreases free testosterone.

(Choice A) A CT scan of the adrenal gland can be used in the evaluation of adrenocortical tumors as causes of hyperandrogenism. Patients with adrenocortical tumors typically have virilization (eg, clitoromegaly, deepening voice), abdominal striae, and elevated dehydroepiandrosterone sulfate levels.

(Choice B) Clomiphene citrate is administered for ovulation induction in PCOS to treat infertility. It does not regulate menses.

(Choice D) Leuprolide, a gonadotropin-releasing hormone agonist, is used in the treatment of endometriosis. Patients with endometriosis have dysmenorrhea, chronic pelvic pain, and no evidence of hyperandrogenism.

(Choice E) Levothyroxine is used to treat hypothyroidism, which can cause irregular menses, but patients also

production of sex hormone-binding globulin, which binds and decreases free testosterone.

(Choice A) A CT scan of the adrenal gland can be used in the evaluation of adrenocortical tumors as causes of hyperandrogenism. Patients with adrenocortical tumors typically have virilization (eg, clitoromegaly, deepening voice), abdominal striae, and elevated dehydroepiandrosterone sulfate levels.

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(Choice D) Leuprolide, a gonadotropin-releasing hormone agonist, is used in the treatment of endometriosis. Patients with endometriosis have dysmenorrhea, chronic pelvic pain, and no evidence of hyperandrogenism.

(Choice E) Levothyroxine is used to treat hypothyroidism, which can cause irregular menses, but patients also have elevated TSH levels. This patient has a normal TSH level.

(Choice F) Spironolactone, an androgen receptor antagonist, is indicated for treatment of hirsutism; it does not regulate menstrual cycles.

Educational objective:
Polycystic ovary syndrome may present with irregular menses and signs of hyperandrogenism (eg, hirsutism). Treatment involves weight loss and oral contraceptives containing estrogen and progestin to regulate menstrual cycles.

References

- Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline

A 28-year-old avid mountain climber and his friend are vacationing in the Andes in Peru. During their climbing expedition, the pair becomes lost in the mountains for several days. It has been over 16 hours since their food supply ran out. Their glycogen stores are becoming depleted, and their bodies are beginning to upregulate the process of gluconeogenesis. Alanine is converted into which of the following intermediates during this process?

- A. Citrate
- B. Glycerol-3-phosphate
- C. Lactate
- D. Pyruvate
- E. Succinate

Submit

A 28-year-old avid mountain climber and his friend are vacationing in the Andes in Peru. During their climbing expedition, the pair becomes lost in the mountains for several days. It has been over 16 hours since their food supply ran out. Their glycogen stores are becoming depleted, and their bodies are beginning to upregulate the process of gluconeogenesis. Alanine is converted into which of the following intermediates during this process?

- A. Citrate [6%]
- ✗ B. Glycerol-3-phosphate [10%]
- C. Lactate [9%]
- ✓ D. Pyruvate [66%]
- E. Succinate [7%]

Incorrect
Correct answer
D

66%
Answered correctly

4 Seconds
TimeSpent

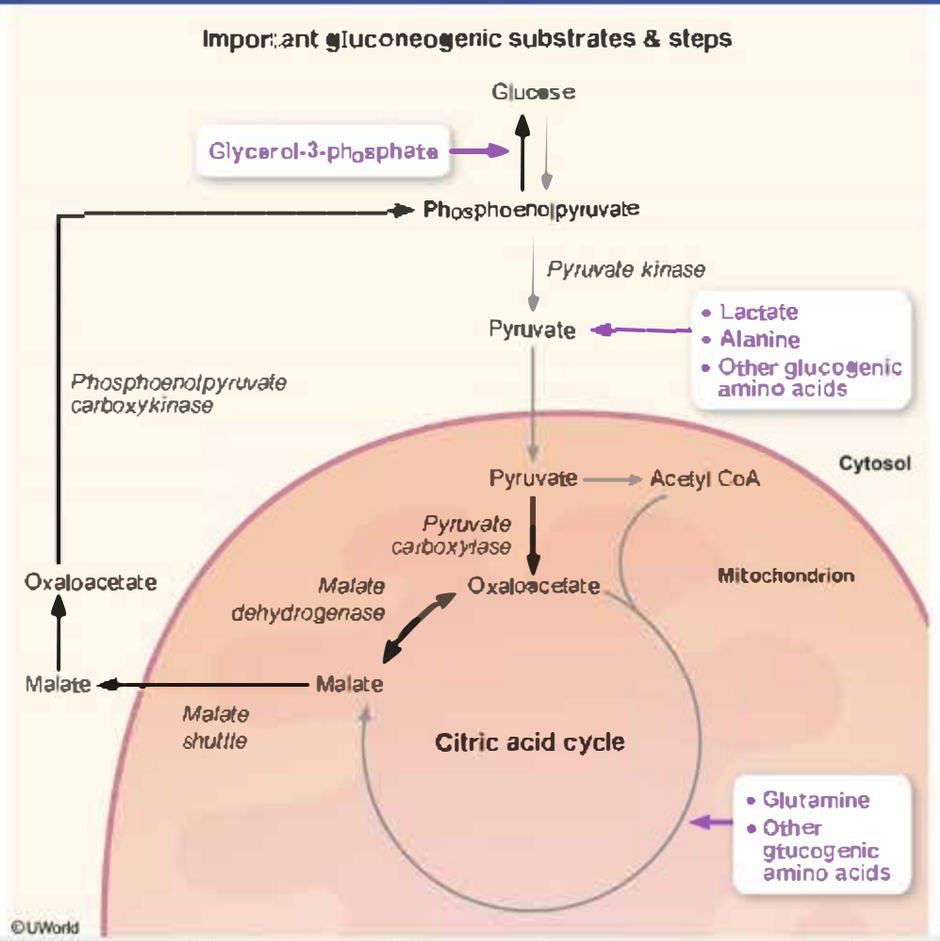
10/24/2018
Last Updated

Explanation

Important gluconeogenic substrates & steps

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

Exhibit Display



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• Other

The liver maintains glucose levels in the blood via **glycogenolysis** and **gluconeogenesis**. During fasting states, glycogen reserves drop dramatically in the first 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.

(Choices A and E) Citrate and succinate are intermediates in the Krebs cycle.

(Choice B) Glycerol-3-phosphate is a substrate for gluconeogenesis that is released during the breakdown of adipose.

(Choice C) Lactate derived from anaerobic glycolysis is also converted to pyruvate during gluconeogenesis.

Educational objective:
The main substrates of gluconeogenesis are alanine, glutamine, lactate, and glycerol 3-phosphate. Alanine is converted to pyruvate during the process of gluconeogenesis.

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A 66-year-old woman is brought to the emergency department due to agitation, restlessness, and poor sleep. Over the past 3 months, she has had headaches and gained 6.3 kg (13.9 lb). The patient's medical history is unremarkable, and she takes no medications. She has smoked a pack of cigarettes daily for the last 50 years but does not use illicit drugs. Blood pressure is 160/110 mm Hg and pulse is 90/min. Skin examination shows facial plethora and scattered bruises on her extremities. Laboratory results are as follows:

Sodium	147 mEq/L
Potassium	3.2 mEq/L
Chloride	98 mEq/L
Bicarbonate	26 mEq/L
Blood urea nitrogen	12 mg/dL
Creatinine	0.9 mg/dL
	205

Blood urea nitrogen	12 mg/dL
Creatinine	0.9 mg/dL
Glucose	205 mg/dL
Calcium	9.4 mg/dL

Which of the following is the most likely cause of this patient's hypertension?

- A. Adrenal medullary disease
- B. Aortic dissection
- C. Cushing syndrome
- D. Hypothyroidism
- E. Parathyroid gland disease
- F. Renal artery stenosis
- G. Renal parenchymal disease

	mg/dL
Glucose	205 mg/dL
Calcium	9.4 mg/dL

Which of the following is the most likely cause of this patient's hypertension?

- A. Adrenal medullary disease [7%]
- ✗ B. Aortic dissection [0%]
- ✓ C. Cushing syndrome [84%]
- D. Hypothyroidism [1%]
- E. Parathyroid gland disease [0%]
- F. Renal artery stenosis [4%]
- G. Renal parenchymal disease [1%]

Incorrect
Correct answer

84%
Answered correctly

12 Seconds
Time Spent

07/07/2018
Last Updated

Secondary causes of hypertension	
Condition	**Clinical clues/features**
Renal parenchymal disease	• Elevated serum creatinine • Abnormal urinalysis (proteinuria, red blood cell casts)
Renovascular disease	• Severe hypertension (≥180 mm Hg systolic &/or 120 mm Hg diastolic) after age 55 • Possible recurrent flash pulmonary edema or resistant heart failure • Unexplained rise in serum creatinine • Abdominal bruit
Primary aldosteronism	• Easily provoked hypokalemia • Slight hypernatremia • Hypertension with adrenal incidentaloma
Pheochromocytoma	• Paroxysmal elevated blood pressure with tachycardia • Pounding headaches, palpitations, diaphoresis • Hypertension with an adrenal incidentaloma
Cushing syndrome	• Central obesity, facial plethora • Proximal muscle weakness, abdominal striae • Ecchymosis, amenorrhea/erectile dysfunction

Primary aldosteronism	• Slight hypernatremia • Hypertension with adrenal incidentaloma
Pheochromocytoma	• Paroxysmal elevated blood pressure with tachycardia • Pounding headaches, palpitations, diaphoresis • Hypertension with an adrenal incidentaloma
Cushing syndrome	• Central obesity, facial plethora • Proximal muscle weakness, abdominal striae • Ecchymosis, amenorrhea/erectile dysfunction • Hypertension with adrenal incidentaloma
Hypothyroidism	• Fatigue, dry skin, cold intolerance • Constipation, weight gain, bradycardia
Primary hyperparathyroidism	• Hypercalcemia (polyuria, polydipsia) • Kidney stones • Neuropsychiatric presentations (confusion, depression, psychosis)
Coarctation of the aorta	• Differential hypertension with brachial-femoral pulse delay

This patient's **hypertension**, neuropsychiatric disturbances, **hyperglycemia**, and weight gain suggest hypercortisolism (**Cushing syndrome**). Other manifestations can include proximal muscle weakness, central adiposity with enlargement of the supraclavicular and dorsal neck fat pads, abdominal stria, facial rounding, and

This patient's **hypertension**, neuropsychiatric disturbances, **hyperglycemia**, and weight gain suggest hypercortisolism (**Cushing syndrome**). Other manifestations can include proximal muscle weakness, central adiposity with enlargement of the supraclavicular and dorsal neck fat pads, abdominal stria, facial rounding, and ecchymosis. Most cases of Cushing syndrome are due to exogenous glucocorticoid intake, ectopic ACTH production (eg, small cell lung cancer), or ACTH-producing pituitary adenomas (Cushing disease). Primary adrenal hypercortisolism (eg, adrenal adenoma) is less common. Associated **hypokalemia** suggests severe hypercortisolism and is most often seen with ectopic ACTH-producing tumors.

Initial testing for suspected hypercortisolism can include a 24-hour assay for **urine free cortisol**, a late-night salivary cortisol measurement, or a low-dose dexamethasone suppression test. Once hypercortisolism is established, an **ACTH level** can determine whether it is ACTH-dependent (Cushing disease or ectopic ACTH production) or ACTH-independent (adrenal disease or exogenous glucocorticoid intake). Patients with an elevated ACTH should have a high-dose **dexamethasone suppression test** to determine whether ACTH production is pituitary (dexamethasone suppresses cortisol production) or ectopic (dexamethasone does not suppress cortisol).

(Choice A) Pheochromocytoma is a catecholamine-producing adrenal medullary tumor. (Extra-adrenal tumors are termed paragangliomas). In addition to severe hypertension, associated symptoms can include weight loss, tachycardia, diaphoresis, and anxiety.

(Choice B) Aortic dissection causes severe chest pain radiating to the back. Although it occurs most commonly in patients with hypertension, this patient has no other features of aortic dissection.

(Choice D) Hypothyroidism can cause hypertension due to increased norepinephrine and aldosterone levels, leading to increased systemic vascular resistance. However, other expected findings would include fatigue,

tachycardia, diaphoresis, and anxiety.

(Choice B) Aortic dissection causes severe chest pain radiating to the back. Although it occurs most commonly in patients with hypertension, this patient has no other features of aortic dissection.

(Choice D) Hypothyroidism can cause hypertension due to increased norepinephrine and aldosterone levels, leading to increased systemic vascular resistance. However, other expected findings would include fatigue, bradycardia, depression, and skin and hair changes.

(Choice E) Hyperparathyroidism typically presents with asymptomatic hypercalcemia. Hyperparathyroidism can cause elevated blood pressure, but this patient's normal serum calcium makes this less likely.

(Choice F) Renal artery stenosis (RAS) can cause severe hypertension often associated with flash pulmonary edema, resistant heart failure, and chronic kidney disease. Patients may also have an abdominal bruit. RAS is usually seen in patients with other features of atherosclerosis.

(Choice G) Renal parenchymal disease with decreased glomerular filtration rate can cause resistant hypertension, but this patient's normal blood urea nitrogen and creatinine rule out significant renal disease.

Educational objective:
Cushing syndrome is characterized by hypertension, hyperglycemia, and weight gain. Common causes include excess glucocorticoid intake, ACTH-producing pituitary adenoma, and ectopic ACTH production.

References

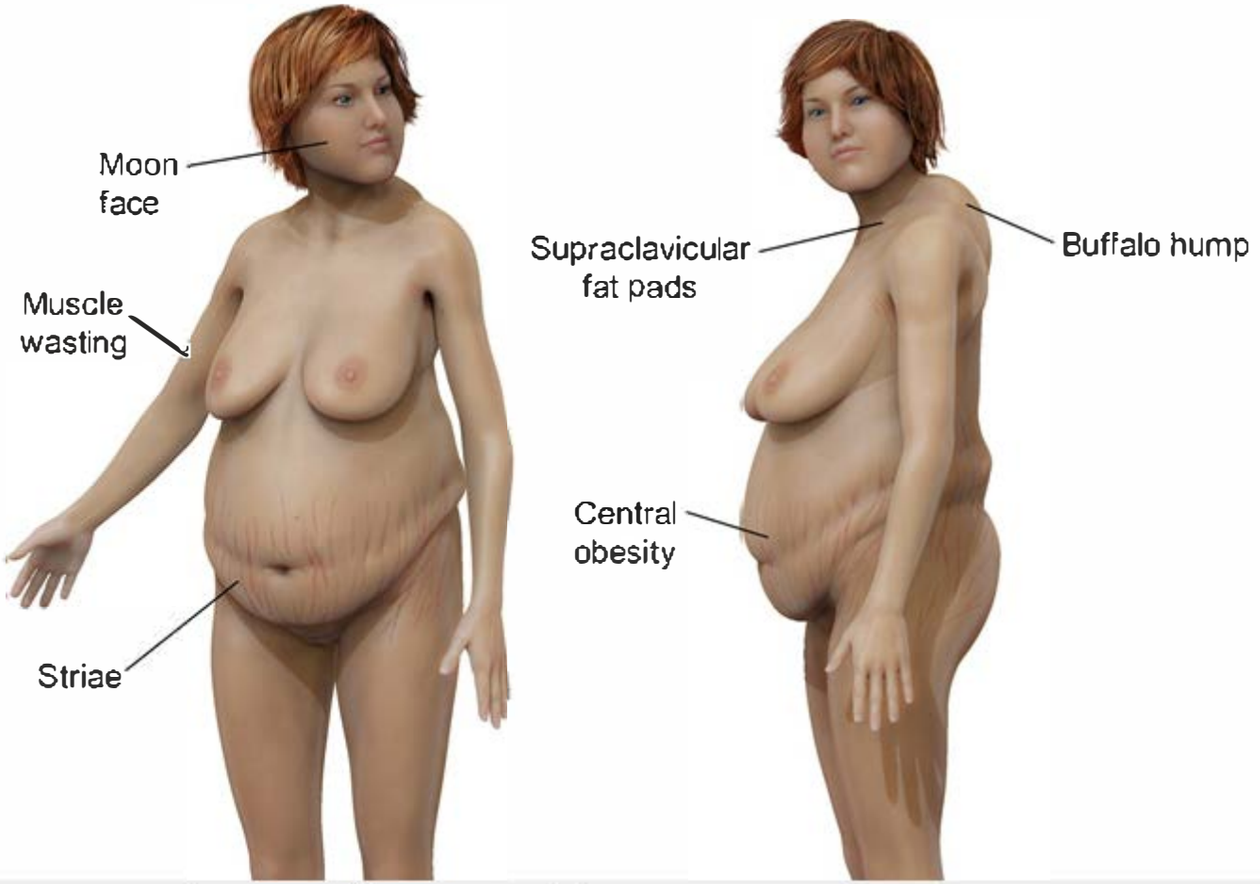
- The diagnosis of Cushing's syndrome

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

- Hypertension with an adrenal incidentaloma

Exhibit Display

Features of Cushing syndrome



Zoom In | Zoom Out | Reset | Add To Flash Card

hyperparathyroidism

- Kidney stones

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

Exhibit Display

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A 65-year-old man with acute myocardial infarction complicated by cardiogenic shock is admitted to the coronary care unit. His hospital course is complicated by acute renal failure and lower gastrointestinal bleeding from anticoagulation therapy. The patient has no previous history of thyroid disease. Physical examination of the thyroid gland is normal. Laboratory results are as follows:

Thyroxine (T4), free	1.3 ng/dL (normal, 0.9-2.4 ng/dL)
Triiodothyronine (T3), total	70 ng/dL (normal, 80-180 ng/dL)
TSH	2.0 mU/L (normal, 0.5-5.0 mU/L)

Which of the following is the most likely diagnosis?

A. Central hypothyroidism
B. Euthyroid sick syndrome
C. Primary hypothyroidism
D. Riedel's thyroiditis
E. Subclinical hypothyroidism

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TSH	2.0 mU/L (normal, 0.5-5.0 mU/L)

Which of the following is the most likely diagnosis?

- ✗ A. Central hypothyroidism [2%]
- ✓ B. Euthyroid sick syndrome [69%]
- C. Primary hypothyroidism [1%]
- D. Riedel's thyroiditis [1%]
- E. Subclinical hypothyroidism [25%]

Incorrect
Correct answer

69%
Answered correctly

11 Seconds
Time Spent

08/15/2018
Last Updated

Any patient with an acute, severe illness may have abnormal thyroid function tests (ie, abnormal thyroid hormone and TSH levels). The most common pattern is a fall in **total and free T3 levels**, with normal levels of T4 and TSH. This condition, often referred to as euthyroid sick syndrome, or "**low T3 syndrome**," is thought to be a result of decreased peripheral 5'-deiodination of T4 due to caloric deprivation, elevated glucocorticoid and inflammatory cytokine levels, and inhibitors of 5'monodeiodinase (eg, free fatty acids, certain medications). There is a rough correlation between the severity of the underlying, non-thyroidal illness and the fall in T3 levels. If the non-thyroidal illness continues, serum T4 and TSH levels may eventually decrease as well.

Thyroid function testing is unreliable in patients with acute illness, and thyroid hormone supplementation in those with euthyroid sick syndrome has not been found to improve clinical outcomes; therefore, thyroid function testing is generally not recommended in acutely ill patients. On recovery from the non-thyroidal illness, patients may experience a modest, transient increase in serum TSH level. This is often misinterpreted as subclinical hypothyroidism, and testing should be delayed, if possible, until the patient has returned to baseline health.

(Choice A) Central hypothyroidism is characterized by low (or inappropriately normal) TSH levels associated with low T4 and low or low-normal T3.

(Choices C and E) Overt primary hypothyroidism is characterized by decreased free T4 levels with an elevated TSH. Subclinical hypothyroidism is characterized by an elevated TSH with normal T4 levels. Serum T3 levels remain normal until the late stages of hypothyroidism, and measurement of T3 levels is generally not useful in these patients.

(Choice D) Riedel's (fibrous) thyroiditis is an inflammatory disorder characterized by fibrosclerosis of the thyroid,

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(Choice A) Central hypothyroidism is characterized by low (or inappropriately normal) TSH levels associated with low T4 and low or low-normal T3.

(Choices C and E) Overt primary hypothyroidism is characterized by decreased free T4 levels with an elevated TSH. Subclinical hypothyroidism is characterized by an elevated TSH with normal T4 levels. Serum T3 levels remain normal until the late stages of hypothyroidism, and measurement of T3 levels is generally not useful in these patients.

(Choice D) Riedel's (fibrous) thyroiditis is an inflammatory disorder characterized by fibrosclerosis of the thyroid, surrounding tissues, and often remote nonthyroidal structures (eg, retroperitoneum). Subclinical or overt hypothyroidism may be seen, but most patients have a hard goiter.

Educational objective:
Any patient with an acute, severe illness may have abnormal thyroid function tests. Euthyroid sick syndrome ("low T3 syndrome") is characterized by a fall in total and free T3 levels with normal T4 and TSH levels.

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A 33-year-old woman comes to the office for follow-up of a thyroid nodule that was discovered incidentally on a routine physical examination 3 weeks ago. The patient feels well and has experienced no weight changes, temperature intolerance, or menstrual irregularities. Medical history is notable for primary hypothyroidism treated with levothyroxine. Family history is notable for hypertension and hypothyroidism in her mother, but the patient has no relatives with a history of thyroid cancer. TSH is normal. Neck ultrasound reveals a 2.0-cm hypoechoic nodule in the right lobe of her thyroid without any enlarged lymph nodes. Fine-needle aspiration biopsy reveals large cells with ground glass cytoplasm, and pale nuclei containing inclusion bodies and central grooving consistent with papillary thyroid cancer. Which of the following is the best next step in management of this patient?

- A. Antithyroid peroxidase antibody assay
- B. Genetic mutation analysis in fine-needle aspiration biopsy sample
- C. Measurement of serum calcitonin
- D. Radioactive iodine ablation
- E. Surgical resection
- F. Thyroid scintigraphy

Submit

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- A. Antithyroid peroxidase antibody assay [0%]
- B. Genetic mutation analysis in fine-needle aspiration biopsy sample [2%]
- C. Measurement of serum calcitonin [2%]
- D. Radioactive iodine ablation [6%]
- ✔ E. Surgical resection [84%]
- F. Thyroid scintigraphy [3%]

Correct

84%
Answered correctly

6 Seconds
Time Spent

10/12/2018
Last Updated

Surgical resection is the primary treatment for **papillary thyroid cancer**. The extent of surgery depends on the tumor size, extrathyroidal invasion, patient age, and lymph node involvement. Small tumors (<1-2 cm) without evidence of lymph node involvement or contralateral thyroid abnormalities can usually be managed with partial thyroidectomy/lobectomy, whereas larger tumors usually warrant total thyroidectomy. In addition, regional lymph node or central compartment lymph node dissection is usually performed for papillary cancer with lymph node metastasis or extrathyroidal invasion.

Following surgery, adjuvant therapy with **radioiodine** ablation is warranted for patients with increased risk of tumor recurrence (eg, large tumors, extrathyroidal invasion, lymph node metastasis, incomplete resection) **(Choice D)**. TSH can stimulate growth of occult residual or metastatic disease. For this reason, patients at increased risk of recurrence should also receive adequate doses of **thyroid replacement** to **suppress TSH** secretion.

(Choice A) Thyroid peroxidase (TPO) antibodies are a marker for chronic lymphocytic (Hashimoto) thyroiditis. TPO antibodies are useful in the initial evaluation of hypothyroidism and diffuse goiter but have no utility in evaluation of papillary thyroid cancer.

(Choice B) Mutations of several genes (eg, BRAF, RET) are common in papillary thyroid cancer. Genetic mutation profiling may be performed when the cytology results from fine-needle aspiration biopsy are indeterminate but are not needed if cytology confirms papillary cancer.

(Choice C) Calcitonin is a marker for medullary thyroid cancer, which arises from the parafollicular C cells of the thyroid gland. Papillary and follicular cancers arise from thyroid epithelial cells.

(Choice F) Thyroid scintigraphy is performed in the initial evaluation of thyroid nodules in patients with subnormal

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(Choice C) Calcitonin is a marker for medullary thyroid cancer, which arises from the parafollicular C cells of the thyroid gland. Papillary and follicular cancers arise from thyroid epithelial cells.

(Choice F) Thyroid scintigraphy is performed in the initial evaluation of thyroid nodules in patients with subnormal TSH levels. A hyperfunctioning ("hot") nodule with increased uptake of the radiomarker is less likely to be malignant than a hypofunctioning ("cold") nodule.

Educational objective:
Surgical resection is the primary treatment modality for papillary thyroid carcinoma. Postoperative adjuvant therapies for patients at increased risk of recurrence include radioiodine ablation and suppressive doses of thyroid hormone.

References

- 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer.

A newborn girl is evaluated in the delivery room immediately after delivery. The infant was born at 41 weeks gestation to a 23-year-old woman, gravida 2 para 1, via uncomplicated vaginal delivery. The mother was previously healthy and had routine prenatal care. Serology was normal. The pregnancy was complicated by polyhydramnios and gestational diabetes necessitating insulin. The infant's vital signs are normal and birth weight is 3.6 kg (7 lb 15 oz). Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. Physical examination shows an active, crying infant. Cardiac auscultation reveals a soft, 1/6 systolic murmur. The infant's hands and feet are cyanotic; the mucosal membranes are pink. The remainder of the examination is normal. Which of the following tests is most likely to be abnormal?

- A. Blood culture
- B. Clavicle x-ray
- C. Contrast enema
- D. Glucose level
- E. Hearing screening
- F. Pulse oximetry

Submit

A newborn girl is evaluated in the delivery room immediately after delivery. The infant was born at 41 weeks gestation to a 23-year-old woman, gravida 2 para 1, via uncomplicated vaginal delivery. The mother was previously healthy and had routine prenatal care. Serology was normal. The pregnancy was complicated by polyhydramnios and gestational diabetes necessitating insulin. The infant's vital signs are normal and birth weight is 3.6 kg (7 lb 15 oz). Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. Physical examination shows an active, crying infant. Cardiac auscultation reveals a soft, 1/6 systolic murmur. The infant's hands and feet are cyanotic; the mucosal membranes are pink. The remainder of the examination is normal. Which of the following tests is most likely to be abnormal?

- ✗ A. Blood culture [0%]
- B. Clavicle x-ray [3%]
- C. Contrast enema [3%]
- ✓ D. Glucose level [70%]
- E. Hearing screening [1%]
- F. Pulse oximetry [20%]

Incorrect
Correct answer

70%
Answered correctly

5 Seconds
Time Spent

09/22/2018
Last Updated

Infant of diabetic mother - complications

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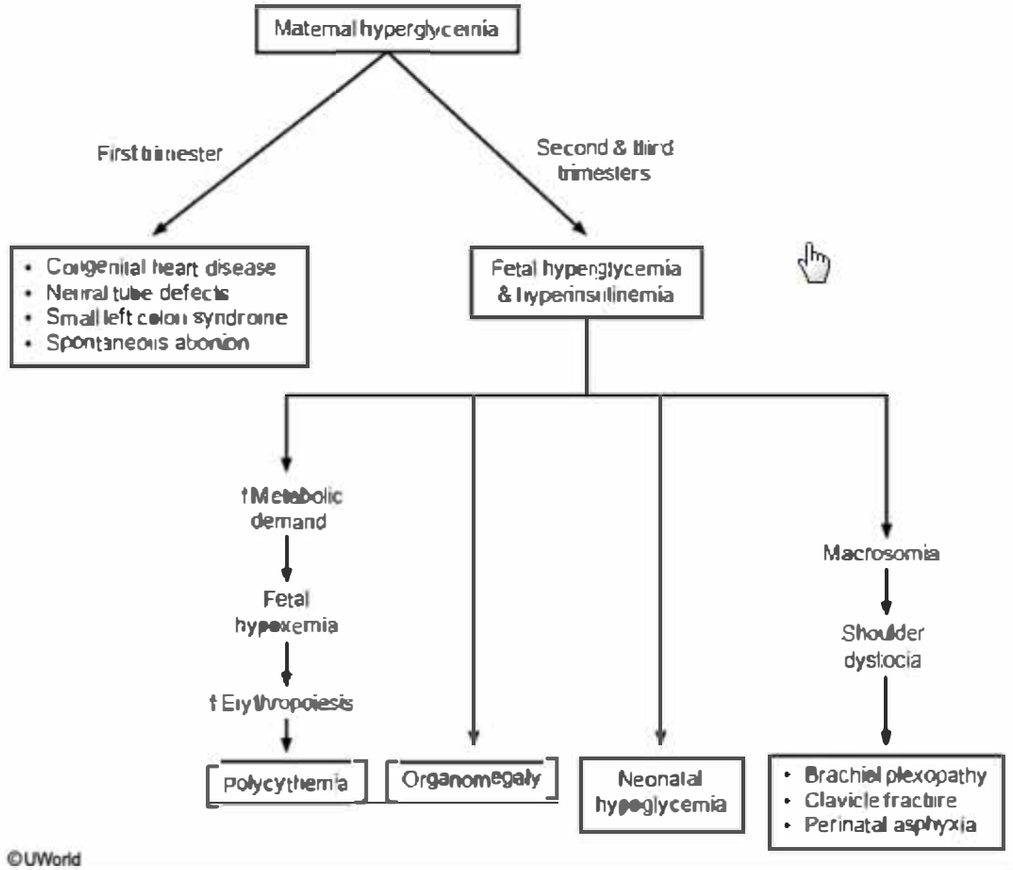

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Polycythemia | Organomegaly | Neonatal | Brachial plexopathy

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Infants of diabetic mothers (IDMs) are at increased risk for a variety of complications. Because glucose is actively transported across the placenta to the fetus, maternal hyperglycemia leads to fetal hyperglycemia. The effects of fetal hyperglycemia vary, depending on the developmental stage of the fetus:

- First trimester: The fetus cannot produce insulin during the first trimester and therefore cannot protect itself from hyperglycemia. Hyperglycemia during the first trimester can disrupt organogenesis, resulting in **malformations** (eg, congenital heart disease).
- Second and third trimesters: Once the fetal pancreas is sufficiently developed, hyperglycemia triggers the release of insulin, which results in increased glycogen and fat storage (**organomegaly**), increased growth factor production (**macrosomia**), and increased oxygen consumption (**polycythemia**).
- Delivery: IDMs who are macrosomic are more difficult to deliver vaginally, leading to higher rates of cesarean delivery (due to failure to progress) or device-assisted delivery (eg, forceps, vacuum). Clavicle fractures, brachial plexus injuries, and asphyxia are associated with macrosomia.
- After delivery: Fetal insulin production takes time to decrease after delivery, but maternal glucose exposure ends as soon as the umbilical cord is clamped. This often results in a period of **neonatal hypoglycemia** until insulin levels normalize. Hypoglycemia is the most common complication among IDMs.

(Choice A) Risk factors for neonatal sepsis include maternal colonization with group B *Streptococcus*, prolonged rupture of membranes, and chorioamnionitis. IDMs are not at increased risk for sepsis, which would be very unlikely in this well-appearing infant with a normal examination.

(Choice B) Clavicle fracture is most common in macrosomic infants, usually defined as weight >4 kg (8 lb 14 oz). This infant is not macrosomic and had an uncomplicated delivery, so she is at low risk for clavicle fracture.

(Choice A) Risk factors for neonatal sepsis include maternal colonization with group B *Streptococcus*, prolonged rupture of membranes, and chorioamnionitis. IDMs are not at increased risk for sepsis, which would be very unlikely in this well-appearing infant with a normal examination.

(Choice B) Clavicle fracture is most common in macrosomic infants, usually defined as weight >4 kg (8 lb 14 oz). This infant is not macrosomic and had an uncomplicated delivery, so she is at low risk for clavicle fracture.

(Choices C and F) Infants exposed to hyperglycemia in the first trimester as a result of poorly controlled prepregnancy diabetes are at higher risk for congenital malformations. These include congenital heart disease (abnormal echocardiogram) and microcolon (contrast enema). IDMs are also at increased risk for hypertrophic cardiomyopathy, but oxygen saturation is typically normal. This infant has acrocyanosis (cyanosis of the hands and feet, which is normal in the newborn period) but no central cyanosis.

(Choice E) Risk factors for congenital hearing loss include congenital cytomegalovirus infection and family history of hearing loss. IDMs are not at increased risk for hearing loss, although this infant should receive hearing screening as recommended for all newborns.

Educational objective:
Fetal hyperglycemia during the first trimester is associated with malformations; fetal hyperglycemia after the first trimester is associated with perinatal complications such as macrosomia, birth injury, and hypoglycemia. Neonatal hypoglycemia is the most common complication among infants of diabetic mothers.

References

A 48-year-old overweight man comes to the physician for evaluation of a right foot ulcer that he first noticed 3 weeks ago. He has a history of hypertension, type 2 diabetes mellitus, and hypercholesterolemia. His current medications include ramipril, aspirin, metformin, sitagliptin, and rosuvastatin. He has a 20-pack-year smoking history and occasionally drinks alcohol but does not use illicit drugs. The patient is afebrile. His blood pressure is 132/80 mm Hg and pulse is 76/min. Examination shows a 1.7 x 2 cm ulcer on the plantar surface of the great toe. Which of the following tests will best assess this patient's risk of foot ulcers?

- A. 6-minute walk test
- B. Ankle-brachial index
- C. Capillary refill time
- D. Knee reflex assessment
- E. Monofilament testing

Submit

A 48-year-old overweight man comes to the physician for evaluation of a right foot ulcer that he first noticed 3 weeks ago. He has a history of hypertension, type 2 diabetes mellitus, and hypercholesterolemia. His current medications include ramipril, aspirin, metformin, sitagliptin, and rosuvastatin. He has a 20-pack-year smoking history and occasionally drinks alcohol but does not use illicit drugs. The patient is afebrile. His blood pressure is 132/80 mm Hg and pulse is 76/min. Examination shows a 1.7 x 2 cm ulcer on the plantar surface of the great toe. Which of the following tests will best assess this patient's risk of foot ulcers?

- A. 6-minute walk test [0%]
- B. Ankle-brachial index [21%]
- ✗ C. Capillary refill time [5%]
- D. Knee reflex assessment [2%]
- ✓ E. Monofilament testing [69%]

Incorrect
Correct answer
E

69%
Answered correctly

4 Seconds
TimeSpent

07/03/2018
Last Updated

Explanation

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

Monofilament test

This patient has a diabetic foot ulcer, which can eventually lead to nontraumatic lower limb amputation. Risk factors for diabetic foot ulcers include diabetic neuropathy, previous foot ulceration, vascular disease, and foot deformity. **Diabetic neuropathy** is the most common underlying cause and is found in >80% of patients with diabetic foot ulcers. Neuropathy decreases pain sensation and pressure perception, it causes muscle imbalance leading to foot deformities, and impairs the microcirculation and integrity of the skin.

Neuropathic ulcers most commonly occur in the feet under bony prominences, such as the metatarsal heads. They typically have a punched-out or undermined border. Peripheral sensory neuropathy can be documented by testing for pressure sensation with a 10-g **monofilament** (placed on the plantar surface at a right angle with increasing pressure until filament buckles). Patients with neuropathy have a higher pressure threshold and loss of monofilament sensation, which are associated with an increased risk of foot ulcerations. Other sensory deficits may include decreased vibratory sensation (tested with a tuning fork), decreased pinprick pain, or decreased temperature sensation.

(Choice A) The 6-minute walk test is an assessment of functional status that measures how far a patient can walk in a standardized time. It is typically used for patients with chronic lung or heart disease or with chronic pain conditions (eg, fibromyalgia, osteoarthritis). It is not as useful for patients with diabetic neuropathy or foot ulcers.

(Choice B) Peripheral arterial disease (PAD) can be assessed by calculating the **ankle-brachial index (ABI)**. However, ABI is primarily a measure of large vessel PAD and does not accurately assess small vessel disease, which often contributes to ulcers in diabetic patients. In addition, **arterial ulcers** are usually located on the tips of the toes, rather than the plantar surface.

(Choice A) The 6-minute walk test is an assessment of functional status that measures how far a patient can walk in a standardized time. It is typically used for patients with chronic lung or heart disease or with chronic pain conditions (eg, fibromyalgia, osteoarthritis). It is not as useful for patients with diabetic neuropathy or foot ulcers.

(Choice B) Peripheral arterial disease (PAD) can be assessed by calculating the **ankle-brachial index (ABI)**. However, ABI is primarily a measure of large vessel PAD and does not accurately assess small vessel disease, which often contributes to ulcers in diabetic patients. In addition, **arterial ulcers** are usually located on the tips of the toes, rather than the plantar surface.

(Choice C) Delayed capillary refill time (>3 seconds) indicates impaired limb perfusion and may suggest underlying peripheral arterial disease. However, delayed capillary refill is a nonspecific finding, and is also seen in hypotension or volume depletion.

(Choice D) Diabetic neuropathy can affect the large nerve fibers in the lower extremities, causing decreased/absent ankle reflexes. However, the knee reflex is usually not affected.

Educational objective:
Risk factors for diabetic foot ulcers include diabetic neuropathy, previous foot ulceration, vascular disease, and foot deformity. Diabetic neuropathy is the most important contributing factor and is found in >80% of patients with ulcers. Monofilament testing predicts the risk of future ulcers.

References

- The Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy.

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Exhibit Display

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temperature sensation.

Exhibit Display

Ankle-brachial index interpretation

Ankle-brachial index is calculated by dividing the higher ankle (dorsalis pedis or posterior tibial) systolic pressure in each lower extremity by the higher brachial artery (left or right) systolic pressure.

ABI	Interpretation
≤0.90	Abnormal
0.91-1.30	Normal
≥1.30	Suggestive of calcified & uncompressible vessels; additional vascular studies should be considered

ABI = ankle-brachial index.

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References

temperature sensation.

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References

A 28-year-old woman is hospitalized following a motor vehicle accident. She was returning home following a wine-tasting event when she veered off the road and rolled her car. Initial evaluation in the emergency department found severe hypotension, a hip fracture, multiple rib fractures, and evidence of blunt abdominal trauma. The patient underwent emergent laparotomy, which revealed a liver laceration and extensive hemoperitoneum. Her condition was stabilized with surgical intervention, fluid resuscitation, and blood transfusions. In the early postoperative period soon after extubation, the patient developed numbness in the fingertips and around her lips. She also developed forceful flexion of the wrist with abduction of the thumb while her nurse was measuring her blood pressure. Temperature is 37.4 C (99.3 F), blood pressure is 120/68 mm Hg, pulse is 80/min, and respirations are 12/min. Neurologic examination shows hyperactive reflexes diffusely with 5/5 muscle strength in all extremities. Which of the following is the most likely diagnosis?

- A. Alcohol withdrawal
- B. Anxiety
- C. Fat embolism
- D. Hypermagnesemia
- E. Hypocalcemia

Submit

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- ✗ A. Alcohol withdrawal [1%]
- B. Anxiety [0%]
- C. Fat embolism [1%]
- D. Hypermagnesemia [3%]
- ✓ E. Hypocalcemia [93%]

Incorrect

93%

5 Seconds

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; **IV** = intravenous.	

This patient has paresthesias, **carpal spasm (Trousseau sign)**, and hyperreflexia. In the setting of high-volume transfusion, these neurologic features are most likely due to **hypocalcemia**. Other potential features of severe hypocalcemia include tetany, laryngospasm, seizures, encephalopathy, and heart failure. Patients with chronic hypocalcemia may have only mild symptoms, but patients with acute hypocalcemia will have more severe

This patient has paresthesias, carpal spasm (Trousseau sign), and hyperreflexia. In the setting of high-volume transfusion, these neurologic features are most likely due to **hypocalcemia**. Other potential features of severe hypocalcemia include tetany, laryngospasm, seizures, encephalopathy, and heart failure. Patients with chronic hypocalcemia may have only mild symptoms, but patients with acute hypocalcemia will have more severe manifestations at the same calcium concentration.

Citrate in **transfused blood** binds **ionized calcium**, which is the biologically active fraction (total calcium levels will not be significantly affected). 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 A) Alcohol withdrawal is most pronounced 12-48 hours following the last drink. Clinical features may include hyperreflexia, tremor, diaphoresis, and gastrointestinal upset, but carpal spasm and paresthesias are more consistent with hypocalcemia.

(Choice B) Hyperventilation due to anxiety can cause acute respiratory alkalosis, increasing the binding of calcium to albumin and reducing ionized calcium concentrations. However, this patient's respiratory rate is only 12/min.

(Choice C) Fat embolism can occur following pelvic or long bone fractures. Manifestations of fat embolism include respiratory insufficiency, hypoxemia, altered mental state, and petechial rash.

(Choice D) Hypomagnesemia (not hypermagnesemia) can present similarly to hypocalcemia. Severe

consistent with hypocalcemia.

(Choice B) Hyperventilation due to anxiety can cause acute respiratory alkalosis, increasing the binding of calcium to albumin and reducing ionized calcium concentrations. However, this patient's respiratory rate is only 12/min.

(Choice C) Fat embolism can occur following pelvic or long bone fractures. Manifestations of fat embolism include respiratory insufficiency, hypoxemia, altered mental state, and petechial rash.

(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.

Educational objective:
High-volume blood transfusion can cause symptomatic hypocalcemia due to chelation of ionized calcium by citrate in transfused blood. Patients with impaired hepatic function are at increased risk due to decreased clearance of citrate by the liver.

References

- Effects of liver function on ionized hypocalcaemia following rapid blood transfusion

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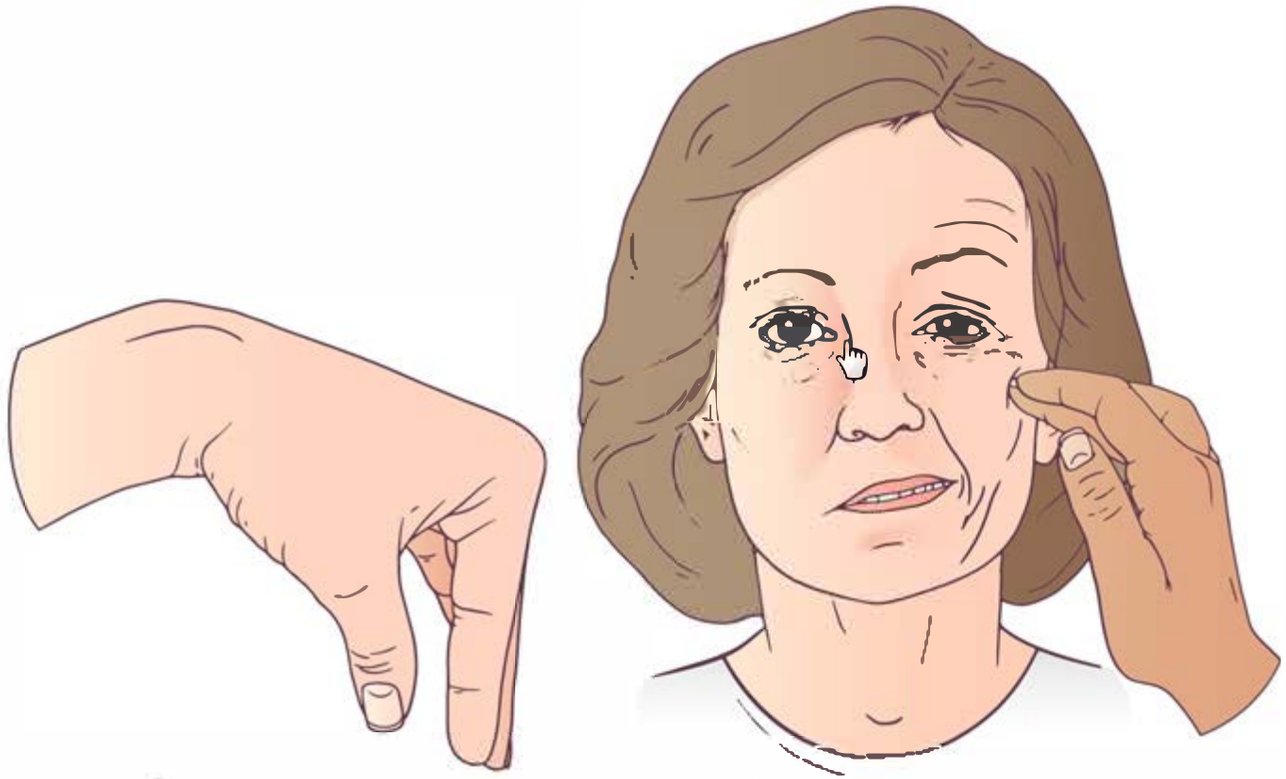
- Tumor lysis syndrome

Exhibit Display

Signs of hypocalcemia



1 Trousseau sign

2 Chvostek sign

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A 60-year-old asymptomatic man presents to your office for a routine check-up. He has a 10-year history of type 2 DM, and a 12-year history of hypertension. His current medications include low-dose glyburide and a low-dose thiazide diuretic. His blood pressure is 140/90 mm Hg and heart rate is 65/min. Physical examination shows a soft ejection systolic murmur at the base of the heart. Ophthalmoscopic evaluation reveals no abnormalities. ECG recorded 6 months ago showed left ventricular hypertrophy and non-specific ST segment and T-wave abnormalities. His recent fasting glucose level was in the range of 120 to 150 mg/dL, and HbA1c was 7.1 % (normal < 6%). 24-hour urine collection reveals microalbuminuria. Which of the following is the best measure to slow end-organ damage in this patient?

- (●) A. Increase the dose of glyburide
- ( ) B. Increase the dose of thiazide diuretic
- ( ) C. Switch to insulin
- ( ) D. Add ACE inhibitor
- ( ) E. Add beta-blocker

Submit

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- ✗ A. Increase the dose of glyburide [2%]
- B. Increase the dose of thiazide diuretic [1%]
- C. Switch to insulin [3%]
- ✓ D. Add ACE inhibitor [91%]
- E. Add beta-blocker [1%]

Incorrect
Correct answer
D

91%
Answered correctly

19 Seconds
TimeSpent

08/09/2018
Last Updated

Several randomized controlled clinical trials have demonstrated the beneficial effects of ACE inhibitors in slowing the progression of diabetic nephropathy. The use of ACE inhibitors reduces urinary albumin excretion and the decline in creatinine clearance. Its use is recommended in patients with microalbuminuria even if their blood pressure is normal, since microalbuminuria is a sensitive marker of renal microvascular damage. The beneficial effect of ACE inhibitors is due to the reduction in blood pressure as well as the direct effect on reducing intraglomerular pressure.

In this case, the patient has microalbuminuria; therefore, addition of an ACE inhibitor to his regimen is likely to ameliorate microalbuminuria, as well as slow down the progression of renal damage.

(Choice B and E) Improving the control of blood pressure by increasing the dose of the thiazide diuretic or adding a beta-blocker seems reasonable, but an ACE inhibitor is a more appropriate choice due to its effect on disease progression.

(Choice A and C) Increasing the dose of an oral hypoglycemic agent to improve glycemic control is a reasonable approach to the management of diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) has shown that the risk of microvascular complications in diabetics can be reduced with tight blood glucose control as well as tight blood pressure control.

In this case, however, increasing the dosage of glyburide or adding insulin is not warranted at this time. The patient's HBA1c is only marginally elevated (The target limit suggested by the American Diabetes Association is less than 7%), and in such a scenario, the initial step is counseling regarding lifestyle changes. Furthermore, the use of ACE inhibitor might help decrease the HBA1c by their salutary effect on reducing insulin resistance.

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Educational Objective:
Several randomized controlled clinical trials have demonstrated the beneficial effect of ACE inhibitors on slowing the progression of diabetic nephropathy.

* The use of ACE inhibitors in patients with DM is a very high-yield topic in the USMLE.

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A 52-year-old man comes to the office due to decreased libido and inability to achieve and maintain erections for the past several months. He has also had fatigue, anorexia, and a 5-kg (11-lb) weight loss over the same duration. The patient is married and has one child. He drinks alcohol but does not use tobacco or illicit drugs. Blood pressure is 110/70 mm Hg and pulse is 82/min. Physical examination shows bilateral gynecomastia and firm and small testes. Laboratory testing shows normal TSH with decreased levels of total triiodothyronine (T3) and thyroxine (T4). Which of the following is the most likely diagnosis?

