

ENDOCRINE AND METABOLIC DISORDERS

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**TEXAS TECH UNIVERSITY HEALTH SCIENCES CENTER
SCHOOL OF PHARMACY
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Learning Objectives

1. Differentiate between the diagnostic and classification criteria for various endocrine and metabolic disorders, including type 1 and type 2 diabetes mellitus, obesity, and disorders of the thyroid, adrenal, and pituitary glands.
2. Compare the various therapeutic agents used in treating endocrine and metabolic disorders.
3. Select appropriate treatment and monitoring options for a given patient presenting with one of the above disorders.
4. Recommend appropriate therapeutic management for secondary complications from diabetes or thyroid disorders.

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. A 66-year-old Hispanic man with a history of myocardial infarction, dyslipidemia, and hypertension received a diagnosis of type 2 diabetes mellitus (DM). After 1 month of exercise and dietary changes and no diabetes medications, his hemoglobin A1C and fasting glucose concentration today are 11.5% and 322 mg/dL, respectively. He weighs 123.8 kg, with a body mass index (BMI) of 42 kg/m². Which set of drugs is best to initiate?
 - A. Metformin and glipizide.
 - B. Glipizide and insulin glulisine.
 - C. Pioglitazone and acarbose.
 - D. Insulin detemir and glulisine.
2. A 21-year-old patient is given a diagnosis of type 1 DM after the discovery of elevated glucose concentrations (average 326 mg/dL) and is showing signs and symptoms of hyperglycemia. Her weight is 80 kg. Which is the most appropriate initial dose of rapid-acting insulin before breakfast for this patient? Assume a total daily insulin (TDI) regimen of 0.5 unit/kg/day.
 - A. 2 units.
 - B. 4 units.
 - C. 7 units.
 - D. 14 units.
3. A patient with type 2 DM has a blood pressure reading of 152/84 mm Hg, a serum creatinine of 1.8 mg/dL, and two recent spot urine albumin/creatinine concentrations of 420 and 395 mg/g. Which class of drugs (barring any contraindications) is best to initiate in this patient?
 - A. Thiazide diuretic.
 - B. Dihydropyridine calcium channel blocker.
 - C. Angiotensin receptor blocker (ARB).
 - D. Nondihydropyridine calcium channel blocker.
4. Regarding propylthiouracil (PTU) and methimazole in the treatment of hyperthyroidism, which statement is most appropriate?
 - A. PTU is clinically superior to methimazole in efficacy.
 - B. PTU may be associated with greater liver toxicity than methimazole.
 - C. Both agents are equally efficacious in the treatment of Hashimoto's disease.
 - D. Both medications should be administered three times daily.
5. Which medication is the most appropriate choice for a patient with a diagnosis of Cushing's syndrome who did not experience adequate symptom relief after surgical resection for a pituitary adenoma?
 - A. Ketoconazole.
 - B. Spironolactone.
 - C. Hydrocortisone.
 - D. Bromocriptine.
6. A physician is asking for a recommendation for initial therapy for a patient with type 2 DM. The physician states that metformin is no longer an option for this patient. An A1C obtained today is 9.4% (personal goal 7%), and the patient's estimated glomerular filtration rate (eGFR) is 29 mL/min. Which of the following agents would be the best recommendation?
 - A. Canagliflozin.
 - B. Alogliptin.
 - C. Glargine.
 - D. Exenatide.