- A. Adrenal insufficiency
- B. Chronic liver disease
- C. Exogenous thyroxine intake
- D. Hashimoto thyroiditis
- E. Penile vascular occlusion
- F. Testosterone insensitivity

Submit

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- A. Adrenal insufficiency [11%]
- ✔ B. Chronic liver disease [61%]
- ✘ C. Exogenous thyroxine intake [5%]
- D. Hashimoto thyroiditis [11%]
- E. Penile vascular occlusion [0%]
- F. Testosterone insensitivity [9%]

Incorrect
Correct answer
B

61%
Answered correctly

7 Seconds
TimeSpent

09/14/2018
Last Updated

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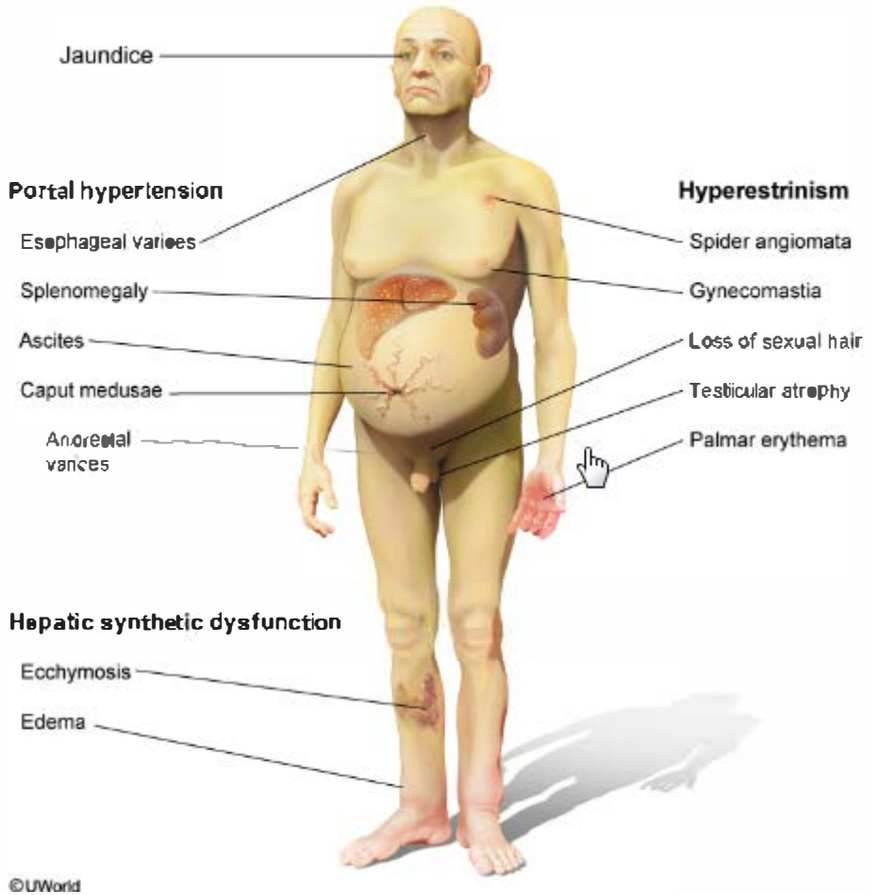
Signs of liver cirrhosis



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Ecchymosis

This patient's erectile dysfunction and testicular atrophy are most likely due to **hypogonadism**, which is a common complication of chronic liver disease with cirrhosis. **Cirrhosis** (especially due to alcoholic liver disease or hemochromatosis) can cause hypogonadism due to primary gonadal injury or hypothalamic-pituitary dysfunction. Cirrhosis is also associated with elevated circulating levels of **estradiol** due to increased conversion from androgens. Findings due to excess estrogen include telangiectasias, palmar erythema, testicular atrophy, and gynecomastia (usually bilateral but can be unilateral).

In addition, the liver produces serum binding proteins for thyroid hormones (eg, thyroxine-binding globulin, transthyretin, albumin, lipoproteins). Cirrhosis leads to decreased synthesis of these proteins, which lowers the **total** triiodothyronine (T3) and thyroxine (T4) in circulation; however, free T3 and T4 levels are unchanged, and TSH will be normal, reflecting a euthyroid status.

(Choice A) Adrenal insufficiency (AI) can cause fatigue, weakness, anorexia, and weight loss. In women with AI, features of hypogonadism (eg, loss of libido, decreased pubic hair) can be seen due to decreased adrenal androgen production; however, men with AI do not develop these findings as androgens are primarily produced in the testes. In addition, AI would not explain this patient's gynecomastia, testicular atrophy, or thyroid hormone laboratory abnormalities.

(Choice C) Exogenous thyroid hormone intake can cause weight loss, fatigue, and anxiety. However, TSH would be suppressed.

(Choice D) Hashimoto thyroiditis (chronic autoimmune thyroiditis) is due to lymphocytic infiltration of the thyroid causing hypothyroidism. Laboratory studies show elevated TSH, decreased T4, and antithyroid peroxidase

the testes. In addition, AI would not explain this patient's gynecomastia, testicular atrophy, or thyroid hormone laboratory abnormalities.

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(Choice D) Hashimoto thyroiditis (chronic autoimmune thyroiditis) is due to lymphocytic infiltration of the thyroid causing hypothyroidism. Laboratory studies show elevated TSH, decreased T4, and antithyroid peroxidase antibodies.

(Choice E) Arterial insufficiency is a common cause of erectile dysfunction. However, this would not cause gynecomastia or testicular atrophy, and most patients would have other signs of arterial disease.

(Choice F) Androgen insensitivity is caused by mutations in the androgen receptor and would cause primary infertility (eg, primary amenorrhea in a genetically male but phenotypically female individual [complete androgen insensitivity syndrome]). It is unlikely in this patient with recent-onset sexual dysfunction.

Educational objective:
Cirrhosis can cause hypogonadism due to primary gonadal injury or hypothalamic-pituitary dysfunction. Cirrhosis is also associated with elevated circulating levels of estradiol due to increased conversion from androgens.

References

- Male hypogonadism in cirrhosis and after liver transplantation.

A 31-year-old woman comes to the office with a 3-month history of palpitations and weight loss. She weighs 110 kg (243 lb); 3 months ago, she weighed 118 kg (260 lb). There is no associated dysphagia, neck pain, or hoarseness, and her menstrual periods have been regular. The patient was previously healthy and her family history is unremarkable. She does not use tobacco or alcohol. The patient is sexually active with one partner and uses a barrier method for contraception. Temperature is 36.7 C (98.1 F), blood pressure is 140/90 mm Hg, pulse is 102/min, and respirations are 20/min. The thyroid gland cannot be clearly felt on examination due to body habitus. Ocular examination is unremarkable. Laboratory tests show an elevated serum free triiodothyronine and thyroxine and low TSH. A urine pregnancy test is negative. Radioactive iodine scan reveals uptake of tracer only in the right thyroid lobe, as shown in the image below.

Which of the following processes is responsible for this patient's elevated thyroid hormone levels?

A. Antibody-stimulated thyroid hormone production

thyroid lobe, as shown in the image below.

Which of the following processes is responsible for this patient's elevated thyroid hormone levels?

- A. Antibody-stimulated thyroid hormone production
- B. Autonomous thyroid hormone production
- C. Exogenous thyroid hormone intake
- D. Pituitary dysfunction
- E. Release of preformed thyroid hormone

Submit

thyroid lobe, as shown in the image below.

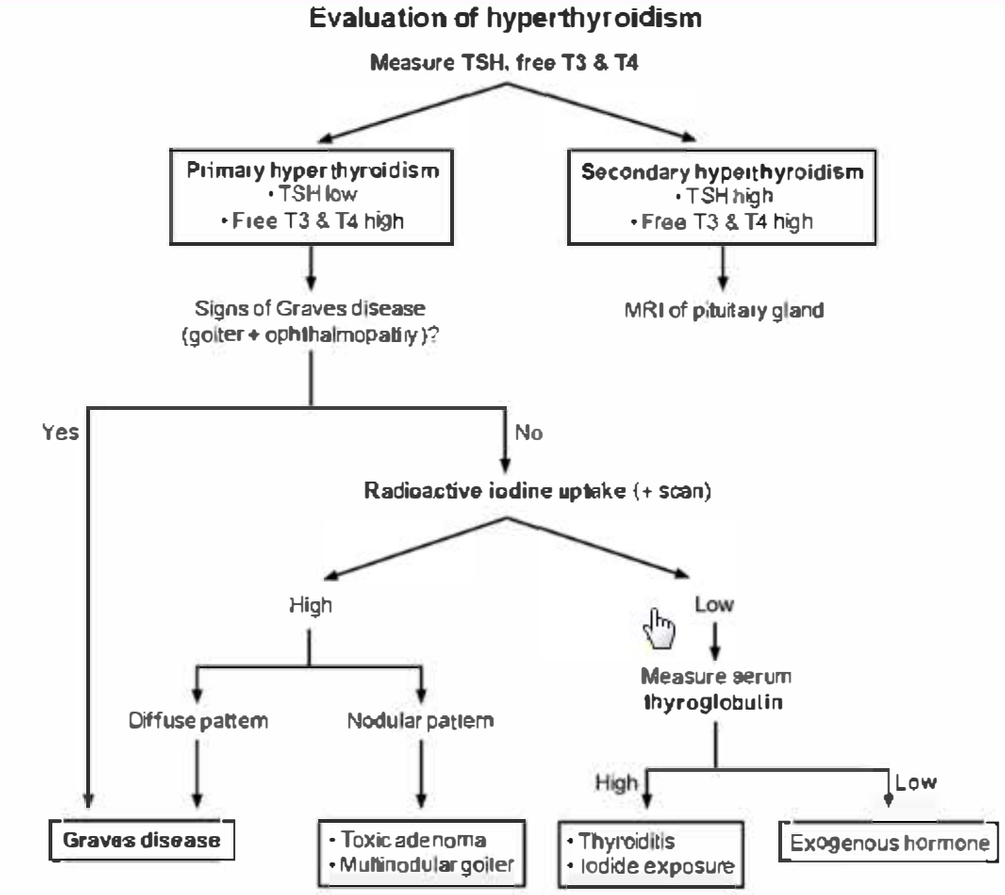
Which of the following processes is responsible for this patient's elevated thyroid hormone levels?

- A. Antibody-stimulated thyroid hormone production [17%]
- ✔ B. Autonomous thyroid hormone production [71%]
- C. Exogenous thyroid hormone intake [2%]
- D. Pituitary dysfunction [0%]
- E. Release of preformed thyroid hormone [7%]

Correct
71%
10 Seconds
10/23/2018

Evaluation of hyperthyroidism

Exhibit Display



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This patient has clinical thyrotoxicosis (eg, palpitations, tachycardia, weight loss) with elevated thyroid hormone levels and a suppressed TSH, consistent with primary hyperthyroidism. The radioactive iodine scan reveals unicentric uptake only in the right lobe, thereby confirming the diagnosis of **toxic adenoma**. Both toxic adenoma and multinodular goiter have a nodular pattern of uptake; however, in contrast to the focal uptake of radioactive iodine in toxic adenoma, uptake in patients with multinodular goiter shows a patchy distribution.

Normally, TSH is the major driver for the production of thyroid hormones. However, the hyperplastic cells in toxic adenoma and toxic multinodular goiter overproduce thyroid hormone **autonomously** without TSH stimulation. Some of these patients have activating somatic mutations of the TSH receptors on the hyperplastic follicular cells, leading to TSH-independent activation of adenylyl cyclase.

(Choice A) Hyperthyroidism in Graves disease results from thyroid-stimulating autoantibody-induced activation of TSH receptors on thyroid follicular cells. Radioiodine uptake is diffuse rather than focal, and patients usually have additional extrathyroidal manifestations (eg, exophthalmos, pretibial myxedema).

(Choice C) Surreptitious intake of thyroid hormone is occasionally seen in patients who are attempting to lose weight. In such cases, radioiodine uptake is diffusely reduced.

(Choice D) TSH is elevated or inappropriately normal in hyperthyroidism resulting from TSH-secreting pituitary tumors.

(Choice E) Release of preformed thyroid hormone is seen in various forms of thyroiditis, including subacute (de Quervain) thyroiditis, silent thyroiditis, and the transient hyperthyroid phase seen in some patients with chronic lymphocytic (Hashimoto) thyroiditis. Radioactive iodine uptake in these cases is markedly reduced.

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Educational objective:
Hyperthyroidism from toxic adenoma is due to autonomous production of thyroid hormones from the hyperplastic thyroid follicular cells. The radioactive iodine uptake scan reveals uptake only in the hyperactive nodule, with suppression of uptake in the rest of the gland.

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A 36-year-old woman comes to the office due to weight loss. She has lost 5 kg (11 lb) over the last 3 months associated with palpitations, heat intolerance, persistent tremors, and excessive sweating. Past medical and family histories are unremarkable, and the patient does not use tobacco, alcohol, or illicit drugs. She is married and has a child. Blood pressure is 140/70 mm Hg and pulse is 104/min and regular. Physical examination shows a 2x2 cm nodule in the left thyroid lobe. The rest of the thyroid gland is normal, and there is no associated cervical lymphadenopathy. Eye examination shows minimal lid lag, but no proptosis or chemosis. There is a fine tremor in both upper extremities. Thyroid function test results are as follows:

Serum TSH	<0.03 μU/mL
Total T3	330 ng/dL
Total T4	14 μg/dL

Radioactive iodine scan shows uptake only in the nodule. The patient wishes to have additional children and is concerned that she will not be able to get pregnant if she is treated for her current condition. If left untreated, this patient is at greatest risk for developing which of the following complications?

A. Bone loss
B. Coronary artery disease
C. Fetal hyperthyroidism
D. Thyroid cancer

lymphadenopathy. Eye examination shows minimal lid lag, but no proptosis or chemosis. There is a fine tremor in both upper extremities. Thyroid function test results are as follows:

Serum TSH	<0.03 µU/mL
Total T3	330 ng/dL
Total T4	14 µg/dL

Radioactive iodine scan shows uptake only in the nodule. The patient wishes to have additional children and is concerned that she will not be able to get pregnant if she is treated for her current condition. If left untreated, this patient is at greatest risk for developing which of the following complications?

- A. Bone loss
- B. Coronary artery disease
- C. Fetal hyperthyroidism
- D. Thyroid cancer
- E. Vision loss

Submit

lymphadenopathy. Eye examination shows minimal lid lag, but no proptosis or chemosis. There is a fine tremor in both upper extremities. Thyroid function test results are as follows:

Serum TSH	<0.03 µU/mL
Total T3	330 ng/dL
Total T4	14 µg/dL

Radioactive iodine scan shows uptake only in the nodule. The patient wishes to have additional children and is concerned that she will not be able to get pregnant if she is treated for her current condition. If left untreated, this patient is at greatest risk for developing which of the following complications?

- ✔ A. Bone loss [41%]
- B. Coronary artery disease [13%]
- ✘ C. Fetal hyperthyroidism [18%]
- D. Thyroid cancer [18%]
- E. Vision loss [6%]

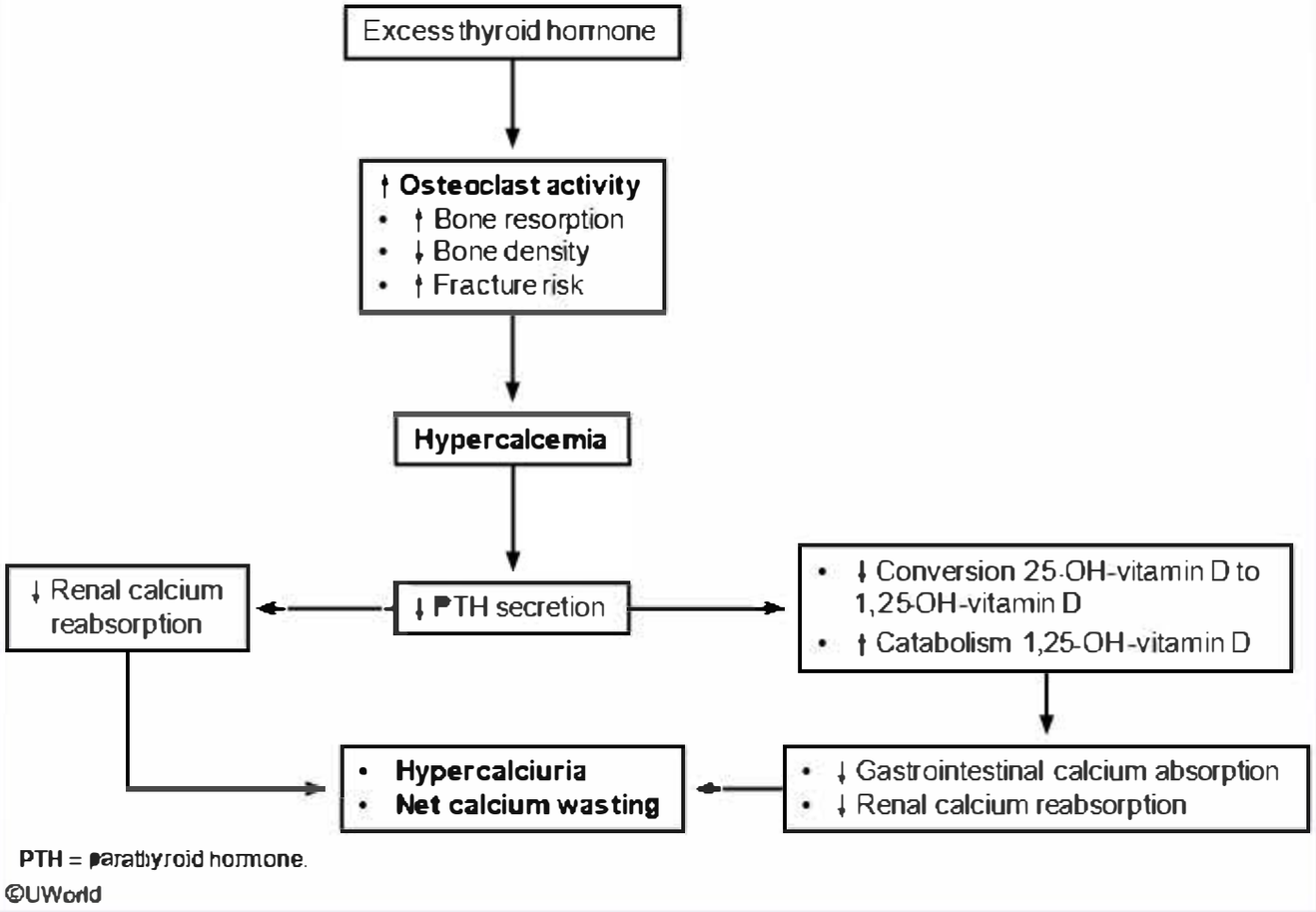
Incorrect
Correct answer

41%
Answered correctly

10 Seconds
Time Spent

08/10/2018
Last Updated

Hyperthyroid bone disease



PTH = parathyroid hormone.

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This patient with hyperthyroid symptoms, suppressed TSH, and a "hot" thyroid nodule has typical features of a toxic adenoma (TA). TA and toxic multinodular goiter (MNG) are the most common causes of hyperthyroidism

This patient with hyperthyroid symptoms, suppressed TSH, and a "hot" thyroid nodule has typical features of a **toxic adenoma** (TA). TA and toxic multinodular goiter (MNG) are the most common causes of **hyperthyroidism** after Graves disease and are most often caused by activating mutations in the TSH receptor. These disorders are characterized by TSH-independent thyroid hormone secretion and focal (TA) or multifocal (MNG) follicular hyperplasia. Initial treatment of TA and MNG includes a beta blocker to alleviate the symptoms of hyperthyroidism and a thionamide (eg, methimazole, propylthiouracil) to decrease thyroid hormone secretion. Options for definitive management of TA include surgery and radioiodine ablation.

If left untreated, patients with hyperthyroidism can develop rapid **bone loss** leading to **osteoporosis** and increased risk of fracture. Direct effects of the thyroid hormones cause increased osteoclastic bone resorption. Patients can also develop hypercalcemia and hypercalciuria due to increased bone turnover.

(Choice B) Common cardiovascular effects of hyperthyroidism include tachycardia, systolic hypertension, increased pulse pressure, and tachyarrhythmias (eg, atrial fibrillation). Thyrotoxicosis per se is not a risk factor for coronary artery disease, although its symptoms can be unmasked or worsened with thyrotoxicosis.

(Choice C) Fetal hyperthyroidism can be seen in patients with active Graves disease, in whom TSH receptor (TSHR) antibodies can cross the placenta and affect the fetal thyroid. TSHR antibodies are not seen in TA.

(Choice D) Large hypofunctioning ("cold") nodules carry an increased risk of malignancy and require additional evaluation. Hyperfunctioning nodules are rarely malignant.

(Choice E) Infiltrative ophthalmopathy in Graves disease leads to proptosis, impaired ocular movement, ocular irritation and redness, and possible vision loss. However, significant ophthalmopathy is not seen in TA.

Patients can also develop hypercalcemia and hypercalciuria due to increased bone turnover.

(Choice B) Common cardiovascular effects of hyperthyroidism include tachycardia, systolic hypertension, increased pulse pressure, and tachyarrhythmias (eg, atrial fibrillation). Thyrotoxicosis per se is not a risk factor for coronary artery disease, although its symptoms can be unmasked or worsened with thyrotoxicosis.

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(Choice D) Large hypofunctioning ("cold") nodules carry an increased risk of malignancy and require additional evaluation. Hyperfunctioning nodules are rarely malignant.

(Choice E) Infiltrative ophthalmopathy in Graves disease leads to proptosis, impaired ocular movement, ocular irritation and redness, and possible vision loss. However, significant ophthalmopathy is not seen in TA.

Educational objective:
Untreated hyperthyroid patients are at risk for rapid bone loss from increased osteoclastic activity in the bone cells. Untreated hyperthyroid patients are also at risk for cardiac tachyarrhythmias, including atrial fibrillation.

References

- Metabolic and clinical consequences of hyperthyroidism on bone density.

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A 45-year-old woman undergoes elective total hysterectomy for uterine fibroids. In the postoperative recovery room, she develops nausea, vomiting, dizziness, and diffuse abdominal pain. The patient's medical history includes systemic lupus erythematosus, pernicious anemia, type 2 diabetes mellitus, and chronic low back pain. Her outpatient medications include monthly vitamin B_{12} injections, metformin, insulin glargine, prednisone, hydroxychloroquine, and acetaminophen. Blood pressure is 85/50 mm Hg and pulse is 110/min. After administration of 4 L of intravenous fluids her blood pressure is 110/70 mm Hg. The patient has a round plethoric face, buffalo hump, and central obesity. Laboratory results are as follows:

Sodium	132 mEq/L
Potassium	4.4 mEq/L
Chloride	104 mEq/L
Bicarbonate	22 mEq/L
Urea nitrogen	34 mg/dL
Creatinine	1.2 mg/dL
Calcium	8.8 mg/dL
Glucose	50 mg/dL

Which of the following is the most likely cause of this patient's acute condition?

Bicarbonate	22 mEq/L
Urea nitrogen	34 mg/dL
Creatinine	1.2 mg/dL
Calcium	8.8 mg/dL
Glucose	50 mg/dL

Which of the following is the most likely cause of this patient's acute condition?

- A. Adrenal insufficiency
- B. Diabetic ketoacidosis
- C. Insulin-induced hypoglycemia
- D. Lactic acidosis
- E. Pelvic abscess
- F. Postoperative bleeding
- G. Postoperative ileus

Submit

Bicarbonate	22 mEq/L
Urea nitrogen	34 mg/dL
Creatinine	1.2 mg/dL
Calcium	8.8 mg/dL
Glucose	50 mg/dL

Which of the following is the most likely cause of this patient's acute condition?

- ✔ A. Adrenal insufficiency [83%]
- ✘ B. Diabetic ketoacidosis [1%]
- C. Insulin-induced hypoglycemia [7%]
- D. Lactic acidosis [1%]
- E. Pelvic abscess [0%]
- F. Postoperative bleeding [4%]
- G. Postoperative ileus [0%]

Incorrect | 83% | 9 Seconds | 06/21/2018

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

Acute adrenal insufficiency (adrenal crisis) is characterized by severe and often refractory **hypotension**, vomiting, abdominal pain, and fever. It can be triggered by acute illness or other major stressor (eg, surgery) and occurs in patients with underlying **primary adrenal insufficiency** (PAI; Addison disease) or suppression of the hypothalamus-pituitary-adrenal (HPA) axis due to chronic **glucocorticoid** use. Those with PAI usually have hyponatremia and **hyperkalemia** due to concurrent mineralocorticoid insufficiency. By contrast, potassium is normal in patients with central adrenal insufficiency although hyponatremia can be present due to increased release of antidiuretic hormone. Treatment for adrenal crisis includes intravenous **hydrocortisone or dexamethasone** with aggressive fluid support and should be started empirically without waiting for laboratory confirmation.

Patients on long-term glucocorticoid therapy who have **Cushingoid features** (eg, central obesity, moon facies) are at very high risk of adrenal crisis. However, HPA suppression can be seen in as little as 3 weeks in patients taking **prednisone ≥20 mg/day** or equivalent. These patients may not respond appropriately to acute stressors and should be given higher doses ("stress doses") of glucocorticoids during the acute condition. Low-dose glucocorticoids (<5 mg/day) have minimal risk and usually do not require stress dosing. Intermediate doses (5-20 mg/day) can cause HPA suppression and require preoperative evaluation with an early-morning cortisol level to determine risk.

(Choices B and D) Diabetic ketoacidosis can present with vomiting and abdominal pain but would be characterized by hyperglycemia and an elevated anion gap acidosis. Lactic acidosis can be seen in patients taking metformin but would also show an elevated anion gap.

(Choice C) Hypoglycemia is common in adrenal crisis. Insulin-induced hypoglycemia can cause dizziness but typically causes systolic hypertension with widened pulse pressure.

(Choice E) Pelvic abscess is a common complication of hysterectomy and can cause fever, tachycardia, and abdominal pain. However, it usually presents several days to weeks after surgery.

(Choice F) Postoperative hemorrhage can cause acute hypotension and tachycardia but would not explain this patient's hypoglycemia, nausea, and vomiting.

(Choice G) Postoperative ileus can cause abdominal pain and vomiting but symptoms are initially mild and nonspecific, and evolve over several hours to days.

Educational objective:

metformin but would also show an elevated anion gap.

(Choice C) Hypoglycemia is common in adrenal crisis. Insulin-induced hypoglycemia can cause dizziness but typically causes systolic hypertension with widened pulse pressure.

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(Choice F) Postoperative hemorrhage can cause acute hypotension and tachycardia but would not explain this patient's hypoglycemia, nausea, and vomiting.

(Choice G) Postoperative ileus can cause abdominal pain and vomiting but symptoms are initially mild and nonspecific, and evolve over several hours to days.

Educational objective:
Acute adrenal insufficiency is characterized by hypotension, vomiting, abdominal pain, and fever. It can be triggered by acute illness or surgery and occurs in those with underlying primary adrenal insufficiency or on chronic glucocorticoid therapy. Treatment includes hydrocortisone or dexamethasone with aggressive fluid support.

References

- Adrenal crisis: still a deadly event in the 21st century.

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A 21-year-old woman comes to the office with 5 months of fatigue, excessive sweating, and palpitations. The patient is slightly overweight and had previously been unsuccessful in losing weight with caloric restriction and exercise. However, she has lost weight during the past 6 months with an over-the-counter weight loss remedy. The patient has had no menstrual periods for the last 3 months. She is not sexually active. Her blood pressure is 136/70 mm Hg and pulse is 100/min. Her BMI is 26 kg/m^2. The patient has lid lag but no proptosis. Examination of the thyroid shows a small gland without nodules or tenderness. Laboratory findings are as follows:

TSH	low
Free T4	high
β-hCG	negative

Radioiodine uptake by the thyroid gland is diffusely decreased. Which of the following would most likely be found in this patient?

A. Elevated antithyroid peroxidase antibody titer
B. Elevated erythrocyte sedimentation rate
C. Elevated serum alpha-subunit level
D. Elevated TSH receptor antibody titer
E. Low serum thyroglobulin level

The patient has had no menstrual periods for the last 3 months. She is not sexually active. Her blood pressure is 136/70 mm Hg and pulse is 100/min. Her BMI is 26 kg/m². The patient has lid lag but no proptosis. Examination of the thyroid shows a small gland without nodules or tenderness. Laboratory findings are as follows:

TSH	low
Free T4	high
β-hCG	negative

Radioiodine uptake by the thyroid gland is diffusely decreased. Which of the following would most likely be found in this patient?

- A. Elevated antithyroid peroxidase antibody titer [14%]
- B. Elevated erythrocyte sedimentation rate [5%]
- C. Elevated serum alpha-subunit level [14%]
- ✗ D. Elevated TSH receptor antibody titer [20%]
- ✓ E. Low serum thyroglobulin level [45%]

Incorrect
Correct answer

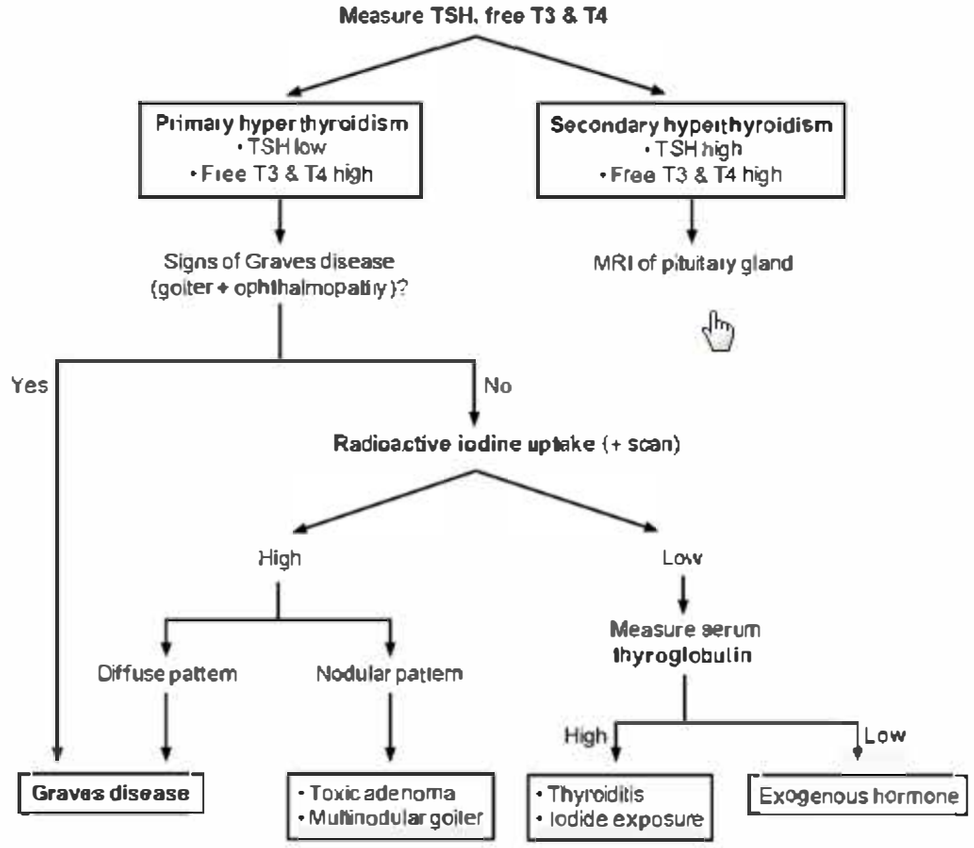
45%
Answered correctly

7 Seconds
Time Spent

08/15/2018
Last Updated

Exhibit Display

Evaluation of hyperthyroidism



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This patient, with fatigue, sweating, palpitations, and weight loss, has features of **hyperthyroidism**. The first step in evaluating hyperthyroidism is to measure serum **TSH** and **free T4** levels. In the absence of a TSH-secreting pituitary adenoma (secondary hyperthyroidism), patients with hyperthyroidism will have an elevated T4 and suppressed TSH. The most common cause of hyperthyroidism is Graves' disease, which is caused by an autoantibody to the TSH receptor and is characterized by a diffuse goiter and ocular abnormalities (proptosis, periorbital edema). Patients with clear features of Graves' disease may be managed accordingly, but those without require further investigation.

Patients with undiagnosed hyperthyroidism may be evaluated further with **radioactive iodine uptake** (RAIU), usually with scan. A high RAIU suggests de novo hormone synthesis due to Graves' disease (diffusely increased uptake) or toxic nodular disease (nodular uptake). In contrast, a low RAIU suggests either release of preformed thyroid hormone (ie, thyroiditis) or exogenous thyroid hormone intake. In such cases, the serum **thyroglobulin** level can make the distinction: elevated thyroglobulin is consistent with endogenous thyroid hormone release whereas decreased thyroglobulin suggests exogenous or factitious thyrotoxicosis. In this patient, it is likely that her weight loss supplement contains thyroid hormone derived from porcine or other animal sources.

(Choice A) Antithyroid peroxidase antibodies are seen in Hashimoto thyroiditis, which usually presents with a palpable goiter and clinical hypothyroidism (rather than hyperthyroidism). RAIU is not typically part of the evaluation of hypothyroidism but would generally show low uptake in patients with Hashimoto thyroiditis due to autoimmune thyroid destruction. Rarely, patients with Hashimoto thyroiditis can present with a transient hyperthyroid state (due to inflammation) early in the course of the disease. Factitious thyrotoxicosis is much more likely in this patient who developed manifestations of hyperthyroidism shortly after she started taking an over-the-

autoimmune thyroid destruction. Rarely, patients with Hashimoto thyroiditis can present with a transient hyperthyroid state (due to inflammation) early in the course of the disease. Factitious thyrotoxicosis is much more likely in this patient who developed manifestations of hyperthyroidism shortly after she started taking an over-the-counter weight loss remedy.

(Choice B) Subacute thyroiditis (de Quervain's thyroiditis) is characterized by fever, neck pain, thyroid tenderness, and an elevated erythrocyte sedimentation rate. In most cases, hyperthyroid symptoms fade in <8 weeks as the thyroid gland becomes depleted of preformed hormone.

(Choice C) TSH is comprised of 2 subunits, an alpha-subunit (common to TSH, FSH, LH, and hCG) and a thyroid-specific beta-subunit. Many TSH-secreting pituitary adenomas overproduce the alpha-subunit, and an elevated ratio of alpha-subunit to TSH suggests a pituitary adenoma. These patients would have an elevated TSH, elevated free T4, and normal or increased RAIU.

(Choice D) This patient's absence of ophthalmopathy (eg, proptosis, periorbital edema) and low RAIU make Graves' disease unlikely.

Educational objective:
In hyperthyroidism, increased radioactive iodine uptake (RAIU) suggests de novo thyroid hormone synthesis, whereas decreased RAIU suggests release of preformed hormone or exogenous hormone intake. Thyrotoxicosis due to exogenous thyroid hormone is characterized by low serum thyroglobulin levels.

References

A 40-year-old man comes to the office for follow-up of hypertension. He was diagnosed with mild hypertension 6 months ago and has had good control with regular exercise and weight loss. The patient feels well and takes no medications. He does not smoke and drinks a few glasses of wine per week. The patient's medical history is otherwise unremarkable. His mother has osteoporosis that is treated with oral alendronate. On examination, inspection and palpation of the neck show no masses. Laboratory results are as follows:

Sodium	140 mEq/L
Potassium	4.0 mEq/L
Bicarbonate	25 mEq/L
Chloride	101 mEq/L
Calcium	11.8 mg/dL
Albumin	4.0 g/dL
Phosphorus	2.2 mg/dL
Creatinine	1.2 mg/dL
25-hydroxyvitamin D	38 ng/mL (normal: 25-80 ng/mL)

Serum parathyroid hormone level is 814 pg/mL. Further testing shows a high 24-hour urine calcium excretion of

Albumin	4.0 g/dL
Phosphorus	2.2 mg/dL
Creatinine	1.2 mg/dL
25-hydroxyvitamin D	38 ng/mL (normal: 25-80 ng/mL)

Serum parathyroid hormone level is 814 pg/mL. Further testing shows a high 24-hour urine calcium excretion of 325 mg. DXA scan reveals normal bone mineral density. Renal ultrasound shows multiple small (<5 mm) stones in both kidneys. Which of the following is the most appropriate next step in management of this patient?

A. Initiate bisphosphonate therapy

B. Obtain CT scan of the chest, abdomen, and pelvis

C. Refer for parathyroid imaging and parathyroidectomy

D. Repeat serum calcium measurement in 3-6 months

E. Start vitamin D supplementation

Submit

Albumin	4.0 g/dL
Phosphorus	2.2 mg/dL
Creatinine	1.2 mg/dL
25-hydroxyvitamin D	38 ng/mL (normal: 25-80 ng/mL)

Serum parathyroid hormone level is 814 pg/mL. Further testing shows a high 24-hour urine calcium excretion of 325 mg. DXA scan reveals normal bone mineral density. Renal ultrasound shows multiple small (<5 mm) stones in both kidneys. Which of the following is the most appropriate next step in management of this patient?

- ✗ A. Initiate bisphosphonate therapy [11%]
- B. Obtain CT scan of the chest, abdomen, and pelvis [21%]
- ✓ C. Refer for parathyroid imaging and parathyroidectomy [55%]
- D. Repeat serum calcium measurement in 3-6 months [9%]
- E. Start vitamin D supplementation [2%]

Incorrect
Correct answer

55%
Answered correctly

18 Seconds
Time Spent

09/14/2018
Last Updated

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
Indications for parathyroidectomy	• Age <50 • Symptomatic hypercalcemia • **Complications:** Osteoporosis (T-score <−2.5, fragility fracture), nephrolithiasis/calcinosis, CKD (GFR <60 mL/min) • **Elevated risk of complications:** Calcium ≥1 mg/dL above normal, urinary calcium excretion >400 mg/day

CKD = chronic kidney disease; **GFR** = glomerular filtration rate; **MEN** = multiple endocrine neoplasia; **PTH** = parathyroid hormone

This patient has **hypercalcemia**, hypophosphatemia, and an **elevated parathyroid hormone** (PTH) level consistent with **primary hyperparathyroidism** (PHPT). PTH causes increased reabsorption of calcium from the distal tubule, but net urinary calcium excretion is increased due to excess resorption of calcium from bones. By contrast, familial hypocalciuric hypercalcemia is characterized by hypercalcemia with an elevated PTH but low urinary calcium excretion (often <100 mg/24 hr).

Parathyroidectomy is recommended for patients with **symptomatic hypercalcemia**. It is also recommended for patients, such as this one, with **complications** (eg, osteoporosis, nephrocalcinosis, **nephrolithiasis**, impaired renal function) or at significant **risk for complications** (eg, serum calcium ≥1 mg/dL above normal, urinary calcium excretion >400 mg/24 hr). In addition, younger patients (age <50) such as this one are likely to have complications during their lifetime and should be offered surgery.

This patient is relatively young and has nephrolithiasis (likely as a complication of PHPT); he should therefore be referred for parathyroidectomy. Parathyroid imaging (eg, sestamibi scan, ultrasonography) helps optimize the surgical approach by potentially determining the affected side and evaluating for the possibility of a minimally invasive intervention.

(Choice A) Parathyroidectomy is the treatment of choice for PHPT. However, bisphosphonate therapy can be used in patients who decline surgery and have osteopenia or osteoporosis.

(Choice B) Extended CT imaging would be indicated for suspected hypercalcemia of malignancy, which typically presents with severe, symptomatic hypercalcemia, low PTH, and elevated PTH-related protein. Imaging to evaluate for multiple endocrine neoplasia syndromes is recommended only if there is evidence of multiglandular hyperparathyroidism or additional endocrine tumors.

used in patients who decline surgery and have osteopenia or osteoporosis.

(Choice B) Extended CT imaging would be indicated for suspected hypercalcemia of malignancy, which typically presents with severe, symptomatic hypercalcemia, low PTH, and elevated PTH-related protein. Imaging to evaluate for multiple endocrine neoplasia syndromes is recommended only if there is evidence of multiglandular hyperparathyroidism or additional endocrine tumors.

(Choice D) Continued observation is appropriate in older asymptomatic patients with near-normal calcium levels and normal bone density.

(Choice E) Vitamin D supplementation is not recommended in patients with PHPT who do not have overt vitamin D deficiency as it may exacerbate hypercalcemia and hypercalciuria. This patient has a normal vitamin D level.

Educational objective:

The most common presentation of primary hyperparathyroidism is asymptomatic hypercalcemia with an elevated parathyroid hormone level. Parathyroidectomy is recommended for patients with symptomatic hypercalcemia and those with complications (eg, nephrolithiasis) or at increased risk for complications. Younger patients (age <50) are likely to have complications during their lifetime and should be offered surgery.

References

- Primary hyperparathyroidism: an update.
- Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop

A 63-year-old man comes to the urgent care center with a 2-week history of an ulcer on his right foot. He has no associated pain, fever, chills, or skin rash. The patient was diagnosed with hypertension 5 years ago but did not follow up with a physician, and he has had no surgeries or hospitalizations. He takes ibuprofen for occasional back pain. The patient has a 30-pack year smoking history but quit 2 years ago. He drinks 1 or 2 beers daily and does not eat red meat or processed foods. The patient considers himself to be in good health and walks several miles a day. Temperature is 36.7 C (98.1 F), blood pressure is 156/98 mm Hg, and pulse is 88/min. BMI is 32 kg/m^2. On examination, the feet are warm and dry. A nontender ulcer with a thick surrounding callus is present on the sole of the foot just below the head of the first metatarsal bone. Which of the following will most likely diagnose the underlying cause of this patient's foot ulcer?

- A. Alcohol screening questionnaire
- B. Ankle-brachial index
- C. Culture from the ulcer bed
- D. Duplex venous ultrasound
- E. Hemoglobin A1c assay
- F. Hepatitis C testing
- G. TSH level

follow up with a physician, and he has had no surgeries or hospitalizations. He takes ibuprofen for occasional back pain. The patient has a 30-pack year smoking history but quit 2 years ago. He drinks 1 or 2 beers daily and does not eat red meat or processed foods. The patient considers himself to be in good health and walks several miles a day. Temperature is 36.7 C (98.1 F), blood pressure is 156/98 mm Hg, and pulse is 88/min. BMI is 32 kg/m^2. On examination, the feet are warm and dry. A nontender ulcer with a thick surrounding callus is present on the sole of the foot just below the head of the first metatarsal bone. Which of the following will most likely diagnose the underlying cause of this patient's foot ulcer?

- A. Alcohol screening questionnaire [0%]
- B. Ankle-brachial index [13%]
- C. Culture from the ulcer bed [1%]
- ✗ D. Duplex venous ultrasound [2%]
- ✓ E. Hemoglobin A1c assay [81%]
- F. Hepatitis C testing [0%]
- G. TSH level [0%]

Incorrect
Correct answer

81%
Answered correctly

7 Seconds
Time Spent

09/30/2018
Last Updated

Diabetic foot ulcers	
Risk factors	• **Diabetic neuropathy** (loss of protective sensation, small muscle atrophy, abnormal vascular tone, decreased sweating with fissures) • **Arterial insufficiency** • End-stage renal disease in a patient on dialysis • Smoking
Location	• Plantar surface, areas under pressure points (eg, bony prominences)
Management	• Mechanical offloading • Debridement • Wound dressings • Antibiotics if infection

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Peripheral neuropathy is the most common cause of foot ulcers in patients with diabetes, and **diabetes** is the most common underlying cause of **neuropathic ulcers**. Whereas neuropathy involving small nerve fibers typically causes positive symptoms (eg, pain, paresthesias), involvement of large fibers produces primarily negative symptoms (eg, sensory loss) that can cause minor injuries to go unrecognized until the development of a foot ulcer. Autonomic dysregulation can lead to decreased sweating and dry feet (susceptible to skin fissure formation) and further increase the risk for ulceration.

ulcer. Autonomic dysregulation can lead to decreased sweating and dry feet (susceptible to skin fissure formation) and further increase the risk for ulceration.

Neuropathic ulcers typically occur at weight-bearing sites (eg, below the head of the first metatarsal) on the **sole of the foot**. The plantar location of this patient's ulcer (with callus formation suggesting a pressure point) and the lack of associated pain are consistent with a neuropathic ulcer. He should therefore be screened for diabetes with a **hemoglobin A1c** assay or **fasting glucose** measurement. Poor diabetic control (eg, elevated hemoglobin A1c) increases the risk for peripheral neuropathy.

(Choice A) Peripheral neuropathy due to alcohol use may resemble diabetic neuropathy (eg, symmetric, distal numbness or paresthesias) but is less frequently associated with ulcer development, possibly as perfusion is more preserved. In addition, this patient's moderate alcohol intake is unlikely to cause neuropathy.

(Choice B) The ankle-brachial index can diagnose peripheral artery disease. Features suggesting an **arterial ulcer** include location at the tips of the digits, diminished pulses, skin pallor, loss of hair, and intermittent claudication. This patient has warm feet (preserved perfusion) and walks several miles daily (preserved exercise tolerance), making significant artery disease unlikely.

(Choice C) Culture from an ulcer bed typically reveals polymicrobial colonization but would not indicate true infection in the absence of more specific symptoms (eg, fever, erythema, purulent drainage). Culture also would not establish the underlying cause of the ulcer.

(Choice D) Duplex sonography can identify venous insufficiency or obstruction. **Venous ulcers** typically occur on the medial aspect of the leg above the malleolus; they are usually associated with edema and stasis dermatitis

preserved. In addition, this patient's moderate alcohol intake is unlikely to cause neuropathy.

(Choice B) The ankle-brachial index can diagnose peripheral artery disease. Features suggesting an **arterial ulcer** include location at the tips of the digits, diminished pulses, skin pallor, loss of hair, and intermittent claudication. This patient has warm feet (preserved perfusion) and walks several miles daily (preserved exercise tolerance), making significant artery disease unlikely.

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(Choice D) Duplex sonography can identify venous insufficiency or obstruction. **Venous ulcers** typically occur on the medial aspect of the leg above the malleolus; they are usually associated with edema and stasis dermatitis.

(Choice F) Mild sensorimotor abnormalities can be detected on electrodiagnostic testing in patients with hepatitis C-induced mixed cryoglobulinemia (which can cause a vasculitic rash), but clinically significant neuropathy and ulceration are uncommon.

(Choice G) Peripheral neuropathy is an uncommon manifestation of hypothyroidism and is usually seen in patients with severe, untreated hypothyroidism.

Educational objective:
Diabetes is the most common cause of neuropathic ulcers. These ulcers typically occur on the sole of the foot at weight-bearing points.

common underlying cause of neuropathic ulcers. Whereas neuropathy involving small nerve fibers typically

Exhibit Display

Zoom In | Zoom Out | Reset | Add To Flash Card

not establish the underlying cause of the ulcer.

Exhibit Display

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Educational objective:

A 46-year-old man undergoes an elective inguinal hernia repair. After induction of general anesthesia, he is noted to be pale and tachycardic. The patient's medical history is significant for frequent headaches, hypertension, and an anxiety disorder. His outpatient medications include lisinopril, alprazolam, and as-needed naproxen. The patient regularly drinks a 6-pack of beer on weekends but does not use tobacco or illicit drugs. Family history is unremarkable. His temperature is 36.9 C (98.4 F), blood pressure is now 250/140 mm Hg (it was 144/90 mm Hg before induction), and pulse is 125/min. ECG shows sinus tachycardia with no ischemic changes. Which of the following is the most likely diagnosis?

- A. Alcohol withdrawal
- B. Anaphylaxis
- C. Panic disorder
- D. Pheochromocytoma
- E. Serotonin syndrome
- F. Thyroid storm

Submit

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- ✗ A. Alcohol withdrawal [6%]
- B. Anaphylaxis [5%]
- C. Panic disorder [2%]
- ✓ D. Pheochromocytoma [52%]
- E. Serotonin syndrome [11%]
- F. Thyroid storm [22%]

Incorrect
Correct answer
D

52%
Answered correctly

299 Seconds
TimeSpent

06/04/2018
Last Updated

In light of this patient's history of hypertension and frequent headaches, his presentation with severe hypertension, pallor, and sinus tachycardia is concerning for an occult **pheochromocytoma** with a **catecholamine surge** due to anesthesia. Pheochromocytomas and paraganglionomas are catecholamine-producing tumors arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia, respectively.

Hypertension in pheochromocytoma can be intermittent or sustained. **Paroxysms** of severe **hypertension** can be precipitated by increases in intra-abdominal pressure (eg, tumor palpation, positional changes), surgical procedures, and a number of medications, particularly **anesthetic** agents. In addition, nonselective **beta blockers** can cause a state of unopposed alpha adrenergic stimulation leading to vasoconstriction and paradoxical hypertension. For this reason, alpha adrenergic blockers (eg, phenoxybenzamine) should be administered prior to beta blockers in patients with pheochromocytoma.

(Choices A, C, and F) Alcohol withdrawal and panic disorder can mimic pheochromocytoma paroxysms but are unlikely to manifest when the patient is under anesthesia. Thyroid storm can be precipitated by surgery in patients with preexisting thyrotoxicosis, but the presentation is usually less acute, and almost all patients will have pyrexia. Severely elevated blood pressure and pallor (from catecholamine-induced vasoconstriction) are more likely due to catecholamine surge from pheochromocytoma.

(Choice B) Anaphylaxis is a severe type 1 hypersensitivity reaction to a drug, environmental agent, or food. Anaphylaxis typically causes hives, angioedema, respiratory compromise, and acute hypotension rather than hypertension.

(Choice E) Serotonin syndrome is characterized by abnormal mental status, autonomic hyperactivity, and

(Choices A, C, and F) Alcohol withdrawal and panic disorder can mimic pheochromocytoma paroxysms but are unlikely to manifest when the patient is under anesthesia. Thyroid storm can be precipitated by surgery in patients with preexisting thyrotoxicosis, but the presentation is usually less acute, and almost all patients will have pyrexia. Severely elevated blood pressure and pallor (from catecholamine-induced vasoconstriction) are more likely due to catecholamine surge from pheochromocytoma.

(Choice B) Anaphylaxis is a severe type 1 hypersensitivity reaction to a drug, environmental agent, or food. Anaphylaxis typically causes hives, angioedema, respiratory compromise, and acute hypotension rather than hypertension.

(Choice E) Serotonin syndrome is characterized by abnormal mental status, autonomic hyperactivity, and muscular rigidity with hyperreflexia. It is typically triggered by initiation or titration of selective serotonin reuptake inhibitors.

Educational objective:
Pheochromocytomas are catecholamine-producing tumors arising from chromaffin cells of the adrenal medulla. Paroxysms of severe hypertension in patients with pheochromocytoma can be precipitated by surgical procedures, induction of anesthesia, and a number of medications.

References

- Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline.

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A 66-year-old man comes to the office with nausea, loss of appetite, fatigue, and marked weakness. His medical history is significant for hypertension treated with amlodipine. The patient also has polymyalgia rheumatica, for which he was on prednisone for 12 months, but he stopped taking the medication 7 days ago because he was unhappy with the associated weight gain. Temperature is 36.7 C (98.1 F), blood pressure is 100/70 mm Hg without orthostatic changes, pulse is 100/min, and respirations are 18/min. His face is round and plethoric, and there is excess supraclavicular fat deposition. Laboratory results are as follows:

Serum sodium	131 mEq/L
Serum potassium	4.3 mEq/L
Chloride	96 mEq/L
Bicarbonate	24 mEq/L
Blood urea nitrogen	10 mg/dL
Serum creatinine	0.9 mg/dL
Calcium	9.6 mg/dL
Blood glucose	71 mg/dL

Chest x-ray is unremarkable. Which of the following biochemical abnormalities is most likely to be present in this patient?

Chloride	96 mEq/L
Bicarbonate	24 mEq/L
Blood urea nitrogen	10 mg/dL
Serum creatinine	0.9 mg/dL
Calcium	9.6 mg/dL
Blood glucose	71 mg/dL

Chest x-ray is unremarkable. Which of the following biochemical abnormalities is most likely to be present in this patient?

A. Decreased ACTH, decreased aldosterone, and decreased cortisol levels
B. Decreased ACTH and decreased aldosterone levels
C. Decreased ACTH and decreased cortisol levels
D. Increased ACTH and decreased cortisol levels
E. Increased ACTH and increased cortisol levels

Submit

Chloride	96 mEq/L
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Blood urea nitrogen	10 mg/dL
Serum creatinine	0.9 mg/dL
Calcium	9.6 mg/dL
Blood glucose	71 mg/dL

Chest x-ray is unremarkable. Which of the following biochemical abnormalities is most likely to be present in this patient?

A. Decreased ACTH, decreased aldosterone, and decreased cortisol levels [23%]
B. Decreased ACTH and decreased aldosterone levels [6%]
✔ C. Decreased ACTH and decreased cortisol levels [43%]
D. Increased ACTH and decreased cortisol levels [20%]
E. Increased ACTH and increased cortisol levels [5%]

Correct 43% 6 Seconds 05/09/2018

Primary versus central adrenal insufficiency		
	Primary	**Central (secondary/pituitary; tertiary/hypothalamic)**
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

This patient - with nausea, weakness, and fatigue following abrupt discontinuation of chronic glucocorticoid therapy - most likely has **central adrenal insufficiency** (AI) due to suppression of the **hypothalamic-pituitary-adrenal (HPA) axis**. Glucocorticoids suppress secretion of corticotropin-releasing hormone from the hypothalamus and ACTH secretion from the pituitary gland. Suppression of adrenal function is likely to develop in patients receiving glucocorticoids for a prolonged period; patients treated with corticosteroids for <3 weeks are less likely to develop HPA suppression. In addition, patients with a **Cushingoid appearance** are more likely to have a suppressed HPA

- most likely has **central adrenal insufficiency** (AI) due to suppression of the **hypothalamic-pituitary-adrenal (HPA) axis**. Glucocorticoids suppress secretion of corticotropin-releasing hormone from the hypothalamus and ACTH secretion from the pituitary gland. Suppression of adrenal function is likely to develop in patients receiving glucocorticoids for a prolonged period; patients treated with corticosteroids for <3 weeks are less likely to develop HPA suppression. In addition, patients with a **Cushingoid appearance** are more likely to have a suppressed HPA axis. Following glucocorticoid discontinuation, normal HPA axis function may not fully return for up to **6-12 months**.

The diagnosis of central AI begins with measurement of **morning cortisol** (low) and **ACTH** (low in central AI; high in primary AI). Aldosterone levels are low in primary AI but normal in central AI as aldosterone is regulated primarily by the renin-angiotensin-aldosterone system, not the pituitary **(Choices A and B)**. In primary AI, aldosterone deficiency causes renal sodium wasting, leading to hyponatremia. Although hyponatremia may occur in central AI (possibly from impaired free water excretion due to cortisol deficiency), it is generally mild. Also, mild hypotension can occur due to decreased peripheral arterial resistance.

(Choice D) Increased ACTH and low cortisol are seen in primary AI. These patients have low levels of all adrenal cortical hormones, including cortisol, adrenal sex steroids, and aldosterone, and typically have hyperpigmentation, hyponatremia, and hyperkalemia. In central AI due to prednisone, it may take several months (not 7 days) following discontinuation of the medication for pituitary ACTH secretion to start to recover.

(Choice E) Increased ACTH and cortisol levels can be seen physiologically in response to stress (eg, hypovolemia) or pathologically in ACTH-dependent Cushing syndrome.

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(Choice E) Increased ACTH and cortisol levels can be seen physiologically in response to stress (eg, hypovolemia) or pathologically in ACTH-dependent Cushing syndrome.

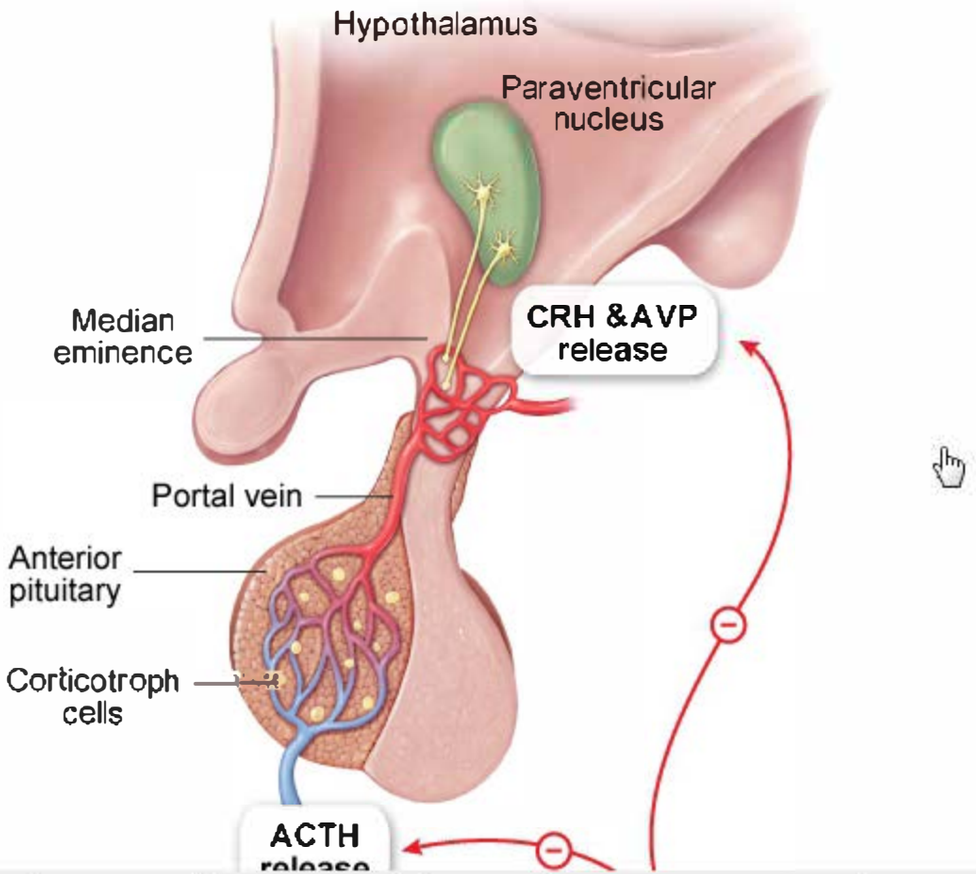
Educational objective:
Chronic supraphysiologic doses of glucocorticoids cause central adrenal insufficiency (AI). Laboratory studies typically show low ACTH and cortisol levels and a normal aldosterone level. In contrast, patients with primary AI have elevated ACTH, low aldosterone, and significant electrolyte effects (hyponatremia, hyperkalemia).

References

- Predisposing factors for adrenal insufficiency.

Exhibit Display

Hypothalamic-pituitary-adrenal axis



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in central AI (possibly from impaired free water excretion due to cortisol deficiency), it is generally mild. Also, mild

A 17-year-old girl is admitted to the hospital for purging behavior, weight loss, and syncope. She is started on nasogastric feeds and her activities are restricted. On the second day of admission, the patient complains of severe shortness of breath and has recurrent episodes of nonsustained ventricular tachycardia. Her blood pressure is 82/55 mm Hg, heart rate is 112/min, and respirations are 22/min. Her body mass index is 14 kg/m^2. Physical examination shows an emaciated girl with bibasilar crackles and jugular venous distension. Serum chemistry results are as follows:

Sodium	138 mEq/L
Potassium	2.1 mEq/L
Chloride	92 mEq/L
Bicarbonate	28 mEq/L
Blood urea nitrogen	14 mg/dL
Creatinine	0.8 mg/dL
Calcium	8 mg/dL
Glucose	90 mg/dL
Magnesium	1 mg/dL
Phosphorus	0.9 mg/dL

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A surge in which of the following hormones best explains this patient's deterioration?

- A. Aldosterone
- B. Cortisol
- C. Glucagon
- D. Insulin
- E. Triiodothyronine

Submit

Blood urea nitrogen	14 mg/dL
Creatinine	0.8 mg/dL
Calcium	8 mg/dL
Glucose	90 mg/dL
Magnesium	1 mg/dL
Phosphorus	0.9 mg/dL

A surge in which of the following hormones best explains this patient's deterioration?

- A. Aldosterone [24%]
- ✗ B. Cortisol [16%]
- C. Glucagon [4%]
- ✓ D. Insulin [46%]
- E. Triiodothyronine [7%]

Incorrect
Correct answer

46%
Answered correctly

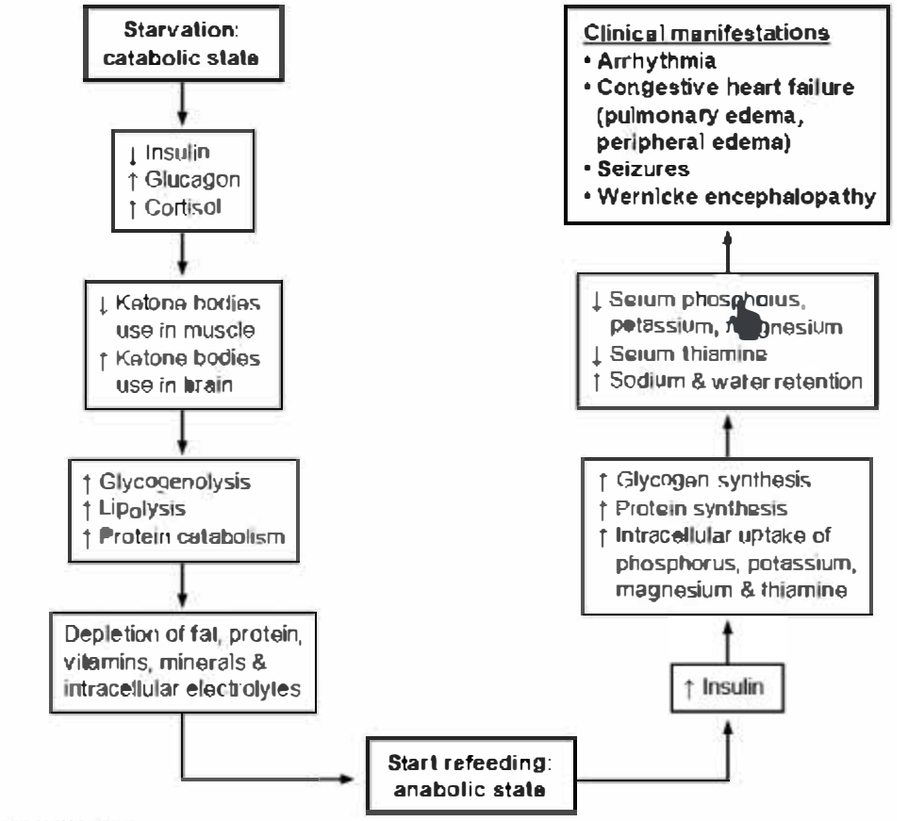
8 Seconds
Time Spent

11/05/2018
Last Updated

Pathogenesis of refeeding syndrome

Exhibit Display

Pathogenesis of refeeding syndrome



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Chronic starvation and acute refeeding are potentially life-threatening in patients with anorexia nervosa. Refeeding syndrome is the constellation of pathologic derangements resulting from a surge in insulin activity as the body resumes anabolism (Flow chart). Carbohydrate ingestion, whether enteral or intravenous, causes pancreatic **insulin secretion** and cellular uptake of phosphorus, potassium, and magnesium. **Phosphorus** is the primary deficient electrolyte as it is required for energy (adenosine triphosphate). Deficiencies in potassium and magnesium potentiate **cardiac arrhythmias** in a heart that is already atrophic from prolonged malnutrition. Therefore, aggressive initiation of nutrition without adequate electrolyte repletion can quickly precipitate **cardiopulmonary failure**. This patient has signs of volume overload from heart failure based on increased pulse and respiratory rate, jugular venous distension, and bibasilar lung crackles.

(Choices A and B) Aldosterone and cortisol stimulate water resorption, sodium conservation, and potassium secretion in an attempt to maintain blood pressure. These steroid hormones are high during starvation but less so during refeeding. In addition, they do not directly impact phosphorus or magnesium uptake.

(Choice C) Glucagon activity is elevated during starvation but decreased during refeeding.

(Choice E) Patients with anorexia nervosa have euthyroid hypothyroxinemia, which is characterized by normal thyroid-stimulating hormone and normal to decreased serum thyroxine and triiodothyronine.

Educational objective:
Refeeding syndrome is a potentially fatal complication of nutritional rehabilitation in anorexia nervosa. Carbohydrate intake stimulates insulin activity, which in turn promotes cellular uptake of phosphorus, potassium, and magnesium. Clinical manifestations include arrhythmias and cardiopulmonary failure.

A 49-year-old man comes to the office due to a 3-month history of fatigue. He also reports diffuse joint pain, finger swelling, and difficulty gripping objects with his right hand. The patient has poorly controlled hypertension despite being compliant with medications, a low-salt diet, and regular exercise. Temperature is 36.7 C (98 F), blood pressure is 146/98 mm Hg, pulse is 90/min, and respirations are 14/min. On examination, facial features appear coarse and differ significantly from his driver's license photograph taken 3 years ago. The palms are sweaty and have a doughy feel. The skin is oily. Multiple skin tags are noted, particularly on the neck area. Tapping the ventral aspect of the right wrist produces shooting pain on the lateral side of the right hand. Which of the following is the best next step in evaluating this patient?

- A. Fasting growth hormone level
- B. Growth hormone level following an oral glucose load
- C. Insulin-like growth factor 1 level
- D. MRI of the pituitary gland
- E. Thyrotropin-releasing hormone stimulation test

Submit

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- A. Fasting growth hormone level [9%]
- ✗ B. Growth hormone level following an oral glucose load [14%]
- ✓ C. Insulin-like growth factor 1 level [69%]
- D. MRI of the pituitary gland [5%]
- E. Thyrotropin-releasing hormone stimulation test [2%]

Incorrect
Correct answer
C

69%
Answered correctly

6 Seconds
TimeSpent

09/14/2018
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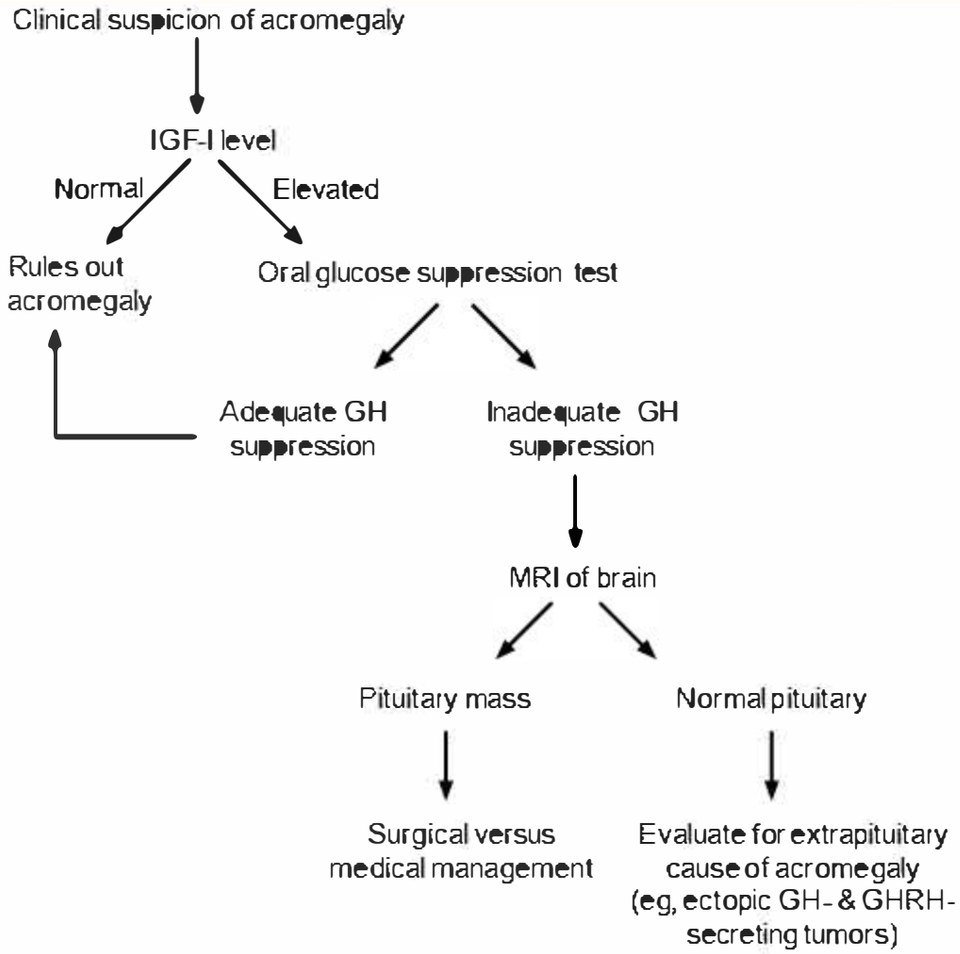

GH = growth hormone; GHRH = growth hormone-releasing hormone; IGF-1 = insulin-like growth factor 1.

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This patient's presentation (coarse facial features, arthralgias, uncontrolled hypertension, enlargement of the digits,

This patient's presentation (coarse facial features, arthralgias, uncontrolled hypertension, enlargement of the digits, carpal tunnel syndrome) is consistent with **acromegaly**. This condition is caused by excessive secretion of **growth hormone (GH)**, usually due to a pituitary **somatotroph adenoma**. Other common features include malocclusion of the jaw, hyperhidrosis, heart failure, macroglossia, and local mass-effect symptoms (eg, headache, visual field defects).

GH stimulates hepatic **insulin-like growth factor 1** (IGF-1) secretion, which is responsible for most of the clinical manifestations of acromegaly. IGF-1 levels in acromegaly are consistently elevated throughout the day. In contrast, GH levels can fluctuate widely and cannot be used alone to diagnose acromegaly **(Choice A)**. As a result, IGF-1 is the preferred initial test. However, IGF-1 levels decrease with age and require interpretation according to age-adjusted norms.

(Choice B) Patients with elevated IGF-1 should undergo confirmatory testing with an oral glucose suppression test. In normal individuals, administration of glucose rapidly suppresses GH secretion; however, in acromegaly, GH will not be suppressed and may paradoxically increase.

(Choice D) Once acromegaly is confirmed with a glucose suppression test, patients should have an MRI of the brain to identify a pituitary mass. However, incidental pituitary lesions are common in normal patients and can be misleading in the diagnostic assessment. As a general rule in endocrinology, imaging is performed after biochemical diagnosis of a disorder is made.

(Choice E) Thyrotropin-releasing hormone administration suppresses GH secretion in normal individuals but stimulates secretion in many patients with acromegaly. However, this test has poor sensitivity and is not routinely performed.

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(Choice E) Thyrotropin-releasing hormone administration suppresses GH secretion in normal individuals but stimulates secretion in many patients with acromegaly. However, this test has poor sensitivity and is not routinely performed.

Educational objective:
Acromegaly is caused by excessive secretion of growth hormone (GH), usually due to a pituitary somatotroph adenoma. Insulin-like growth factor 1 mediates most of the effects of GH and is the preferred initial test in suspected acromegaly. GH is not as sensitive due to wide fluctuations in circulating levels.

References

- Pituitary tumours: acromegaly.

A 12-week-old female infant is brought to the office by her mother due to a three-week history of weakness, poor appetite, and choking spells during feeding. Other accompanying symptoms include excessive sleeping, constipation and apathy. Her prenatal history is unremarkable. She was delivered vaginally at 38 weeks of gestation. She was born outside the United States. Her weight and length at birth were within normal range. She is exclusively breastfed. Her mother's family history is unremarkable. The identity and family history of her father are unknown. The pertinent physical findings include apathy, weakness, hypotonia, large tongue, sluggish movement, abdominal bloating, and an umbilical hernia. Based on the given information, what is the most likely diagnosis?

- A. Infant botulism
- B. Werdnig-Hoffmann syndrome
- C. Myotonic congenital myopathy
- D. Congenital hypothyroidism
- E. Myasthenia gravis

Submit

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- A. Infant botulism [3%]
- ✗ B. Werdnig-Hoffmann syndrome [11%]
- C. Myotonic congenital myopathy [4%]
- ✓ D. Congenital hypothyroidism [79%]
- E. Myasthenia gravis [0%]

Incorrect
Correct answer
D

79%
Answered correctly

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10/27/2018
Last Updated

This clinical case is characteristic of congenital hypothyroidism, which may be familial or sporadic. The most common cause is thyroid dysgenesis (i.e., aplasia, hypoplasia, or ectopic gland), which has been incriminated in 85% of cases. Other causes include inborn errors of thyroxin synthesis (10%), and transplacental maternal thyrotropin-receptor blocking antibodies (5%). Infants initially appear normal at birth, but gradually develop apathy, weakness, hypotonia, large tongue, sluggish movement, abdominal bloating, and an umbilical hernia. Other signs include pathologic jaundice, difficult breathing, noisy respiration, hypothermia, and refractory macrocytic anemia. Infants initially appear normal due to the presence of moderate amounts of maternal hormones in the infant's circulation. For this reason, screening is mandated in all states at birth to allow for the early detection, treatment, and consequent improvement of the prognosis. Screening is done by measuring serum T4 and TSH levels. The treatment is levothyroxine (initial dose of 10 mcg/kg, then titrated accordingly).

(Choice A) Infant botulism occurs most commonly in infants whose diet includes honey or canned food. This infant has been exclusively breastfed since birth. Furthermore, patients with botulism do not present with a large tongue, umbilical hernia, and apathy, which are all classic features of hypothyroidism.

(Choice B) Werdnig-Hoffman syndrome is an autosomal recessive disorder that involves degeneration of the anterior horn cells and cranial nerve motor nuclei. It is a cause of "floppy baby" syndrome (the other cause is infant botulism).

(Choice C) Myotonic congenital myopathy is an autosomal dominant disorder characterized by muscle weakness and atrophy (most predominant in the distal muscles of the upper and lower extremities), myotonia, testicular atrophy, and baldness.

treatment is levothyroxine (initial dose of 10 mcg/kg, then titrated accordingly).

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(Choice C) Myotonic congenital myopathy is an autosomal dominant disorder characterized by muscle weakness and atrophy (most predominant in the distal muscles of the upper and lower extremities), myotonia, testicular atrophy, and baldness.

(Choice E) Myasthenia gravis presents with easy fatigability and weakness that improves with rest. The pediatric form occurs in late childhood or adolescence.

Educational objective:
Infants with congenital hypothyroidism initially appear normal at birth, but gradually develop apathy, weakness, hypotonia, large tongue, sluggish movement, abdominal bloating, and an umbilical hernia. For this reason, screening newborns for hypothyroidism, along with phenylketonuria and galactosemia, is standardly performed in all states.

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A 56-year-old man comes to the physician with a 7-month history of headache, loss of libido, erectile dysfunction, and visual disturbances. His past medical history is unremarkable. He is currently not taking any medications. The patient has a 15-pack-year smoking history and does not use alcohol. On visual field examination, there is a small temporal field defect seen in both eyes. Genitourinary examination shows atrophic testes. An MRI scan reveals a 1.5-cm pituitary tumor. Which of the following biochemical findings will be most consistent with the diagnosis of a prolactinoma in this patient?

	Prolactin (ng/mL) [Normal <15 ng/mL]	LH	TSH
A.	200	Low	Normal
B.	45	Low	Low
C.	35	Normal	Normal
D.	90	Low	High

Submit

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	Prolactin (ng/mL) [Normal <15 ng/mL]	LH	TSH
✔ ○ A. [56%]	200	Low	Normal
✘ ◉ B. [31%]	45	Low	Low
○ C. [2%]	35	Normal	Normal
○ D. [10%]	90	Low	High

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

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Prolactin-producing lactotroph adenomas (prolactinomas) account for approximately 50% of primary pituitary tumors, making them the most common type. Prolactinomas are usually detected early (<10-mm microadenomas) in premenopausal women due to associated endocrine symptoms (oligo/amenorrhea, infertility, galactorrhea). However, in men and post-menopausal women, prolactinomas produce only minimal or nonspecific symptoms at early stages, and many are not diagnosed until they are much larger and produce **compressive symptoms** such as headaches or visual field defects. Men may also develop symptoms of **hypogonadotropic hypogonadism** due to suppression of gonadotropin-releasing hormone secretion from the hypothalamus by prolactin

tumors, making them the most common type. Prolactinomas are usually detected early (<10-mm microadenomas) in premenopausal women due to associated endocrine symptoms (oligo/amenorrhea, infertility, galactorrhea). However, in men and post-menopausal women, prolactinomas produce only minimal or nonspecific symptoms at early stages, and many are not diagnosed until they are much larger and produce **compressive symptoms** such as headaches or visual field defects. Men may also develop symptoms of **hypogonadotropic hypogonadism** due to **suppression of gonadotropin-releasing hormone secretion** from the hypothalamus by prolactin. Gynecomastia is present in about a third of men with prolactinomas; galactorrhea may occur but is uncommon.

The magnitude of prolactin elevation correlates with the size of the prolactinoma, and a level **>200 ng/mL** is virtually diagnostic of prolactinoma. As seen in this patient, hyperprolactinemia at this level will usually cause hypogonadism with low testosterone levels and low or inappropriately-normal LH. TSH may also be normal or low; this depends on the compressive effect on thyrotroph cells.

(Choice B) Very large pituitary masses will cause low TSH and LH levels due to compression of thyrotrophs and gonadotrophs, along with mildly elevated prolactin due to compression of the dopaminergic pathways in the pituitary stalk. This is the characteristic pattern of "nonfunctioning" pituitary macroadenomas (which usually secrete the biologically inert gonadotropin alpha subunit). However, a mildly elevated prolactin level of 45 ng/mL is less consistent with 1.5-cm prolactinoma, which would likely be associated with a prolactin level >200 ng/mL (prolactin levels can be as high as 1000 ng/mL in ~2-cm prolactinomas).

(Choice C) Mild elevations of prolactin in the context of otherwise normal pituitary function are typically due to medications (eg, certain antipsychotic drugs). Other causes include hypothyroidism and renal failure.

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(Choice C) Mild elevations of prolactin in the context of otherwise normal pituitary function are typically due to medications (eg, certain antipsychotic drugs). Other causes include hypothyroidism and renal failure.

(Choice D) Primary hypothyroidism may cause mild-to-moderate hyperprolactinemia, which is thought to be due to thyrotropin releasing hormone-induced stimulation of lactotrophs. LH in such patients may be normal or mildly low.

Educational objective:

Prolactin-producing lactotroph adenoma (prolactinoma) is the most common primary pituitary tumor. Serum prolactin levels correlate with the size of prolactinoma, and levels >200 ng/mL are essentially diagnostic.

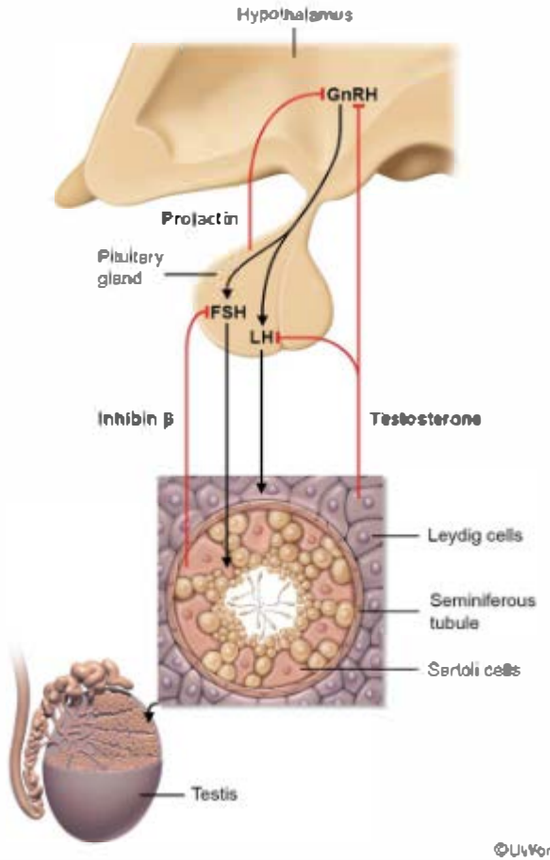
References

Treatment

- Trans-sphenoidal surgery

Exhibit Display

Prolactin and gonadotropin production



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(prolactin levels can be as high as 1000 ng/mL in >2-cm prolactinomas).

A 32-year-old woman comes to the office due to lightheadedness. She had an uncomplicated vaginal delivery 6 weeks ago with minimal blood loss. The patient had mild fatigue and backache during the last trimester of pregnancy, but the fatigue has worsened since the delivery. She has also been having intermittent generalized abdominal pain, loss of appetite, and weakness. She says her skin is tanning even though she has spent only minimal time outdoors. Yesterday, the patient felt like she was "going to pass out" and experienced several episodes of lightheadedness accompanied by nausea and abdominal discomfort. She has no chest pain, shortness of breath, or bleeding. The patient has a history of hypothyroidism and takes levothyroxine. Her temperature is 36.1 C (97 F), blood pressure is 110/60 mm Hg supine and 85/45 mm Hg standing, and pulse is 104/min. Skin shows generalized hyperpigmentation. Lungs are clear, and her heart rate is tachycardic but regular with no gallops or murmurs. Abdominal examination shows mild, diffuse tenderness without guarding and normal bowel sounds. Laboratory results are as follows:

Hematocrit	32%
Leukocytes	9,000/mm^3
Sodium	131 mEq/L
Potassium	5.6 mEq/L
Bicarbonate	18 mEq/L
Creatinine	1.4 mg/dL

Sodium	131 mEq/L
Potassium	5.6 mEq/L
Bicarbonate	18 mEq/L
Creatinine	1.4 mg/dL
TSH	4.6 µU/mL

Which of the following is the most likely diagnosis?

- A. Autoimmune adrenalitis
- B. Inadequate dose of levothyroxine
- C. Lymphocytic hypophysitis
- D. Pituitary infarction
- E. Postpartum cardiomyopathy
- F. Postpartum endometritis

Submit

Sodium	131 mEq/L
Potassium	5.6 mEq/L
Bicarbonate	18 mEq/L
Creatinine	1.4 mg/dL
TSH	4.6 µU/mL

Which of the following is the most likely diagnosis?

- ✔ A. Autoimmune adrenalitis [70%]
- B. Inadequate dose of levothyroxine [2%]
- C. Lymphocytic hypophysitis [2%]
- D. Pituitary infarction [23%]
- E. Postpartum cardiomyopathy [0%]
- F. Postpartum endometritis [0%]

Correct

70%

8 Seconds

05/19/2018

Primary versus central adrenal insufficiency		
	Primary	**Central (secondary/pituitary; tertiary/hypothalamic)**
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

This patient has several symptoms consistent with **adrenal insufficiency (AI)**, including weakness, abdominal pain, loss of appetite, and mild hyponatremia. She also has postural hypotension and hyperkalemia, which further raise suspicion for AI. Common in the postpartum period, AI can be due to adrenal (primary AI) or pituitary (secondary AI) disease.

Patients with **primary AI** have loss of glucocorticoid, mineralocorticoid, and adrenal androgen secretion.

Patients with **primary AI** have loss of glucocorticoid, mineralocorticoid, and adrenal androgen secretion. Symptoms are often severe, and patients may develop significant hypotension, hyperkalemia, and hyperchloremic acidosis. Primary AI is also frequently associated with hyperpigmentation due to increased pituitary secretion of ACTH and melanocyte-stimulating hormone. Autoimmune adrenalitis is the most common etiology for primary adrenal insufficiency and involves both humoral and cell-mediated immune destruction of the adrenal cortex. Up to half of the patients with autoimmune adrenalitis have other autoimmune disorders, which may also flare up in the postpartum period.

In contrast to primary AI, patients with **secondary AI** have only glucocorticoid and adrenal androgen deficiency with preservation of mineralocorticoid production (regulated primarily by the renin-angiotensin system, not the pituitary). Therefore, hyperkalemia, significant hypotension, and hyperchloremic acidosis are not seen. Lymphocytic hypophysitis (lymphocytic infiltration of the pituitary gland) and Sheehan syndrome (pituitary infarction due to hemorrhage/hypotension during labor) are common causes of postpartum secondary AI. This patient has hyperpigmentation and features of mineralocorticoid deficiency suggesting primary rather than secondary AI **(Choices C and D)**.

(Choice B) Undertreated hypothyroidism can cause hypotension and fatigue, but this patient's electrolyte abnormalities and hyperpigmentation are more consistent with primary AI.

(Choice E) Cardiomyopathy in the postpartum/peripartum period presents with systolic heart failure (ie, shortness of breath, edema).

(Choice F) Postpartum endometritis occurs during the first 10 days after delivery, most commonly in patients with

Lymphocytic hypophysitis (lymphocytic infiltration of the pituitary gland) and Sheehan syndrome (pituitary infarction due to hemorrhage/hypotension during labor) are common causes of postpartum secondary AI. This patient has hyperpigmentation and features of mineralocorticoid deficiency suggesting primary rather than secondary AI **(Choices C and D)**.

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(Choice E) Cardiomyopathy in the postpartum/peripartum period presents with systolic heart failure (ie, shortness of breath, edema).

(Choice F) Postpartum endometritis occurs during the first 10 days after delivery, most commonly in patients with prolonged rupture of membranes or cesarian delivery. Typical features include fever, lower abdominal pain, and foul-smelling vaginal discharge.

Educational objective:
Postpartum adrenal insufficiency (AI) may be due to adrenal (primary AI) or pituitary (secondary AI) disease. Hyperpigmentation and signs of mineralocorticoid deficiency suggest primary rather than secondary AI.

References

- Adrenal insufficiency.

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A 50-year-old man comes to the physician complaining of 2 months of muscle cramps. He also complains of weakness and fatigue. He has a 20-pack-year smoking history but does not drink alcohol. The patient's past medical and family histories are noncontributory. His temperature is 36.7 C (98 F), blood pressure is 150/96 mm Hg, and pulse is 78/min. His body mass index is 28 kg/m^2. The rest of the examination is within normal limits. Laboratory results are as follows:

Plasma sodium	147 mEq/L
Potassium	2.6 mEq/L
Serum creatinine	0.8 mg/dL

Which of the following is the most appropriate next step in management of this patient?

A. Chest computed tomography scan
B. Dexamethasone suppression testing
C. Imaging of adrenals by computed tomography scan
D. Measurement of 24-hour urinary potassium excretion
E. Plasma free metanephrines
F. Plasma renin activity and aldosterone concentration

Hg, and pulse is 78/min. His body mass index is 28 kg/m². The rest of the examination is within normal limits. Laboratory results are as follows:

Plasma sodium	147 mEq/L
Potassium	2.6 mEq/L
Serum creatinine	0.8 mg/dL

Which of the following is the most appropriate next step in management of this patient?

- A. Chest computed tomography scan [9%]
- B. Dexamethasone suppression testing [6%]
- ✗ C. Imaging of adrenals by computed tomography scan [3%]
- D. Measurement of 24-hour urinary potassium excretion [2%]
- E. Plasma free metanephrines [0%]
- ✓ F. Plasma renin activity and aldosterone concentration [77%]

Incorrect
Correct answer

77%
Answered correctly

9 Seconds
Time Spent

10/29/2018
Last Updated

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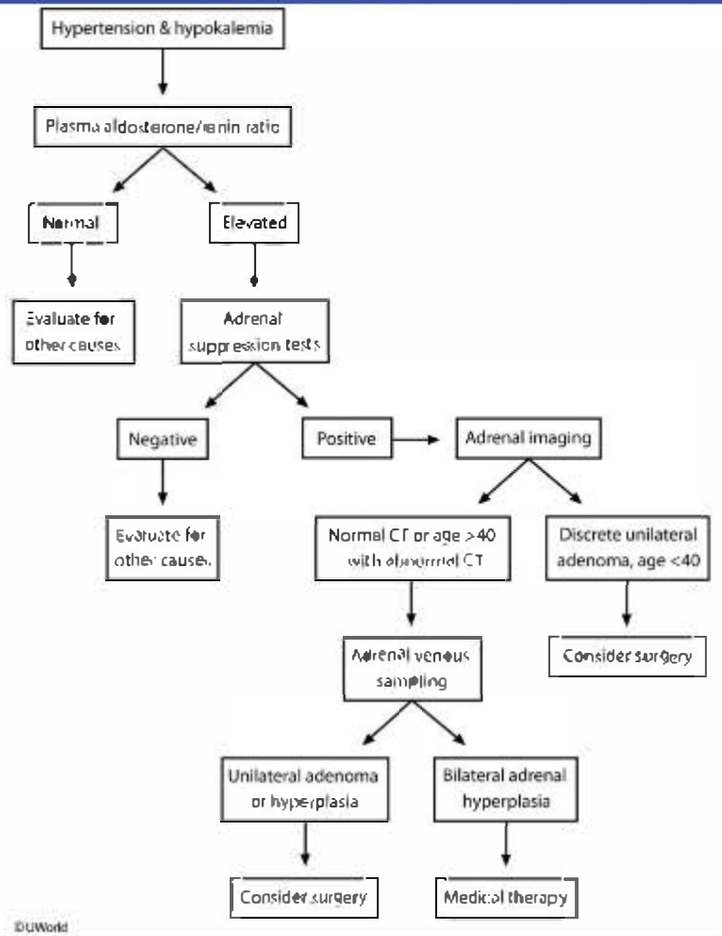

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Primary hyperaldosteronism should be suspected in any hypertensive patient presenting with hypokalemia. Patients with mild primary hyperaldosteronism may not have spontaneous hypokalemia, but they are prone to develop **diuretic-induced hypokalemia**. Severe hypokalemia can cause muscle cramps/weakness. Other findings include **metabolic alkalosis** and **mild hypernatremia** (143-147 mEq/L). Patients usually **do not have peripheral edema** due to spontaneous diuresis (aldosterone escape).

The best screening test is early-morning plasma aldosterone concentration (PAC) to plasma renin activity (PRA) ratio. However, drugs that significantly alter the PAC/PRA ratio (eg, spironolactone, eplerenone, amiloride, triamterene) should be withdrawn for 4 weeks before testing. A **PAC/PRA ratio >20** with plasma aldosterone >15 ng/dL suggests primary hyperaldosteronism and requires further confirmatory adrenal suppression testing. Adrenal suppression testing usually involves salt loading and documenting inability to suppress serum aldosterone. Patients with positive adrenal suppression testing should then undergo adrenal imaging, usually by computed tomography (CT) scan **(Choice C)**.

Hyperaldosteronism is most commonly due to bilateral adrenal hyperplasia (50%-60%) or aldosterone-producing adrenal adenoma (40%-50%). If CT scan does not reveal a discrete unilateral mass, adrenal vein sampling is recommended to differentiate between hyperplasia and adenoma. Surgery is preferred for adenoma, and medical therapy is preferred for hyperplasia.

(Choice A) Chest CT scan can diagnose a lung cancer, which can sometimes be associated with syndrome of inappropriate antidiuretic hormone or Lambert-Eaton syndrome. Lambert-Eaton syndrome usually presents with progressively worsening proximal muscle weakness, fatigue, ptosis, and autonomic dysfunction (eg, dry mouth). Syndrome of inappropriate antidiuretic hormone causes hyponatremia instead of hypernatremia.

(Choice A) Chest CT scan can diagnose a lung cancer, which can sometimes be associated with syndrome of inappropriate antidiuretic hormone or Lambert-Eaton syndrome. Lambert-Eaton syndrome usually presents with progressively worsening proximal muscle weakness, fatigue, ptosis, and autonomic dysfunction (eg, dry mouth). Syndrome of inappropriate antidiuretic hormone causes hyponatremia instead of hypernatremia.

(Choice B) Dexamethasone suppression test can diagnose Cushing's syndrome. Patients typically develop findings such as central obesity, purple striae, proximal muscle wasting, glucose intolerance, and hypertension.

(Choice D) Measurement of 24-hour urinary potassium excretion was used previously to document inappropriate potassium excretion. A 24-hour urinary potassium level >30 mEq in the presence of hypokalemia suggests hyperaldosteronism. However, this test is no longer commonly used.

(Choice E) Plasma free metanephrines would be elevated in pheochromocytoma, a secondary cause of hypertension. Patients usually develop hypertension and the classic triad of episodic headache, sweating, and palpitations with tachycardia. However, pheochromocytoma does not usually cause the degree of hypokalemia seen in this patient.

Educational objective:

The ratio of plasma aldosterone concentration to plasma renin activity is the preferred initial screening test for primary hyperaldosteronism. Adrenal suppression testing can confirm the diagnosis, and positive tests require further adrenal imaging. Adrenal venous sampling is the most sensitive test for differentiating adrenal adenoma and bilateral adrenal hyperplasia in patients without discrete unilateral adrenal mass on imaging.

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A 55-year-old Caucasian male presents to the office for a routine check-up. He has no present complaints. His past medical history is significant for a long history of hypertension. He does not smoke or consume alcohol. His current medications are enalapril and hydrochlorothiazide. His blood pressure is 140/90 mm Hg and heart rate is 80/min. Physical examination reveals a moderately overweight man (BMI = 27 kg/m2) with a waist circumference of 41 inches. The laboratory studies show:

Fasting blood glucose	112 mg/dL
Total cholesterol	220 mg/dL
LDL cholesterol	140 mg/dL
Triglycerides	240 mg/dL

Which of the following is the most important pathogenic factor for this patient's condition?

A. Impaired secretion of insulin

B. Low absolute values of insulin

Fasting blood glucose	112 mg/dL
Total cholesterol	220 mg/dL
LDL cholesterol	140 mg/dL
Triglycerides	240 mg/dL

Which of the following is the most important pathogenic factor for this patient's condition?

A. Impaired secretion of insulin
B. Low absolute values of insulin
C. Insulin resistance
D. Sympathetic hyperactivity
E. Insulin-mediated vasodilatation

glucose	mg/dL
Total cholesterol	220 mg/dL
LDL cholesterol	140 mg/dL
Triglycerides	240 mg/dL

Which of the following is the most important pathogenic factor for this patient's condition?

- A. Impaired secretion of insulin [2%]
- B. Low absolute values of insulin [1%]
- ✔ C. Insulin resistance [89%]
- ✘ D. Sympathetic hyperactivity [6%]
- E. Insulin-mediated vasodilatation [0%]

Incorrect
Correct answer

89%
Answered correctly

7 Seconds
Time Spent

10/10/2018
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This vignette describes a patient with the typical clinical presentation of metabolic syndrome, which includes hypertension, impaired fasting glucose, and dyslipidemia. Patients are also characteristically overweight (as seen in this case), with predominantly central (abdominal) fat distribution that is reflected by an increased waist-to-hip ratio. Insulin resistance plays a central role in the pathogenesis of metabolic syndrome. Metabolic syndrome is diagnosed when at least 3 of the 5 following criteria are met:

1. Abdominal obesity (Men: Waist circumference >40 inches; Women: Waist circumference >35 inches)
2. Fasting glucose >100 - 110 mg/dL
3. Blood pressure > 130/80 mm Hg
4. Triglycerides >150 mg/dL
5. HDL cholesterol (Men: <40 mg/dL; Women: <50 mg/dL)

(Choices A and B) Most health care providers believe that insulin resistance is the first event in the development of type 2 diabetes mellitus (DM); however, type 2 DM does not develop without a beta cell secretory defect. Increased insulin secretion from the beta cells is required to cope with increased insulin resistance. If beta cells are able to compensate for the increased insulin resistance, subjects generally remain normoglycemic at the expense of very high insulin levels; however, if beta cells are unable to compensate fully, glucose intolerance and type 2 DM results.

(Choices D and E) Aside from problems with glucose control, insulin resistance is associated with several other systemic effects (e.g., dyslipidemia, endothelial dysfunction, procoagulable state, increased sympathetic activity, increased markers of inflammation, decreased uric acid excretion, increased sodium absorption, disordered breathing and increased testosterone production from the ovaries). Although sympathetic activity is increased in

5. HDL cholesterol (Men: <40 mg/dL; Women: <50 mg/dL)

(Choices A and B) Most health care providers believe that insulin resistance is the first event in the development of type 2 diabetes mellitus (DM); however, type 2 DM does not develop without a beta cell secretory defect. Increased insulin secretion from the beta cells is required to cope with increased insulin resistance. If beta cells are able to compensate for the increased insulin resistance, subjects generally remain normoglycemic at the expense of very high insulin levels; however, if beta cells are unable to compensate fully, glucose intolerance and type 2 DM results.

(Choices D and E) Aside from problems with glucose control, insulin resistance is associated with several other systemic effects (e.g., dyslipidemia, endothelial dysfunction, procoagulable state, increased sympathetic activity, increased markers of inflammation, decreased uric acid excretion, increased sodium absorption, disordered breathing and increased testosterone production from the ovaries). Although sympathetic activity is increased in insulin resistance it does not play a central role in pathogenesis of metabolic syndrome. The endothelial dependent vasodilatation is impaired in insulin resistance.

Educational Objective:

Insulin resistance typical for patients with central-type obesity is the key pathogenic factor in the development of type-2 diabetes mellitus and associated abnormalities (hypertension, dyslipidemia).

*Extremely high yield question for the USMLE!!!

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A 31-year-old woman comes to the office after 3 months of continuous burning upper abdominal pain that is only partially relieved by over-the-counter ranitidine or antacids. She also has experienced recent-onset constipation and excess urination. The patient reports no weight loss or decreased appetite. Her menstrual periods are regular. The patient's father has a history of "many stomach ulcers and multiple kidney stones." Her temperature is 37.1 C (98.8 F), blood pressure is 130/85 mm Hg, pulse is 78/min, and respirations are 14/min. Abdominal examination shows normal bowel sounds, tenderness in the epigastric region, and no palpable masses. Her stools are positive for occult blood. Laboratory results are as follows:

Sodium	137 mEq/L
Potassium	4.2 mEq/L
Chloride	104 mEq/L
Bicarbonate	24 mEq/L
Calcium	11.4 mg/dL
Phosphorus	1.8 mg/dL
Blood urea nitrogen	21 mg/dL
Creatinine	1.0 mg/dL

Additional evaluation is most likely to reveal which of the following?

Bicarbonate	24 mEq/L
Calcium	11.4 mg/dL
Phosphorus	1.8 mg/dL
Blood urea nitrogen	21 mg/dL
Creatinine	1.0 mg/dL

Additional evaluation is most likely to reveal which of the following?

- A. Adrenal insufficiency
- B. Glucagonoma
- C. Medullary thyroid cancer
- D. Metastatic gastric carcinoma
- E. Milk-alkali syndrome
- F. Primary hyperparathyroidism
- G. Sarcoidosis
- H. Thyroid adenoma

Phosphorus	1.8 mg/dL
Blood urea nitrogen	21 mg/dL
Creatinine	1.0 mg/dL

Additional evaluation is most likely to reveal which of the following?

- A. Adrenal insufficiency [0%]
- B. Glucagonoma [5%]
- ✗ C. Medullary thyroid cancer [4%]
- D. Metastatic gastric carcinoma [5%]
- E. Milk-alkali syndrome [12%]
- ✓ F. Primary hyperparathyroidism [69%]
- G. Sarcoidosis [1%]
- H. Thyroid adenoma [0%]

Incorrect
Correct answer

69%
Answered Correctly

10 Seconds
Time Spent

07/30/2018
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Windows Media Player

Multiple endocrine neoplasia type 1	
Manifestation	**Clinical features**
Pituitary adenomas (10%-20%)	• Secretion of prolactin, growth hormone, ACTH (or "nonfunctioning" tumors) • Mass effects (eg, headache, visual field defects)
Primary hyperparathyroidism (>90%)	• Multiple parathyroid adenomas or parathyroid hyperplasia • Hypercalcemia (eg, polyuria, kidney stones, decreased bone density)
Pancreatic/gastrointestinal neuroendocrine tumors (60%-70%)	• **Gastrinoma** - recurrent peptic ulcers • Insulinoma - hypoglycemia • VIPoma - secretory diarrhea, hypokalemia, hypochlorhydria • Glucagonoma - weight loss, necrolytic migratory erythema, hyperglycemia

This patient most likely has **type 1 multiple endocrine neoplasia syndrome (MEN1)**, an autosomal dominant condition characterized by 3 primary tumor types ("the 3 Ps"):

- **Parathyroid** adenomas/hyperplasia. Constipation, polyuria, and possibly abdominal pain in the setting of a calcium level of 11.4 mg/dL suggest **symptomatic hypercalcemia**, likely from **primary hyperparathyroidism (PHPT)**. PHPT is present in >90% of patients with MEN1, usually occurs by age 40, and results from

Windows Media Player

This patient most likely has **type 1 multiple endocrine neoplasia syndrome (MEN1)**, an autosomal dominant condition characterized by 3 primary tumor types ("the 3 Ps"):

- **Parathyroid** adenomas/hyperplasia. Constipation, polyuria, and possibly abdominal pain in the setting of a calcium level of 11.4 mg/dL suggest **symptomatic hypercalcemia**, likely from **primary hyperparathyroidism (PHPT)**. PHPT is present in >90% of patients with MEN1, usually occurs by age 40, and results from multiglandular parathyroid adenomas or parathyroid hyperplasia.
- Gastrointestinal/**pancreatic** endocrine tumors (eg, gastrinomas). Burning upper abdominal pain that is only partially responsive to ranitidine and antacids and associated with occult gastrointestinal bleeding is concerning for **Zollinger-Ellison syndrome**, characterized by severe and refractory peptic ulcer disease due to gastrin-producing tumors (**gastrinomas**).
- **Pituitary** adenomas.

The patient's father probably also had MEN1 given his history of kidney stones (likely due to hypercalcemia) and recurrent peptic ulcers.

(Choice A) Primary adrenal insufficiency presents with fatigue and weight loss. Typical clinical findings include hypotension, hyperpigmentation, and hyperkalemia.

(Choice B) Glucagonoma is a less common tumor in MEN1 and is characterized by hyperglycemia, necrolytic migratory erythema, weight loss, and anemia.

(Choice C) Medullary thyroid cancer is a component of MEN2 and typically presents as a thyroid nodule.

(Choice D) Gastric cancer can cause abdominal pain with gastrointestinal ulceration and bleeding. However, it is

(Choice B) Glucagonoma is a less common tumor in MEN1 and is characterized by hyperglycemia, necrolytic migratory erythema, weight loss, and anemia.

(Choice C) Medullary thyroid cancer is a component of MEN2 and typically presents as a thyroid nodule.

(Choice D) Gastric cancer can cause abdominal pain with gastrointestinal ulceration and bleeding. However, it is commonly associated with weight loss, early satiety, and dysphagia; would be rare at this patient's age; and is less likely to explain hypercalcemia.

(Choice E) Milk-alkali syndrome is characterized by hypercalcemia, renal insufficiency, and metabolic alkalosis. This patient has a normal serum creatinine and bicarbonate.

(Choice G) Sarcoidosis causes hypercalcemia due to increased conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. However, whereas pulmonary symptoms are common, gastrointestinal manifestations (eg, epigastric pain) are rare. Sarcoidosis also would not explain this patient's family history of recurrent kidney stones and peptic ulcers.

(Choice H) A toxic thyroid adenoma could cause hypercalcemia due to increased bone turnover. However, this patient has no other manifestations of thyrotoxicosis (eg, weight loss, tachycardia).

Educational objective:
Type 1 multiple endocrine neoplasia is characterized by primary hyperparathyroidism, pituitary tumors, and gastrointestinal/pancreatic endocrine tumors (eg, gastrinomas). Common complications include symptomatic hypercalcemia and recurrent peptic ulcer.

hypotension, hyperpigmentation, and hypercalcemia.

Exhibit Display

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

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hypercalcemia and recurrent peptic ulcer.

A 45-year-old woman comes to the office due to progressive fatigue, myalgias, and muscle weakness in both lower extremities for the past month. She has slight difficulty getting up from a chair, and has weakness and cramping in the legs after walking a short distance. The patient's other medical problems include hypertension, which is treated with lisinopril. She does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/80 mm Hg, pulse is 64/min, and respirations are 14/min. Examination shows mildly decreased strength in the proximal muscles of the lower extremities with sluggish ankle jerks bilaterally. Laboratory tests show a normal erythrocyte sedimentation rate and an elevated serum creatine kinase level. Serum sodium, glucose, potassium, and creatinine are normal. Which of the following is the most appropriate next step in management of this patient?

- A. Antinuclear antibody test
- B. Discontinuation of lisinopril
- C. Electromyogram
- D. Muscle biopsy
- E. Serum TSH and free T4 tests

Submit

A 45-year-old woman comes to the office due to progressive fatigue, myalgias, and muscle weakness in both lower extremities for the past month. She has slight difficulty getting up from a chair, and has weakness and cramping in the legs after walking a short distance. The patient's other medical problems include hypertension, which is treated with lisinopril. She does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/80 mm Hg, pulse is 64/min, and respirations are 14/min. Examination shows mildly decreased strength in the proximal muscles of the lower extremities with sluggish ankle jerks bilaterally. Laboratory tests show a normal erythrocyte sedimentation rate and an elevated serum creatine kinase level. Serum sodium, glucose, potassium, and creatinine are normal. Which of the following is the most appropriate next step in management of this patient?

- A. Antinuclear antibody test [9%]
- B. Discontinuation of lisinopril [4%]
- ✗ C. Electromyogram [13%]
- D. Muscle biopsy [27%]
- ✓ E. Serum TSH and free T4 tests [45%]

Incorrect
Correct answer
E

45%
Answered correctly

4 Seconds
TimeSpent

11/08/2018
Last Updated

Common causes of myopathy	
Connective tissue diseases	• Polymyositis/dermatomyositis • Inclusion body myositis • Vasculitis • Overlap syndrome (mixed connective tissue disease)
Endocrine/ metabolic	• Hypothyroidism, thyrotoxicosis • Cushing syndrome • Electrolytes (↓ potassium, calcium, phosphorus)
Drugs/toxins	• Corticosteroids, statins • Zidovudine, colchicine • Alcohol, cocaine, heroin
Miscellaneous	• Infections, trauma, hyperthermia

This patient has **myalgias** and proximal muscle **weakness** with an elevated serum creatine kinase (CK) level. In a relatively young, otherwise healthy woman with fatigue and delayed deep tendon reflexes, this presentation is most consistent with **hypothyroid 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

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.

Initial testing should include **TSH and free T4**. If thyroid studies are normal, additional testing, including serologic markers (eg, antinuclear antibodies, anti-Jo-1 antibodies) and muscle biopsy, may be needed to rule out other causes of myositis **(Choice A)**.

(Choice B) Myopathy with elevated CK concentration usually is not a manifestation of lisinopril toxicity. The most common drugs associated with myopathy are corticosteroids, statins, and colchicine.

(Choice C) Electromyogram in patients with hypothyroid myopathy can be normal or show nonspecific changes. It is more helpful in evaluating patients with polymyositis and can be considered if thyroid studies are normal.

(Choice D) Polymyositis is characterized by symmetric proximal muscle weakness. Sedimentation rate and CK are elevated in approximately half of patients, and the diagnosis can be confirmed with muscle biopsy. However, myalgias are typically absent or mild and deep tendon reflexes are normal.

Educational objective:
Hypothyroid myopathy is characterized by myalgias, proximal muscle weakness, and an elevated serum creatine kinase level. Patients often have additional features of hypothyroidism (eg, fatigue, delayed reflexes). Initial diagnostic testing includes TSH and free T4 levels.

A 39-year-old woman who recently underwent thyroidectomy for Grave's disease complains of anxiety, muscle cramps, and poor sleep. Her medications include daily multivitamin supplements and lansoprazole for acid reflux disease. Her temperature is 36.6 C (98 F), blood pressure is 142/85 mm Hg, and pulse is 82/min. Electrocardiogram shows normal sinus rhythm with prolongation of the corrected QT interval to 510 msec (normal <460 msec). Which of the following is the most likely diagnosis?

- A. Hyperkalemia
- B. Hypocalcemia
- C. Hyponatremia
- D. Persistent hyperthyroidism
- E. Vitamin D toxicity

Submit

A 39-year-old woman who recently underwent thyroidectomy for Grave's disease complains of anxiety, muscle cramps, and poor sleep. Her medications include daily multivitamin supplements and lansoprazole for acid reflux disease. Her temperature is 36.6 C (98 F), blood pressure is 142/85 mm Hg, and pulse is 82/min. Electrocardiogram shows normal sinus rhythm with prolongation of the corrected QT interval to 510 msec (normal <460 msec). Which of the following is the most likely diagnosis?

- ✗ A. Hyperkalemia [9%]
- ✓ B. Hypocalcemia [85%]
- C. Hyponatremia [0%]
- D. Persistent hyperthyroidism [3%]
- E. Vitamin D toxicity [1%]

Incorrect
Correct answer
B

85%
Answered correctly

6 Seconds
TimeSpent

10/13/2018
Last Updated

Explanation

Post-surgical hypoparathyroidism can occur during thyroidectomy or from the removal of 3 1/2 parathyroid glands due to parathyroid hyperplasia. Hypocalcemia is the resultant condition of the hypoparathyroidism and the most common complication of thyroidectomy. Patients with hypocalcemia can be asymptomatic at initial presentation (found incidentally) or may complain only of nonspecific symptoms (eg, fatigue, anxiety, depression). Involuntary contractions (tetany) involving the lips, face, and extremities and seizures are seen in severe hypocalcemia. Electrocardiogram may show QT-interval prolongation.

(Choice A) Hyperkalemia is not a common postoperative complication of thyroidectomy.

(Choices C and D) Persistent hypothyroidism (not hyper) can be seen post-thyroidectomy and can cause hyponatremia without thyroid hormone supplementation. Prolonged QT interval is not seen with hypothyroidism/hyponatremia.

(Choice E) Vitamin D toxicity is associated with hypercalcemia, which results in shortened QT interval.

Educational objective:
Hypoparathyroidism (parathyroid hormone deficiency) is characterized by low calcium and elevated phosphorus levels in the presence of normal renal function. Causes of hypoparathyroidism include post surgical, autoimmune parathyroid destruction, and defective calcium-sensing receptor. Hypocalcemia is the most common complication seen post thyroidectomy.

References

A 48-year-old man comes to the physician complaining of generalized bone pain 4 months after undergoing small-bowel resection for Crohn's disease. His current medications include mesalamine and infliximab. He has not used prednisone for the past 2 months. The patient is very sedentary and spends most of his time watching television. His pain is more severe at the lower spine, pelvis, and lower extremities; examination shows tenderness at these sites. Proximal muscle weakness is noted. X-rays of the lumbar spine show decreased bone density with blurring of the spine. X-rays of the femoral neck show pseudofractures bilaterally. Which of the following laboratory abnormalities is consistent with this patient's diagnosis?

	Serum calcium	Serum phosphate	Serum parathyroid hormone
A.	Increased	Low	Increased
B.	Low	Increased	Low
C.	Low	Low	Increased
D.	Normal	Normal	Normal

Submit

A 48-year-old man comes to the physician complaining of generalized bone pain 4 months after undergoing small-bowel resection for Crohn's disease. His current medications include mesalamine and infliximab. He has not used prednisone for the past 2 months. The patient is very sedentary and spends most of his time watching television. His pain is more severe at the lower spine, pelvis, and lower extremities; examination shows tenderness at these sites. Proximal muscle weakness is noted. X-rays of the lumbar spine show decreased bone density with blurring of the spine. X-rays of the femoral neck show pseudofractures bilaterally. Which of the following laboratory abnormalities is consistent with this patient's diagnosis?

	Serum calcium	Serum phosphate	Serum parathyroid hormone
✗ A. [19%]	Increased	Low	Increased
B. [5%]	Low	Increased	Low
✓ C. [67%]	Low	Low	Increased
D. [8%]	Normal	Normal	Normal

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

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This patient's presentation suggests osteomalacia. Vitamin D deficiency most commonly causes osteomalacia and

This patient's presentation suggests osteomalacia. Vitamin D deficiency most commonly causes osteomalacia and can be due to malabsorption, intestinal bypass surgery, celiac sprue, or chronic liver or kidney disease. Patients can be asymptomatic or present with bone pain, muscle weakness or cramps, and difficulty walking.

Vitamin D deficiency leads to decreased intestinal calcium and phosphorus absorption, resulting in hypocalcemia and hypophosphatemia. Hypocalcemia and low vitamin D levels lead to secondary hyperparathyroidism, which brings the serum calcium levels to normal or near-normal by increasing bone calcium resorption and renal calcium reabsorption. Also, high parathyroid hormone increases urinary phosphate excretion to worsen the hypophosphatemia. As a result, vitamin D deficiency causes more marked hypophosphatemia than hypocalcemia, especially in the early stages. X-ray findings include decreased bone density with thinning of cortex, eventual codfish vertebral bodies (concave shape), and **pseudofractures** (Looser zones).

This patient likely has severe vitamin D deficiency due to small-bowel resection and gastrointestinal malabsorption from Crohn's disease. In addition, he possibly worsened the vitamin D deficiency by spending most of his time indoors without adequate exposure to sunlight.

(Choice A) Increased serum calcium, low serum phosphate, and increased serum parathyroid hormone levels are seen in patients with primary hyperparathyroidism.

(Choice B) Low serum calcium, increased serum phosphate, and low serum parathyroid hormone levels are seen in patients with hypoparathyroidism.

(Choice D) Normal serum calcium, normal serum phosphate, and normal serum parathyroid hormone levels are seen in patients with osteoporosis and Paget's disease. In osteoporosis, bone pain (without fracture) and muscle

indoors without adequate exposure to sunlight.

(Choice A) Increased serum calcium, low serum phosphate, and increased serum parathyroid hormone levels are seen in patients with primary hyperparathyroidism.

(Choice B) Low serum calcium, increased serum phosphate, and low serum parathyroid hormone levels are seen in patients with hypoparathyroidism.

(Choice D) Normal serum calcium, normal serum phosphate, and normal serum parathyroid hormone levels are seen in patients with osteoporosis and Paget's disease. In osteoporosis, bone pain (without fracture) and muscle weakness are not present. The serum alkaline phosphatase level is markedly elevated in Paget's disease. Hypercalcemia can occur in patients with moderately severe Paget's disease following immobilization.

Educational objective:
Patients with osteomalacia due to vitamin D deficiency have low or low-normal serum calcium, low serum phosphate, increased serum parathyroid hormone, low plasma 25-OH vitamin D levels, and elevated alkaline phosphatase. Unlike in osteoporosis, most patients complain of **bone pain** and **muscle weakness**. X-ray findings include decreased bone density with thinning of cortex and **pseudofractures** (Looser zones).

References

- Osteomalacia as a result of vitamin D deficiency.

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A 45-year-old man comes to the physician for follow-up after a recent emergency department visit for abdominal pain. The pain subsided with analgesics. However, he was found to have elevated blood pressure and an incidental right adrenal mass on abdominal imaging. The patient has no prior abnormal findings. He has no symptoms except mild headache, which he attributes to stress at work. He does not use tobacco, alcohol, or illicit drugs. The patient's blood pressure today is 160/94 mm Hg. Serum potassium is 3.0 mEq/L and sodium is 146 mEq/L. Further workup shows a plasma aldosterone/plasma renin activity ratio of 45. He refuses to undergo surgery for removal of the adrenal mass. Which of the following is the best initial therapy for this patient?

- A. Chlorthalidone
- B. Clonidine
- C. Eplerenone
- D. Hydralazine
- E. Ramipril
- F. Verapamil

Submit

A 45-year-old man comes to the physician for follow-up after a recent emergency department visit for abdominal pain. The pain subsided with analgesics. However, he was found to have elevated blood pressure and an incidental right adrenal mass on abdominal imaging. The patient has no prior abnormal findings. He has no symptoms except mild headache, which he attributes to stress at work. He does not use tobacco, alcohol, or illicit drugs. The patient's blood pressure today is 160/94 mm Hg. Serum potassium is 3.0 mEq/L and sodium is 146 mEq/L. Further workup shows a plasma aldosterone/plasma renin activity ratio of 45. He refuses to undergo surgery for removal of the adrenal mass. Which of the following is the best initial therapy for this patient?

- ✗ A. Chlorthalidone [3%]
- B. Clonidine [6%]
- ✓ C. Eplerenone [75%]
- D. Hydralazine [3%]
- E. Ramipril [9%]
- F. Verapamil [1%]

Incorrect
Correct answer
C

75%
Answered correctly

4 Seconds
Time Spent

10/28/2018
Last Updated

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

This patient's presentation of hypertension, hypokalemia, and computed tomography (CT) scan showing an adrenal mass is consistent with primary hyperaldosteronism. The condition is usually due to an adrenal adenoma or bilateral adrenal hyperplasia. Diagnosis is suggested by elevated plasma aldosterone concentration with plasma aldosterone to renin ratio >20. The elevated aldosterone leads directly to decreased renin through a feedback inhibition. Adrenal suppression testing after oral saline load can confirm the diagnosis. Adrenal imaging with CT scan and adrenal venous sampling can usually distinguish between unilateral adrenal adenoma and

feedback inhibition. Adrenal suppression testing after oral saline load can confirm the diagnosis. Adrenal imaging with CT scan and adrenal venous sampling can usually distinguish between unilateral adrenal adenoma and bilateral adrenal hyperplasia. Surgery is preferred for unilateral adrenal adenoma. Medical therapy is recommended for patients with bilateral adrenal hyperplasia or with unilateral adrenal adenoma who refuse surgery or are poor surgical candidates.

Spironolactone is an aldosterone antagonist and the preferred initial medical therapy. However, spironolactone is also a progesterone and androgen receptor antagonist that can cause significant side effects in both men (eg, decreased libido, **gynecomastia**) and women (eg, breast tenderness, menstrual irregularities). **Eplerenone** is a very **selective mineralocorticoid antagonist** with a very low affinity for progesterone or androgen receptors. It has fewer endocrine side effects and is an alternate therapy.

(Choices A and E) Some patients may still have persistent hypertension despite aldosterone antagonist therapy. Additional antihypertensives such as thiazide diuretics (eg, chlorthalidone) or angiotensin-converting-enzyme inhibitors (eg, ramipril) are usually recommended for blood pressure control in these patients. However, they are not the best initial therapy.

(Choices B, D, and F) Clonidine, hydralazine, and verapamil are not initially preferred as medical therapy for primary hyperaldosteronism. They are 2nd- or 3rd-line antihypertensives that may be used in some patients with persistent hypertension despite adequate 1st-line medical therapy.

Educational objective:

Primary hyperaldosteronism is usually due to an adrenal adenoma or bilateral adrenal hyperplasia. Surgery is preferred for unilateral adrenal adenoma. Medical therapy with aldosterone antagonists (eg, spironolactone

Spironolactone is an aldosterone antagonist and the preferred initial medical therapy. However, spironolactone is also a progesterone and androgen receptor antagonist that can cause significant side effects in both men (eg, decreased libido, **gynecomastia**) and women (eg, breast tenderness, menstrual irregularities). **Eplerenone** is a very **selective mineralocorticoid antagonist** with a very low affinity for progesterone or androgen receptors. It has fewer endocrine side effects and is an alternate therapy.

(Choices A and E) Some patients may still have persistent hypertension despite aldosterone antagonist therapy. Additional antihypertensives such as thiazide diuretics (eg, chlorthalidone) or angiotensin-converting-enzyme inhibitors (eg, ramipril) are usually recommended for blood pressure control in these patients. However, they are not the best initial therapy.

(Choices B, D, and F) Clonidine, hydralazine, and verapamil are not initially preferred as medical therapy for primary hyperaldosteronism. They are 2nd- or 3rd-line antihypertensives that may be used in some patients with persistent hypertension despite adequate 1st-line medical therapy.

Educational objective:
Primary hyperaldosteronism is usually due to an adrenal adenoma or bilateral adrenal hyperplasia. Surgery is preferred for unilateral adrenal adenoma. Medical therapy with aldosterone antagonists (eg, spironolactone, eplerenone) is recommended for patients with bilateral adrenal hyperplasia or with unilateral adrenal adenoma who either refuse surgery or are poor surgical candidates.

References

A 75-year-old man is brought to the emergency department due to a 2-day history of progressive lethargy and confusion. His family reports that he has experienced fatigue and blurred vision over the last several days since being started on prednisone for newly diagnosed polymyalgia rheumatica. The patient's medical history is notable for diet-controlled type 2 diabetes mellitus, as well as hypertension and hyperlipidemia for which he takes lisinopril and atorvastatin, respectively. Temperature is 37.9 C (100.2 F), blood pressure is 90/60 mm Hg, pulse is 112/min, and respirations are 18/min. Oral mucous membranes are dry. The lungs are clear to auscultation, and the heart has a regular tachycardia with no murmur. The neck is supple. The patient is very drowsy but arousable and moves all extremities on command. Laboratory results are as follows:

Sodium	128 mEq/L
Potassium	3.5 mEq/L
Chloride	94 mEq/L
Bicarbonate	24 mEq/L
Blood urea nitrogen	36 mg/dL
Creatinine	1.9 mg/dL
Calcium	8.8 mg/dL
Glucose	830 mg/dL

Urine ketones are positive in trace amounts. Which of the following is the most likely cause of this patient's altered

Bicarbonate	24 mEq/L
Blood urea nitrogen	36 mg/dL
Creatinine	1.9 mg/dL
Calcium	8.8 mg/dL
Glucose	830 mg/dL

Urine ketones are positive in trace amounts. Which of the following is the most likely cause of this patient's altered sensorium?

- A. Corticosteroid-induced psychosis
- B. Hyperosmolality
- C. Hyponatremia
- D. Ketoacidosis
- E. Meningitis
- F. Metabolic acidosis

Submit

Bicarbonate	24 mEq/L
Blood urea nitrogen	36 mg/dL
Creatinine	1.9 mg/dL
Calcium	8.8 mg/dL
Glucose	830 mg/dL

Urine ketones are positive in trace amounts. Which of the following is the most likely cause of this patient's altered sensorium?

- A. Corticosteroid-induced psychosis [4%]
- ✔ B. Hyperosmolality [51%]
- C. Hyponatremia [27%]
- D. Ketoacidosis [11%]
- E. Meningitis [0%]
- ✘ F. Metabolic acidosis [4%]

Incorrect
Correct answer

51%
Answered correctly

11 Seconds
Time Spent

07/29/2018
Last Updated

	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state
Patient characteristics	• Type 1 diabetes usually • Younger age	• Type 2 diabetes 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 (13.9-27.8 mmol/L) • Bicarbonate <18 mEq/L (18 mmol/L) • Elevated anion gap • Positive serum ketones • Serum osmolality <320 mOsm/kg (320 mmol/kg)	• Glucose >600 mg/dL (33.3 mmol/L) • Bicarbonate >18 mEq/L (18 mmol/L) • Normal anion gap • Negative or small serum ketones • Serum osmolality >320 mOsm/kg (320 mmol/kg)

This patient with type 2 diabetes mellitus has **hyperosmolar hyperglycemic state** (HHS), likely due to exogenous glucocorticoid use in the setting of polymyalgia rheumatica. HHS is characterized by **severe hyperglycemia** and **high serum osmolality** due to relative insulin deficiency and/or elevated counterregulatory hormones (glucagon, catecholamines, cortisol, growth hormone). Common precipitating factors include:

This patient with type 2 diabetes mellitus has **hyperosmolar hyperglycemic state** (HHS), likely due to exogenous glucocorticoid use in the setting of polymyalgia rheumatica. HHS is characterized by **severe hyperglycemia** and **high serum osmolality** due to relative insulin deficiency and/or elevated counterregulatory hormones (glucagon, catecholamines, cortisol, growth hormone). Common precipitating factors include:

- Infection (most common)
- Medications (eg, glucocorticoids, thiazide diuretics, pentamidine, atypical antipsychotics)
- Interruption of insulin therapy
- Trauma or acute illness (eg, stroke, myocardial infarction)

Severe hyperglycemia causes glycosuria and osmotic diuresis, resulting in hypovolemia and dehydration. As hypovolemia worsens, the glomerular filtration rate declines, leading to reduced renal glucose excretion and worsening hyperglycemia. Elderly individuals are at increased risk due to altered perception of thirst and restricted fluid intake. **Neurologic symptoms** ranging from confusion to coma are common and are primarily due to the high serum osmolality (usually >320 mOsm/kg). In contrast to diabetic ketoacidosis, which typically develops rapidly over hours, HHS develops over a few days to weeks.

(Choice A) Corticosteroid-induced psychosis is characterized by delusions, hallucinations, disorganized thought processes, and aggression. This patient does not have these features.

(Choice C) Mental status changes in hyponatremia are due to cerebral edema caused by movement of water into brain cells from low osmolar extracellular fluid. However, this patient's moderate hyponatremia actually represents pseudohyponatremia from hyperglycemia, as his corrected serum sodium, estimated by the formula (measured

(Choice C) Mental status changes in hyponatremia are due to cerebral edema caused by movement of water into brain cells from low osmolar extracellular fluid. However, this patient's moderate hyponatremia actually represents pseudohyponatremia from hyperglycemia, as his corrected serum sodium, estimated by the formula (measured sodium in mEq/L + 2 mEq/L sodium for each 100 mg/dL that glucose is above 100 mg/dL), is normal: 128 + 2 x 7.3 = ~143 mEq/L. Pseudohyponatremia would not contribute directly to neurologic symptoms.

(Choices D and F) Mild ketosis may occur in HHS primarily due to decreased food intake (starvation ketosis). However, unlike diabetic ketoacidosis in patients with type I diabetes, more prominent ketosis does not occur in HHS because even relatively low insulin levels are able to suppress ketogenesis. This patient is unlikely to have diabetic ketoacidosis or other metabolic acidosis in light of his normal bicarbonate concentration and anion gap.

(Choice E) Although this patient has mental obtundation, other features of meningitis such as headache, high fever (often >38 C [100.4 F]), and neck rigidity are not present.

Educational objective:
Hyperosmolar hyperglycemic state in type 2 diabetes mellitus is characterized by severe hyperglycemia and hyperosmolality without significant ketosis. Altered sensorium is attributed to high serum osmolality. Common precipitating factors include infection, medications (eg, glucocorticoids), interruption of insulin therapy, and injury or acute illness.

References

- Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment.

A 2-day-old boy is evaluated in the newborn nursery for jaundice. He was born to a 24-year-old primigravid woman who is in good health. The mother consumed a well-balanced diet and took prenatal vitamins throughout the pregnancy. The infant is breastfeeding poorly, with a weak latch and suck. On examination, the patient has jaundice, scleral icterus, a large tongue, and a hoarse cry. His tone is normal but his activity is decreased. Laboratory results are as follows:

Total bilirubin	15.3 mg/dL
Direct bilirubin	0.7 mg/dL
TSH	110 µU/mL
Thyroxine (T_4), serum	0.6 µg/dL

Which of the following is the most likely cause of this infant's condition?

A. Defective synthesis of thyroxine

B. Iodine deficiency (endemic goiter)

C. Panhypopituitarism

Laboratory results are as follows:

Total bilirubin	15.3 mg/dL
Direct bilirubin	0.7 mg/dL
TSH	110 μU/mL
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Which of the following is the most likely cause of this infant's condition?

A. Defective synthesis of thyroxine
B. Iodine deficiency (endemic goiter)
C. Panhypopituitarism
D. Thyroid dysgenesis
E. Transplacental TSH-receptor antibody

Laboratory results are as follows:

Total bilirubin	15.3 mg/dL
Direct bilirubin	0.7 mg/dL
TSH	110 μU/mL
Thyroxine (T_4), serum	0.6 μg/dL

Which of the following is the most likely cause of this infant's condition?

- A. Defective synthesis of thyroxine [23%]
- ✗ B. Iodine deficiency (endemic goiter) [5%]
- C. Panhypopituitarism [1%]
- ✓ D. Thyroid dysgenesis [59%]
- E. Transplacental TSH-receptor antibody [10%]

Congenital hypothyroidism	

Clinical manifestations	• Initially normal at birth
	• Symptoms develop after maternal T_4 wanes:
	  ◦ Lethargy
	  ◦ Enlarged fontanelle
	  ◦ Protruding tongue
	  ◦ Umbilical hernia
	  ◦ Poor feeding
	  ◦ Constipation
	  ◦ Dry skin
	  ◦ Jaundice

Diagnosis	• ↑ TSH & ↓ free T_4 levels • Newborn screening
Treatment	• Levothyroxine

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Newborn screening programs universally test for congenital hypothyroidism, which is characterized by **elevated TSH** levels and **decreased T_4** levels. This infant's jaundice, decreased activity, poor feeding, and hoarse cry are typical symptoms of congenital hypothyroidism. However, most infants with hypothyroidism are **asymptomatic** and identified through **newborn screening**. The most common cause of congenital hypothyroidism worldwide is **thyroid dysgenesis** (eg, aplasia, hypoplasia, ectopic gland). Prompt recognition and thyroid hormone replacement (eg, **levothyroxine**) is necessary to prevent permanent **neurodevelopmental injury**.

(Choice A) A variety of defects in the synthesis of thyroid hormone can lead to congenital hypothyroidism, but these conditions are rare relative to thyroid dysgenesis. All known conditions of defective synthesis are inherited in an autosomal recessive pattern.

(Choice B) Maternal iodine deficiency can cause neonatal hypothyroidism; introduction of iodine into the infant diet can reverse this condition. However, iodine deficiency or endemic goiter is uncommon in the developed world, and this mother's nutritional status was good throughout the pregnancy.

(Choice C) Deficiency of TSH due to pituitary failure (panhypopituitarism) is a serious condition, as it is usually associated with ACTH deficiency and impending adrenal shock. However, this infant has elevated levels of TSH, demonstrating that the pituitary is functioning.

(Choice E) Maternal Graves' disease can lead to transplacental passage of TSH-receptor antibodies. Affected infants have signs of hyperthyroidism (thyrotoxicosis) including jitteriness, tachycardia, weight loss, and poor feeding.

Educational objective:

Congenital hypothyroidism is associated with neurodevelopmental injury if not recognized and treated early. Decreased activity, hoarse cry, and jaundice are commonly associated with congenital hypothyroidism, but the majority of infants with congenital hypothyroidism are asymptomatic. Thyroid dysgenesis is the most common cause of congenital hypothyroidism worldwide.

References

A 29-year-old white female presents to the emergency department with nausea, vomiting, severe generalized abdominal pain, and hypotension. She is subsequently admitted to the intensive care unit. Her past medical history is significant for hypothyroidism secondary to Hashimoto's thyroiditis, for which she has been taking levothyroxine. She denies smoking cigarettes, drinking alcohol, and using any intravenous drugs. Her mother also has hypothyroidism. Her blood pressure is 70/50 mm Hg, heart rate is 110/min, temperature is 98.4° F (37.0° C) and respiratory rate is 24/min. Physical examination reveals dry and pigmented mucous membranes. The skin creases also show increased pigmentation. Lab studies show:

Serum chemistry

Serum Na	130 mEq/L
Serum K	6.1 mEq/L
Chloride	96 mEq/L
Bicarbonate	18 mEq/L
BUN	33 mg/dL
Serum creatinine	1.3 mg/dL
Blood glucose	56 mg/dL

CBC

CBC

Hemoglobin	10.8 g/L
Platelets	300,000/mm3
Leukocyte count	6,500/mm3
Neutrophils	70%
Eosinophils	10%
Lymphocytes	20%

The random serum cortisol level is 3.2 mcg/dL (normal = 5 to 25 mcg/dL), and ACTH level is 142 pg/mL (normal = 9 to 52 pg/mL). What is the most likely involved pathophysiologic mechanism of this patient's disorder?

- A. Autoimmune
- B. Infective
- C. Infiltrative
- D. Hemorrhagic
- E. Congenital

Platelets	300,000/mm3
Leukocyte count	6,500/mm3
Neutrophils	70%
Eosinophils	10%
Lymphocytes	20%

The random serum cortisol level is 3.2 mcg/dL (normal = 5 to 25 mcg/dL), and ACTH level is 142 pg/mL (normal = 9 to 52 pg/mL). What is the most likely involved pathophysiologic mechanism of this patient's disorder?

- ✔ A. Autoimmune [86%]
- B. Infective [2%]
- C. Infiltrative [3%]
- D. Hemorrhagic [4%]
- E. Congenital [3%]

Correct

86% Answered correctly

13 Seconds TimeSpent

08/09/2018 Last Updated

The patient in this vignette has features consistent with primary adrenal insufficiency (e.g., hypotension, pigmentation, hyponatremia, hyperkalemia, eosinophilia, markedly elevated ACTH levels, and low serum cortisol levels despite hypotension and stress). The most common cause of primary adrenal insufficiency in developed countries is autoimmune adrenalitis (responsible for more than 80% of patients with primary adrenal cortical insufficiency). The presence of autoantibodies against one or more adrenal steroidogenic enzymes has been postulated to be a cause of autoimmune adrenal destruction. In addition, approximately 50% of patients with autoimmune primary adrenal insufficiency (Addison's disease) have autoimmune diseases involving other endocrine glands, such as the thyroid, parathyroid, and ovaries. Other non-endocrine autoimmune conditions, such as pernicious anemia and vitiligo, are also common.

(Choice B) A number of infections can cause primary adrenal insufficiency. These infections include cytomegalovirus infection, fungal infection, and tuberculosis.

(Choice C) Malignant infiltration of the adrenal glands can occur, and is actually fairly common in certain cancers (e.g., small cell lung cancer); however, patients typically do not have primary adrenal insufficiency, unless more than 90% of the adrenal glands has been destroyed.

(Choice D) Patients on Coumadin (warfarin) can have adrenal hemorrhage with acute stress such as sepsis. This can occur even when the INR is in the therapeutic range. Stress increases the ACTH levels, which in turn increases the adrenal blood flow, thus predisposing such patients to adrenal hemorrhage. Hemorrhagic necrosis of the adrenal glands may also be seen in patients with some systemic infections (e.g., children with meningococcemia or *Pseudomonas* sepsis).

(e.g., small cell lung cancer); however, patients typically do not have primary adrenal insufficiency, unless more than 90% of the adrenal glands has been destroyed.

(Choice D) Patients on Coumadin (warfarin) can have adrenal hemorrhage with acute stress such as sepsis. This can occur even when the INR is in the therapeutic range. Stress increases the ACTH levels, which in turn increases the adrenal blood flow, thus predisposing such patients to adrenal hemorrhage. Hemorrhagic necrosis of the adrenal glands may also be seen in patients with some systemic infections (e.g., children with meningococcemia or *Pseudomonas* sepsis).

(Choice E) Adrenoleukodystrophy is the common cause of congenital problems which lead to adrenal insufficiency. It is typically seen in young males, and its pathophysiology involves the accumulation of very long chain fatty acids within the adrenal glands. Females can serve as carriers; they do not show any clinical manifestations of adrenoleukodystrophy. Adrenal insufficiency soon after birth is also seen in congenital adrenal hyperplasia due to classic 21-hydroxylase deficiency. In this case, the patient is unlikely to have a congenital cause of adrenal insufficiency because she became symptomatic in her late 20s. Autoimmune adrenalitis remains as the most likely cause of her adrenal insufficiency.

Educational Objective:

In developed countries, more than 80% of patients have primary adrenal insufficiency due to autoimmune adrenalitis. Patients with autoimmune adrenalitis have autoimmune involvement of other endocrine glands, such as the thyroid, parathyroid, and ovaries.

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A 75-year-old man with known type 2 diabetes mellitus is brought to the emergency department with weakness and blurred vision. Over the last several days, he has had a hacking cough, a sore throat, and poor appetite. His temperature is 38.0 C (100.5 F), blood pressure is 100/60 mm Hg, pulse is 112/min and regular, and respirations are 18/min. Mucous membranes are dry. Lungs are clear to auscultation. There is no heart murmur. The abdomen is soft, nontender, and nondistended. No skin rashes are present. There is mild generalized weakness on neurologic examination. Laboratory results are as follows:

Serum chemistry

Sodium	134 mEq/L
Potassium	5.9 mEq/L
Chloride	101 mEq/L
Bicarbonate	22 mEq/L
Blood urea nitrogen	52 mg/dL
Creatinine	1.5 mg/dL
Calcium	9.1 mg/dL

Glucose	1070 mg/dL
Liver function studies	
Aspartate aminotransferase (SGOT)	17 U/L
Alanine aminotransferase (SGPT)	15 U/L

Which of the following is most likely present in this patient?

A. Decreased serum ionized calcium concentration
B. Renal phosphate retention
C. Renal sodium loss that exceeds water loss
D. Suppression of antidiuretic hormone release
E. Total body potassium depletion

Submit

Glucose	1070 mg/dL
Liver function studies	
Aspartate aminotransferase (SGOT)	17 U/L
Alanine aminotransferase (SGPT)	15 U/L

Which of the following is most likely present in this patient?

- A. Decreased serum ionized calcium concentration [3%]
- ✗ B. Renal phosphate retention [6%]
- C. Renal sodium loss that exceeds water loss [10%]
- D. Suppression of antidiuretic hormone release [7%]
- ✓ E. Total body potassium depletion [71%]

Incorrect

71%

9 Seconds

06/30/2018

	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state
Patient characteristics	• Type 1 diabetes usually • Younger age	• Type 2 diabetes 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 (13.9-27.8 mmol/L) • Bicarbonate <18 mEq/L (18 mmol/L) • Elevated anion gap • Positive serum ketones • Serum osmolality <320 mOsm/kg (320 mmol/kg)	• Glucose >600 mg/dL (33.3 mmol/L) • Bicarbonate >18 mEq/L (18 mmol/L) • Normal anion gap • Negative or small serum ketones • Serum osmolality >320 mOsm/kg (320 mmol/kg)

This patient's clinical presentation is consistent with a hyperosmolar hyperglycemic state (HHS), most likely precipitated by his recent upper respiratory tract infection. Diabetic ketoacidosis (DKA) and HHS are the 2 most serious acute complications of diabetes. DKA is characterized by the triad of hyperglycemia, ketonemia, and anion gap metabolic acidosis. HHS is characterized by severe hyperglycemia (frequently >1000 mg/dL) and increased

precipitated by his recent upper respiratory tract infection. Diabetic ketoacidosis (DKA) and HHS are the 2 most serious acute complications of diabetes. DKA is characterized by the triad of hyperglycemia, ketonemia, and anion gap metabolic acidosis. HHS is characterized by severe hyperglycemia (frequently >1000 mg/dL) and increased serum osmolality (>320 mOsm/kg). There is little or no ketonemia or acidosis present, and most patients have pH >7.3 and serum bicarbonate >20 mEq/L. Patients with HHS also frequently develop neurologic symptoms (focal signs, lethargy, blurry vision, and obtundation) due to severe hyperglycemia and elevated serum osmolality.

Most patients with HHS or DKA have normal or elevated serum potassium levels at initial evaluation. This is due to the combined effects of insulin deficiency and hyperosmolality, which promote the movement of potassium out of cells into the extracellular 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.

(Choice A) An increase in extracellular pH (alkalemia) promotes the binding of calcium to albumin and lowers serum ionized calcium concentration. Patients with HHS have normal pH or slight acidemia, and serum ionized calcium concentration should remain unchanged.

(Choice B) Patients with severe hyperglycemia (due to HHS or DKA) have total phosphate depletion due to phosphaturia caused by osmotic diuresis. Renal phosphate retention is not seen in these patients. This patient has severe prerenal azotemia due to dehydration. If not corrected, this can lead to acute kidney injury and later relative renal phosphate retention (once the glomerular filtration rate falls below 20–25 mL/min).

(Choice C) Hyperglycemia and glucosuria-induced osmotic diuresis cause free water loss that exceeds sodium

(Choice B) Patients with severe hyperglycemia (due to HHS or DKA) have total phosphate depletion due to phosphaturia caused by osmotic diuresis. Renal phosphate retention is not seen in these patients. This patient has severe prerenal azotemia due to dehydration. If not corrected, this can lead to acute kidney injury and later relative renal phosphate retention (once the glomerular filtration rate falls below 20–25 mL/min).

(Choice C) Hyperglycemia and glucosuria-induced osmotic diuresis cause free water loss that exceeds sodium loss.

(Choice D) Suppression of antidiuretic hormone (ADH) secretion is seen in patients with hyponatremia due to excess free water intake. The hyponatremia in HHS is due to the osmotic shift of water from the intracellular to extracellular space, in addition to renal sodium losses from osmotic diuresis. In HHS, secretion of ADH by the posterior pituitary is stimulated by the increased plasma osmolality and hypovolemia/hypotension, though patients with chronic hyperglycemia will have a lesser ADH release and antidiuretic response.

Educational objective:
Despite normal or elevated serum potassium levels, patients with hyperosmolar hyperglycemic state (HHS) or diabetic ketoacidosis have a total body potassium deficit due to excessive urinary loss caused by glucosuria-induced osmotic diuresis. Aggressive insulin therapy for HHS can lower serum potassium levels further and cause severe hypokalemia.

References

- Hyperosmolar hyperglycemic state.

A 56-year-old woman comes to the office due to eye irritation, painful eye movements, and diplopia. Over the last few weeks, she has also experienced weight loss and fatigue. The patient smokes a pack of cigarettes a day and has a 25-pack-year history. Other medical problems include chronic obstructive pulmonary disease treated with an inhaled corticosteroid and bronchodilators. She also suffered a head injury in a motor vehicle accident 6 months ago. Blood pressure is 146/70 mm Hg, pulse is 110/min, and respirations are 18/min. On physical examination, the patient is unable to maintain eye convergence and experiences diplopia on upward gaze. Her eyes are shown in the image below.

Which of the following is the most likely cause of this patient's examination findings?

Which of the following is the most likely cause of this patient's examination findings?

- A. Brain stem injury
- B. Increased intracranial pressure
- C. Increased intraocular pressure
- D. Neuromuscular junction disorder
- E. Orbital tissue expansion
- F. Paraneoplastic syndrome

Submit

Which of the following is the most likely cause of this patient's examination findings?

- A. Brain stem injury [4%]
- ✗ B. Increased intracranial pressure [6%]
- C. Increased intraocular pressure [5%]
- D. Neuromuscular junction disorder [6%]
- ✓ E. Orbital tissue expansion [61%]
- F. Paraneoplastic syndrome [16%]

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

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This patient has clinical features of hyperthyroidism (ie, weight loss, tachycardia) with proptosis and impaired extraocular motion (decreased convergence, diplopia) consistent with **Graves ophthalmopathy**. Other common symptoms include irritation (eg, gritty or sandy sensation), redness, photophobia, pain, and tearing. Ophthalmopathy in Graves disease is typically diagnosed at the same time as hyperthyroidism but may occur

extraocular motion (decreased convergence, diplopia) consistent with **Graves ophthalmopathy**. Other common symptoms include irritation (eg, gritty or sandy sensation), redness, photophobia, pain, and tearing. Ophthalmopathy in Graves disease is typically diagnosed at the same time as hyperthyroidism but may occur before or after the onset of hyperthyroidism. Risk factors include female sex, advancing age, and smoking.

In Graves disease, **thyrotropin (TSH) receptor autoantibodies** (TRAB) stimulate thyroid hormone production, resulting in hyperthyroidism. Thyroid hormone increases sensitivity to catecholamines, and thyrotoxicosis of any etiology may cause lid lag and retraction due to sympathetic activation and contraction of the superior tarsal muscle. However, true **exophthalmos** with impaired extraocular motion is seen only in Graves disease and is due to T cell activation and stimulation of orbital fibroblasts and adipocytes by TRAB, resulting in **orbital tissue expansion** and lymphocytic infiltration.

(Choice A) Brain stem dysfunction can cause diplopia but not proptosis. Furthermore, because many neural tracts are tightly packed in the brain stem, other neurologic findings (eg, weakness, sensory deficits, altered sensorium) are usually present.

(Choice B) Increased intracranial pressure (eg, pseudotumor cerebri) can cause papilledema but would not cause proptosis.

(Choice C) Graves ophthalmopathy can cause increased intraocular pressure due to orbital tissue expansion and compression of the globe. However, increased intraocular pressure alone (eg, glaucoma) does not cause proptosis.

(Choices D and F) Myasthenia gravis (MG) is a disorder of the neuromuscular junction caused by autoantibodies

(Choice A) Brain stem dysfunction can cause diplopia but not proptosis. Furthermore, because many neural tracts are tightly packed in the brain stem, other neurologic findings (eg, weakness, sensory deficits, altered sensorium) are usually present.

(Choice B) Increased intracranial pressure (eg, pseudotumor cerebri) can cause papilledema but would not cause proptosis.

(Choice C) Graves ophthalmopathy can cause increased intraocular pressure due to orbital tissue expansion and compression of the globe. However, increased intraocular pressure alone (eg, glaucoma) does not cause proptosis.

(Choices D and F) Myasthenia gravis (MG) is a disorder of the neuromuscular junction caused by autoantibodies against acetylcholine receptors on the motor end plate. Ocular involvement may cause fluctuating diplopia and ptosis. Lambert-Eaton myasthenic syndrome (LEMS) is a paraneoplastic syndrome that may also cause diplopia. However, ocular involvement by LEMS is less common than involvement of the proximal limb muscles, and neither MG nor LEMS would cause ocular irritation, painful movement, or proptosis.

Educational objective:
Graves ophthalmopathy is characterized by ocular irritation, impaired extraocular motion, and proptosis. It is caused by T cell activation and stimulation of orbital fibroblasts by thyrotropin (TSH) receptor autoantibodies, leading to expansion of orbital tissues.

References

A 56-year-old woman comes to the office for a follow-up visit. She has chronic kidney disease due to systemic lupus erythematosus (SLE) and nonsteroidal anti-inflammatory drug use. Medical history is notable for recurrent kidney stones, and the patient experienced natural menopause at age 49. Her only current medication is hydroxychloroquine. The patient quit smoking 10 years ago when she was diagnosed with SLE. Family history is noncontributory. Laboratory results are as follows:

Calcium	10.8 mg/dL
Albumin	3.9 g/dL
Creatinine	1.6 mg/dL
Phosphorus	3.0 mg/dL
Parathyroid hormone	800 pg/mL

DXA bone densitometry scan shows a T score of -2.5 at the lumbar spine, which is consistent with osteoporosis. Which of the following is the most likely cause of this patient's hypercalcemia?

A. Chronic kidney disease
B. Hypercalcemia of malignancy
C. Milk-alkali syndrome
D. Osteoporosis

Calcium	10.8 mg/dL
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Which of the following is the most likely cause of this patient's hypercalcemia?

- A. Chronic kidney disease
- B. Hypercalcemia of malignancy
- C. Milk-alkali syndrome
- D. Osteoporosis
- E. Primary hyperparathyroidism
- F. Sarcoidosis
- G. Vitamin D toxicity

Creatinine	1.6 mg/dL
Phosphorus	3.0 mg/dL
Parathyroid hormone	800 pg/mL

DXA bone densitometry scan shows a T score of -2.5 at the lumbar spine, which is consistent with osteoporosis.

Which of the following is the most likely cause of this patient's hypercalcemia?

- A. Chronic kidney disease [34%]
- B. Hypercalcemia of malignancy [1%]
- C. Milk-alkali syndrome [0%]
- D. Osteoporosis [3%]
- ✔ E. Primary hyperparathyroidism [59%]
- F. Sarcoidosis [0%]
- ✘ G. Vitamin D toxicity [0%]

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Correct answer

59%
Answered correctly

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06/08/2018
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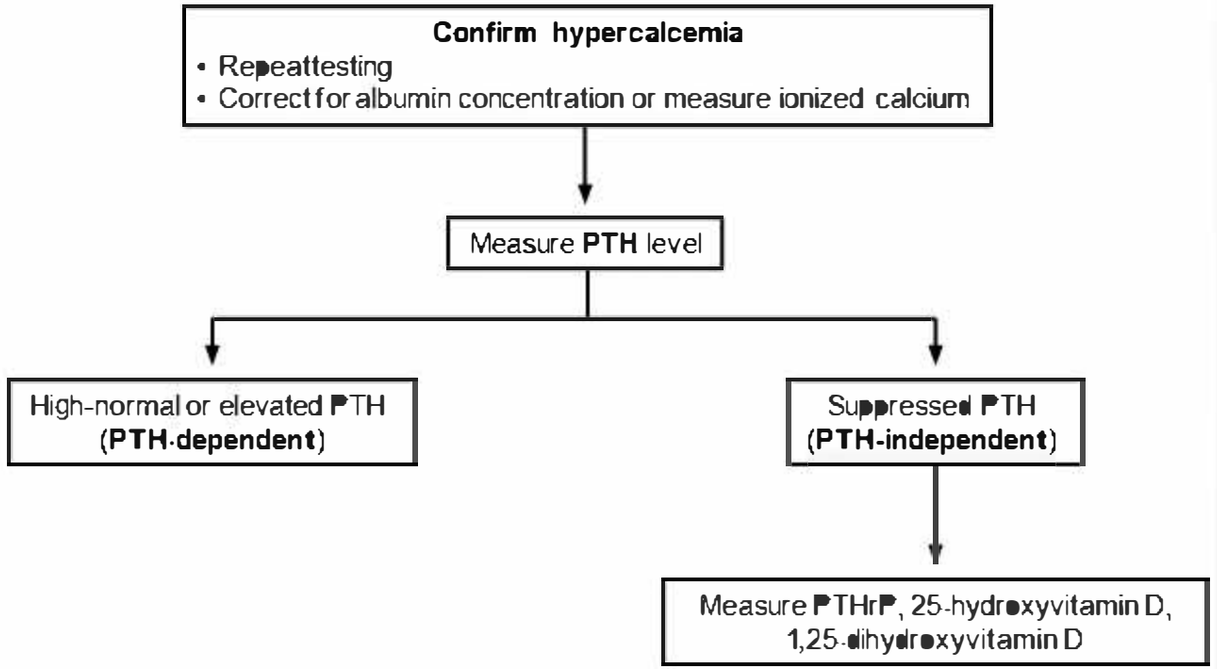
Diagnosis of hypercalcemia



Causes
- **Primary** (or tertiary) **hyperparathyroidism**
- Familial hypocalciuric hypercalcemia
- Lithium

Causes
- **Malignancy**
- Vitamin D toxicity
- Granulomatous diseases
- Drug-induced (eg, thiazides)
- Milk-alkali syndrome
- Thyrotoxicosis
- Vitamin A toxicity
- Immobilization

Causes of **hypercalcemia** can be categorized on the basis of parathyroid hormone (PTH) levels as PTH-dependent or PTH-independent:

- **PTH-independent** hypercalcemia (suppressed PTH) is usually due to malignancy, vitamin D toxicity, or extrarenal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in granulomatous diseases (eg, sarcoidosis) **(Choices F and G)**.
- **PTH-dependent** hypercalcemia (elevated or inappropriately normal PTH) is usually due to **primary hyperparathyroidism** (PHPT).

This patient has hypercalcemia with an elevated PTH level, suggesting PHPT. Normally, elevated plasma calcium **suppresses PTH secretion**. However in PHPT, PTH secretion from autonomously functioning parathyroid adenomas or parathyroid hyperplasia is not suppressed. Most patients with PHPT present with mild, asymptomatic hypercalcemia, but potential clinical features include nephrolithiasis, osteoporosis, nausea, constipation, and neuropsychiatric symptoms ("stones, bones, abdominal moans, psychic groans"). Serum phosphorus is often normal but can be low in moderate-to-severe PHPT.

(Choice A) Secondary hyperparathyroidism is characterized by increased secretion of PTH in response to hypocalcemia. It is a common finding in chronic kidney disease due to inadequate phosphate excretion and low 1,25-hydroxyvitamin D levels. Serum phosphorus will be high and calcium will be low or low-normal. Long-standing secondary hyperparathyroidism can lead to autonomous PTH secretion (tertiary hyperparathyroidism), but this is typically seen in patients with end-stage renal disease (eg, on hemodialysis) and would be very unusual with a creatinine of 1.6 mg/dL. It is associated with very high PTH levels.

(Choice B) Hypercalcemia of malignancy is usually due to secretion of PTH-related protein and is characterized

(Choice A) Secondary hyperparathyroidism is characterized by increased secretion of PTH in response to hypocalcemia. It is a common finding in chronic kidney disease due to inadequate phosphate excretion and low 1,25-hydroxyvitamin D levels. Serum phosphorus will be high and calcium will be low or low-normal. Long-standing secondary hyperparathyroidism can lead to autonomous PTH secretion (tertiary hyperparathyroidism), but this is typically seen in patients with end-stage renal disease (eg, on hemodialysis) and would be very unusual with a creatinine of 1.6 mg/dL. It is associated with very high PTH levels.

(Choice B) Hypercalcemia of malignancy is usually due to secretion of PTH-related protein and is characterized by severe hypercalcemia (typically >14 mg/dL) and a suppressed PTH level.

(Choice C) Milk-alkali syndrome is caused by excessive ingestion of calcium and absorbable alkali (eg, calcium-containing antacids). Calcium would be elevated, but PTH would be suppressed.

(Choice D) Circulating levels of calcium and PTH are normal in primary osteoporosis.

Educational objective:

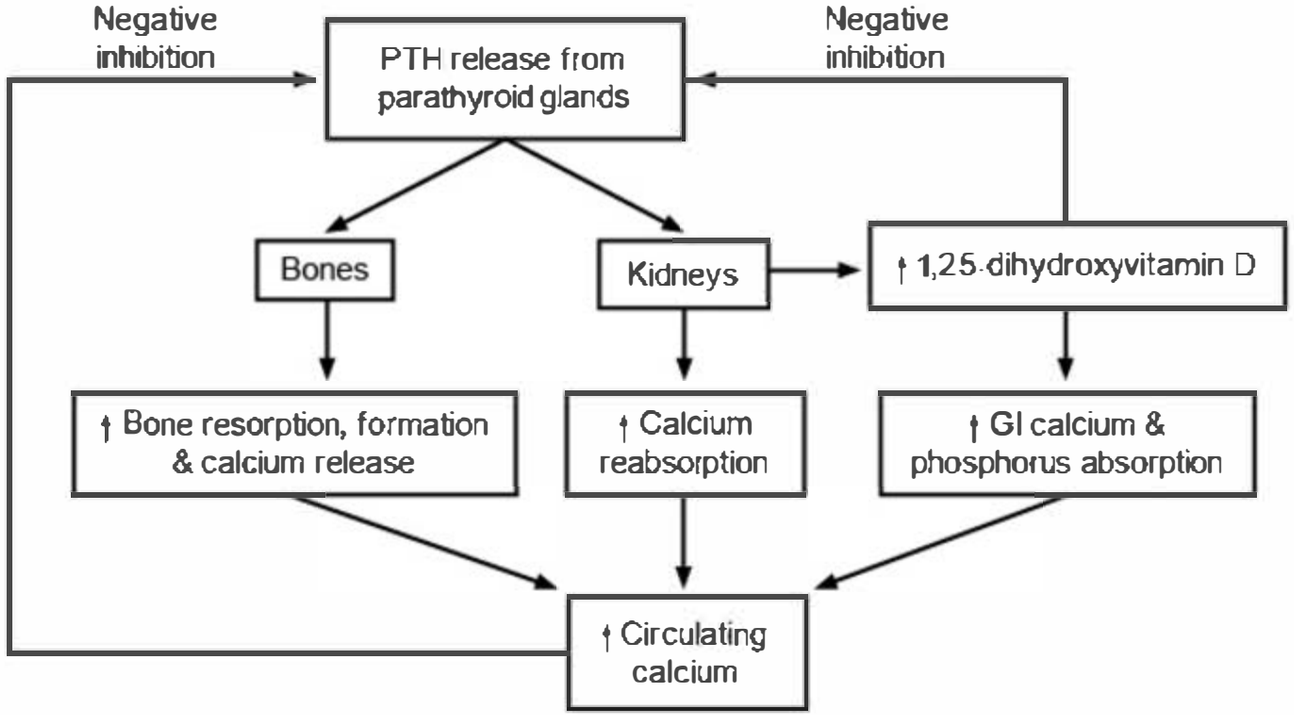
Primary hyperparathyroidism is characterized by autonomous secretion of parathyroid hormone from parathyroid adenomas or parathyroid hyperplasia. Most patients have mild, asymptomatic hypercalcemia, but potential clinical features include nephrolithiasis, osteoporosis, nausea, constipation, and neuropsychiatric symptoms.

References

- Primary hyperparathyroidism.
- A practical approach to problems of hypercalcaemia.

Exhibit Display

PTH, vitamin D & calcium axis



GI = gastrointestinal; PTH = parathyroid hormone.

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neuropsychiatric symptoms (stones, bones, abdominal moans, psychic groans). Serum phosphorus is often

A 58-year-old woman comes to the office due to recent-onset tremor, palpitations, weight loss, and fatigue. She has no other medical conditions and takes no medications or over-the-counter supplements. The patient's mother had hypothyroidism and osteoporosis. Blood pressure is 144/80 mm Hg, pulse is 110/min, and respirations are 18/min. On examination, there is diffuse, nontender enlargement of the thyroid gland. Ocular examination shows bilateral proptosis, lid lag, and periorbital puffiness. The patient has diplopia and ocular discomfort on extremes of lateral gaze. Laboratory tests show a suppressed TSH and elevated thyroid hormone levels. Which of the following treatment options is most likely to worsen this patient's eye disease?

- A. Prednisone
- B. Propranolol
- C. Propylthiouracil
- D. Radioactive iodine
- E. Thyroidectomy

Submit

A 58-year-old woman comes to the office due to recent-onset tremor, palpitations, weight loss, and fatigue. She has no other medical conditions and takes no medications or over-the-counter supplements. The patient's mother had hypothyroidism and osteoporosis. Blood pressure is 144/80 mm Hg, pulse is 110/min, and respirations are 18/min. On examination, there is diffuse, nontender enlargement of the thyroid gland. Ocular examination shows bilateral proptosis, lid lag, and periorbital puffiness. The patient has diplopia and ocular discomfort on extremes of lateral gaze. Laboratory tests show a suppressed TSH and elevated thyroid hormone levels. Which of the following treatment options is most likely to worsen this patient's eye disease?

- A. Prednisone [23%]
- B. Propranolol [12%]
- ✗ C. Propylthiouracil [14%]
- ✓ D. Radioactive iodine [44%]
- E. Thyroidectomy [6%]

Incorrect
Correct answer
D

44%
Answered correctly

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Last Updated

Complications of Graves disease treatment	
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.

This patient has hyperthyroidism with a diffuse goiter, consistent with **Graves disease**. In addition, she has signs of Graves **ophthalmopathy**, including proptosis, swelling of the periorbital tissues, and involvement of the extraocular muscles (eg, diplopia, discomfort with ocular movements). Graves ophthalmopathy is due to the effects of activated T cells and thyrotropin receptor antibodies (TRAB) on TSH receptors on retro-orbital fibroblasts and adipocytes.

The 3 primary treatment options for Graves disease include **radioactive iodine** (RAI), antithyroid drugs (eg, propylthiouracil, methimazole), and thyroidectomy. Patients with mild disease often achieve permanent remission with antithyroid drugs alone, but those with more severe disease require definitive treatment with thyroidectomy or RAI. However, titers of TRAB increase significantly following RAI therapy, and RAI can cause worsening of ophthalmopathy. For this reason, administration of **glucocorticoids** with RAI is often advised to prevent complications in patients with mild ophthalmopathy **(Choice A)**; **thyroidectomy** is preferred over RAI for those with moderate or severe ophthalmopathy **(Choice E)**.

(Choice B) Beta blockers (eg, propranolol) are usually given to minimize the cardiovascular effects (eg, hypertension, tachycardia) of hyperthyroidism.

(Choice C) Destruction of thyroid follicles by RAI can cause unregulated release of thyroid hormone, temporarily worsening the hyperthyroid state. Younger patients without cardiovascular disease usually tolerate RAI without major problems. However, elderly patients and those with cardiovascular disease may not tolerate the temporary increase in thyroid hormone and often are given an **antithyroid drug** to deplete existing thyroid hormone stores prior to RAI.

Educational objective:
Graves ophthalmopathy is due to the effects of activated T cells and thyrotropin receptor antibodies (TRAB) on TSH receptors on retro-orbital fibroblasts and adipocytes. Radioactive iodine (RAI) treatment can raise titers of TRAB and worsen the ophthalmopathy. Glucocorticoids and antithyroid drugs can be used to minimize the effects of RAI.

A 29-year-old nulligravid woman comes to the office because she has not menstruated since stopping her birth control. Menarche was at age 14, and she had irregular, heavy menstrual periods from age 14-16. The patient then took combination oral contraceptives until 6 months ago. Since stopping her medication, she has had more frequent headaches and increasing acne but has had no weight changes, pelvic pain, or abnormal hair loss or growth. The patient is a high school teacher and coaches the cross-country and track teams. She runs recreationally and eats a well-balanced diet. She does not use tobacco, alcohol, or illicit drugs. Vital signs are normal and BMI is 22 kg/m^2. A few open comedones are seen on the forehead. The remainder of the physical examination, including pelvic examination, is normal. Urine pregnancy test is negative and pelvic ultrasound is normal. Which of the following is the best next step in evaluation of this patient?

- A. Karyotype analysis
- B. MRI of the pituitary
- C. No further evaluation indicated
- D. Serum 17-hydroxyprogesterone level
- E. Serum prolactin level

Submit

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- A. Karyotype analysis [0%]
- B. MRI of the pituitary [9%]
- ✗ C. No further evaluation indicated [32%]
- D. Serum 17-hydroxyprogesterone level [21%]
- ✓ E. Serum prolactin level [35%]

Incorrect
Correct answer

35%
Answered correctly

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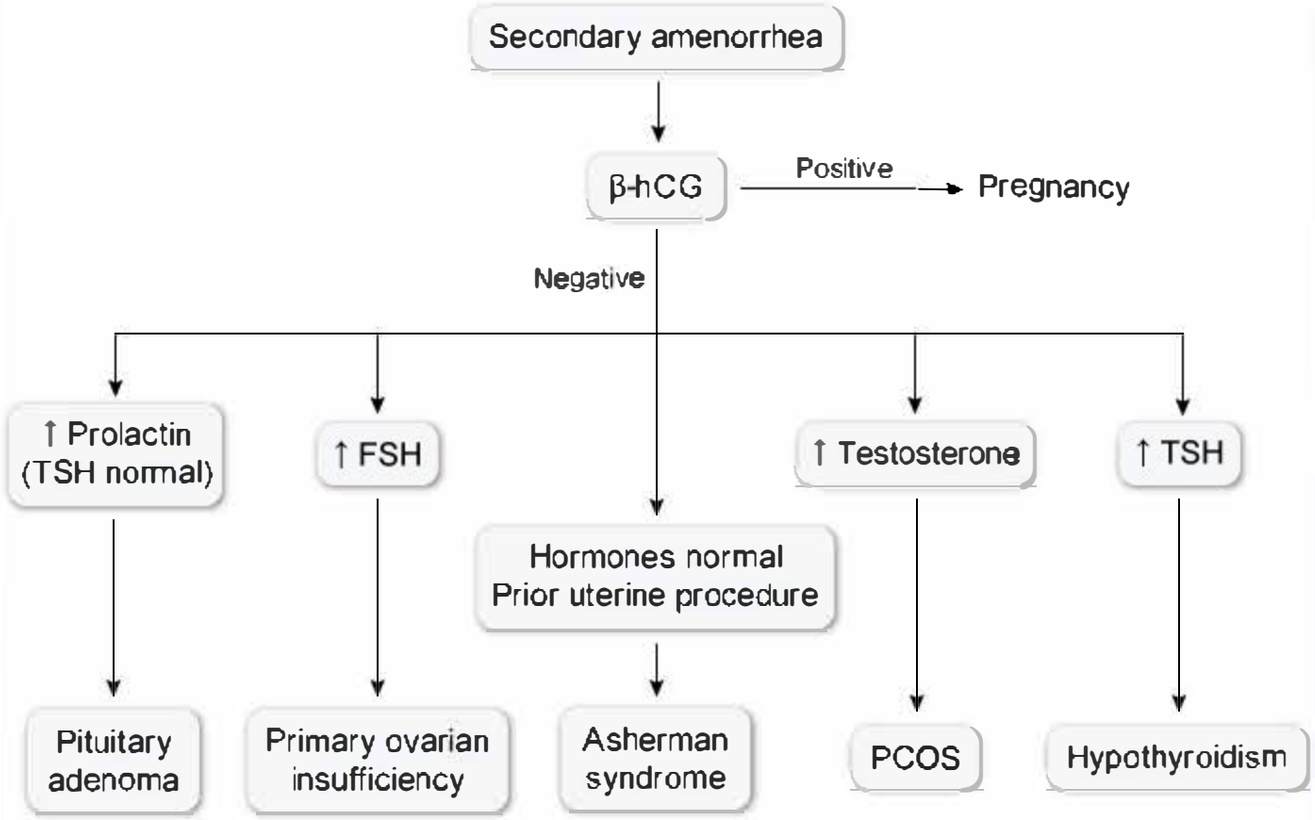
Last Updated

Secondary amenorrhea evaluation



PCOS = polycystic ovarian syndrome.

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This patient has **secondary amenorrhea**, defined as amenorrhea for ≥3 months in women with previously regular menses (or ≥6 months in women with previously irregular menses). Most women have return of spontaneous

This patient has **secondary amenorrhea**, defined as amenorrhea for ≥3 months in women with previously regular menses (or ≥6 months in women with previously irregular menses). Most women have return of spontaneous menses within 1-3 months after cessation of oral contraceptives; those who do not have a return of menses (as with this patient) require further evaluation **(Choice C)**.

The most common cause of secondary amenorrhea is pregnancy, followed by **hypothalamic-pituitary-ovarian (HPO) axis dysfunction** (eg, functional hypothalamic amenorrhea, primary ovarian insufficiency) and **endocrine abnormalities** that affect the HPO axis (eg, pituitary or thyroid dysfunction). Therefore, initial evaluation is with a pregnancy test followed by serum **FSH, TSH, and prolactin levels**, which help differentiate between the causes of secondary amenorrhea. The results of this initial testing determine the next steps in evaluation (eg, karyotype analysis, imaging).

(Choice A) Karyotype analysis is performed in patients with primary ovarian insufficiency (POI), as POI is associated with chromosomal abnormalities (eg, Turner syndrome, fragile X syndrome). However, the diagnosis of POI is made with an elevated FSH level (to postmenopausal levels) in women age <40 who have oligo- or amenorrhea.

(Choice B) Prolactinomas can cause secondary amenorrhea and frequent headaches (as in this patient). However, an MRI of the pituitary is performed after patients are found to have elevated prolactin levels. In addition, this patient's headache is nonspecific and could be related to estrogen fluctuations after discontinuation of her oral contraceptives.

(Choice D) Serum 17-hydroxyprogesterone is elevated in nonclassic congenital adrenal hyperplasia (21-hydroxylase deficiency), which can cause abnormal uterine bleeding and hyperandrogenism (eg, acne, hirsutism)

associated with chromosomal abnormalities (eg, Turner syndrome, fragile X syndrome). However, the diagnosis of POI is made with an elevated FSH level (to postmenopausal levels) in women age <40 who have oligo- or amenorrhea.

(Choice B) Prolactinomas can cause secondary amenorrhea and frequent headaches (as in this patient). However, an MRI of the pituitary is performed after patients are found to have elevated prolactin levels. In addition, this patient's headache is nonspecific and could be related to estrogen fluctuations after discontinuation of her oral contraceptives.

(Choice D) Serum 17-hydroxyprogesterone is elevated in nonclassic congenital adrenal hyperplasia (21-hydroxylase deficiency), which can cause abnormal uterine bleeding and hyperandrogenism (eg, acne, hirsutism). Although this patient has increasing acne, the cessation of hormonal contraception typically worsens acne (due to the anti-androgenic properties of contraceptives). In addition, this patient's acne is mild and likely represents a normal variant.

Educational objective:
Secondary amenorrhea is amenorrhea for ≥3 months in women with previously regular menses (or ≥6 months in women with previously irregular menses). Initial evaluation includes a pregnancy test, followed by serum prolactin, TSH, and FSH level testing.

References

- Amenorrhea: an approach to diagnosis and management.

A 34-year-old woman comes to the office due to a 6-month history of easy bruising with minimal or no trauma. She also has had difficulty climbing stairs due to muscle weakness and frequent nocturnal muscle cramps. The patient has experienced a 7-kg (15-lb) weight gain despite following a restricted-calorie vegan diet. Her medical history is notable for an uncomplicated root canal procedure 6 months ago but is otherwise unremarkable. She takes no prescription or over-the-counter medications. The patient is not currently sexually active and has never been pregnant. Her last menstrual period was 3 months ago. There is no family history of bleeding disorders. Her blood pressure is 146/94 mm Hg and pulse is 78/min. BMI is 29 kg/m^2. Examination shows facial plethora with dark terminal hair on her upper lip and chin. There is inflammatory acne on her face and back, extensive tinea versicolor on the trunk, and scattered bruises over the extremities. Fasting laboratory results are as follows:

Complete blood count	
Hemoglobin	14 g/dL
Platelets	160,000/mm^3
Leukocytes	9,500/mm^3
Neutrophils	80%
Eosinophils	0%
Lymphocytes	17%
Monocytes	2%

Eosinophils	0%
Lymphocytes	17%
Monocytes	2%
Basophils	1%

Serum chemistry

Sodium	140 mEq/L
Potassium	3.6 mEq/L
Chloride	100 mEq/L
Bicarbonate	28 mEq/L
Creatinine	0.8 mg/dL
Calcium	9 mg/dL
Glucose	122 mg/dL

Which of the following is the most likely cause of this patient's symptoms?

A. Cushing syndrome

Chloride	100 mEq/L
Bicarbonate	28 mEq/L
Creatinine	0.8 mg/dL
Calcium	9 mg/dL
Glucose	122 mg/dL

Which of the following is the most likely cause of this patient's symptoms?

- A. Cushing syndrome
- B. Cutaneous small vessel vasculitis
- C. Polycystic ovary syndrome
- D. Vitamin C deficiency
- E. Vitamin K deficiency
- F. Von Willebrand disease

Submit

Chloride	100 mEq/L
Bicarbonate	28 mEq/L
Creatinine	0.8 mg/dL
Calcium	9 mg/dL
Glucose	122 mg/dL

Which of the following is the most likely cause of this patient's symptoms?

- ✔ A. Cushing syndrome [70%]
- B. Cutaneous small vessel vasculitis [1%]
- C. Polycystic ovary syndrome [23%]
- ✘ D. Vitamin C deficiency [1%]
- E. Vitamin K deficiency [2%]
- F. Von Willebrand disease [0%]

Incorrect
Correct answer

70%
Answered correctly

19 Seconds
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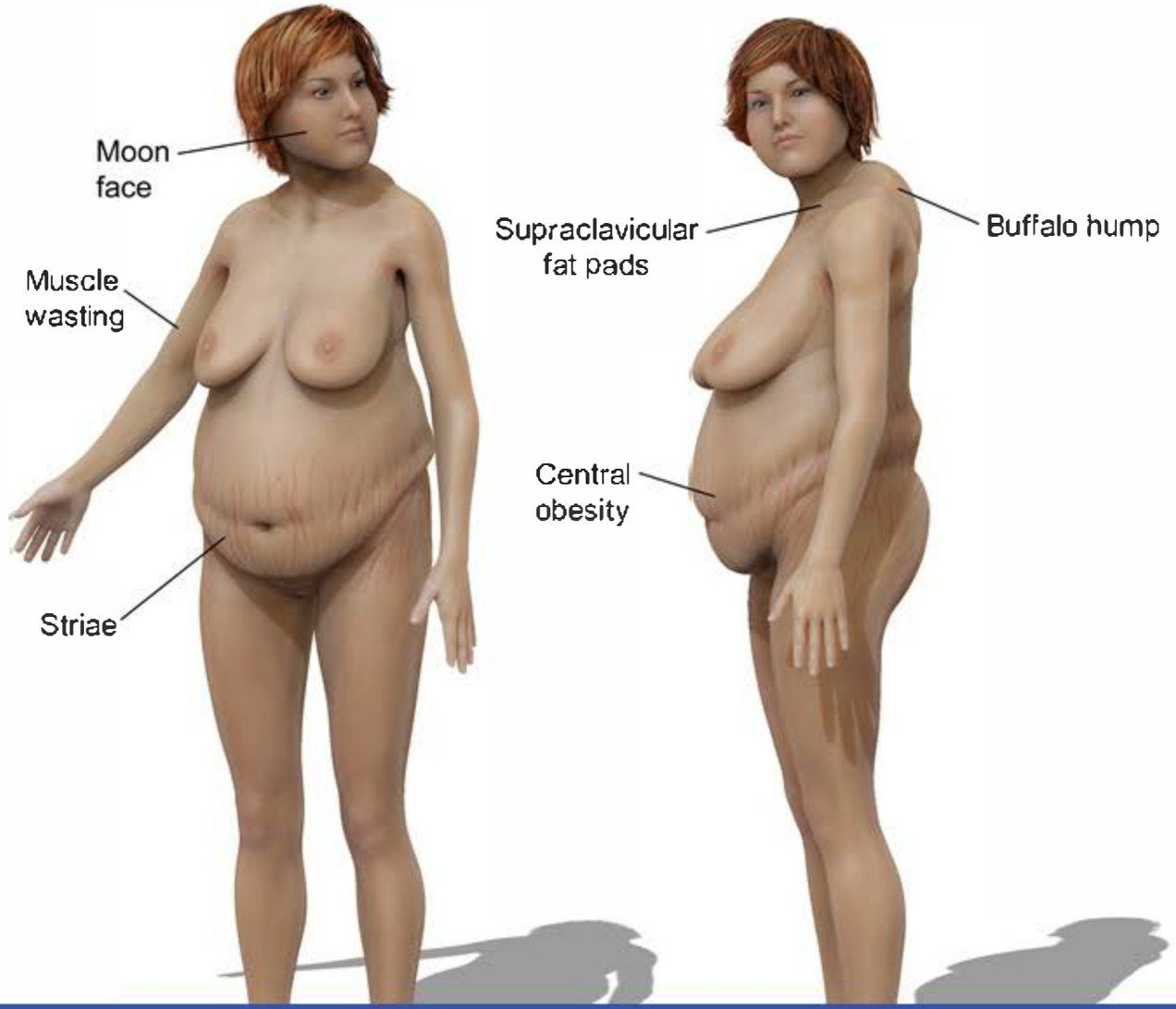
Features of Cushing syndrome



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.

Hyperglycemia is common (due to peripheral insulin resistance and hypercortisolism-induced gluconeogenesis). Hypokalemia and alkalosis may be present (due to the partial mineralocorticoid effects of cortisol) if cortisol levels are very high. Once there is laboratory confirmation of **hypercortisolism** (eg, late-night salivary cortisol assay, 24-hour urine free cortisol measurement, overnight low-dose dexamethasone suppression test), **ACTH levels** are measured to differentiate ACTH-dependent (eg, ACTH-secreting pituitary tumor, ectopic ACTH) from ACTH-independent (eg, adrenal adenoma) causes.

(Choice B) Cutaneous small-vessel vasculitis can be triggered by infections, medications, inflammatory conditions, or malignancy. It presents with nonblanching violaceous petechiae that can coalesce into palpable purpura. Weight gain, hyperglycemia, and hyperandrogenic symptoms would not be common.

(Choice C) Polycystic ovary syndrome shares a number of features with Cushing syndrome, including obesity, irregular menstrual periods, and hyperandrogenism. However, skin atrophy, muscle weakness, and bruisability are not characteristic.

purpura. Weight gain, hyperglycemia, and hyperandrogenic symptoms would not be common.

(Choice C) Polycystic ovary syndrome shares a number of features with Cushing syndrome, including obesity, irregular menstrual periods, and hyperandrogenism. However, skin atrophy, muscle weakness, and bruisability are not characteristic.

(Choices D, E, and F) Vitamin C deficiency causes microvascular bleeding due to impaired synthesis of collagen. Vitamin K deficiency also causes bleeding, due to reduced levels of coagulation factors II, VII, IX, and X. Von Willebrand disease is an autosomal dominant disorder characterized by impaired platelet function and excessive bleeding. However, none of these conditions would explain this patient's weight gain, muscle weakness, hyperandrogenism, hyperglycemia, and metabolic alkalosis. In addition, vitamin C or K deficiencies are not common in vegans.

Educational objective:

Cushing syndrome is characterized by weight gain, muscle weakness, and hypertension. Patients can experience easy bruisability, dermal atrophy, and striae due to the catabolic effects of cortisol on connective tissue. Women can have features of hyperandrogenism due to co-secretion of adrenal androgens with cortisol.

References

- The diagnosis of Cushing's syndrome.

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platelet function and coagulation proteins are normal. Dermatologic signs may include **hyperpigmentation** (in

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A 35-year-old woman comes to her primary care physician complaining of palpitations, weight loss, increased appetite, and diarrhea for the past 2 months. She does not use alcohol or tobacco. Her temperature is 37.1° C (98° F), blood pressure is 135/80 mm Hg, pulse is 100/min, and respirations are 14/min. Physical examination shows exophthalmos, lid lag, lid retraction, and a diffusely enlarged and nontender thyroid gland. Laboratory studies show very low serum thyroid-stimulating hormone and increased serum free T4 and T3. The patient is diagnosed with Graves' disease. Various treatment options are discussed, and she opts for long-term treatment with methimazole. Which of the following conditions is this patient at risk for developing from the medication?

- A. Agranulocytosis
- B. Hypocalcemia
- C. Pancreatitis
- D. Permanent hypothyroidism
- E. Recurrent laryngeal nerve palsy
- F. Renal impairment
- G. Thyroid cancer
- H. Worsening of ophthalmopathy

appetite, and diarrhea for the past 2 months. She does not use alcohol or tobacco. Her temperature is 37.1° C (98° F), blood pressure is 135/80 mm Hg, pulse is 100/min, and respirations are 14/min. Physical examination shows exophthalmos, lid lag, lid retraction, and a diffusely enlarged and nontender thyroid gland. Laboratory studies show very low serum thyroid-stimulating hormone and increased serum free T4 and T3. The patient is diagnosed with Graves' disease. Various treatment options are discussed, and she opts for long-term treatment with methimazole. Which of the following conditions is this patient at risk for developing from the medication?

- ✔ A. Agranulocytosis [79%]
- B. Hypocalcemia [1%]
- C. Pancreatitis [2%]
- D. Permanent hypothyroidism [4%]
- ✘ E. Recurrent laryngeal nerve palsy [0%]
- F. Renal impairment [4%]
- G. Thyroid cancer [0%]
- H. Worsening of ophthalmopathy [6%]

Incorrect
Correct answer

79%
Answered correctly

5 Seconds
Time Spent

06/30/2018
Last Updated

Complications of Graves disease treatment	
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 3 major treatment options for Graves' disease are:

1. Radioactive iodine ablation (preferred in the United States)
2. Antithyroid drug (ATD) therapy
3. Thyroidectomy

All 3 modalities are equally effective, but surgery and radioactive iodine ablation can permanently treat

All 3 modalities are equally effective, but surgery and radioactive iodine ablation can permanently treat hyperthyroidism. However, the physician should discuss the options with the patient to make a mutual decision. The two available ATDs in the United States are propylthiouracil (PTU) and methimazole (MMI). PTU is usually not the preferred drug due to a black box warning of severe liver injury and acute liver failure. However, PTU is preferred during the first trimester of pregnancy due to fetal teratogenicity with MMI. Approximately 30%-40% of patients treated with ATDs for 1 year go into permanent remission.

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. Those developing sore throat and fever should stop the ATD and see a physician to check their white blood cell count. However, routine monitoring of the white blood cell count is not needed due to the rarity of the condition.

(Choices B and E) Hypocalcemia and recurrent laryngeal nerve damage are complications of thyroidectomy.

(Choice D) Permanent hypothyroidism may result after radioiodine treatment or thyroidectomy.

(Choice G) Use of ATDs is not associated with a higher risk of thyroid cancer.

(Choices C and F) Pancreatitis and renal damage are not common side effects of ATD therapy or other treatments for Graves' disease.

(Choice H) Radioactive iodine therapy can be associated with development or worsening of ophthalmopathy in Graves' disease patients.

Educational objective:

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. Those developing sore throat and fever should stop the ATD and see a physician to check their white blood cell count. However, routine monitoring of the white blood cell count is not needed due to the rarity of the condition.

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(Choice H) Radioactive iodine therapy can be associated with development or worsening of ophthalmopathy in Graves' disease patients.

Educational objective:
Graves' disease can be treated with anti-thyroid drugs, radioactive iodine therapy, or thyroidectomy. The most serious side effect of anti-thyroid drugs is agranulocytosis (0.3% of patients). Patients developing sore throat and fever should stop the drug and see a physician to check their white blood cell count.

References

- Treatment of Graves' hyperthyroidism: evidence-based and emerging modalities.

A 31-year-old woman comes to the office due to a 6.8-kg (15-lb) weight gain over the last few months. She has been unable to lose weight despite rigorous dieting and regular exercise. The patient also has experienced weakness and cannot lift weights that she was able to lift before the onset of her symptoms. Her menstrual periods have been irregular for the last few months, and she has had increasing anxiety and insomnia for which she has started seeing a clinical psychologist. Medical history is unremarkable. She drinks wine only on rare occasions and quit smoking 7 years ago after a 5-pack-year history. On examination, blood pressure is 160/100 mm Hg and pulse is 88/min and regular. Neurologic examination shows proximal muscle weakness. Dark terminal hair is present on the lower abdomen. Fasting laboratory results are as follows:

Glucose	130 mg/dL
Sodium	142 mEq/L
Potassium	3.6 mEq/L
Chloride	98 mEq/L
Bicarbonate	28 mEq/L
Calcium	9.2 mg/dL
TSH	2.2 mIU/L

Which of the following is the most appropriate next step in evaluating this patient's condition?

Glucose	156 mg/dL
Sodium	142 mEq/L
Potassium	3.6 mEq/L
Chloride	98 mEq/L
Bicarbonate	28 mEq/L
Calcium	9.2 mg/dL
TSH	2.2 mIU/L

Which of the following is the most appropriate next step in evaluating this patient's condition?

- A. Early-morning cortisol level
- B. Overnight low-dose dexamethasone suppression test
- C. Serum ACTH level
- D. Serum aldosterone to plasma renin activity ratio
- E. Serum testosterone level

Submit

Glucose	156 mg/dL
Sodium	142 mEq/L
Potassium	3.6 mEq/L
Chloride	98 mEq/L
Bicarbonate	28 mEq/L
Calcium	9.2 mg/dL
TSH	2.2 mIU/L

Which of the following is the most appropriate next step in evaluating this patient's condition?

- ✗ A. Early-morning cortisol level [39%]
- ✓ B. Overnight low-dose dexamethasone suppression test [32%]
- C. Serum ACTH level [15%]
- D. Serum aldosterone to plasma renin activity ratio [5%]
- E. Serum testosterone level [7%]

Incorrect

32%

7 Seconds

07/21/2018

Features of Cushing syndrome	
Clinical manifestations	• **Central obesity** (eg, fat accumulation in the cheeks & dorsocervical & supraclavicular fat pads) • Skin atrophy & wide, purplish **striae** • Proximal muscle weakness • Hypertension • **Glucose intolerance** • Skin hyperpigmentation (if ACTH excess)
Diagnosis	• 24-hour urinary cortisol excretion • Late-night salivary cortisol assay • Low-dose dexamethasone suppression test

This patient has weight gain, psychiatric symptoms, hirsutism, hypertension, and hyperglycemia. This constellation of findings is consistent with hypercortisolism (**Cushing syndrome**). This condition is most commonly due to exogenous administration of glucocorticoids, but can also be due to an ACTH-producing pituitary tumor (Cushing disease), ectopic ACTH production (eg, small cell lung cancer), or 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,

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(Choice A) Early-morning cortisol levels will be low or low-normal in patients with primary adrenal insufficiency. However, there is considerable overlap in cortisol levels in normal subjects and those with Cushing syndrome, and this test has low utility in the evaluation of hypercortisolism.

(Choice D) The ratio of plasma aldosterone to plasma renin activity is useful to evaluate primary hyperaldosteronism, which typically presents with hypertension and hypokalemia. This patient's hyperglycemia and psychiatric and menstrual symptoms are more consistent with hypercortisolism.

(Choice E) Hyperandrogenism can be seen in Cushing syndrome due to ACTH-induced adrenal androgen production or co-secretion of cortisol and testosterone by an adrenal tumor. Testosterone levels may be useful in evaluating hirsutism, but would not explain this patient's constellation of findings consistent with Cushing syndrome.

Educational objective:
The initial step in the evaluation of Cushing syndrome is to confirm hypercortisolism with a late-night salivary cortisol assay, 24-hour urine free cortisol measurement, and/or overnight low-dose dexamethasone test. If hypercortisolism is confirmed, ACTH levels are measured to differentiate ACTH-dependent from ACTH-independent causes.

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The initial step in the evaluation of Cushing syndrome is to confirm hypercortisolism with a late-night salivary cortisol assay, 24-hour urine free cortisol measurement, and/or overnight low-dose dexamethasone test. If hypercortisolism is confirmed, ACTH levels are measured to differentiate ACTH-dependent from ACTH-independent causes.

A 45-year-old woman comes to the physician for a routine preventive examination. The patient was diagnosed with hypertension 6 months ago and is currently taking chlorthalidone. Her last Papanicolaou test 2 years ago was normal with negative human papillomavirus screening. The patient received an influenza vaccination 3 weeks ago through her employer and the tetanus and diphtheria vaccination 5 years ago. She has a 20-pack-year smoking history but quit 6 years ago. The patient does not use alcohol or illicit drugs. Her mother and maternal uncle have type 2 diabetes mellitus. There is no history of cancer in the family. The patient's temperature is 37 C (98 F), blood pressure is 140/86 mm Hg, pulse is 80/min, and respirations are 14/min. Her BMI is 28.3 kg/m^2. Physical examination is unremarkable. Which of the following is the most appropriate next step in management of this patient?

- A. Chest x-ray
- B. Fasting glucose measurement
- C. Human papilloma virus vaccine
- D. Papanicolaou test
- E. Pneumococcal vaccination

Submit

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A. Chest x-ray [2%]
✔ B. Fasting glucose measurement [87%]
C. Human papilloma virus vaccine [0%]
D. Papanicolaou test [4%]
E. Pneumococcal vaccination [5%]

Correct
87% Answered correctly
5 Seconds TimeSpent
05/22/2018 Last Updated

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**.

Recommended **screening tests** include fasting plasma glucose (FPG), 2-hour oral glucose tolerance test (OGTT) or hemoglobin A_{1c}. This patient has multiple risk factors for diabetes—hypertension, overweight, family history—and should be offered screening for diabetes.

(Choice A) This patient is at a moderately increased risk for developing lung cancer due to tobacco use. Studies have not shown a significant benefit in lung cancer screening with chest x-ray alone or combined with sputum cytology in high-risk populations. Revised guidelines based on the National Lung Screening Trial recommend annual low-dose CT scan screening for lung cancer in adults age 55-80 with a ≥30-pack-year smoking history who currently smoke or have quit in the last 15 years.

(Choice C) The human papilloma virus (HPV) vaccine is approved for use in male and female patients age 9-26.

(Choice D) For women with average risk for cervical cancer, a Papanicolaou (Pap) test is recommended every 3 years from age 21-29. Between ages 30-65, patients with initial negative testing may have either a Pap test alone

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(Choice D) For women with average risk for cervical cancer, a Papanicolaou (Pap) test is recommended every 3 years from age 21-29. Between ages 30-65, patients with initial negative testing may have either a Pap test alone every 3 years or a combination of Pap test and HPV testing every 5 years (preferred).

(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.

Educational objective:

Screening for diabetes is recommended in patients with sustained blood pressure >135/80 mm Hg and may be considered in all patients over age 45, as well as those with additional risk factors for diabetes. Screening options include fasting plasma glucose, 2-hour oral glucose tolerance test and hemoglobin A_{1c}.

D. Papanicolaou test [4%]

Exhibit Display

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

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D. Papanicolaou test [4%]

E. Pneumococca

Correct

Explanation

Diabetes mellitus increas e of
diabetes in the United St tes in
asymptomatic patients:

- The **US Preventive** d blood
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at any age with additional risk factors for diabetes.

Recommended screening tests include fasting plasma glucose (FPG), 2-hour oral glucose tolerance test (OGTT) or hemoglobin A_{1c}. This patient has multiple risk factors for diabetes—hypertension, overweight, family history—

Exhibit Display

Screening tests for diabetes mellitus

Test	Interpretation
Hemoglobin A1c	• 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 hr • **≥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	• Most sensitive test • 75-g glucose load with glucose testing for 2 hr

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Exhibit Display

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Oral glucose tolerance test	• Most sensitive test • 75-g glucose load with glucose testing for 2 hr • **≥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.

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A 23-year-old man is brought to the emergency department due to muscle weakness, vomiting, and abdominal pain. Over the last 6 weeks, he has lost a considerable amount of weight despite eating excessively. The patient also has experienced increased frequency of urination, leg cramps, and blurry vision. His medical history is unremarkable, and he does not use tobacco, alcohol, or illicit drugs. The patient's mother has hypothyroidism and his father died of lung cancer. He is sexually active with a female partner. Temperature is 37.8 C (100 F), blood pressure is 110/70 mm Hg, pulse is 110/min, and respirations are 27/min. His oral mucosa is dry. Laboratory results are as follows:

Sodium	132 mEq/L
Potassium	5.4 mEq/L
Chloride	96 mEq/L
Bicarbonate	12 mEq/L
Blood urea nitrogen	19 mg/dL
Creatinine	1.1 mg/dL
Calcium	8.9 mg/dL
Glucose	470 mg/dL

Which of the following is the most likely cause of the increased potassium level in this patient?

Chloride	96 mEq/L
Bicarbonate	12 mEq/L
Blood urea nitrogen	19 mg/dL
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Calcium	8.9 mg/dL
Glucose	470 mg/dL

Which of the following is the most likely cause of the increased potassium level in this patient?

- A. Extracellular shift
- B. Increased renal reabsorption of potassium
- C. Intracellular potassium excess
- D. Osmotic diuresis
- E. Tissue destruction

Submit

Chloride	96 mEq/L
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Blood urea nitrogen	19 mg/dL
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Which of the following is the most likely cause of the increased potassium level in this patient?

- ✔ A. Extracellular shift [88%]
- B. Increased renal reabsorption of potassium [3%]
- C. Intracellular potassium excess [1%]
- D. Osmotic diuresis [4%]
- E. Tissue destruction [2%]

Correct

88% Answered correctly

9 Seconds TimeSpent

07/17/2018 Last Updated

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.

The patient has severe hyperglycemia associated with neurologic and abdominal symptoms. His laboratory

The patient has severe hyperglycemia associated with neurologic and abdominal symptoms. His laboratory studies show a low bicarbonate level, consistent with metabolic acidosis, and an elevated anion gap, calculated by sodium – (chloride + bicarbonate) = 132 – (96 + 12) = 24 (normal 10-14). This is consistent with new-onset type 1 diabetes with **diabetic ketoacidosis** (DKA). In DKA, measured serum potassium levels are often initially **high** due to:

- **Extracellular shift** of potassium driven by increased plasma tonicity
- Loss of insulin-dependent potassium uptake across cell membranes **(Choice C)**

Hyperkalemia develops despite a significant **total body potassium deficit** (eg, ≥500 mEq) due to potassium loss in the urine (from glucose-induced osmotic diuresis) and renal elimination of potassium ketoacid salts **(Choices B and D)**.

Administration of insulin in treatment of DKA **drives potassium into cells** and can rapidly lead to **hypokalemia**. For this reason, potassium should be monitored closely and added to intravenous fluids once serum potassium is ≤5.2 mEq/L.

(Choice E) Massive tissue destruction can cause hyperkalemia due to the release of intracellular potassium from dying cells. This can be seen in large burns, crush injury, rhabdomyolysis, intravascular hemolysis, and tumor lysis syndrome. However, these conditions typically cause additional abnormalities (eg, hypocalcemia, elevated blood urea nitrogen), and this patient's significant hyperglycemia is more consistent with DKA.

Educational objective:
Patients with diabetic ketoacidosis can have a significant deficit in total body potassium. However, serum levels

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Educational objective:
Patients with diabetic ketoacidosis can have a significant deficit in total body potassium. However, serum levels may be normal or elevated due to an extracellular shift of potassium caused by increased plasma tonicity and loss of insulin-dependent potassium uptake. Administration of insulin drives potassium into cells and can lead to hypokalemia.

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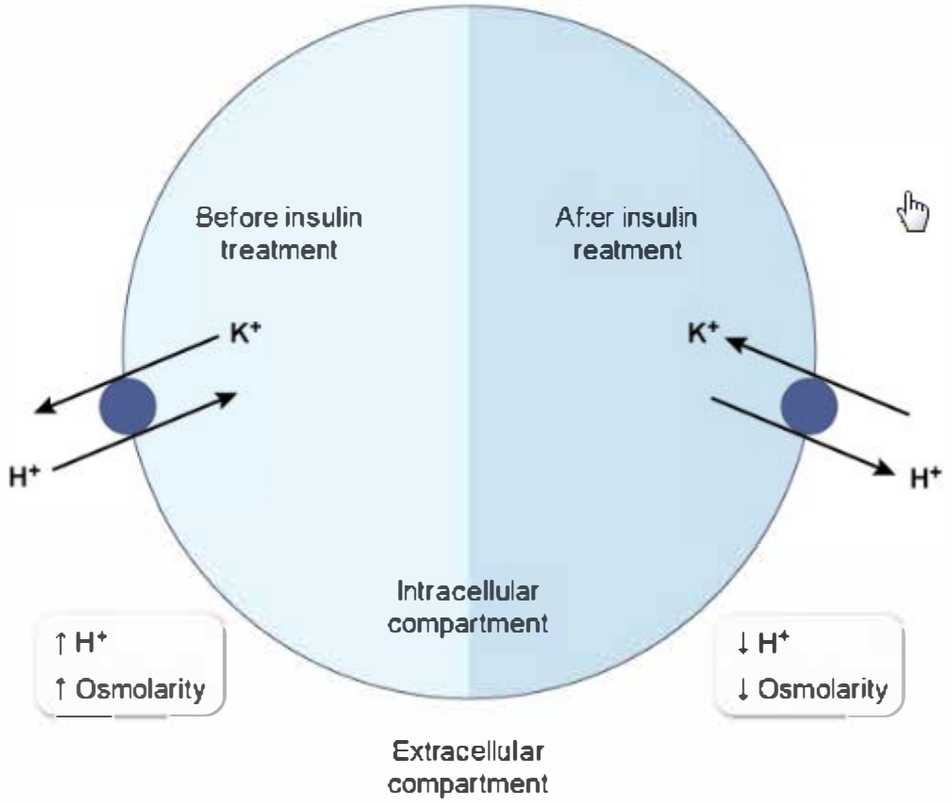
The patient has severe hyperglycemia associated with neurologic and abdominal symptoms. His laboratory

Exhibit Display

Diabetic ketoacidosis



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A 27-year-old man with type 1 diabetes mellitus that was diagnosed 15 years ago comes to the emergency department due to abdominal pain, nausea, and vomiting. The patient takes insulin glargine at night and insulin lispro before meals 3 times a day, but has not been compliant with his insulin injections. He stopped taking his insulin for the last 2 days due to not feeling well and inability to eat. The patient's medical history is otherwise unremarkable. He does not use tobacco or alcohol. Temperature is 36 C (96.8 F), blood pressure is 102/60 mm Hg, pulse is 110/min, and respirations are 26/min. The patient appears lethargic and dehydrated. The lungs are clear to auscultation. The abdomen is soft, nontender, and nondistended. Laboratory results are as follows:

Sodium	128 mEq/L
Potassium	5.4 mEq/L
Chloride	90 mEq/L
Bicarbonate	10 mEq/L
Blood glucose	550 mg/dL

Which of the following is the most appropriate next step in management of this patient?

A. 0.45% saline and regular insulin infusion

B. 5% dextrose and NPH insulin subcutaneously

C. Hypertonic saline and regular insulin infusion

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- A. 0.45% saline and regular insulin infusion
- B. 5% dextrose and NPH insulin subcutaneously
- C. Hypertonic saline and regular insulin infusion
- D. Normal saline and regular insulin infusion
- E. Normal saline and resume his home insulin regimen
- F. Sodium bicarbonate infusion

Sodium	128 mEq/L
Potassium	5.4 mEq/L
Chloride	90 mEq/L
Bicarbonate	10 mEq/L
Blood glucose	550 mg/dL

Which of the following is the most appropriate next step in management of this patient?

A. 0.45% saline and regular insulin infusion [4%]
B. 5% dextrose and NPH insulin subcutaneously [2%]
C. Hypertonic saline and regular insulin infusion [3%]
✔ D. Normal saline and regular insulin infusion [87%]
E. Normal saline and resume his home insulin regimen [1%]
F. Sodium bicarbonate infusion [0%]

Correct

87%
Answered correctly

11 Seconds
TimeSpent

07/29/2018
Last Updated

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
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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.

This patient with nausea, vomiting, and abdominal pain has **metabolic acidosis** (low bicarbonate) with an **elevated anion gap** (sodium – [chloride + bicarbonate]: 128 – [90 + 10] = 28 [normal 10-14]). In light of his

This patient with nausea, vomiting, and abdominal pain has **metabolic acidosis** (low bicarbonate) with an **elevated anion gap** (sodium – [chloride + bicarbonate]; 128 – [90 + 10] = 28 [normal 10-14]). In light of his hyperglycemia and type 1 diabetes, this is consistent with **diabetic ketoacidosis** (DKA). DKA can be precipitated by discontinuation of insulin, especially in the setting of infection or other stressors. It is more common in patients with type 1 diabetes due to absolute insulin deficiency, which leads to accumulation of ketoacids. A diagnosis can often be made provisionally based on bedside capillary blood glucose and confirmed with venous glucose, serum or urine ketones, and arterial blood gas analysis.

Essential measures in DKA include:

1. Hydration to restore intravascular volume, with **0.9% (normal) saline** recommended in the first 1-2 hours
2. Correction of hyperglycemia and ketosis with **intravenous regular insulin**
3. Serial assessment of electrolytes, especially potassium
4. Treatment of the underlying precipitating factors

Insulin deficiency causes an extracellular shift of potassium, and serum potassium levels may be normal or elevated despite a total body deficit. Administration of insulin drives potassium into cells, resulting in hypokalemia. Potassium should be added to intravenous fluids once serum potassium is ≤5.2 mEq/L. When glucose reaches <200 mg/dL, patients also should be given dextrose-containing fluids to avoid hypoglycemia, but insulin should be continued to ensure resolution of ketosis.

(Choice A) After intravascular volume is restored, if serum sodium is normal or elevated, the intravenous fluid is changed to 0.45% saline. Normal saline is used initially regardless of sodium levels.

(Choice A) After intravascular volume is restored, if serum sodium is normal or elevated, the intravenous fluid is changed to 0.45% saline. Normal saline is used initially regardless of sodium levels.

(Choices B and E) A solution of 5% dextrose provides only limited volume resuscitation because as dextrose is metabolized the solution becomes hypotonic, promoting water shift out of the intravascular space. NPH and glargine have a long duration of action and do not allow rapid dose titration; they are usually restarted when DKA has resolved. Finally, intravenous insulin is preferred to subcutaneous insulin (except in very mild DKA) due to the latter's unpredictable absorption (erratic skin perfusion).

(Choice C) Patients with DKA can have pseudohyponatremia due to hyperglycemia; this patient's corrected sodium (observed sodium + ~2 mEq/L for every 100 mg/dL glucose is over 100 mg/dL) is normal (128 + ~2 x 4.5 = 128 + ~9 = ~137 mEq/L). Hypertonic saline is reserved for moderate to severe (true) hyponatremia.

(Choice F) In most patients with DKA, administration of bicarbonate is not beneficial and may lead to cerebral edema, reduced tissue oxygenation, hypokalemia, and alkalosis. Bicarbonate is reserved for severe acidosis (pH ≤6.9), plasma bicarbonate <5 mEq/L, or severe hyperkalemia.

Educational objective:
Essential measures in diabetic ketoacidosis include:

1. Hydration to restore intravascular volume, with 0.9% (normal) saline recommended in the first 1-2 hours
2. Correction of hyperglycemia and ketosis with intravenous regular insulin
3. Serial assessment of electrolytes, especially potassium
4. Treatment of the underlying precipitating factors

A 23-year-old African American man is treated with an antibiotic for a urinary tract infection. Several days later, he comes to the physician saying that his initial symptoms have improved but his urine now appears dark. He has no significant past medical history and does not use tobacco, alcohol, or illicit drugs. His temperature is 36.8 C (98.2 F), pulse is 88/min, respirations are 14/min, and blood pressure is 130/76 mm Hg. Physical examination is within normal limits. The urine sample stains positive with Prussian blue and the sediment microscopy is unrevealing. What is the mechanism behind the cell damage responsible for this patient's current symptoms?

- A. Autoantibody production
- B. Circulating immune complexes
- C. Inflammatory cytokine production
- D. Microvascular obstruction
- E. Oxidative stress
- F. Spread of the infection

Submit

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- A. Autoantibody production [2%]
- ✗ B. Circulating immune complexes [8%]
- C. Inflammatory cytokine production [3%]
- D. Microvascular obstruction [3%]
- ✓ E. Oxidative stress [81%]
- F. Spread of the infection [0%]

Incorrect
Correct answer
E

81%
Answered correctly

5 Seconds
TimeSpent

10/22/2018
Last Updated

This patient has signs and symptoms of hemolysis due to glucose-6-phosphate dehydrogenase **(G6PD) deficiency**. Hemolytic episodes in these patients are most commonly precipitated by **infections** or **medications** that increase oxidative stress (particularly sulfa drugs, antimalarials, and nitrofurantoin). This patient's episode was most likely caused by trimethoprim-sulfamethoxazole, a sulfa-containing antibiotic that is often used to treat urinary tract infections. The positive Prussian blue stain indicates the presence of hemosiderin, which is found in the urine during hemolytic episodes.

The underlying pathophysiology behind this disease is **oxidative stress** leading to hemolysis. In normal patients, G6PD is responsible for catalyzing the reduction of NADP to NADPH, the first step in the hexose monophosphate shunt. This is the only source of NADPH in red blood cells (RBCs). NADPH is necessary to form reduced glutathione, which protects RBCs from oxidative injury. In the absence of G6PD and in the presence of oxidizing agents (eg, bacterial toxins, sulfa-containing drugs), hemoglobin becomes oxidized to form methemoglobin, denatured globin, and sulfhemoglobin. These molecules form insoluble masses (**Heinz bodies**) that attach to the RBC membrane, decrease membrane pliability, and promote RBC removal in the spleen's reticuloendothelial system (RES).

(Choice A) Autoimmune hemolysis occurs when IgG autoantibodies bind to the RBC membrane and promote removal from circulation in the spleen's RES. The direct Coombs test will be positive. Alpha-methyldopa and penicillin can cause this type of reaction; there is no indication that this patient has taken these medications.

(Choice B) Circulating immune complexes cause glomerulonephritis. Urine microscopy usually shows hematuria and RBC casts.

system (RES).

(Choice A) Autoimmune hemolysis occurs when IgG autoantibodies bind to the RBC membrane and promote removal from circulation in the spleen's RES. The direct Coombs test will be positive. Alpha-methyldopa and penicillin can cause this type of reaction; there is no indication that this patient has taken these medications.

(Choice B) Circulating immune complexes cause glomerulonephritis. Urine microscopy usually shows hematuria and RBC casts.

(Choice C) Inflammatory cytokines (eg, TNF-α, IL-1, IL-2) can be upregulated in conditions associated with hemolysis; however, the cytokines themselves are not directly responsible for the hemolytic process.

(Choice D) Microvascular obstruction can be associated with microangiopathic hemolytic anemia and hemolytic crises in sickle cell anemia. This patient does not have renal failure or other symptoms suggestive of microangiopathic anemia.

(Choice F) Serious infections with damage to the epithelium of the urinary tract can cause hematuria. One would expect to see white blood cells and RBCs in the urinary sediment if the patient's dark urine was due to infection-induced bleeding.

Educational objective:
G6PD deficiency causes hemolytic anemia due to oxidative injury to red blood cells. Hemolytic episodes can be precipitated by infection or medications (especially sulfa drugs, antimalarials, and nitrofurantoin).

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A 58-year-old man comes to the physician with a one-year history of diarrhea. The stools are watery and accompanied by abdominal cramps. He has no fever, blood from the rectum, or foul-smelling stools. He has also experienced frequent episodes of dizziness, flushing, wheezing, and a feeling of warmth. The patient has taken herbal medicines, which failed to relieve his symptoms. He is depressed about his illness and feels hopeless about diagnosis and treatment. He appears ill. Cardiac auscultation shows a 2/6 systolic murmur over the left lower sternal border that increases with inspiration. Abdominal examination shows hepatomegaly 3 cm below the right costal margin and no abdominal tenderness. Laboratory results are as follows:

Hemoglobin	14.0 g/dL
Mean corpuscular volume	90 fL
Platelets	200,000/µL
Leukocytes	6,100/µL
Alkaline phosphatase	400 U/L
Aspartate aminotransferase (SGOT)	101 U/L
Alanine aminotransferase (SGPT)	99 U/L

	µL
Leukocytes	6,100/µL
Alkaline phosphatase	400 U/L
Aspartate aminotransferase (SGOT)	101 U/L
Alanine aminotransferase (SGPT)	99 U/L

This patient is at risk of developing a deficiency of which of the following vitamins or minerals?

- A. Calcium
- B. Iron
- C. Niacin
- D. Vitamin A
- E. Vitamin C

Submit

	µL
Leukocytes	6,100/µL
Alkaline phosphatase	400 U/L
Aspartate aminotransferase (SGOT)	101 U/L
Alanine aminotransferase (SGPT)	99 U/L

This patient is at risk of developing a deficiency of which of the following vitamins or minerals?

- A. Calcium [10%]
- B. Iron [6%]
- ✔ C. Niacin [50%]
- D. Vitamin A [31%]
- E. Vitamin C [1%]

Correct

50% Answered correctly

9 Seconds TimeSpent

07/29/2018 Last Updated

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

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The patient's clinical features - episodic flushing and wheezing, diarrhea, and valvular heart disease with tricuspid regurgitation - are consistent with **carcinoid syndrome**. Carcinoids are slow-growing tumors found most commonly in the distal small intestine, proximal colon, and lung. These tumors can secrete several products, including histamine, serotonin, and vasoactive intestinal peptide, that are metabolized in the liver. Gastrointestinal

regurgitation - are consistent with **carcinoid syndrome**. Carcinoids are slow-growing tumors found most commonly in the distal small intestine, proximal colon, and lung. These tumors can secrete several products, including histamine, serotonin, and vasoactive intestinal peptide, that are metabolized in the liver. Gastrointestinal carcinoid tumors often metastasize to the liver. In such cases, the liver is unable to metabolize these hormones before they are released into the systemic circulation, leading to the carcinoid syndrome. Other clinical features include cutaneous telangiectasias and tricuspid regurgitation.

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).

(Choices A and E) Neither calcium nor vitamin C deficiency is associated with carcinoid syndrome.

(Choice B) Iron deficiency is typically not seen in patients with carcinoid syndrome. In addition, this patient's serum hemoglobin and mean corpuscular volume are within normal limits, making iron deficiency even less likely.

(Choice D) Vitamin A deficiency is not seen in association with carcinoid syndrome. It occurs most commonly due to dietary deficiency or in association with fat malabsorption (eg, celiac disease, small-bowel Crohn's disease, pancreatic insufficiency). Fatty diarrhea or steatorrhea typically causes pale, greasy, and malodorous stools, unlike the watery diarrhea seen in patients with carcinoid syndrome.

Educational objective:

Carcinoid tumors are rare neuroendocrine tumors that cause episodic flushing, secretory diarrhea, bronchospasm,

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).

(Choices A and E) Neither calcium nor vitamin C deficiency is associated with carcinoid syndrome.

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Educational objective:

Carcinoid tumors are rare neuroendocrine tumors that cause episodic flushing, secretory diarrhea, bronchospasm, and cardiac valvular abnormalities. Carcinoid cells cause increased production of serotonin from tryptophan (required for niacin synthesis), resulting in niacin deficiency (ie, pellagra, with dermatitis, diarrhea, and dementia).

References

- Carcinoid syndrome: diagnosis and medical management.

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A 40-year-old, previously healthy woman comes to the office due to a 3-month history of progressive weakness, frequent insomnia, palpitations, and an unintentional 4-kg (8.8-lb) weight loss. She also has a constant feeling of anxiety and increased sensitivity to warm temperatures. Blood pressure is 140/70 mm Hg and pulse is 110/min. Physical examination shows lid lag without exophthalmos and a fine tremor of the patient's outstretched hands. The thyroid gland is enlarged and nontender. Laboratory results are as follows:

TSH	0.1 µU/mL
T4, serum	20 µg/dL
Thyroid-stimulating immunoglobulins	340% (normal: <110%)

Treatment options are discussed with the patient, and she elects to proceed with radioiodine therapy. Which of the following is the most likely outcome after treatment in this patient?

A. Development of hypothyroidism over months to years
B. Disappearance of thyroid-stimulating immunoglobulins
C. Increased risk of papillary thyroid cancer
D. Iodine-induced blockage of thyroid hormone synthesis
E. Rapid normalization of thyroid hormone levels
F. Symptom improvement without hormonal changes

Physical examination shows lid lag without exophthalmos and a fine tremor of the patient's outstretched hands. The thyroid gland is enlarged and nontender. Laboratory results are as follows:

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T4, serum	20 µg/dL
Thyroid-stimulating immunoglobulins	340% (normal: <110%)

Treatment options are discussed with the patient, and she elects to proceed with radioiodine therapy. Which of the following is the most likely outcome after treatment in this patient?

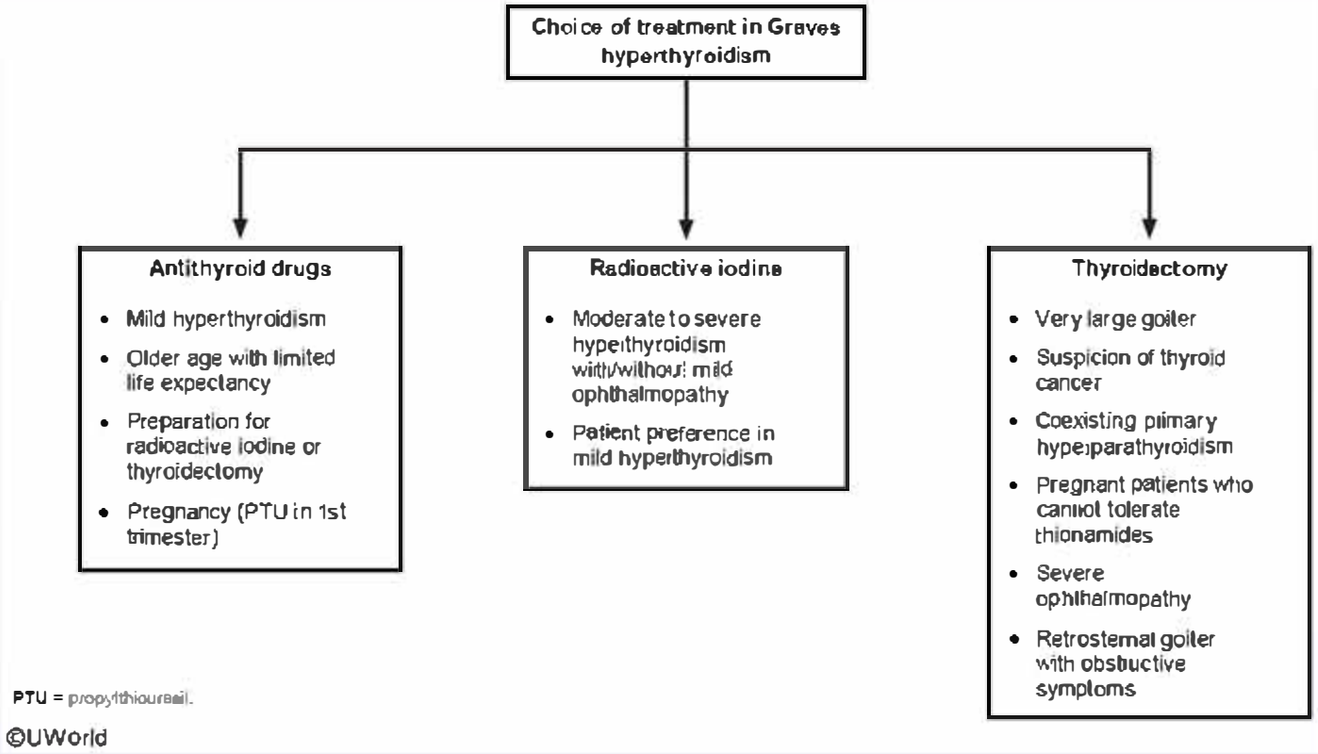
- ✔ A. Development of hypothyroidism over months to years [71%]
- B. Disappearance of thyroid-stimulating immunoglobulins [0%]
- ✘ C. Increased risk of papillary thyroid cancer [4%]
- D. Iodine-induced blockage of thyroid hormone synthesis [17%]
- E. Rapid normalization of thyroid hormone levels [3%]
- F. Symptom improvement without hormonal changes [1%]

Incorrect
Correct answer

71%
Answered correctly

9 Seconds
Time Spent

07/31/2018
Last Updated



This patient has symptomatic hyperthyroidism (low TSH and elevated T4 levels) associated with an elevated titer of thyroid-stimulating immunoglobulins, consistent with **Graves disease**. The 3 primary treatment options in Graves disease include **radioactive iodine (RAI) therapy**, antithyroid drugs, and surgical thyroidectomy. RAI (^{131}I) is taken up by the thyroid follicular cells in a manner similar to that of natural iodine, and the subsequent beta emission induces slow necrosis of the thyroid follicular cells. This leads to clinical and biochemical resolution of hyperthyroidism over the subsequent 6-18 weeks (not rapidly) **(Choice E)**.

The goal of RAI in Graves disease is to administer a sufficient dose of radiation to prevent recurrence of hyperthyroidism. However, the diffuse uptake of radioiodine eventually leads to **permanent hypothyroidism** within months in >90% of patients. In contrast, when RAI is used to treat toxic nodular goiter and toxic adenoma, the radioisotope is taken up only by the autonomous thyroid tissue, and the function of the remaining normal tissue is usually adequate to prevent permanent hypothyroidism.

(Choice B) RAI can acutely worsen Graves ophthalmopathy due to increased titers of thyroid-stimulating immunoglobulins (autoantibodies). Thyroidectomy is preferred in those with significant ocular manifestations.

(Choice C) There is no significant increased risk of thyroid cancer or overall cancer mortality in patients treated with RAI for Graves disease.

(Choice D) Pharmacologic doses of iodine (eg, in potassium iodide solutions) are occasionally used to transiently reduce the synthesis and release of thyroid hormones in patients with Graves disease. In contrast, the dose of iodine used in RAI, although sufficient to induce radiation necrosis, is much lower than that required to biochemically inhibit thyroid hormone synthesis.

(Choice F) Thyroid hormone increases sensitivity to catecholamines, and many of the symptoms of hyperthyroidism are mediated by the resulting hyperadrenergic state. Beta blockers can be used to blunt these symptoms without altering thyroid hormone levels, but RAI therapy drastically decreases hormone production.

Educational objective:
Radioiodine therapy for Graves disease leads to resolution of hyperthyroidism in 6-18 weeks, but the dose needed for treatment gradually leads to permanent hypothyroidism in most patients. This therapy can also acutely worsen

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(Choice F) Thyroid hormone increases sensitivity to catecholamines, and many of the symptoms of hyperthyroidism are mediated by the resulting hyperadrenergic state. Beta blockers can be used to blunt these symptoms without altering thyroid hormone levels, but RAI therapy drastically decreases hormone production.

Educational objective:
Radioiodine therapy for Graves disease leads to resolution of hyperthyroidism in 6-18 weeks, but the dose needed for treatment gradually leads to permanent hypothyroidism in most patients. This therapy can also acutely worsen Graves ophthalmopathy due to increased titers of thyroid-stimulating autoantibodies.

References

- Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists.
- Radioiodine therapy for hyperthyroidism.

A 32-year-old woman with a 13-year history of type 1 diabetes mellitus comes to the hospital with palpitations and shortness of breath. She has had these symptoms for the last several months, but they have worsened recently. The patient also has experienced anxiety, poor sleep, and unintentional weight loss that she attributes to drinking too much coffee at work. She drinks 2 8-oz cups of coffee daily and a glass of red wine on weekends. The patient's diabetes is managed with a regimen of insulin glargine and insulin lispro, and she has had good glycemic control in the past. However, in the last few months she has had rising home glucose readings and has required increasing insulin doses to maintain control. The patient has also had irregular menstrual periods, for which she was started on a combination estrogen-progesterone oral contraceptive pill 2 months ago. CT scan of the chest with contrast performed in the emergency department shows no evidence of pulmonary embolism, and the patient is admitted for additional evaluation. Following admission, she develops nausea and vomiting. Six hours later, the patient is found to be confused, diaphoretic, and agitated. Her temperature is 38.9 C (102 F), blood pressure is 145/65 mm Hg, and pulse is 154/min. The chest is clear to auscultation. Examination of skin and abdomen is unremarkable. Laboratory results are as follows:

Serum chemistry

Sodium	136 mEq/L
Potassium	4 mEq/L
Chloride	106 mEq/L

Chloride	106 mEq/L
Bicarbonate	22 mEq/L
Blood urea nitrogen	28 mg/dL
Creatinine	1.2 mg/dL
Calcium	9.6 mg/dL
Glucose	320 mg/dL

Liver function studies

Albumin	3.7 g/dL
Total bilirubin	2.3 mg/dL
	1.3

Liver function studies

Albumin	3.7 g/dL
Total bilirubin	2.3 mg/dL
Direct bilirubin	1.3 mg/dL
Aspartate aminotransferase (AST)	62 U/L
Alanine aminotransferase (ALT)	74 U/L

Which of the following is the most likely diagnosis?

A. Delayed iodine allergy
B. Diabetic ketoacidosis
C. Hepatic encephalopathy
D. Subsegmental pulmonary emboli
E. Thyrotoxic crisis

A 66-year-old man with a 10-year history of type 2 diabetes mellitus comes to the office due to burning and stabbing pain in his feet for the past few months. The pain is severe enough to interfere with his daily activities and is worse at night. His medical history is notable for hypertension, hyperlipidemia, and coronary artery disease with a non-ST elevation myocardial infarction 4 years ago. The patient is on a mixed regimen of insulin glargine and insulin aspart, in addition to other medications, including metoprolol, valsartan, atorvastatin, and aspirin. On physical examination, there is loss of ankle reflexes bilaterally, with loss of vibratory sensation and altered proprioception below the knees. Hemoglobin A1c is 8.6% and serum creatinine is 1.55 mg/dL. In addition to optimizing glycemic control, which of the following is the most appropriate medication for management of this patient's current symptoms?

A. Amitriptyline
B. Ketorolac
C. Oxycodone
D. Prednisone
E. Pregabalin

Submit

A 66-year-old man with a 10-year history of type 2 diabetes mellitus comes to the office due to burning and stabbing pain in his feet for the past few months. The pain is severe enough to interfere with his daily activities and is worse at night. His medical history is notable for hypertension, hyperlipidemia, and coronary artery disease with a non-ST elevation myocardial infarction 4 years ago. The patient is on a mixed regimen of insulin glargine and insulin aspart, in addition to other medications, including metoprolol, valsartan, atorvastatin, and aspirin. On physical examination, there is loss of ankle reflexes bilaterally, with loss of vibratory sensation and altered proprioception below the knees. Hemoglobin A1c is 8.6% and serum creatinine is 1.55 mg/dL. In addition to optimizing glycemic control, which of the following is the most appropriate medication for management of this patient's current symptoms?

- A. Amitriptyline [18%]
- B. Ketorolac [1%]
- ✗ C. Oxycodone [1%]
- D. Prednisone [0%]
- ✓ E. Pregabalin [78%]

Incorrect
Correct answer
E

78%
Answered correctly

5 Seconds
Time Spent

10/05/2018
Last Updated

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

CNS = central nervous system.

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This patient with uncontrolled diabetes mellitus (elevated hemoglobin A1c) has neuropathic pain and symmetric distal neurologic deficits (eg, loss of reflexes, altered vibration and proprioception) consistent with sensorimotor

This patient with uncontrolled diabetes mellitus (elevated hemoglobin A1c) has neuropathic pain and symmetric distal neurologic deficits (eg, loss of reflexes, altered vibration and proprioception) consistent with sensorimotor **polyneuropathy due to diabetes mellitus**. The clinical features of diabetic neuropathy depend on the type of nerve fibers involved; small fiber neuropathy predominantly causes pain, allodynia, and paresthesias, whereas large fiber involvement causes more numbness, loss of proprioception, diminished vibration sense, and loss of ankle reflexes. Both types are commonly seen together. As diabetic neuropathy progresses, the pain may diminish but the sensory deficits persist.

Initial treatment options for painful diabetic neuropathy include tricyclic antidepressants (eg, amitriptyline), dual serotonin norepinephrine reuptake inhibitors (eg, duloxetine), and anticonvulsants (eg, pregabalin, gabapentin). **Pregabalin** is a structural analogue of gamma-aminobutyric acid and decreases pain by inhibiting the release of excitatory neurotransmitters by binding to voltage-gated calcium modulators on nerve terminals. Common side effects are drowsiness, weight gain, and fluid retention.

(Choice A) Although amitriptyline is effective for reducing neuropathic pain, it should be used with caution in patients age >65 due to its anticholinergic effects, and it is not recommended in patients with pre-existing cardiac disease due to the risk of precipitating conduction abnormalities.

(Choice B) NSAIDs (eg, ketorolac) are more effective for somatic (eg, joint pain) than neuropathic pain. Also, they are relatively contraindicated in patients on antiplatelet therapy for coronary artery disease and those with renal insufficiency.

(Choice C) Opioids (eg, oxycodone) are possibly effective for painful diabetic neuropathy, but evidence for their effectiveness is limited, and they are not recommended as initial treatment due to the risk of abuse and

(Choice A) Although amitriptyline is effective for reducing neuropathic pain, it should be used with caution in patients age >65 due to its anticholinergic effects, and it is not recommended in patients with pre-existing cardiac disease due to the risk of precipitating conduction abnormalities.

(Choice B) NSAIDs (eg, ketorolac) are more effective for somatic (eg, joint pain) than neuropathic pain. Also, they are relatively contraindicated in patients on antiplatelet therapy for coronary artery disease and those with renal insufficiency.

(Choice C) Opioids (eg, oxycodone) are possibly effective for painful diabetic neuropathy, but evidence for their effectiveness is limited, and they are not recommended as initial treatment due to the risk of abuse and dependence.

(Choice D) Systemic glucocorticoids (eg, prednisone) can be used for chronic inflammatory demyelinating neuropathy, a rare disorder that can cause distal paresthesias and numbness; these patients typically have motor weakness in the upper and lower extremities.

Educational objective:
Initial treatment options for painful diabetic neuropathy include tricyclic antidepressants, dual serotonin norepinephrine reuptake inhibitors, and anticonvulsants. Pregabalin decreases pain by inhibiting the release of excitatory neurotransmitters.

References

A 24-year-old primigravida comes to the office for her first prenatal visit. Her last menstrual period was 8 weeks ago and 2 home pregnancy tests have been positive. The patient feels generally well, although she has experienced mild intermittent nausea and anxiety during the pregnancy. Medical history is unremarkable, and her only medication is an over-the-counter prenatal vitamin. Thyroid function tests were normal on evaluation for fatigue and mild palpitations 6 months ago. The patient stopped drinking alcohol after finding out she was pregnant, and she does not use tobacco or illicit drugs. Blood pressure is 120/80 mm Hg and pulse is 82/min. Physical examination findings are normal. Pelvic ultrasound shows a gestational sac containing a fetal pole and a yolk sac. Thyroid function study results are as follows:

	Today	Six months ago
TSH	0.3 µU/mL	2.0 µU/mL
Total thyroxine (T4)	15 µg/dL	8 µg/dL
Total triiodothyronine (T3)	220 ng/dL	130 ng/dL

Which of the following is the most likely cause of this patient's current laboratory findings?

A. Euthyroid sick syndrome

yolk sac. Thyroid function study results are as follows:

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TSH	0.3 µU/mL	2.0 µU/mL
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Which of the following is the most likely cause of this patient's current laboratory findings?

- A. Euthyroid sick syndrome
- B. Graves disease
- C. Hashimoto disease
- D. Iodine deficiency
- E. Normal physiologic changes
- F. Subacute thyroiditis

		ago
TSH	0.3 μU/mL	2.0 μU/mL
Total thyroxine (T4)	15 μg/dL	8 μg/dL
Total triiodothyronine (T3)	220 ng/dL	130 ng/dL

Which of the following is the most likely cause of this patient's current laboratory findings?

- ✗ A. Euthyroid sick syndrome [2%]
- B. Graves disease [13%]
- C. Hashimoto disease [2%]
- D. Iodine deficiency [0%]
- ✓ E. Normal physiologic changes [74%]
- F. Subacute thyroiditis [6%]

Incorrect
Correct answer

74%
Answered Correctly

8 Seconds
Time Spent

09/14/2018
Last Updated

Maternal thyroid testing in pregnancy, first trimester		
Hormone	**Change**	**Mechanism**
Total T4	Increased	• β-hCG stimulates thyroid hormone production in first trimester • Estrogen stimulates TBG; thyroid increases hormone production to maintain steady free T4 levels
Free T4	Unchanged or mildly increased	
TSH	Decreased	• Increased β-hCG & thyroid hormone suppress TSH secretion

β-hCG = β-human chorionic gonadotropin; TBG = thyroxine-binding globulin.

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Thyroid hormone production increases during pregnancy to cope with metabolic demands. This is accomplished by 2 mechanisms:

- **Estrogen** stimulates synthesis of **thyroxine-binding globulin** (TBG) and decreases TBG clearance, leading to an increased pool of bound thyroid hormone. Patients with normal thyroid reserve subsequently increase thyroid hormone production to maintain free hormone levels.
- **hCG** (which shares a common alpha subunit with TSH and a very similar beta subunit) directly stimulates **TSH receptors**. This results in increased hormone production with feedback suppression of pituitary TSH release.

In patients with normal thyroid function, the net effect (as seen in this patient) can resemble subclinical

In patients with normal thyroid function, the net effect (as seen in this patient) can resemble subclinical hyperthyroidism with **increased** circulating **total T3 and T4**, **normal** (or mildly elevated) **free T4**, and **suppressed TSH**, although the patient remains clinically euthyroid. However, patients with impaired thyroid function (eg, chronic lymphocytic [Hashimoto] thyroiditis) cannot increase thyroid hormone production, resulting in a relative hypothyroid state **(Choice C)**. For this reason, patients with baseline hypothyroidism who become pregnant should have their replacement thyroxine dose increased.

(Choice A) Euthyroid sick syndrome is an alteration in biochemical thyroid function tests in the setting of severe nonthyroid illness. Common findings include a low total and free T3 with a normal T4 and TSH.

(Choice B) Graves disease causes an increase in total and free thyroid hormone levels. However, most patients will have additional manifestations, such as proptosis, diffuse goiter, hypertension, and tachycardia.

(Choice D) Iodine requirements increase during pregnancy, and inadequate iodine intake can cause maternal and fetal hypothyroidism. Such patients would have an elevated TSH with decreased thyroid hormone levels.

(Choice F) Subacute (granulomatous or De Quervain) thyroiditis can cause hyperthyroidism with a suppressed TSH. However, it most commonly follows an acute viral illness and is associated with a painful, tender goiter.

Educational objective:
Thyroid hormone production increases during pregnancy to cope with metabolic demands. Estrogen causes an increase in thyroxine-binding globulin, leading to increased total (but not free) thyroid hormone levels. hCG directly stimulates TSH receptors, causing increased production of thyroid hormones.

A 42-year-old woman comes to the emergency department due to 2 syncopal episodes in the last 3 days. The patient was well until approximately a month ago when she began to feel increasingly fatigued and weak. For the past 2 weeks, she has had anorexia, nausea, and abdominal pain. The patient's medical history is unremarkable, and she takes no medications. She drinks wine only on social occasions, and does not use tobacco or illicit drugs. Temperature is 36.7 C (98 F), blood pressure is 86/52 mm Hg, pulse is 90/min, and respirations are 18/min. Cardiopulmonary examination is normal. The abdomen is mildly tender with otherwise normal findings. The skin shows hyperpigmentation in the palmar creases. Which of the following additional findings is most likely present in this patient?

- A. Hyperglycemia
- B. Hyperkalemia
- C. Hypernatremia
- D. Hypocalcemia
- E. Hypochloremia

Submit

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- ✗ A. Hyperglycemia [13%]
- ✓ B. Hyperkalemia [70%]
- C. Hypernatremia [7%]
- D. Hypocalcemia [4%]
- E. Hypochloremia [3%]

Incorrect
Correct answer
B

70%
Answered correctly

5 Seconds
TimeSpent

06/18/2018
Last Updated

Clinical features of primary adrenal insufficiency	
Etiology	• **Autoimmune** • Infections (eg, tuberculosis, HIV, disseminated fungal) • Hemorrhagic infarction • Metastatic
Clinical presentation	• 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** & high-dose (250 µg) **ACTH stimulation test** • Primary adrenal insufficiency: Low cortisol, high ACTH • Secondary/tertiary adrenal insufficiency: Low cortisol, low ACTH

This patient has typical features of **primary adrenal insufficiency** (PAI), also known as Addison disease. The initial symptoms of PAI often are nonspecific and can include **fatigue**, malaise, weakness, and **weight loss**. **Gastrointestinal symptoms** (eg, nausea, abdominal pain, diarrhea) occur in up to 90% of patients. Aldosterone deficiency causes **volume depletion** and can manifest as hypotension, postural dizziness, or syncope. Skin signs

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Hyponatremia is the most common electrolyte abnormality in PAI, affecting up to 90% of patients **(Choice C)**. In PAI, loss of mineralocorticoid secretion leads to urinary loss of sodium, volume depletion, and a compensatory increase in the release of antidiuretic hormone (ADH). In addition, cortisol deficiency triggers increased secretion of corticotropin-releasing hormone, which directly stimulates ADH release. The resulting retention of free water leads to dilutional hyponatremia. Conversely, aldosterone deficiency causes **hyperkalemia** in a majority of patients, sometimes accompanied by a mild hyperchloremic acidosis **(Choice E)**.

(Choice A) Hypoglycemia is a potential complication of PAI and can be triggered by fasting, infection, or alcohol consumption. Hyperglycemia is not seen in the absence of preexisting type 1 diabetes mellitus.

(Choice D) PAI can cause mild hypercalcemia due to increased release of calcium from the bones, increased proximal tubular reabsorption, and volume contraction. PAI with concurrent hypoparathyroidism leading to hypocalcemia can be seen in the polyglandular autoimmune syndrome type 1 but is extremely rare.

Educational objective:

Chronic adrenal insufficiency presents with weight loss, fatigue, and gastrointestinal symptoms. Volume depletion

deficiency causes **volume depletion** and can manifest as hypotension, postural dizziness, or syncope. Skin signs can include generalized or patchy hyperpigmentation (due to cosecretion of melanocyte-stimulating hormone with ACTH) and vitiligo (due to autoimmune destruction of melanocytes).

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Educational objective:
Chronic adrenal insufficiency presents with weight loss, fatigue, and gastrointestinal symptoms. Volume depletion can cause hypotension and syncope. Most patients have hyponatremia due to renal sodium loss and increased release of antidiuretic hormone. Hyperkalemia is also common due to mineralocorticoid deficiency.

A 75-year-old woman comes to the office after 2 months of heat intolerance, sweating, and palpitations. The patient has lost significant weight recently despite increasing her dietary intake. Medical history is notable only for hypertension, for which she takes amlodipine. Temperature is 37.2 C (99 F), blood pressure is 116/80 mm Hg, pulse is 120/min and regular, and respirations are 18/min. Physical examination shows a nontender, diffuse swelling in the front of her neck that moves upward with swallowing. There is no proptosis or pretibial myxedema. Fine hand tremors and hyperreflexia are noted on neurological examination. Laboratory results are as follows:

Leukocytes	Normal
Serum creatinine	1.0 mg/dL
TSH	<0.001 µU/mL
Triiodothyronine (T3)	500 ng/dL
Free thyroxine (T4)	4.7 ng/dL (0.9-1.7 ng/dL)

Radioactive iodine uptake at 24 hours is significantly increased and homogenously distributed throughout the thyroid gland. The patient is started on a beta blocker. Which of the following is the best next step in management of this patient?

A. No additional treatment

B. Radioactive iodine therapy

Leukocytes	Normal
Serum creatinine	1.0 mg/dL
TSH	<0.001 µU/mL
Triiodothyronine (T3)	500 ng/dL
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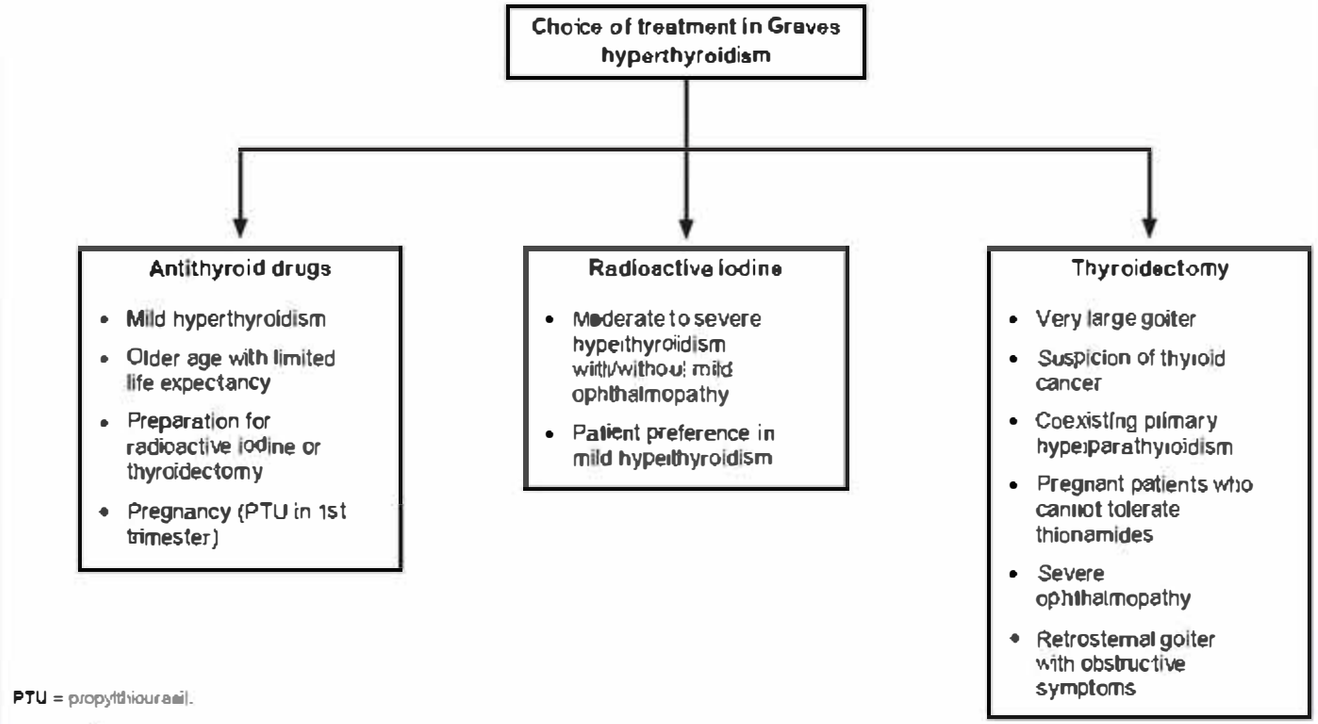
- A. No additional treatment
- B. Radioactive iodine therapy
- C. Start methimazole
- D. Start potassium iodine
- E. Start prednisone
- F. Thyroidectomy

Leukocytes	Normal
Serum creatinine	1.0 mg/dL
TSH	<0.001 µU/mL
Triiodothyronine (T3)	500 ng/dL
Free thyroxine (T4)	4.7 ng/dL (0.9-1.7 ng/dL)

Radioactive iodine uptake at 24 hours is significantly increased and homogenously distributed throughout the thyroid gland. The patient is started on a beta blocker. Which of the following is the best next step in management of this patient?

- A. No additional treatment [2%]
- ✗ B. Radioactive iodine therapy [36%]
- ✓ C. Start methimazole [49%]
- D. Start potassium iodine [2%]
- E. Start prednisone [2%]
- F. Thyroidectomy [6%]



This patient has severe hyperthyroidism along with a diffuse goiter and homogeneous radioiodine uptake consistent with **Graves disease**. The 3 modalities for treatment of Graves disease include **antithyroid drugs** (ATDs) (eg, propylthiouracil, methimazole), **radioactive iodine** (RAI), and **thyroidectomy**. Most patients will require RAI or thyroidectomy.

Patients with mild disease, small goiters, and low TSH receptor antibody titers can be managed with an ATD alone and have a 50% likelihood of permanent remission. ATD therapy alone is also used in pregnant women or older

Patients with mild disease, small goiters, and low TSH receptor antibody titers can be managed with an ATD alone and have a 50% likelihood of permanent remission. ATD therapy alone is also used in pregnant women or older patients with limited life expectancy.

In patients who have significant symptoms and thyroid hormone levels ≥2-3 times normal, an ATD with a beta blocker is initially recommended to stabilize the patient before definitive treatment with RAI or thyroidectomy. Pretreatment with ATDs is also recommended for patients at increased risk (eg, elderly, significant comorbidities) for complications due to the transient worsening of hyperthyroidism following RAI treatment. In light of this patient's age and severe thyrotoxicosis, treatment with an ATD is recommended prior to definitive treatment with RAI **(Choice B)**.

(Choice A) Beta blockers alone are usually sufficient during the thyrotoxic phase of silent or painless thyroiditis but would not be adequate treatment for patients with Graves disease and significant thyrotoxicosis.

(Choice D) Potassium iodide inhibits thyroid hormone synthesis and release. It is used mainly in preparation for thyroidectomy in Graves disease and for treating thyroid storm.

(Choice E) Systemic glucocorticoids are used for thyroid storm, type 2 amiodarone-induced thyrotoxicosis, and severe cases of subacute (de Quervain) thyroiditis.

(Choice F) Thyroidectomy is preferred over RAI in some patients with Graves hyperthyroidism, especially those with a large goiter or a coexisting thyroid nodule suspicious for cancer. Thyroidectomy is also advised for patients with severe Graves ophthalmopathy in whom RAI is contraindicated.

Educational objective:

patient's age and severe thyrotoxicosis, treatment with an ATD is recommended prior to definitive treatment with RAI **(Choice B)**.

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Educational objective:
Graves disease can be treated with antithyroid drugs, radioactive iodine, or thyroidectomy. Antithyroid drugs are used for patients with mild disease who are likely to have a permanent remission. They are also used in preparation for treatment with radioactive iodine in patients with significant hyperthyroidism or who are at increased risk of complications.

References

A 17-year-old boy is brought to the emergency department following a motor vehicle accident. He is found to have an extensive cerebral hemorrhage leading to deep coma, as well as fractures of the C4 vertebra, pelvis, and right femur. Following admission to the hospital, he is intubated and central lines are placed. The patient develops acute renal failure due to rhabdomyolysis, which improves rapidly with treatment. He is extubated after regaining consciousness. He also undergoes percutaneous endoscopic gastrostomy tube placement due to persistent problems with swallowing. The patient is unable to ambulate due to quadriparesis resulting from cervical cord injury. Four weeks after his initial injury, he develops nausea and polyuria. His laboratory results are as follows:

Calcium	12.1 mg/dL
Albumin	3.0 g/dL
Creatinine	1.4 mg/dL
Phosphorus	3.1 mg/dL
Glucose	108 mg/dL
Parathyroid hormone	9 pg/mL
Parathyroid hormone-related protein	undetectable

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1,25-dihydroxyvitamin D	19 pg/mL (normal: 20-60 pg/mL)

Which of the following is the most likely cause of this patient's hypercalcemia?

- A. Hypoalbuminemia
- B. Immobilization
- C. Malignancy
- D. Primary hyperparathyroidism
- E. Rhabdomyolysis
- F. Vitamin D-induced hypercalcemia

Submit

Parathyroid hormone-related protein	undetectable
1,25-dihydroxyvitamin D	19 pg/mL (normal: 20-60 pg/mL)

Which of the following is the most likely cause of this patient's hypercalcemia?

- ✗ A. Hypoalbuminemia [17%]
- ✓ B. Immobilization [60%]
- C. Malignancy [0%]
- D. Primary hyperparathyroidism [2%]
- E. Rhabdomyolysis [17%]
- F. Vitamin D-induced hypercalcemia [1%]

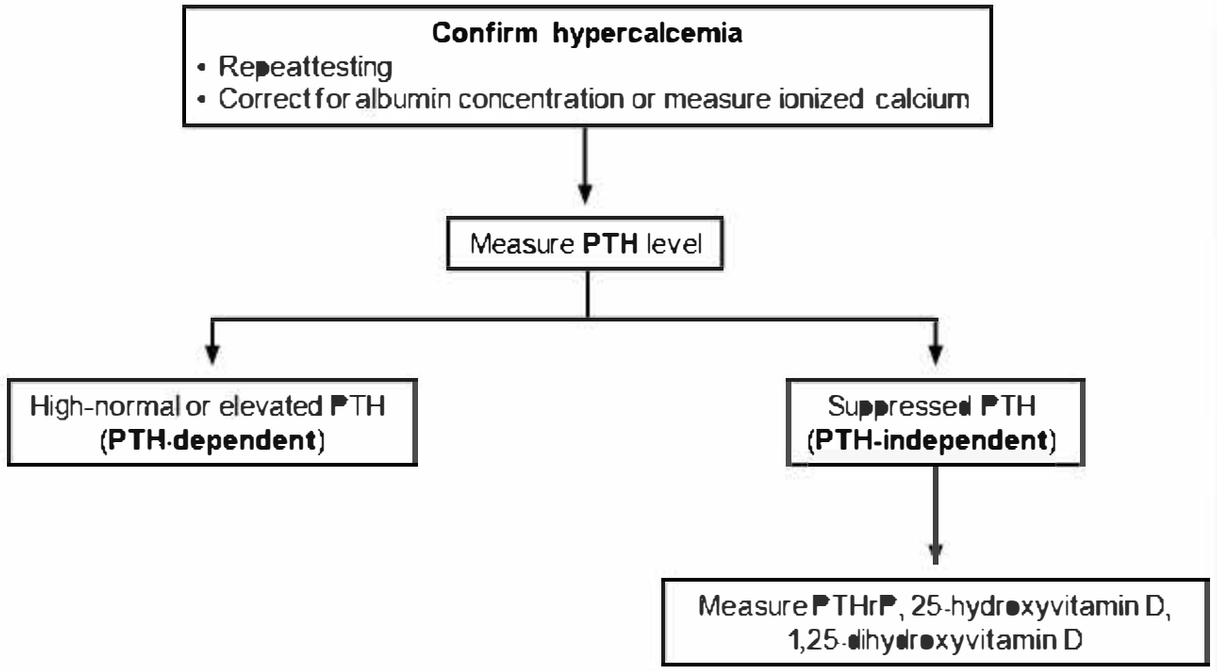
Incorrect
Correct answer

60%
Answered Correctly

9 Seconds
Time Spent

07/28/2018
Last Updated

Diagnosis of hypercalcemia



Causes
- **Primary** (or tertiary) **hyperparathyroidism**
- Familial hypocalciuric hypercalcemia
- Lithium

Causes
- **Malignancy**
- Vitamin D toxicity
- Granulomatous diseases
- Drug-induced (eg, thiazides)
- Milk-alkali syndrome
- Thyrotoxicosis
- Vitamin A toxicity
- Immobilization

This patient with quadriparesis has a corrected calcium level of 12.9 mg/dL:

$$\text{corrected calcium} = \text{measured calcium} + 0.8 \times (4 - \text{albumin})$$

$$12.1 + 0.8 \times (4 - 3) = 12.1 + 0.8 = 12.9 \text{ mg/dL}$$

with symptomatic **hypercalcemia** (nausea, polyuria) and **suppressed parathyroid hormone (PTH)** level likely due to **immobilization**. Hypercalcemia of immobilization is likely due to increased **osteoclastic bone resorption**. The risk is increased in patients with a pre-existing high rate of bone turnover (eg, younger individuals, Paget disease). The onset of hypercalcemia is usually around 4 weeks after immobilization, although patients with chronic renal insufficiency may develop hypercalcemia in as little as 3 days.

The onset of hypercalcemia due to immobilization is often insidious, and the presenting symptoms can be nonspecific. **Bisphosphonates** inhibit osteoclastic bone resorption and are effective in treating hypercalcemia of immobilization and reducing the associated bone loss.

(Choice A) Approximately 40% of circulating calcium is bound to proteins (predominantly albumin). Hypoalbuminemia will lower the total serum calcium level; therefore, measured calcium levels are corrected upward based on the extent of hypoalbuminemia. Conversely, hyperalbuminemia is associated with an increase in total calcium. In either case, the ionized fraction is unaffected, and patients will not have calcium-related symptoms directly related to the change in albumin levels.

(Choices C and F) Hypercalcemia in malignancy can be due to osteolytic metastasis, secretion of PTH-related

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(Choices C and F) Hypercalcemia in malignancy can be due to osteolytic metastasis, secretion of PTH-related protein (PTHrP), or increased formation of 1,25-dihydroxyvitamin D. This patient's PTHrP and 1,25-dihydroxyvitamin D levels are low.

(Choice D) This patient's PTH level is suppressed, which makes primary hyperparathyroidism unlikely.

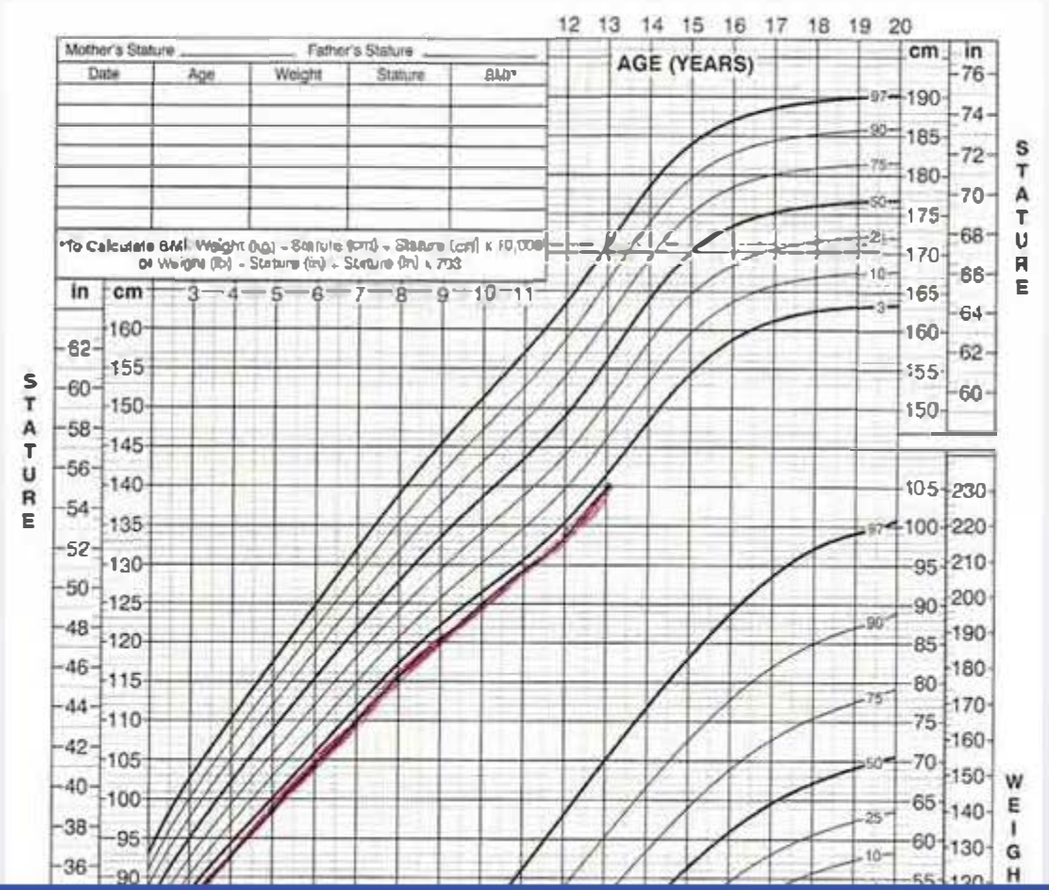
(Choice E) Acute rhabdomyolysis causes hypocalcemia due to precipitation of calcium and phosphorus in damaged muscles. Hypercalcemia can occur due to remobilization of calcium during the diuretic/recovery phase of the illness, often with concurrent hyperphosphatemia. However, this patient recovered from rhabdomyolysis several weeks before the onset of hypercalcemia.

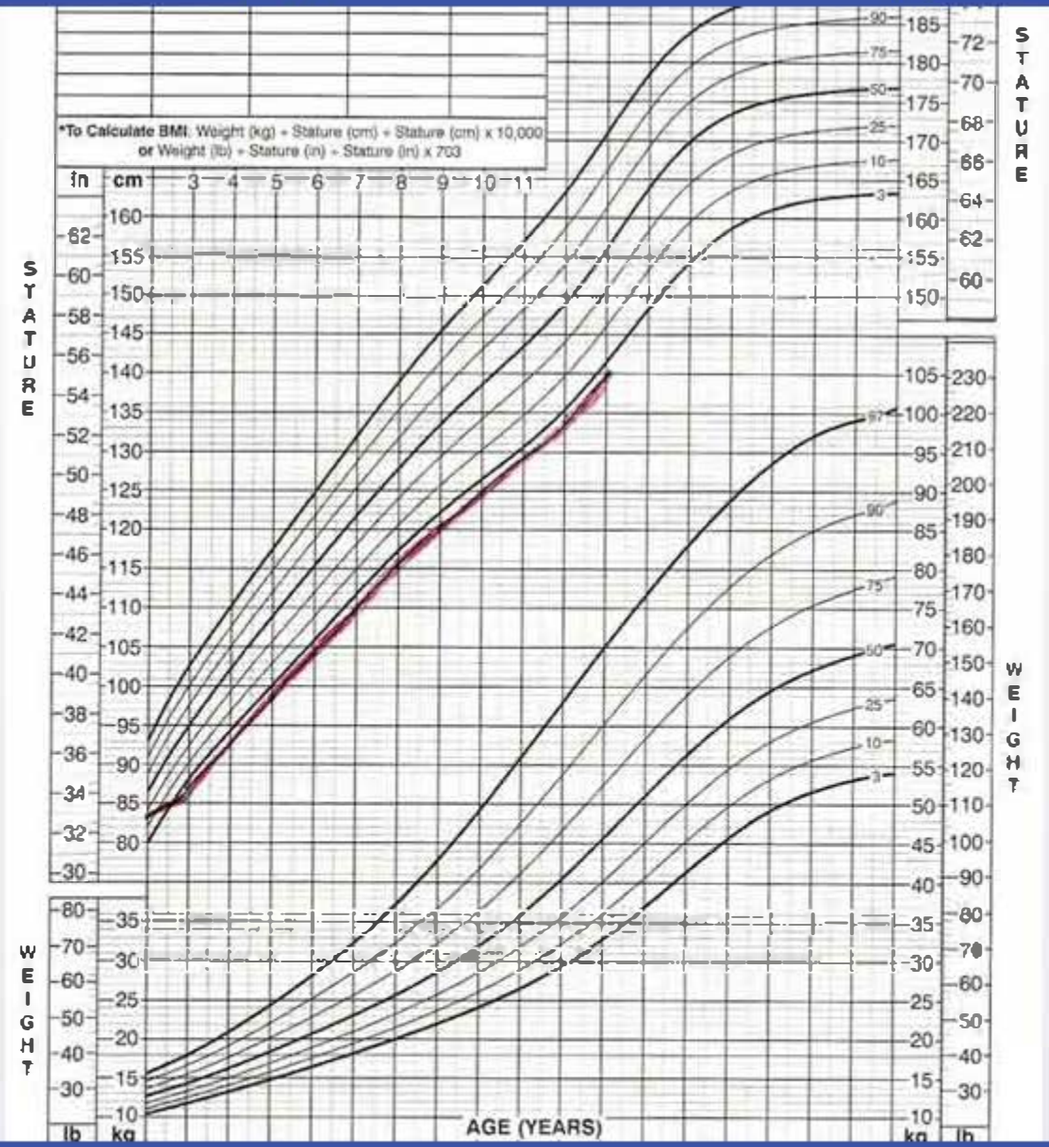
Educational objective:
Hypercalcemia can occur in prolonged immobilization due to increased osteoclastic activity, especially in individuals with a high baseline rate of bone turnover. Bisphosphonates can reduce this hypercalcemia and prevent bone loss.

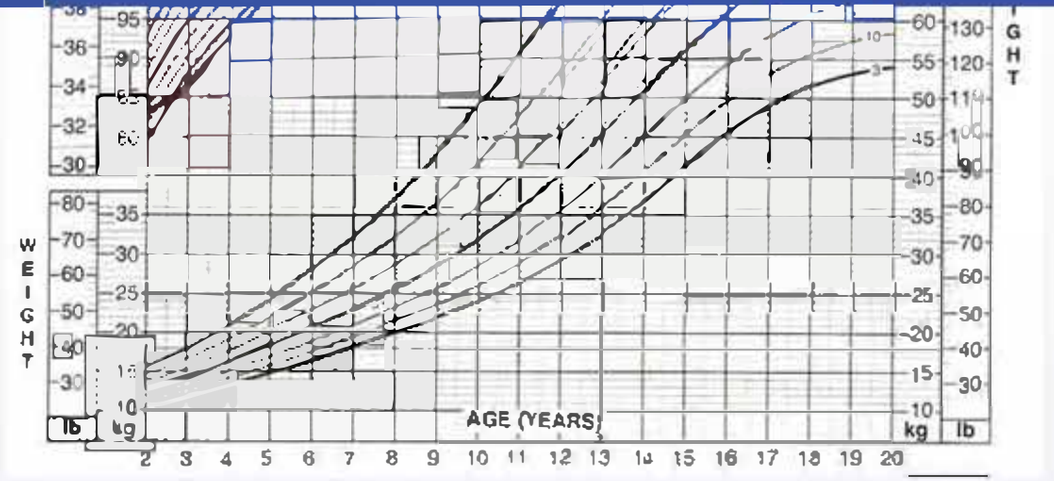
References

- Immobilization induced hypercalcemia.

A previously healthy 13-year-old boy is brought to the physician for evaluation of delayed puberty. He is worried because he is the shortest male in his class. He feels well otherwise. On examination, he is 55in (140cm) tall and weighs 40kg (88lb). His mother is 65in (165cm) tall and his father is 72in (183cm) tall. His sexual maturity score is a 2. A radiograph of his left hand is consistent with a bone age of 10-years-old. His growth chart is shown below.




*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
STATURE
WEIGHT
AGE (YEARS)
in
cm
lb
kg



Which of the following is the best next step in the management of this patient?

A. Start testosterone supplementation

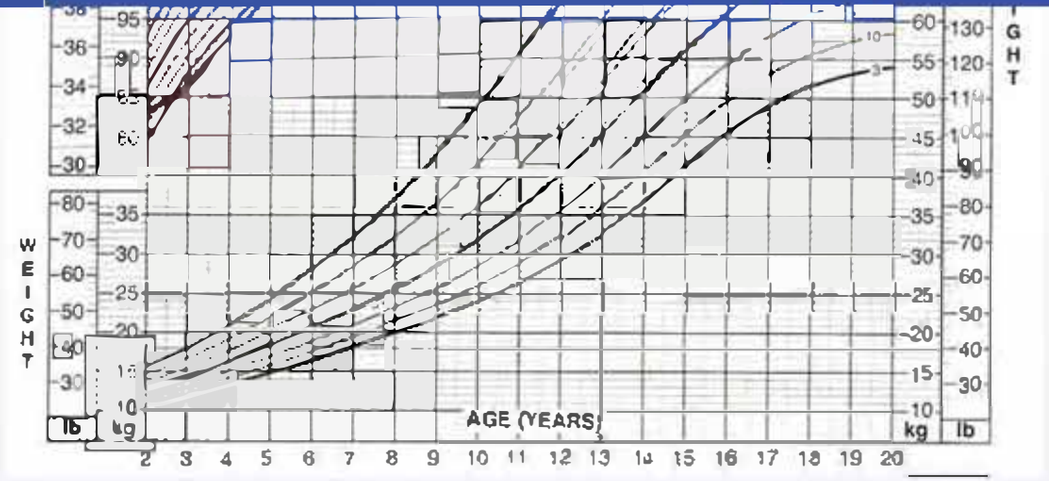
B. Begin growth hormone therapy

C. Check thyroid stimulating hormone and free thyroxine levels

D. Explain to the child that he will remain short

E. Schedule a follow up visit in 6 months

Submit



Which of the following is the best next step in the management of this patient?

- A. Start testosterone supplementation [2%]
- B. Begin growth hormone therapy [12%]
- ✗ C. Check thyroid stimulating hormone and free thyroxine levels [21%]
- D. Explain to the child that he will remain short [5%]
- ✓ E. Schedule a follow up visit in 6 months [57%]

Incorrect
Correct answer

57%
Answered correctly

24 Seconds
Time Spent

11/05/2018
Last Updated

Constitutional growth delay is the most common cause of short stature and pubertal delay in adolescents. Affected individuals have a normal birth weight and height, but between 6 months to 3 years of age, the height growth velocity slows, and the child drops percentiles on their growth curve. Around 3 years of age, the child regains a normal growth velocity and follows the growth curve at the 5^{th} to 10^{th} percentile. Puberty and the adolescent growth spurt are delayed, but eventually occur. The child will have a normal growth spurt and reach a normal adult height. Bone age radiographs show a bone age that is delayed compared to the chronological age.

(Choice A) Testosterone supplementation is not necessary with constitutional growth delay. Hormone supplementation may speed up puberty, but this will shorten the growth spurt and may result in a shorter final adult height.

(Choice B) Patients with constitutional growth delay are not deficient in growth hormone and therefore, supplementation is not necessary.

(Choice C) Hypothyroidism can cause growth delay and should be considered in the differential diagnosis for this child. However, the expected pattern would be normal childhood growth followed by an abrupt "falling off the growth curve" when the hypothyroidism develops. An affected patient would also be expected to have other symptoms like fatigue, constipation, cold intolerance, and dry hair and skin.

(Choice D) This patient has a delayed bone age, is not in puberty, and has not yet had his pubertal growth spurt. Once he reaches puberty, a normal growth spurt will occur and he will attain a normal adult height.

Educational objective:

Constitutional growth delay is characterized by a delayed growth spurt, delayed puberty, and delayed bone age.

A 4-month-old boy is brought to the emergency department after an episode of generalized tonic-clonic seizure 30 minutes ago. The patient was born at 40 weeks gestation by spontaneous vaginal delivery. He was at the 50th percentile for height and weight, and had a normal physical examination. Since birth, the patient has had 3 episodes of upper respiratory infection and otitis media. His parents and older sister have no medical problems. On examination, the patient is lethargic. He weighs 4.2 kg (9.3 lb, <5th percentile). The anterior fontanelle is flat. Pupils are reactive with normal fundi. His tympanic membranes and pharynx are normal. He has round cheeks and a doll-like face. Heart sounds are normal without murmurs. Lungs are clear. The abdomen is protuberant and the liver is palpable 4 cm below the right costal margin. Extremities are thin. Laboratory results are as follows:

Serum chemistry		
Sodium	136 mEq/L	
Chloride	96 mEq/L	
Bicarbonate	16 mEq/L	
Glucose	38 mg/dL	
Lactic acid	24 mg/dL	(normal: 6-16 mg/dL)

Urine dipstick is positive for ketones. Serum triglyceride and uric acid levels are increased. Which of the following is the most likely cause of this patient's condition?

A. Excessive endogenous insulin production

the liver is palpable 5 cm below the right costal margin. Extremities are thin. Laboratory results are as follows:

Serum chemistry		
Sodium	136 mEq/L	
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A. Excessive endogenous insulin production
B. Glucocerebrosidase enzyme deficiency
C. Impaired glycogen to glucose conversion
D. Inability to break fatty acid chains
E. Inadequate total body glycogen stores

Submit

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Urine dipstick is positive for ketones. Serum triglyceride and uric acid levels are increased. Which of the following is the most likely cause of this patient's condition?

- ✗ A. Excessive endogenous insulin production [3%]
- B. Glucocerebrosidase enzyme deficiency [18%]
- ✓ C. Impaired glycogen to glucose conversion [56%]
- D. Inability to break fatty acid chains [14%]
- E. Inadequate total body glycogen stores [6%]

Windows Media Player

Glucose-6-phosphatase deficiency (type I glycogen storage disease, von Gierke disease) is caused by deficient glucose-6-phosphatase in the liver, kidneys, and intestinal mucosa. This results in impaired conversion of glycogen to glucose, leading to **glycogen accumulation** in the affected organs. Patients typically present at age 3-4 months with **hypoglycemia** (often resulting in **seizures**) and **lactic acidosis** (due to buildup in the liver). Other laboratory findings include **hyperuricemia** and hyperlipidemia. Physical examination demonstrates a **doll-like** face with rounded cheeks, thin extremities, short stature, and a protuberant abdomen due to **hepatomegaly**. The spleen and heart are not involved.

(Choice A) Excessive endogenous insulin production at this age could be a result of persistent hyperinsulinemic hypoglycemia of infancy (PHHI), which would also cause hypoglycemia, poor feeding, and poor tone. However, PHHI is often associated with infants of mothers who are diabetic (whereas this patient's mother has no medical problems) and usually presents in the first few days of life with macrosomia (rather than failure to thrive).

(Choice B) Glucocerebrosidase enzyme deficiency results in Gaucher disease. Glucocerebroside accumulates in macrophages of the liver, spleen, and bone marrow, causing bone pain and cytopenias. Hepatosplenomegaly is present, but hypoglycemia and lactic acidosis are not typical.

(Choice D) The inability to break down fatty acid chains is a feature of fatty acid cycle disorders such as medium-chain acyl-CoA dehydrogenase deficiency (MCAD). MCAD results in episodes of hypoketotic hypoglycemia during fasting states (eg, illness). Elevated lactic acid, elevated uric acid, and characteristic facial features are not typically seen.

(Choice E) Inadequate total body glycogen stores may occur in newborns as a result of prematurity or intrauterine

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(Choice E) Inadequate total body glycogen stores may occur in newborns as a result of prematurity or intrauterine growth restriction. Hypoglycemia is very common in these newborns; however, it typically occurs within the first 24 hours of life, would not persist at age 4 months, and would not be associated with specific facial features.

Educational objective:
Glucose-6-phosphatase deficiency (type I glycogen storage disease, von Gierke disease) presents at age 3-4 months with hypoglycemia (often with seizures), lactic acidosis, hyperuricemia, and hyperlipidemia. Patients typically have a doll-like face, thin extremities, short stature, and a protuberant abdomen (due to hepatomegaly).

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A 60-year-old man is admitted to the hospital with right lower lobe pneumonia. His medical history is significant for hypertension, diabetes mellitus, stage 3 chronic kidney disease, severe degenerative disease of the spine, and hypothyroidism due to thyroidectomy 5 years ago. He is a chronic smoker with a 40-pack-year history. During his hospitalization, the laboratory report shows decreased serum calcium and increased phosphate levels. Further evaluation shows an increased serum parathyroid hormone level. Which of the following medical conditions is most likely responsible for this patient's abnormal laboratory findings?

- A. Hypomagnesemia
- B. Primary hyperparathyroidism
- C. Renal failure
- D. Thyroidectomy
- E. Vitamin D deficiency

Submit

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- ✗ A. Hypomagnesemia [4%]
- B. Primary hyperparathyroidism [3%]
- ✓ C. Renal failure [79%]
- D. Thyroidectomy [5%]
- E. Vitamin D deficiency [8%]

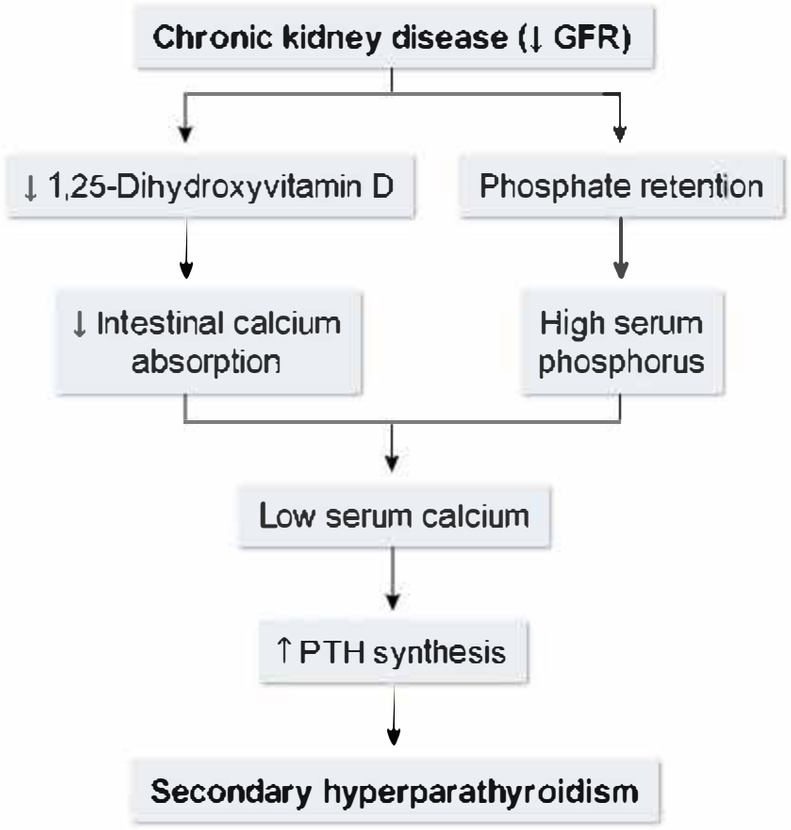
Incorrect
Correct answer
C

79%
Answered correctly

5 Seconds
TimeSpent

08/22/2018
Last Updated

Explanation



GFR = glomerular filtration rate; PTH = parathyroid hormone.

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This patient's laboratory findings are most likely due to renal failure leading to phosphate retention and resultant secondary hyperparathyroidism. Circulating parathyroid hormone (PTH) levels increase with declining glomerular

This patient's laboratory findings are most likely due to renal failure leading to phosphate retention and resultant secondary hyperparathyroidism. Circulating parathyroid hormone (PTH) levels increase with declining glomerular filtration rate (GFR), and the magnitude of PTH elevation usually correlates with severity of renal failure. Secondary hyperparathyroidism is the body's response to normalize serum calcium, phosphorus, and calcitriol in renal failure. Phosphate retention begins early with decreasing GFR and decreased renal phosphate excretion. Phosphate binds to circulating calcium and also interferes with renal production of 1,25 dihydroxyvitamin D (calcitriol). Decreased calcitriol leads to decreased intestinal calcium absorption. Both of these mechanisms cause hypocalcemia, which also stimulates PTH release from the parathyroid glands. Hyperphosphatemia directly stimulates the parathyroid glands to synthesize and release PTH.

(Choice A) Hypomagnesemia causes hypocalcemia by inducing PTH resistance and decreasing PTH secretion. As a result, hypomagnesemia could have variable PTH levels. Despite PTH resistance in hypomagnesemia, serum phosphate levels are typically normal or low in contrast to hyperphosphatemia in renal failure.

(Choice B) Typical biochemical abnormalities in primary hyperparathyroidism include hypercalcemia, elevated or inappropriately normal circulating PTH, and low to low-normal serum phosphate.

(Choice D) Thyroidectomy can cause hypoparathyroidism (not hyperparathyroidism) due to inadvertent removal of the parathyroids during surgery. However, this would lead to low PTH levels rather than the high PTH seen in this patient.

(Choice E) In addition to chronic kidney disease, vitamin D deficiency is one of the most common causes of secondary hyperparathyroidism. It usually causes low to low-normal serum phosphate and normal serum calcium

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(Choice D) Thyroidectomy can cause hypoparathyroidism (not hyperparathyroidism) due to inadvertent removal of the parathyroids during surgery. However, this would lead to low PTH levels rather than the high PTH seen in this patient.

(Choice E) In addition to chronic kidney disease, vitamin D deficiency is one of the most common causes of secondary hyperparathyroidism. It usually causes low to low-normal serum phosphate and normal serum calcium in most adult patients. Vitamin D deficiency is diagnosed by measuring 25 hydroxyvitamin D levels.

Educational objective:
Hypocalcemia, hyperphosphatemia, and increased parathyroid hormone levels are characteristic biochemical abnormalities of secondary hyperparathyroidism in chronic renal failure.

References

- Pathogenesis of secondary hyperparathyroidism.

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A 34-year-old woman comes to the office due to fatigue for the last several months. She becomes tired easily after walking short distances. She also has difficulty combing her hair due to problems holding her hands over her head for long periods. The patient reports anxiety, irritability, and an unintentional weight loss of 3.6 kg (8 lb) over the last 2 months. She has no fever or loss of appetite. The patient does not use tobacco or alcohol. Her father died of a stroke at age 54 and her mother has diabetes mellitus. On examination, the patient is afebrile with a pulse of 115/min. Cardiac examination reveals regular tachycardia with no murmur. The lungs are clear to auscultation. The patient's gait is normal, but she awkwardly drops into the chair when asked to slowly sit. The patient appears to have decreased muscle mass in her shoulders, but her muscles are nontender. Deep tendon reflexes are normal. Which of the following is the most likely cause of this patient's symptoms?

- A. Basal ganglia lesion
- B. Cerebellar dysfunction
- C. Inflammatory muscle disease
- D. Neuromuscular junction disorder
- E. Polyneuropathy
- F. Thyroid disease
- G. Upper motor neuron disease

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- A. Basal ganglia lesion [0%]
- B. Cerebellar dysfunction [0%]
- ✗ C. Inflammatory muscle disease [30%]
- D. Neuromuscular junction disorder [21%]
- E. Polyneuropathy [2%]
- ✓ F. Thyroid disease [43%]
- G. Upper motor neuron disease [1%]

Incorrect
Correct answer

43%
Answered correctly

6 Seconds
Time Spent

10/29/2018
Last Updated

General manifestations of hyperthyroidism	
Symptoms	• Anxiety & insomnia • Palpitations • Heat intolerance • Increased perspiration • Weight loss without decreased appetite
Physical examination	• Goiter • Hypertension • Tremors involving fingers/hands • Hyperreflexia • Proximal muscle weakness • Lid lag • Atrial fibrillation

This patient has proximal muscle weakness (eg, difficulty combing hair, weakness getting into or out of a chair) consistent with myopathy. This type of myopathy can be due to drugs (eg, glucocorticoids) or to connective tissue (eg, polymyositis/dermatomyositis), endocrine (eg, hypothyroidism or hyperthyroidism, Cushing disease), and neuromuscular (eg, Lambert-Eaton syndrome, myasthenia gravis) diseases. This patient has multiple features suggesting hyperthyroidism as the cause of her myopathy, including anxiety, tachycardia, and weight loss. Fatigue

This patient has proximal muscle weakness (eg, difficulty combing hair, weakness getting into or out of a chair) consistent with myopathy. This type of myopathy can be due to drugs (eg, glucocorticoids) or to connective tissue (eg, polymyositis/dermatomyositis), endocrine (eg, hypothyroidism or hyperthyroidism, Cushing disease), and neuromuscular (eg, Lambert-Eaton syndrome, myasthenia gravis) diseases. This patient has multiple features suggesting hyperthyroidism as the cause of her myopathy, including anxiety, tachycardia, and weight loss. Fatigue is common in hyperthyroidism due to chronic sympathetic hyperstimulation. Although hyperthyroidism is classically associated with hyper-reflexia, reflexes are frequently normal.

Acute **thyrotoxic myopathy** can present with severe distal or proximal **muscle weakness**, usually without bulbar or respiratory muscle involvement. Chronic hyperthyroid myopathy presents with proximal muscle weakness weeks to months after the onset of hyperthyroidism. Objective findings may include **muscle atrophy**. Treatment of hyperthyroidism usually improves the myopathy.

(Choice A) Parkinson disease involves primarily the basal ganglia. However, it is uncommon in individuals age <40, and this patient also has no other characteristic findings (eg, resting tremor, rigidity, postural instability).

(Choice B) Cerebellar disorders typically present with gait and balance problems due to unsteadiness or incoordination in the legs. Proximal muscle weakness and/or atrophy are unusual.

(Choice C) Polymyositis, an inflammatory myopathy most common in middle-age women, presents with symmetric proximal muscle weakness and tenderness. However, muscle atrophy is a late finding, and this patient has other features (eg, tachycardia, weight loss) that make thyroid disease more likely.

(Choice D) Myasthenia gravis is due to autoantibodies against the postsynaptic membrane of the neuromuscular

<10, and this patient also has no other characteristic findings (eg, resting tremor, rigidity, postural instability).

(Choice B) Cerebellar disorders typically present with gait and balance problems due to unsteadiness or incoordination in the legs. Proximal muscle weakness and/or atrophy are unusual.

(Choice C) Polymyositis, an inflammatory myopathy most common in middle-age women, presents with symmetric proximal muscle weakness and tenderness. However, muscle atrophy is a late finding, and this patient has other features (eg, tachycardia, weight loss) that make thyroid disease more likely.

(Choice D) Myasthenia gravis is due to autoantibodies against the postsynaptic membrane of the neuromuscular junction. Features include ocular (ptosis, diplopia) and facial weakness as well as bulbar muscle weakness that is worse on repetitive tasks. Isolated proximal muscle weakness is atypical.

(Choice E) Peripheral motor neuropathies typically present with distal muscle weakness and decreased deep tendon reflexes and frequently have associated sensory symptoms.

(Choice G) Upper motor neuron disease (eg, primary lateral sclerosis) causes slowness, stiffness, and clumsiness of movement rather than proximal muscle weakness and atrophy. Examination typically shows long tract signs (eg, hyper-reflexia, spasticity).

Educational objective:
Chronic hyperthyroid myopathy is characterized by proximal muscle weakness in the setting of clinical features of hyperthyroidism. Objective findings may include muscle atrophy. Treatment of hyperthyroidism usually improves the myopathy.

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A 45-year-old woman comes to the physician complaining of fatigue, weakness, and diffuse bone pain. She was diagnosed with celiac sprue 5 years ago and admits to being noncompliant with her diet. She takes over-the-counter folic acid and iron supplements. Laboratory results are as follows:

Hemoglobin	12.2 g/dL
Calcium	9.0 mg/dL
Phosphate	2.6 mg/dL (normal 3-4.5 mg/dL)
Parathyroid hormone	122 pg/mL (normal 10-65 pg/dL)
Alkaline phosphatase	234 U/L (normal 36-92 U/L)

Which of the following is directly responsible for this patient's condition?

A. Accelerated focal bone remodeling
B. Defective formation of collagen
C. Impaired osteoid matrix mineralization
D. Low bone mass with normal mineralization
E. Lytic lesions due to malignant cell infiltration

Hemoglobin	12.2 g/dL
Calcium	9.0 mg/dL
Phosphate	2.6 mg/dL (normal 3-4.5 mg/dL)
Parathyroid hormone	122 pg/mL (normal 10-65 pg/dL)
Alkaline phosphatase	234 U/L (normal 36-92 U/L)

Which of the following is directly responsible for this patient's condition?

- A. Accelerated focal bone remodeling [28%]
- B. Defective formation of collagen [0%]
- ✔ C. Impaired osteoid matrix mineralization [52%]
- D. Low bone mass with normal mineralization [13%]
- ✘ E. Lytic lesions due to malignant cell infiltration [4%]

Incorrect
Correct answer

52%
Answered correctly

32 Seconds
Time Spent

07/03/2018
Last Updated

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

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This patient's presentation suggests osteomalacia, which is due to defective mineralization of the organic bone

This patient's presentation suggests osteomalacia, which is due to defective mineralization of the organic bone matrix. During new bone formation and remodeling, osteoclasts create a cavity at the bone surface that osteoblasts fill with organic matrix (osteoid). Calcium and phosphorus then deposit in the matrix to provide adequate mineralization. As a result, calcium or phosphorus deficiency at the mineralization front will lead to inadequate mineralization of the organic matrix. Osteomalacia can occur in both children and adults (rickets - defective mineralization of the growth plate - occurs only in children). Osteomalacia is most commonly due to severe vitamin D deficiency, which may be caused by malabsorption, intestinal bypass surgery, celiac sprue, or chronic liver or kidney disease. Osteomalacia may also be caused by renal tubular acidosis (proximal, type 2) and inadequate calcium intake.

Vitamin D deficiency leads to decreased intestinal calcium and phosphorus absorption, resulting in hypocalcemia and hypophosphatemia. Hypocalcemia and low vitamin D lead to secondary hyperparathyroidism, which brings the serum calcium levels to normal or near-normal by increasing calcium reabsorption in the bone and kidney. This also leads to elevated alkaline phosphatase. The hyperparathyroidism increases urinary phosphate excretion to worsen the hypophosphatemia. As a result, vitamin D deficiency causes more marked hypophosphatemia than hypocalcemia, especially in the early stages.

Patients can be asymptomatic or develop bone pain, muscle weakness or cramps, and difficulty walking. They can eventually develop fractures (due to bone softening), particularly in the weight-bearing bones of the lower extremities. X-ray findings include decreased bone density with thinning of cortex, eventual codfish vertebral bodies (concave shape), and **pseudofractures** (Looser zones).

(Choice A) Paget's disease of the bone occurs due to accelerated focal bone remodeling. It starts with increased

(Choice A) Paget's disease of the bone occurs due to accelerated focal bone remodeling. It starts with increased osteoclastic activity, followed by rapid and disorganized new bone formation by osteoblasts. Patients typically have normal serum calcium, phosphorus, and parathyroid hormone. However, markers of bone resorption (c-telopeptide, n- telopeptide) and bone formation (alkaline phosphatase, osteocalcin) are significantly elevated.

(Choice B) Osteogenesis imperfecta is due to defective type 1 collagen formation, which is required for development of bone, tendons, ligaments, skin, teeth, and sclera. It has a wide variation in phenotype and degree of severity. However, all patients can develop fractures (starting in childhood) due to increased bone fragility.

(Choice D) Osteoporosis is characterized by low bone mass, but the bone usually has adequate mineralization. Laboratory evaluation shows normal serum calcium, phosphorus, parathyroid hormone, and alkaline phosphatase.

(Choice E) Lytic bone lesions due to malignant cell infiltration can occur in solid tumors (eg, breast, renal cell) or multiple myeloma. These tumors can also release cytokines and other factors that activate local osteoclasts to cause lytic lesions. However, these patients typically have elevated serum calcium.

Educational objective:

Osteomalacia is due to defective mineralization of the organic bone matrix. It is most commonly due to severe vitamin D deficiency, which leads to decreased intestinal calcium and phosphorus absorption with resultant secondary hyperparathyroidism. Typical laboratory findings include hypophosphatemia, hypocalcemia, and elevated alkaline phosphatase.

References

A 24-year-old woman is evaluated for a lump in her neck. She discovered the lump a week ago while showering. The patient feels well and has no associated pain, fever, night sweats, or weight changes. Her medical history is unremarkable, although she has had irregular menses for a year since insertion of an intrauterine device. The patient does not use tobacco, alcohol, or illicit drugs. Her mother died during surgery for thyroid cancer. Blood pressure is 133/80 mm Hg and pulse is 78/min. On examination, there is a palpable 2-cm nodule in the right thyroid lobe. The remainder of the examination, including chest, abdomen, extremities, and skin, is normal. Serum TSH and calcium levels are normal and calcitonin is elevated. Ultrasound-guided aspiration biopsy reveals malignant cells. Which of the following tests is the best next step in evaluation of this patient?

- A. Aldosterone-renin activity ratio
- B. Late-night salivary cortisol
- C. Low-dose dexamethasone suppression test
- D. Plasma fractionated metanephrine assay
- E. Plasma insulin-like growth factor-1
- F. Serum prolactin assay

Submit

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✗ A. Aldosterone-renin activity ratio [3%]

B. Late-night salivary cortisol [1%]

C. Low-dose dexamethasone suppression test [4%]

✓ D. Plasma fractionated metanephrine assay [68%]

E. Plasma insulin-like growth factor-1 [6%]

F. Serum prolactin assay [15%]

Incorrect
Correct answer

68%
Answered correctly

5 Seconds
Time Spent

06/23/2018
Last Updated

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

This patient with a malignant thyroid mass, elevated serum calcitonin level, and family history of thyroid malignancy likely has an inherited form of **medullary thyroid cancer** (MTC). MTC is a calcitonin-producing tumor arising from neuroendocrine parafollicular C cells of the thyroid gland. Although most MTC is sporadic, approximately one third of MTC is inherited as a component of **multiple endocrine neoplasia (MEN) types 2A and 2B**.

MEN 2A and 2B (usually due to *RET* proto-oncogene mutations) are also associated with **pheochromocytoma**, which can be asymptomatic at the time of diagnosis but cause life-threatening **hypertensive crisis** during surgical procedures (eg, thyroidectomy). In light of this risk, most patients with MTC should undergo *RET* mutation testing

MEN 2A and 2B (usually due to *RET* proto-oncogene mutations) are also associated with **pheochromocytoma**, which can be asymptomatic at the time of diagnosis but cause life-threatening **hypertensive crisis** during surgical procedures (eg, thyroidectomy). In light of this risk, most patients with MTC should undergo *RET* mutation testing and screening for pheochromocytoma with a **plasma fractionated metanephrine** assay. If found, pheochromocytoma should be resected prior to thyroidectomy.

(Choices A, B, and C) The aldosterone-renin activity ratio can help evaluate hyperaldosteronism (eg, hypertension, hypernatremia, hypokalemia). The low-dose dexamethasone suppression test and the salivary cortisol test are helpful in screening for Cushing syndrome (eg, obesity, facial plethora, easy bruising). This patient has no manifestations of these conditions. In addition, adrenocortical tumors are uncommon in MEN syndromes, with biochemical testing recommended only in patients with manifestations of excessive hormonal production.

(Choices E and F) Serum prolactin and insulin-like growth factor-1 are screening tests for prolactin and growth hormone-secreting pituitary tumors. Pituitary tumors occur in MEN1 but are not a feature of MEN2.

Educational objective:
Medullary thyroid cancer (MTC) is a calcitonin-producing tumor of the thyroid parafollicular C cells. It often occurs as a component of multiple endocrine neoplasia types 2A and 2B, which are also associated with pheochromocytoma. Patients with MTC should be screened for pheochromocytoma prior to thyroidectomy with a plasma fractionated metanephrine assay.

References

A 30-year-old woman comes to the physician complaining of a significant increase in her daily urinary volume and intense thirst. The symptoms started a few weeks ago, and she has to get up frequently at night to urinate and drink fluids. She has no other medical problems. The patient does not use tobacco, alcohol, or illicit drugs and has no known drug allergies. Her mother developed diabetes mellitus as an adolescent. Temperature is 36.7 C (98 F), blood pressure is 110/70 mm Hg, pulse is 75/min, and respirations are 15/min. Fasting serum laboratory results are as follows:

Sodium	146 mEq/L
Potassium	4.0 mEq/L
Bicarbonate	24 mEq/L
Blood urea nitrogen	15 mg/dL
Creatinine	0.9 mg/dL
Glucose	90 mg/dL
Serum osmolality	300 mOsm/kg
Urine osmolality	126 mOsm/kg

After 6 hours of water deprivation, laboratory results are as follows:

Urine osmolality	126 mOsm/kg

After 6 hours of water deprivation, laboratory results are as follows:

Sodium	153 mEq/L
Serum osmolality	320 mOsm/kg
Urine osmolality	132 mOsm/kg

One hour after the subcutaneous administration of arginine vasopressin, the urine osmolality is 395 mOsm/kg.
Which of the following is the most appropriate treatment for this patient?

- A. Demeclocycline
- B. Desmopressin
- C. Hydrochlorothiazide
- D. Psychotherapy
- E. Tolvaptan

Submit

Urine osmolality	126 mOsm/kg

After 6 hours of water deprivation, laboratory results are as follows:

Sodium	153 mEq/L
Serum osmolality	320 mOsm/kg
Urine osmolality	132 mOsm/kg

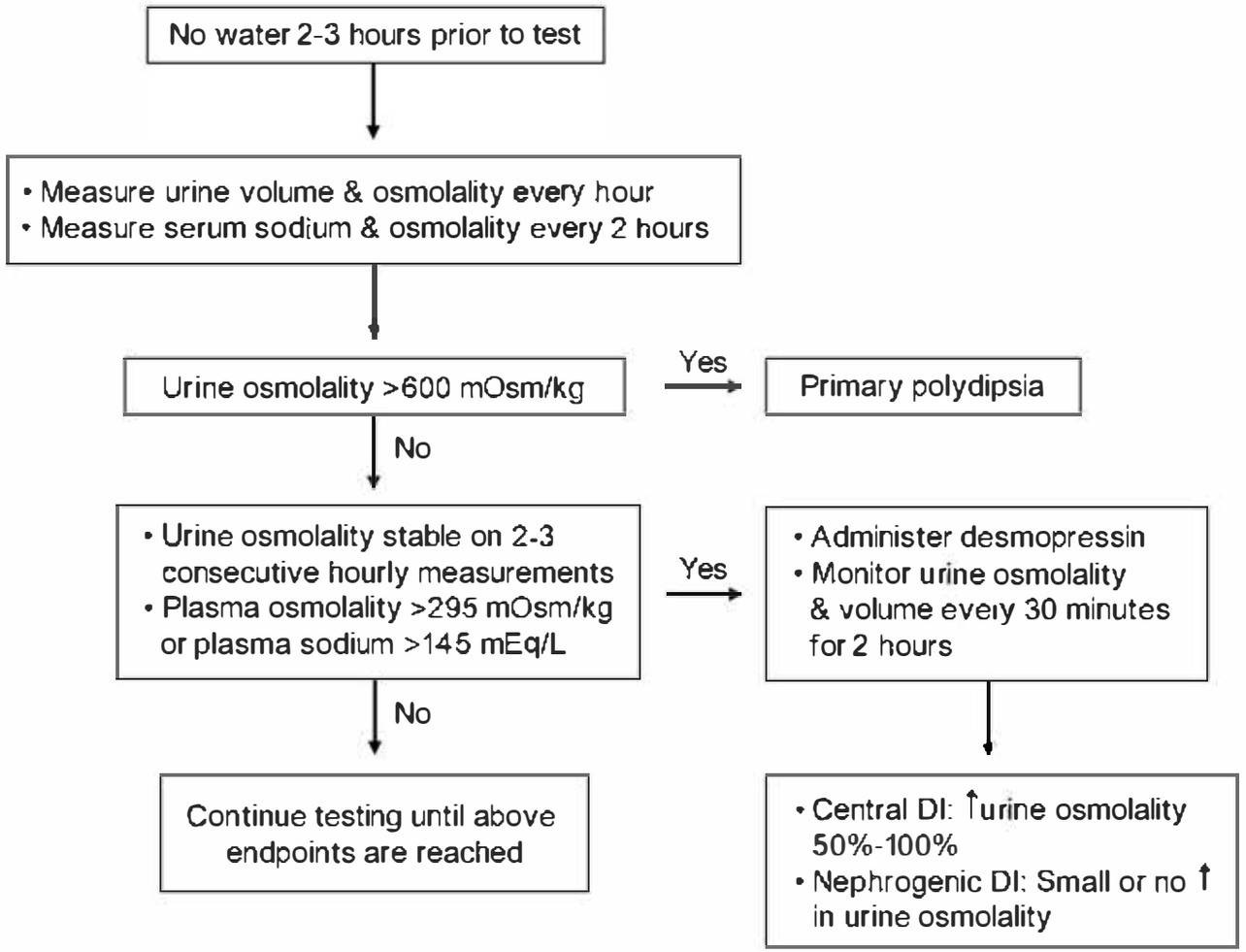
One hour after the subcutaneous administration of arginine vasopressin, the urine osmolality is 395 mOsm/kg.
Which of the following is the most appropriate treatment for this patient?

- A. Demeclocycline [4%]
- ✔ B. Desmopressin [87%]
- ✘ C. Hydrochlorothiazide [2%]
- D. Psychotherapy [2%]
- E. Tolvaptan [2%]

Incorrect
Correct Answer

87%
10 Seconds
05/21/2018

Water deprivation test



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This patient has polyuria, polydipsia, and mild hypernatremia/hypertonicity. Polyuria in the nonhospitalized patient can be due to diabetes mellitus, primary polydipsia, and diabetes insipidus. This patient's normal serum glucose makes diabetes unlikely. Primary polydipsia is due to increased water intake that surpasses the kidney's ability to excrete it. The increased water leads to hyponatremia (sodium <137 mEq/L), a very dilute urine (osmolality <100 mOsm/kg), and urine osmolality < serum osmolality. This patient's sodium >145 mEq/L and urine osmolality < serum osmolality favor diabetes insipidus (DI).

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.

The patient must first abstain from water for at least 2-3 hours. The serum and urine osmolality are measured periodically. Urine osmolality >600 mOsm/kg suggests primary polydipsia due to intact ADH and ability to concentrate urine in the absence of water intake. Patients with continued dilute urine likely have DI. These patients then receive desmopressin to distinguish between central and nephrogenic DI. Central DI typically has >50% (sometimes up to 200%-400%) increase in urine osmolality with desmopressin. Nephrogenic DI has minimal change in urine osmolality with desmopressin. This patient's increased urine osmolality from 132 to 395 mOsm/kg is consistent with central DI. The preferred initial therapy is desmopressin, given intranasally (preferred) or orally.

(Choice A) Demeclocycline is used for treating syndrome of inappropriate antidiuretic hormone (SIADH). It inhibits the ADH-mediated aquaporin insertion in the cortical collecting tubule and helps dilute the urine. However,

(Choice A) Demeclocycline is used for treating syndrome of inappropriate antidiuretic hormone (SIADH). It inhibits the ADH-mediated aquaporin insertion in the cortical collecting tubule and helps dilute the urine. However, SIADH causes hyponatremia with a concentrated urine (urine osmolality > serum osmolality).

(Choice C) Hydrochlorothiazide (HCTZ) is not as effective as desmopressin as monotherapy for central DI. HCTZ can be combined with desmopressin for an additive effect. However, HCTZ is preferred for nephrogenic DI. HCTZ causes mild volume depletion that increases proximal water and sodium reabsorption.

(Choice D) Psychotherapy is helpful in treating patients with primary (psychogenic) polydipsia. However, psychotherapy is not effective in managing central DI. In addition, this patient's water deprivation test is not consistent with primary polydipsia.

(Choice E) Tolvaptan is a V2 vasopressin receptor antagonist that causes a selective water loss in the kidney without affecting sodium or potassium excretion. Due to its cost and side effects (eg, increased liver enzymes), it is usually reserved for significant hypervolemic (due to heart failure) or euvolemic (due to SIADH) hyponatremia that does not improve with standard therapy (eg, fluid restriction).

Educational objective:

A water deprivation test can distinguish between central and nephrogenic diabetes insipidus (DI) and also definitively exclude primary polydipsia. Administration of desmopressin after water deprivation can distinguish between central and nephrogenic DI. Patients with central DI increase their urine osmolality by at least 50% following the administration of desmopressin acetate tablets; patients with nephrogenic DI will not show much change. Desmopressin (intranasal form preferred) is the first-line treatment for central DI.

A 36-year-old woman comes to the physician for a routine health examination. She has no complaints or previous medical problems and takes no medications. She does not use tobacco, alcohol, or illicit drugs. Her menstrual cycles are regular. The patient is an architect at a local construction firm. She has had no exposure to excessive radiation in the past. Her family history is negative for thyroid problems. Her temperature is 36.7° C (98° F), blood pressure is 130/80 mm Hg, pulse is 80/min, and respirations are 16/min. Examination of the neck shows a 2x2 cm, discrete, nontender, firm, and mobile nodule in the left thyroid lobe without cervical lymphadenopathy. The remainder of the examination is within normal limits. Which of the following is the most appropriate initial step in evaluation of this patient?

- A. Computed tomography scan of the neck
- B. Fine-needle aspiration biopsy
- C. Measurement of thyroid-stimulating hormone and thyroid ultrasound
- D. Radionuclide scan
- E. Serum anti-thyroid peroxidase antibodies and thyroglobulin

Submit

A 36-year-old woman comes to the physician for a routine health examination. She has no complaints or previous medical problems and takes no medications. She does not use tobacco, alcohol, or illicit drugs. Her menstrual cycles are regular. The patient is an architect at a local construction firm. She has had no exposure to excessive radiation in the past. Her family history is negative for thyroid problems. Her temperature is 36.7° C (98° F), blood pressure is 130/80 mm Hg, pulse is 80/min, and respirations are 16/min. Examination of the neck shows a 2x2 cm, discrete, nontender, firm, and mobile nodule in the left thyroid lobe without cervical lymphadenopathy. The remainder of the examination is within normal limits. Which of the following is the most appropriate initial step in evaluation of this patient?

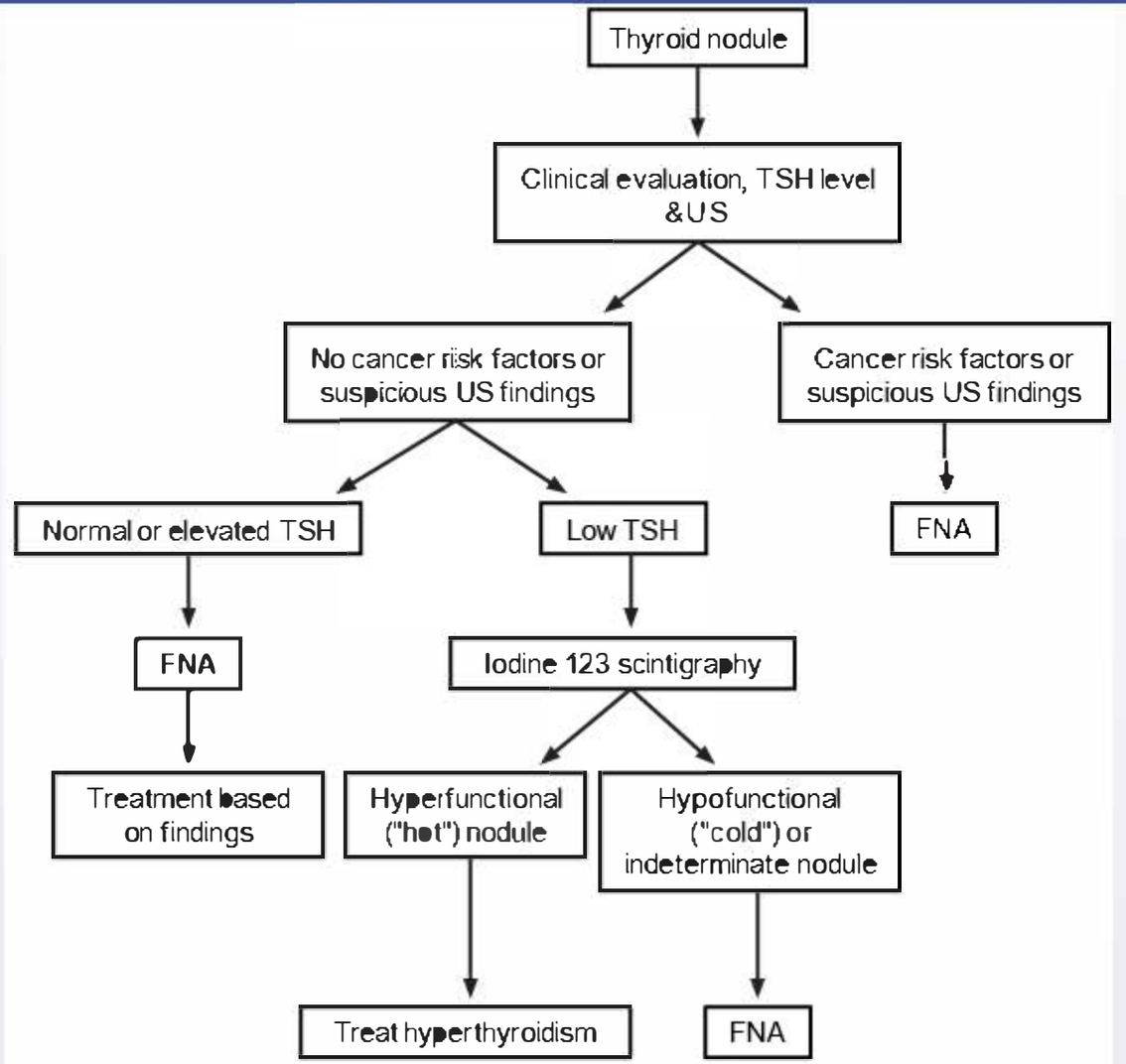
- A. Computed tomography scan of the neck [0%]
- B. Fine-needle aspiration biopsy [13%]
- ✔ C. Measurement of thyroid-stimulating hormone and thyroid ultrasound [80%]
- ✘ D. Radionuclide scan [5%]
- E. Serum anti-thyroid peroxidase antibodies and thyroglobulin [0%]

Incorrect
Correct answer
C

80%
Answered correctly

4 Seconds
TimeSpent

06/12/2018
Last Updated



FNA = fine needle aspiration; US = ultrasound.

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Patients with thyroid nodules should be evaluated based on their cancer risk factors (eg, family history, radiation exposure in childhood, cervical lymphadenopathy), compressive symptoms (eg, hoarseness, difficulty swallowing), and current thyroid status (eg, euthyroid, hypo/hyperthyroid). In addition, serum thyroid-stimulating hormone (TSH) levels and an ultrasound of the nodule should be obtained first. Patients with suspicious ultrasound findings (eg, hypoechoic, microcalcifications, internal vascularity) or cancer risk factors should undergo fine-needle aspiration (FNA). This patient presents with a painless mobile thyroid nodule without clinical risk factors for thyroid cancer, compressive symptoms, or features suggesting hypo/hyperthyroidism.

Patients without cancer risk factors or suspicious ultrasound findings, but with normal or elevated TSH, should also undergo FNA. Patients with low TSH levels should be evaluated with thyroid scintigraphy, preferably with iodine-123 **(Choice D)**. A hyperfunctioning ("hot") nodule (increased isotope uptake in the nodule with decreased surrounding uptake) indicates a low cancer risk and may be treated for hyperthyroidism. An indeterminate or hypofunctioning ("cold") nodule (decreased isotope uptake compared to surrounding tissue) indicates a higher risk of cancer and should be evaluated further with FNA.

(Choice A) Computed tomography scan is inferior to ultrasound in delineating thyroid nodules. Therefore, scanning is not performed in most patients with thyroid nodules unless significant retrosternal extension is suspected.

(Choice B) Although FNA is the most accurate modality for assessing thyroid nodules measuring ≥1 cm, ultrasound and TSH are recommended first in patients without thyroid cancer risk factors to better differentiate which need FNA. However, FNA is indicated in all patients with thyroid cancer risk factors or suspicious ultrasound findings, even if the nodule is <1 cm

(Choice B) Although FNA is the most accurate modality for assessing thyroid nodules measuring ≥1 cm, ultrasound and TSH are recommended first in patients without thyroid cancer risk factors to better differentiate which need FNA. However, FNA is indicated in all patients with thyroid cancer risk factors or suspicious ultrasound findings, even if the nodule is <1 cm.

(Choice E) Anti-thyroid peroxidase antibodies can identify Hashimoto's thyroiditis in patients with high TSH, and serum thyroglobulin can be elevated in many thyroid conditions. Neither test effectively differentiates between benign and malignant lesions and is not routinely recommended for evaluating thyroid nodules.

Educational objective:

Although the prevalence of thyroid nodules in the adult population is high, the majority are benign. Thyroid-stimulating hormone (TSH) measurement and ultrasound are the first steps in evaluation. Radionuclide scan is indicated for patients with low TSH. Hot nodules are almost always benign and can be treated for hyperthyroidism. Fine-needle aspiration is indicated for patients with normal or high TSH, cold nodules, thyroid cancer family history, or suspicious thyroid ultrasound findings.

References

- Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer.

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A 65-year-old man comes to the physician complaining of decreased appetite, nausea, abdominal bloating, and early satiety for the past several months. He has no heartburn or epigastric pain but does have occasional vomiting. The patient has longstanding type 2 diabetes mellitus complicated by nonproliferative retinopathy and has taken insulin for the last 15 years. His blood glucose readings using the home monitor are 40-400 mg/dL. Most of the low blood glucose readings occur after meals. Which of the following would be most helpful in treating this patient's condition?

- A. Diphenhydramine
- B. *Helicobacter pylori* eradication therapy
- C. Lansoprazole
- D. Megestrol acetate
- E. Metoclopramide
- F. Ondansetron
- G. Promethazine
- H. Ranitidine

Submit

A 65-year-old man comes to the physician complaining of decreased appetite, nausea, abdominal bloating, and early satiety for the past several months. He has no heartburn or epigastric pain but does have occasional vomiting. The patient has longstanding type 2 diabetes mellitus complicated by nonproliferative retinopathy and has taken insulin for the last 15 years. His blood glucose readings using the home monitor are 40-400 mg/dL. Most of the low blood glucose readings occur after meals. Which of the following would be most helpful in treating this patient's condition?

- A. Diphenhydramine [0%]
- B. *Helicobacter pylori* eradication therapy [5%]
- C. Lansoprazole [2%]
- D. Megestrol acetate [6%]
- ✔ E. Metoclopramide [71%]
- F. Ondansetron [7%]
- G. Promethazine [3%]
- H. Ranitidine [1%]

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).

(Choices A, F, and G) Antihistamines (eg, promethazine, diphenhydramine) or 5HT3 antagonists (eg, ondansetron, granisetron) are antiemetic agents that can be used in combination with prokinetic agents in gastroparesis patients. They are more useful in those with emesis as a predominant symptom.

(Choice B) This patient's symptoms are not suggestive of dyspepsia or peptic ulcer disease, and *Helicobacter pylori* eradication therapy is not indicated without prior testing.

cisapride (restricted use in the United States due to the risk of cardiac arrhythmias and death).

(Choices A, F, and G) Antihistamines (eg, promethazine, diphenhydramine) or 5HT3 antagonists (eg, ondansetron, granisetron) are antiemetic agents that can be used in combination with prokinetic agents in gastroparesis patients. They are more useful in those with emesis as a predominant symptom.

(Choice B) This patient's symptoms are not suggestive of dyspepsia or peptic ulcer disease, and *Helicobacter pylori* eradication therapy is not indicated without prior testing.

(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.

(Choices C and H) Histamine H2 antagonists (eg, ranitidine) or proton pump inhibitors (eg, lansoprazole) are helpful in symptomatic control of gastroesophageal reflux disease or erosive esophagitis associated with esophageal motility disorder secondary to diabetic autonomic neuropathy. They are not useful in patients with gastroparesis.

Educational objective:

Diabetic gastroparesis (delayed gastric emptying) presents with symptoms of anorexia, nausea, vomiting, early satiety, postprandial fullness, and impaired glycemic control. Prokinetic agents (eg, metoclopramide, erythromycin, cisapride) are useful in the management of symptoms.

References

A 25-year-old woman comes to the physician with a 3-month history of weight loss, irritability, insomnia, and palpitations. Her past medical history is insignificant. She is not currently taking any medications. The patient does not use tobacco, alcohol, or illicit drugs. Blood pressure is 155/70 mm Hg and pulse is 110/min. Physical examination shows lid retraction, dry skin, and fine tremor of the hands. Which of the following is the most likely cause of this patient's hypertension?

A. Elevated serum calcium level

B. Increased myocardial contractility

C. Increased peripheral vascular resistance

D. Increased synthesis of catecholamines

E. Nocturnal hypoventilation

Submit

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- A. Elevated serum calcium level [2%]
- ✔ B. Increased myocardial contractility [37%]
- ✘ C. Increased peripheral vascular resistance [24%]
- D. Increased synthesis of catecholamines [35%]
- E. Nocturnal hypoventilation [0%]

Incorrect
Correct answer
B

37%
Answered correctly

4 Seconds
TimeSpent

05/24/2018
Last Updated

Explanation

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

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This patient – with weight loss, tachycardia, tremor, and lid retraction – has common features of **thyrotoxicosis**. Thyrotoxicosis can produce a number of cardiovascular complications directly through the effects of tri-iodothyronine (T_3) on cardiac myocytes and blood vessels, as well as indirectly by increasing sensitivity to circulating catecholamines. Generally, thyrotoxicosis causes positive inotropic and chronotropic effects, leading to a hyperdynamic cardiovascular state characterized by **tachycardia, systolic hypertension**, and **widened pulse pressure**. Arrhythmias are common and may include sinus tachycardia, **atrial fibrillation/flutter**, and atrial and

Thyrotoxicosis can produce a number of cardiovascular complications directly through the effects of tri-iodothyronine (T_3) on cardiac myocytes and blood vessels, as well as indirectly by increasing sensitivity to circulating catecholamines. Generally, thyrotoxicosis causes positive inotropic and chronotropic effects, leading to a hyperdynamic cardiovascular state characterized by **tachycardia, systolic hypertension**, and **widened pulse pressure**. Arrhythmias are common and may include sinus tachycardia, **atrial fibrillation/flutter**, and atrial and ventricular ectopy. Valvular abnormalities such as mitral valve prolapse and mitral or tricuspid regurgitation are also associated.

Increased oxygen demand in thyrotoxicosis is due to increased cardiac output and increased systemic oxygen consumption; this can lead to anginal symptoms in patients with underlying coronary atherosclerosis. Angina may also occur due to coronary vasospasm (especially in young female patients). Thyrotoxicosis may also cause new-onset heart failure or decompensation of pre-existing heart failure.

(Choice A) Longstanding hypercalcemia, as seen in hyperparathyroidism, is associated with hypertension, possibly due to effects on contractility and arterial compliance. Thyrotoxicosis may cause hypercalcemia due to increased bone turnover, but this is generally mild and is not a significant contributor to systemic hypertension.

(Choice C) Systemic hypertension may be seen in both hyper- and hypo-thyroidism. Hyperthyroidism causes a decrease in systemic vascular resistance, but blood pressure (primarily systolic) rises due to positive inotropic and chronotropic effects. In contrast, hypothyroidism causes hypertension due to an increase in systemic vascular resistance.

(Choice D) Thyrotoxicosis causes increased sensitivity to catecholamines due to increased expression of β1-

onset heart failure or decompensation of pre-existing heart failure.

(Choice A) Longstanding hypercalcemia, as seen in hyperparathyroidism, is associated with hypertension, possibly due to effects on contractility and arterial compliance. Thyrotoxicosis may cause hypercalcemia due to increased bone turnover, but this is generally mild and is not a significant contributor to systemic hypertension.

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(Choice D) Thyrotoxicosis causes increased sensitivity to catecholamines due to increased expression of β1-adrenergic receptors as well as changes in proteins controlling post β1-adrenergic receptor activity. However, T_3 does not stimulate catecholamine production.

(Choice E) Nocturnal hypoventilation is a common cause of secondary hypertension that is seen in obstructive sleep apnea (OSA). Patients with OSA may experience disordered sleep, irritability, and palpitations. However, weight loss, lid retraction, and tremor are more suggestive of thyrotoxicosis.

Educational objective:
Systolic hypertension in thyrotoxicosis is caused by hyperdynamic circulation resulting from increased myocardial contractility and heart rate.

References

A 45-year-old woman comes to the office due to 3 months of excessive hair growth over her face and body. Her last menstrual period was 4 months ago. The patient's menstrual cycle had previously been regular, and she has had 2 successful pregnancies. Medical history includes hypothyroidism, for which she takes a stable dose of levothyroxine; a recent TSH level was normal. The patient has smoked half a pack of cigarettes daily for 25 years. Blood pressure is 124/82 mm Hg and pulse is 72/min. BMI is 24 kg/m^2. The patient is muscular and has an enlarged clitoris. There is temporal balding, and a large amount of coarse terminal hair is present on the face, back, chest, and lower abdomen. The remainder of the physical examination is normal. Urine pregnancy test is negative. Which of the following is the best next step in evaluation of this patient?

- A. ACTH stimulation test
- B. CT scan of the abdomen
- C. Insulin-like growth factor 1 level
- D. LH to FSH ratio
- E. Testosterone and dehydroepiandrosterone sulfate levels

Submit

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- A. ACTH stimulation test [3%]
- ✗ B. CT scan of the abdomen [5%]
- C. Insulin-like growth factor 1 level [1%]
- D. LH to FSH ratio [12%]
- ✓ E. Testosterone and dehydroepiandrosterone sulfate levels [76%]

Incorrect
Correct answer
E

76%
Answered correctly

4 Seconds
TimeSpent

06/21/2018
Last Updated

Causes of hyperandrogenism in women	
Diagnosis	**Clinical features**
PCOS	Oligo-ovulation, clinical or biochemical hyperandrogenemia, polycystic ovaries on imaging, no evidence of another diagnosis
Nonclassic CAH	Oligo-ovulation, hyperandrogenemia, ↑ 17-hydroxyprogesterone levels
Ovarian/adrenal tumors	Older age, rapidly progressive symptoms, ↑ androgen levels (>3 times upper limit of normal)
Hyperprolactinemia	Amenorrhea, galactorrhea, ↑ prolactin levels
Cushing syndrome	Cushingoid features, nonsuppressible dexamethasone suppression test, ↑ 24-hour urinary free cortisol
Acromegaly	Excessive growth, ↑ GH & IGF-1 levels
CAH = congenital adrenal hyperplasia; **GH** = growth hormone; **IGF-1** = insulin-like growth factor 1; **PCOS** = polycystic ovary syndrome.	

Although most women with hirsutism (excessive terminal hair growth) have polycystic ovary syndrome (PCOS)

Although most women with hirsutism (excessive terminal hair growth) have polycystic ovary syndrome (PCOS), **rapid-onset hirsutism** (eg, <1 year), particularly with **virilization** (eg, temporal balding, excessive muscular development, enlarged clitoris), suggests very high androgen levels due to an **androgen-secreting neoplasm** of the ovaries or adrenal glands.

The primary ovarian androgens are testosterone, androstenedione, and dehydroepiandrosterone (DHEA). The adrenals also produce these androgens as well as DHEA sulfate (DHEAS). Therefore, women with a suspected androgen-producing tumor should be evaluated with serum **testosterone and DHEAS levels**:

- Elevated testosterone levels with normal DHEAS levels suggest an ovarian source (more common).
- Elevated DHEAS levels suggest an adrenal tumor (far less common).

DHEAS and DHEA have negligible intrinsic androgenic action but are converted to androstenedione and subsequently to testosterone in peripheral tissues.

(Choice A) Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency causes elevated androgen precursors (eg, 17-hydroxyprogesterone). Female infants with classic CAH present at birth with ambiguous genitalia. In contrast, women with nonclassic CAH due to partial 21-hydroxylase deficiency develop hyperandrogenism from late childhood to early adulthood. However, symptoms are typically slowly progressive over years. Initial testing is with a basal 17-hydroxyprogesterone level; an ACTH stimulation test may be performed in patients with a moderately elevated basal screening for diagnosis.

(Choice B) Imaging studies prior to biochemical confirmation of hyperandrogenism can be misleading because many patients have nonfunctioning adrenal and ovarian masses that have no disease manifestations. If DHEAS

performed in patients with a moderately elevated basal screening for diagnosis.

(Choice B) Imaging studies prior to biochemical confirmation of hyperandrogenism can be misleading because many patients have nonfunctioning adrenal and ovarian masses that have no disease manifestations. If DHEAS levels are elevated, an abdominal CT scan is performed to evaluate the adrenal glands.

(Choice C) Excessive body hair is common in women with acromegaly (elevated growth hormone increases insulin-like growth factor 1 levels). However, hair growth is usually not rapidly progressive, and other clinical features of acromegaly (eg, enlarging facial features, macroglossia) are typically seen.

(Choice D) An increased LH to FSH ratio is sometimes seen in PCOS; however, it is not diagnostic as results are inconsistent. Hirsutism is common in patients with PCOS but is typically chronic and slowly progressive, beginning around puberty.

Educational objective:
Rapid-onset hyperandrogenism, particularly with virilization, suggests an androgen-secreting ovarian or adrenal neoplasm. Serum testosterone and DHEAS levels are used to delineate the site of androgen production. Elevated testosterone with normal DHEAS suggests an ovarian source, whereas elevated DHEAS suggests an adrenal source.

References

- Causes, patterns, and severity of androgen excess in 1205 consecutively recruited women.
- Endocrinology update: hirsutism

A 6-year-old girl is brought to the office for evaluation of breast and pubic hair development. Her parents noticed that she started developing breasts several months ago, and she recently started growing coarse axillary and pubic hair. The patient has had no changes in her behavior or school performance. She has no headaches, visual changes, vomiting, or vaginal bleeding. The patient has no chronic medical conditions and no previous surgery. She takes no daily medications and has no known allergies. BMI is at the 50th percentile for age. Physical examination reveals axillary hair; pubic hair is Tanner stage 3; and breasts are Tanner stage 3. The remainder of the examination is unremarkable. Bone age is consistent with age 8. Basal LH level is high. Which of the following is the best next step in evaluation of this patient?

- A. Adrenal CT scan
- B. Dexamethasone suppression test
- C. Karyotype analysis
- D. MRI of the brain
- E. Pelvic ultrasound
- F. Reassurance and follow-up in 6 months

Submit

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- A. Adrenal CT scan [9%]
- ✗ B. Dexamethasone suppression test [8%]
- C. Karyotype analysis [2%]
- ✓ D. MRI of the brain [56%]
- E. Pelvic ultrasound [16%]
- F. Reassurance and follow-up in 6 months [6%]

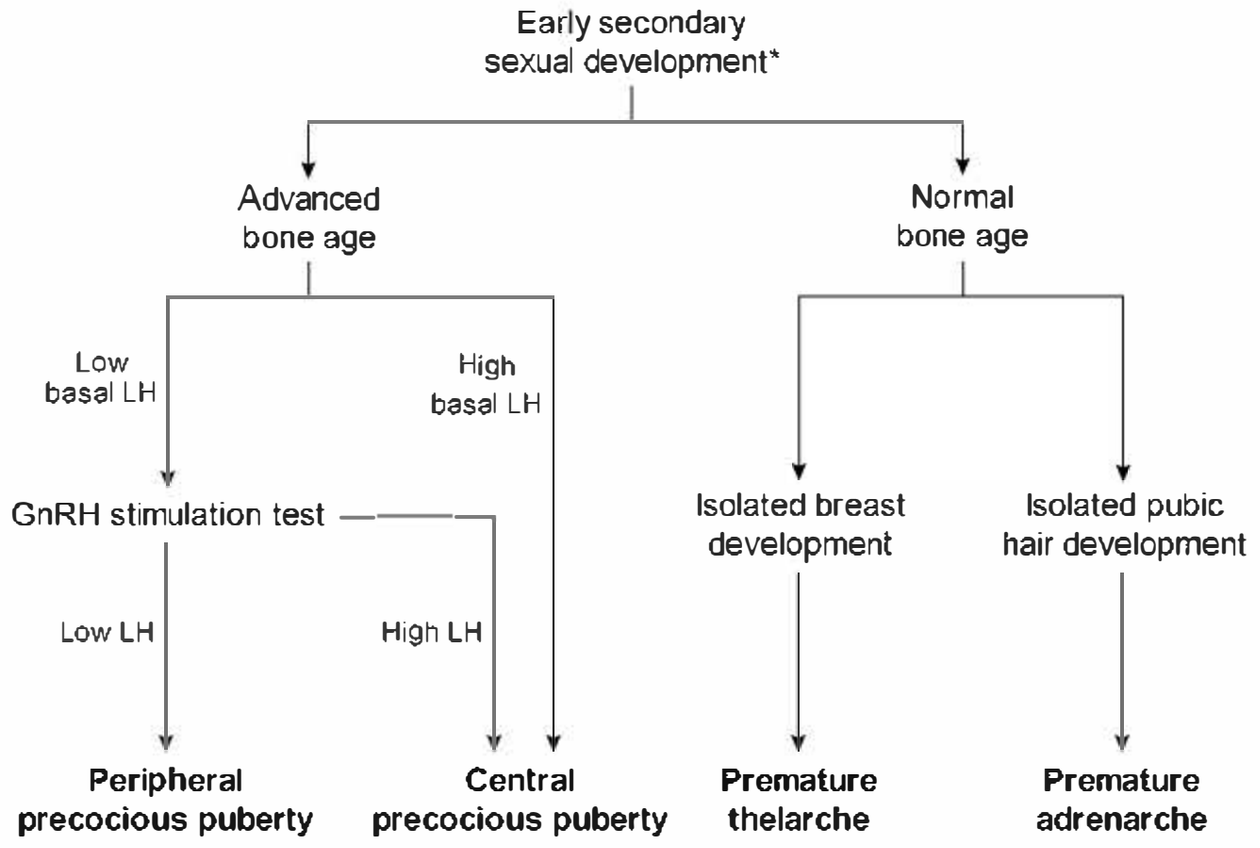
Incorrect
Correct answer

56%
Answered correctly

4 Seconds
Time Spent

07/17/2018
Last Updated

Evaluation of precocious puberty



*Secondary sexual development in girls age <8 or boys age <9.

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Central (gonadotropin-dependent) **precocious puberty** (PP) results from the premature activation of the

Central (gonadotropin-dependent) **precocious puberty** (PP) results from the premature activation of the hypothalamic-pituitary-gonadal (HPG) axis in girls age <8 and boys age <9. Early exposure to increased gonadal hormones results in **breast development** or testicular enlargement and axillary/pubic **hair growth** at a young age. High levels of androgens and estrogens also promote increased bone formation and cartilage growth, which leads to early pubertal growth spurts (increased height velocity) and **advanced bone age**. However, estrogen stimulates growth plate closure, so patients will often have shorter than expected adult height.

Central PP is distinguished from peripheral PP by an **elevated LH** level at baseline (due to hypothalamic secretion of GnRH) or following stimulation with a GnRH agonist. In contrast, elevated sex hormones in patients with peripheral PP suppress LH levels via negative feedback.

Although central PP is typically idiopathic, it can be the first manifestation of an intracranial process even in asymptomatic patients, as in this child. Central nervous system (CNS) lesions can cause PP through endogenous hormone production (eg, GnRH-secreting hypothalamic hamartoma, FSH- and LH-secreting pituitary adenomas) or by indirectly affecting the HPG axis due to mass effect or increased intracranial pressure (eg, craniopharyngioma). Patients with central PP require an **MRI of the brain** to evaluate for **hypothalamic or pituitary tumor**.

Medical and psychosocial consequences exist for PP as affected children appear different than their peers, and physical changes precede emotional maturity. Once a CNS tumor is excluded, the primary treatment for idiopathic central PP is **GnRH agonist therapy**, which prevents premature epiphyseal plate fusion and maximizes adult height potential.

(Choices A and E) Adrenal CT scan or pelvic ultrasound evaluates for adrenal or gonadal tumors, respectively,

Medical and psychosocial consequences exist for PP as affected children appear different than their peers, and physical changes precede emotional maturity. Once a CNS tumor is excluded, the primary treatment for idiopathic central PP is **GnRH agonist therapy**, which prevents premature epiphyseal plate fusion and maximizes adult height potential.

(Choices A and E) Adrenal CT scan or pelvic ultrasound evaluates for adrenal or gonadal tumors, respectively, which may cause peripheral PP. Patients with peripheral PP have low LH and FSH levels.

(Choice B) Dexamethasone suppression test is used to diagnose Cushing syndrome. Patients may have signs of isolated adrenal androgen overproduction (eg, acne, hirsutism); there is no associated premature breast development.

(Choice C) Karyotype analysis is not indicated in PP but is used for delayed puberty to detect chromosomal abnormalities such as Klinefelter syndrome (XXY) and Turner syndrome (XO).

(Choice F) Reassurance can be provided in cases of isolated premature thelarche or adrenarche when bone age is normal.

Educational objective:
Central (gonadotropin-dependent) precocious puberty (PP) is characterized by premature breast and pubic/axillary hair development, advanced bone age, and an elevated LH level. Patients with central PP require an MRI of the brain to evaluate for a tumor prior to starting GnRH agonist therapy.

A 56-year-old man with type 2 diabetes mellitus of 15 years duration is being treated with metformin, glimepiride, and sitagliptin. The patient also has hypertension, hyperlipidemia, and coronary artery disease. His current hemoglobin A1c level is 7.5%. Switching to insulin therapy to attain better glycemic control is discussed with the patient. Intensive glycemic control with a goal hemoglobin A1c of <6.5% is most likely to reduce the risk of which of the following complications?

- A. All-cause mortality
- B. Hypoglycemia
- C. Myocardial infarction
- D. Retinopathy
- E. Stroke

Submit

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- A. All-cause mortality [37%]
- ✗ B. Hypoglycemia [0%]
- C. Myocardial infarction [18%]
- ✓ D. Retinopathy [41%]
- E. Stroke [2%]

Incorrect
Correct answer
D

41%
Answered correctly

5 Seconds
TimeSpent

09/05/2018
Last Updated

Explanation

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)	↓

Optimization of glycemic control in diabetes mellitus is associated with a reduced risk of **microvascular** complications (eg, nephropathy, retinopathy). However, the benefits in preventing **macrovascular** complications (eg, myocardial infarction, stroke, peripheral arterial disease) have not been firmly established, and results from large prospective trials have been mixed **(Choices C and E)**. Two large trials (United Kingdom Prospective Diabetes Study and Diabetes Control and Complications Trial) that enrolled subjects early in the course of their disease initially found no reduction in macrovascular risk with intensive control but did find a reduction during long-term follow-up after the initial studies were completed. In contrast, 3 other large studies that enrolled subjects with long-standing diabetes found a reduction in risk of only microvascular, not macrovascular, complications.

Given the established benefits of tight control on the risk of microvascular complications, the recommended target hemoglobin A1c for most patients should be 6%-7%. However, efforts to reduce the risk of macrovascular complications will depend on careful management of other cardiac risk factors (ie, smoking, blood pressure, lipids).

(Choices A and B) Tight glycemic control is associated with an increased risk of hypoglycemia. Tight control has not been shown to decrease overall mortality, possibly because the microvascular benefits are offset by

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(Choices A and B) Tight glycemic control is associated with an increased risk of hypoglycemia. Tight control has not been shown to decrease overall mortality, possibly because the microvascular benefits are offset by complications of hypoglycemia. Most experts recommend an A1c target of 7%-8% in patients with an elevated risk of hypoglycemia (eg, elderly patients).

Educational objective:

Tight blood glucose control in patients with diabetes decreases the risk of microvascular complications (eg, retinopathy, nephropathy), increases the risk of hypoglycemia, and has an uncertain effect on macrovascular complications (eg, myocardial infarction, stroke) and all-cause mortality.

References

- Individualizing targets and tactics for high-risk patients with type 2 diabetes: practical lessons from ACCORD and other cardiovascular trials.

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A 20-year-old woman is brought to the emergency department due to lethargy. According to her mother, the patient had a "stomach bug" 4 days ago with nausea, vomiting, and abdominal pain that began after eating in a local restaurant. Since that time her vomiting has resolved, but the patient has had worsening symptoms and decreased oral intake. In addition, over the last few weeks the patient has experienced a 4-kg (9-lb) weight loss associated with excessive thirst. Medical history is unremarkable. She is not sexually active, and her last menstrual period was 10 days ago. The patient occasionally drinks beer but does not smoke or use illicit drugs. Temperature is 37.2 C (99 F), blood pressure is 100/56 mm Hg, pulse is 120/min (regular and weak), and respirations are 28/min (rapid and deep). Pulse oximetry is 97% on room air. On examination, the patient is lethargic but easily arousable, responds to questions in short sentences, and moves all of her extremities spontaneously. Mucous membranes are dry, and the neck is supple. Other than tachycardia, cardiopulmonary examination is normal. She has diffuse abdominal tenderness without rebound tenderness, guarding, or rigidity. Which of the following is the most appropriate immediate next step in management of this patient's illness?

- A. 12-lead ECG
- B. Bedside abdominal ultrasound
- C. CT scan of head
- D. Endotracheal intubation
- E. Fingerstick glucose
- F. Lumbar puncture

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- A. 12-lead ECG [3%]
- B. Bedside abdominal ultrasound [6%]
- ✗ C. CT scan of head [1%]
- D. Endotracheal intubation [3%]
- ✓ E. Fingerstick glucose [83%]
- F. Lumbar puncture [1%]

Incorrect
Correct answer

83%
Answered correctly

9 Seconds
Time Spent

11/0 1/2018
Last Updated

Diabetic ketoacidosis	
Patient characteristics	• Young age • Brittle type 1 diabetes • May be initial manifestation of diabetes
Clinical symptoms	• Acute to subacute onset o **Initial**: Polydipsia/polyuria, blurred vision, weight loss o **Later**: Altered mentation, hyperventilation, abdominal pain
Diagnosis	• **Glucose 250-500 mg/dL** • Bicarbonate <18 mEq/L • Elevated anion gap • Positive serum ketones
Treatment	• High-flow IV fluids • IV insulin • Follow & replace potassium

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This patient has features suggesting new-onset **type 1 diabetes**, including young age, polydipsia, and weight loss. Patients with diabetes who have significant hyperglycemia (typically >180 mg/dL) can develop polyuria due to inability of the renal sodium-glucose cotransporter to reabsorb the filtered glucose load. They can often keep up with initial fluid losses by increasing oral intake, but any condition that disrupts oral hydration (eg, acute

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A provisional diagnosis of **diabetic ketoacidosis** (DKA) can be made based on clinical presentation and bedside **capillary blood glucose**, which can be obtained in seconds. Patients will require **aggressive intravenous hydration** and **insulin**, and treatment should be initiated while awaiting the results of confirmatory tests (eg, venous glucose, urine or plasma ketones, arterial blood gas analysis).

(Choice A) Regular tachycardia with an otherwise normal cardiac examination most likely represents a physiologic response to illness, and an ECG is unnecessary.

(Choice B) Abdominal pain and tenderness are common in DKA and correlate with the severity of acidosis. This patient has otherwise benign findings on examination, and no imaging will be needed if her pain improves rapidly with treatment of DKA.

(Choices C and F) Mild alterations in mental status typically occur in DKA (and hyperglycemic hyperosmolar state) when plasma osmolality is >330 mOsm/kg. However, she has a nonfocal examination with no other findings to suggest a structural brain lesion and no fever or meningeal signs to suggest meningitis.

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(Choice D) The patient is hyperventilating due to metabolic acidosis but is responsive, has adequate oxygenation, and is not currently vomiting. Endotracheal intubation would be advised only if she were obtunded, unable to protect her airway, or developed respiratory failure.

Educational objective:
Diabetic ketoacidosis can be the initial manifestation of type 1 diabetes. Typical symptoms include weight loss, abdominal pain, hyperventilation, and altered mentation. Capillary blood glucose can rapidly provide a presumptive diagnosis, and treatment should begin immediately with intravenous fluids and insulin.

References

A 27-year-old woman comes to the office due to a 2-month history of dark hair growth on her cheeks, chin, and upper lip. Her last menstrual period was 12 weeks ago, but she did not seek medical care because a home pregnancy test was negative. The patient is gravida 0 para 0; her menstrual cycles began at age 11 and have previously been regular. She has no associated weight changes, visual disturbances, skin striae, headaches, or proximal muscle weakness. She takes no medications, including over-the-counter medications. Family history is unremarkable. Physical examination shows a BMI of 24 kg/m^2. Her skin is oily with acne on the forehead and cheeks. Dark terminal hairs are noted on the upper lip, cheeks, chin, chest, and lower abdomen. Examination of the genitals shows clitoromegaly. Abdominal examination is normal. Pelvic ultrasound reveals a normal uterus and ovaries. CT scan of the abdomen reveals a left adrenal mass. Which of the following patterns of plasma hormone levels is likely to be present in this patient?

	Dehydroepiandrosterone sulfate	Testosterone	Luteinizing hormone
A.	High	High	Low
B.	Low	Low	Low
C.	Normal	High	Low
D.	Normal or high	High	High
E.	Normal	Normal	Normal

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	Dehydroepiandrosterone sulfate	Testosterone	Luteinizing hormone
✔ A. [77%]	High	High	Low
B. [0%]	Low	Low	Low
C. [12%]	Normal	High	Low
D. [9%]	Normal or high	High	High
✘ E.	Normal	Normal	Normal

Causes of hirsutism in women	
Etiology	**Clinical features**
Polycystic ovary syndrome	• Oligomenorrhea, hyperandrogenism, obesity • Associated with type 2 diabetes, dyslipidemia, hypertension
Idiopathic hirsutism	• Normal menstruation • Normal serum androgens
Nonclassic 21-hydroxylase deficiency	• Similar to polycystic ovary syndrome • 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 of the face, neck, trunk, abdomen) • Increased libido, virilization, irregular menses

Women normally produce a number of androgens, including testosterone (T), androstenedione (AS), dehydroepiandrosterone (DHEA), and **dehydroepiandrosterone sulfate** (DHEAS). AS, DHEA, and T are produced by both the ovaries and the adrenals. In contrast, DHEAS is produced predominantly in the **adrenal glands**.

This patient has an adrenal mass with rapidly progressive (ie, over weeks) **hirsutism** (excess terminal hair growth) and **virilization** (eg, clitoromegaly), suggesting very high androgen levels due to an androgen-producing neoplasm. Most androgen-producing adrenal tumors overproduce DHEAS. Although DHEA and DHEAS are used as diagnostic markers, they have negligible androgenic activity, and the clinical features are due to the conversion of DHEA and DHEAS to more potent androgens (ie, AS and T). Therefore, this patient would most likely have elevated DHEAS and T levels. LH would be low due to negative feedback by T.

(Choice B) Low androgen with low LH levels would be seen in hypopituitarism with hypogonadotropic hypogonadism, which can cause amenorrhea but would have other manifestations of ovarian insufficiency (eg, hot flashes, vaginal dryness) rather than hirsutism and virilization.

(Choice C) Virilizing ovarian tumors can release large amounts of T, leading to suppression of LH release. DHEAS would be normal as adrenal androgen secretion is regulated primarily by ACTH rather than LH. However, this patient's pelvic ultrasound does not reveal an ovarian tumor.

(Choice D) Polycystic ovary syndrome (PCOS) can cause hyperandrogenism with ovulatory dysfunction. T and LH would be increased, and some patients have increased adrenal androgen production as well. However, this patient's ovaries have normal morphology, and rapidly progressive hirsutism with virilization would be unusual in PCOS.

(Choice E) Patients with idiopathic hirsutism have normal androgen and LH levels. However, symptoms would be more slowly progressive, and menstrual cycles would be normal.

Educational objective:

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(Choice E) Patients with idiopathic hirsutism have normal androgen and LH levels. However, symptoms would be more slowly progressive, and menstrual cycles would be normal.

Educational objective:
Rapidly progressive hirsutism with virilization suggests very high androgen levels due to an androgen-producing neoplasm. Elevated dehydroepiandrosterone sulfate levels are seen in androgen-producing adrenal tumors.

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A 60-year-old man comes to the physician after experiencing edema of his face and ankles for 2 weeks. He has no chest pain or breathlessness. For the past 15 years, the patient has had diabetes mellitus, which is managed with exercise, dietary modification, and glyburide. His glycosylated hemoglobin level a month ago was 6.9%. Temperature is 37.0 C (98.6 F), blood pressure is 146/87 mm Hg, pulse is 75/min, and respirations are 15/min. Examination is unremarkable except for bilateral pitting edema around the ankles and periorbital edema. Laboratory results are as follows:

Serum sodium	140 mEq/L
Potassium	4.3 mEq/L
Bicarbonate	20 mEq/L
Blood glucose	120 mg/dL
Blood urea nitrogen	37 mg/dL
Serum creatinine	2.4 mg/dL
Total cholesterol	300 mg/dL

The patient's electrocardiogram is normal. His urine protein results show 3700 mg/24 hr. What is the most appropriate next step in management to alter the course of this patient's diabetic nephropathy?

A. Aggressive lipid management

Bicarbonate	20 mEq/L
Blood glucose	120 mg/dL
Blood urea nitrogen	37 mg/dL
Serum creatinine	2.4 mg/dL
Total cholesterol	300 mg/dL

The patient's electrocardiogram is normal. His urine protein results show 3700 mg/24 hr. What is the most appropriate next step in management to alter the course of this patient's diabetic nephropathy?

- A. Aggressive lipid management
- B. Aspirin therapy
- C. Intensive blood pressure control
- D. Intensive glycemic control
- E. Very low protein diet

Submit

Bicarbonate	20 mEq/L
Blood glucose	120 mg/dL
Blood urea nitrogen	37 mg/dL
Serum creatinine	2.4 mg/dL
Total cholesterol	300 mg/dL

The patient's electrocardiogram is normal. His urine protein results show 3700 mg/24 hr. What is the most appropriate next step in management to alter the course of this patient's diabetic nephropathy?

- ✗ A. Aggressive lipid management [9%]
- B. Aspirin therapy [1%]
- ✓ C. Intensive blood pressure control [59%]
- D. Intensive glycemic control [24%]
- E. Very low protein diet [5%]

Incorrect
Correct answer

59%
Answered correctly

8 Seconds
Time Spent

03/28/2018
Last Updated

Diabetic nephropathy begins with hyperfiltration (increased glomerular filtration rate - GFR) and microalbuminuria (incipient nephropathy). If not treated adequately, microalbuminuria may progress to macroproteinuria, defined as urine protein excretion >300 mg/24 hr. This increase in urinary protein is accompanied by a progressive decline in GFR.

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.

(Choices A and B) Intensive lipid control is likely to reduce the risk for coronary heart disease and improve patient survival; statin therapy is recommended currently for all patients age 40–75 with diabetes mellitus regardless of baseline lipid levels. However, lipid-lowering therapy has not clearly been shown to reduce the progression of nephropathy. Similarly, aspirin reduces the incidence of coronary events without affecting the progression of nephropathy.

(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

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(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.

Educational objective:

The most beneficial therapy to reduce the progression of diabetic nephropathy is strict blood pressure control. Patients with diabetic nephropathy should be treated toward a target blood pressure of 130/80 mm Hg.

References

- Blood pressure, hypertension, RAAS blockade, and drug therapy in diabetic kidney disease.

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C

Explanation

Diabetic nephropathy be inuria (incipient nephropathy). ned as urine protein excretion > cline in GFR.

Intensive blood pressure otemia develops. Most patients patients with diabetic ne mend a target BP of 130/80 mm enzyme (ACE) inhibitors sive drugs for patients with di reducing intraglomerular nts with diabetic nephropathy mu mia.

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Joint National Committee 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 (ACEI/ARB, not first-line)
	Other ethnicities	Thiazide diuretic, ACEI, ARB, or CCB, alone or in combination
		ACEI or ARB

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C

Explanation

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	>90 mm Hg diastolic BP	
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 (ACEI/ARB, not first-line)
	Other ethnicities	Thiazide diuretic, ACEI, ARB, or CCB, alone or in combination
	All ethnicities with chronic kidney disease	ACEI or ARB, alone or in combination with other drug classes

ACEI = ACE inhibitor; ARB = angiotensin II receptor blocker; BP = blood pressure; CCB = calcium channel blocker.

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A 24-year-old woman comes to the clinic after 3 weeks of heat intolerance and increased appetite. Despite increased caloric intake, she has lost weight. The patient's medical history is insignificant, and she takes no prescription or over-the-counter medications. She does not use tobacco or illicit drugs, and consumes alcohol only on rare occasions. The patient's last menstrual period was 3 days ago and was unusually light. Temperature is 37.2 C (99 F), blood pressure is 130/75 mm Hg, pulse is 110/min and regular, and respiratory rate is 14/min. On examination, the thyroid gland is mildly enlarged, mobile, and nontender. Cranial nerve examination is normal, although there is mild lid lag. Laboratory results are as follows:

Free T4	Increased
Total T3	Increased
TSH	Decreased

Radioactive iodine uptake is <5% (normal: 8%-25%). The thyroid gland is not visualized on thyroid scan. Which of the following is the most likely diagnosis for this patient?

A. Graves disease
B. Painless thyroiditis
C. Struma ovarii
D. Subacute thyroiditis
E. Toxic nodular goiter

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Free T4	Increased
Total T3	Increased
TSH	Decreased

Radioactive iodine uptake is <5% (normal: 8%-25%). The thyroid gland is not visualized on thyroid scan. Which of the following is the most likely diagnosis for this patient?

- A. Graves disease [18%]
- ✔ B. Painless thyroiditis [38%]
- C. Struma ovarii [29%]
- D. Subacute thyroiditis [9%]
- E. Toxic nodular goiter [4%]

Correct

38%
Answered correctly

12 Seconds
TimeSpent

06/17/2018
Last Updated

Thyroiditis		
	Clinical features	**Diagnostic testing**
Chronic autoimmune thyroiditis (Hashimoto thyroiditis)	• Predominant **hypothyroid** features • Diffuse goiter	• Positive **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

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **TPO** = thyroid peroxidase.

This patient has **painless thyroiditis** (silent thyroiditis), characterized by acute **thyrotoxicosis** with mild thyroid gland enlargement and suppressed TSH. Painless thyroiditis is an autoimmune disorder thought to be a variant of Hashimoto thyroiditis, although the latter classically presents with chronic hypothyroidism. A similar disorder can also be seen within a year following pregnancy but would be properly termed postpartum thyroiditis. The follicular

This patient has **painless thyroiditis** (silent thyroiditis), characterized by acute **thyrotoxicosis** with mild thyroid gland enlargement and suppressed TSH. Painless thyroiditis is an autoimmune disorder thought to be a variant of Hashimoto thyroiditis, although the latter classically presents with chronic hypothyroidism. A similar disorder can also be seen within a year following pregnancy but would be properly termed postpartum thyroiditis. The follicular inflammatory reaction in painless thyroiditis may occasionally lead to a persistent hypothyroid phase, but most patients recover normal thyroid function.

Patients with hyperthyroidism and a suppressed TSH should undergo thyroid radioiodine scintigraphy to distinguish painless thyroiditis from Graves disease. With painless thyroiditis, radioiodine uptake is decreased suggesting the release of **preformed thyroid hormone**. In contrast, Graves disease causes hyperthyroidism due to increased synthesis of thyroid hormone. Radioiodine uptake will be diffusely increased, and extra-thyroidal manifestations (eg, **exophthalmos**, pretibial myxedema) are often present **(Choice A)**.

(Choice C) Struma ovarii is a very rare cause of thyrotoxicosis and is due to production of thyroid hormone by an ovarian teratoma. It typically presents in women over age 40 with a pelvic mass, ascites, or abdominal pain. The thyroid gland is not enlarged with this condition.

(Choice D) Subacute thyroiditis (granulomatous or De Quervain thyroiditis) also causes hyperthyroidism with a suppressed TSH and decreased radioiodine uptake. However, it is associated with a painful, tender goiter.

(Choice E) Nodular thyroid disease is a more common cause of hyperthyroidism in older individuals. A thyroid scan will show increased uptake in either a focal (**toxic adenoma**) or heterogeneous (toxic multinodular goiter) pattern.

release of **preformed thyroid hormone**. In contrast, Graves disease causes hyperthyroidism due to increased synthesis of thyroid hormone. Radioiodine uptake will be diffusely increased, and extra-thyroidal manifestations (eg, **exophthalmos**, pretibial myxedema) are often present **(Choice A)**.

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(Choice E) Nodular thyroid disease is a more common cause of hyperthyroidism in older individuals. A thyroid scan will show increased uptake in either a focal (**toxic adenoma**) or heterogeneous (toxic multinodular goiter) pattern.

Educational objective:
Painless thyroiditis (silent thyroiditis) is characterized by acute thyrotoxicosis with mild thyroid enlargement and suppressed TSH. Thyroid scintigraphy shows decreased radioiodine uptake.

References

- Subacute, silent, and postpartum thyroiditis.

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pattern.

release of **preformed thyroid hormone**. In contrast, Graves disease causes hyperthyroidism due to increased

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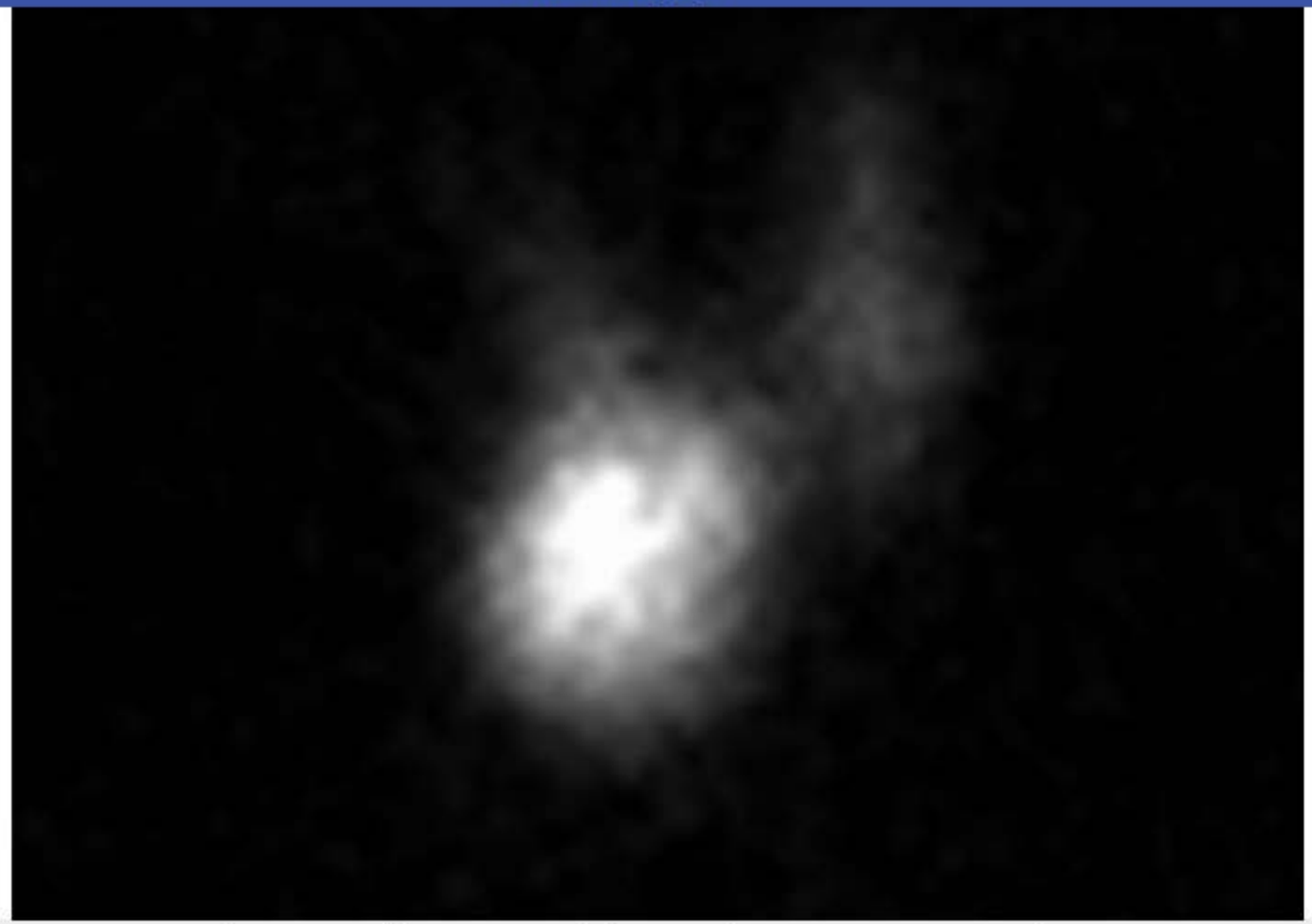

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A 34-year-old woman comes to the physician complaining of diarrhea, weight loss, and fatigue over the last year. The diarrhea occurs 2 or 3 times daily and is accompanied by crampy abdominal pain. She has diarrhea occasionally at night. She has no tenesmus or blood in the stool. The patient describes her stools as very foul-smelling and floating. She also complains of diffuse bone pain. Physical examination is unremarkable. Laboratory results show hemoglobin of 9.8 g/dL with a mean corpuscular volume of 72 fL. Which of the following additional findings would be expected in this patient?

	Calcium	Phosphate	Parathyroid Hormone
A.	Low	Low	High
B.	Low	Low	Low
C.	Low	High	Low
D.	Low	High	High
E.	High	Low	High

Submit

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	Calcium	Phosphate	Parathyroid Hormone
✔ A. [59%]	Low	Low	High
B. [1%]	Low	Low	Low
C. [5%]	Low	High	Low
D. [14%]	Low	High	High
E. [19%]	High	Low	High

Explanation

This patient's presentation of a year of foul-smelling diarrhea, weight loss, and fatigue is consistent with likely steatorrhea and malabsorption. Steatorrhea prevents usual fat emulsification and disrupts chylomicron-mediated absorption of vitamin D in the intestine, resulting in vitamin D deficiency. Because vitamin D mediates intestinal calcium and phosphorus absorption, patients develop hypocalcemia and decreased phosphorus levels. The hypocalcemia leads to secondary hyperparathyroidism with elevated parathyroid hormone levels. Vitamin D deficiency can lead to osteomalacia with findings that include bone pain or tenderness, muscle weakness or cramps, gait abnormalities, and increased fracture risk. However, some patients can be asymptomatic.

Educational objective:

Chronic gastrointestinal disease (eg, steatorrhea, celiac disease) can cause vitamin D deficiency due to malabsorption. Patients usually develop hypocalcemia, low phosphorus, and elevated parathyroid hormone. Patients can be asymptomatic or complain of bone pain or tenderness, muscle weakness or cramps, and gait abnormalities.

References

- Hypocalcemia: updates in diagnosis and management for primary care.

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