7. A 76-year-old woman recently given a diagnosis of Hashimoto's disease presents with mild symptoms of lethargy, weight gain, and intolerance to cold. Her thyroid-stimulating hormone (TSH) level is 12.2 mIU/L, and her free thyroxine (T_4) is below normal limits. Her current weight is 47 kg. She has a history of hypertension and underwent a coronary artery bypass surgery 2 years ago. Which would be the most appropriate initial treatment for this patient?
- Levothyroxine 25 mcg once daily.
 - Levothyroxine 75 mcg once daily.
 - Liothyronine 25 mcg once daily.
 - Liothyronine 75 mcg once daily.
8. A woman with type 2 DM has an A1C of 8.6%. She is receiving insulin glargine (60 units once daily at bedtime) and insulin aspart (8 units before breakfast, 7 units before lunch, and 12 units before dinner). She is consistent in her carbohydrate intake at each meal. Her morning fasting plasma glucose (FPG) and premeal blood glucose (BG) readings have consistently averaged 112 mg/dL. Her bedtime readings are averaging between 185 and 200 mg/dL. Which is the best insulin adjustment to improve her overall glycemic control?
- Increase her prebreakfast aspart to 10 units.
 - Increase her predinner aspart to 14 units.
 - Increase her bedtime glargine to 65 units.
 - Increase her prelunch aspart to 9 units.
9. A 53-year-old woman with a history of Graves' disease underwent ablative therapy 3 years ago. She experienced significant symptom relief and became euthyroid. Her thyroid laboratory values today include TSH 0.12 mIU/L (normal 0.5–4.5 mIU/L) and a free T_4 concentration of 3.8 g/dL (normal 0.8–1.9 ng/dL). She states that many of her previous symptoms have returned but are mild. Which would be the most appropriate treatment for her condition?
- Methimazole.
 - Thyroidectomy.
 - Propylthiouracil.
 - Metoprolol.
10. A 65-year-old man with type 2 DM for 6 years has been receiving metformin 1000 mg twice daily for the past 2 years. His A1C today is 7.8%. His morning fasting blood glucose (FBG) readings are consistently at goal. His after-meal glucose readings average 190–200 mg/dL. Which option would be most appropriate for this patient?
- Increase metformin to 1000 mg three times daily.
 - Add insulin glargine 10 units once daily.
 - Switch from metformin to insulin glargine 10 units once daily.
 - Add saxagliptin 5 mg once daily.
11. A 34-year-old woman has a BMI of 33 kg/m². With dietary changes, she has lost 2 lb in 6 months. She exercises regularly but is unable to do more because she has two jobs and young children. Her medical history is significant for depression, type 2 DM, and substance abuse. Her current medications include metformin 1000 mg twice daily, aspirin 81 mg once daily, and sertraline 100 mg once daily. She is most concerned about weight loss. Which would be the best recommendation to help her lose weight?
- Continue her diet and exercise routine; additional intervention is unwarranted.
 - Initiate lorcaserin 10 mg twice daily.
 - Initiate phentermine/topiramate 3.75/23 mg once daily.
 - Initiate orlistat 120 mg three times daily with meals.
12. A 53-year-old Hispanic woman has a BMI of 44 kg/m² and a history of gestational diabetes. Her mother and sister both have type 2 DM. She had an A1C of 7.4% 2 weeks ago. Her fasting glucose concentration is 178 mg/dL. She is asymptomatic. Which is the best course of action?
- Diagnose type 2 DM and begin treatment.
 - Diagnose type 1 DM and begin treatment.
 - Obtain another A1C today.
 - Obtain another glucose concentration another day.

13. A 66-year-old man has a history of type 2 DM. His current therapy includes metformin 1000 mg twice daily, glyburide 10 mg twice daily, aspirin 81 mg once daily, and lisinopril 20 mg once daily. Today, his A1C is 6.9%, blood pressure is 126/78 mm Hg, and fasting lipid panel is as follows: total cholesterol 212 mg/dL, low-density lipoprotein cholesterol (LDL-C) 128 mg/dL, high-density lipoprotein cholesterol (HDL-C) 45 mg/dL, and triglycerides (TG) 145 mg/dL. Which would be the most appropriate choice for this patient?
- A. Add insulin detemir 10 units once daily.
 - B. Add hydrochlorothiazide 25 mg once daily.
 - C. Add atorvastatin 10 mg once daily.
 - D. Add fenofibrate 145 mg once daily.

I. THYROID DISORDERS

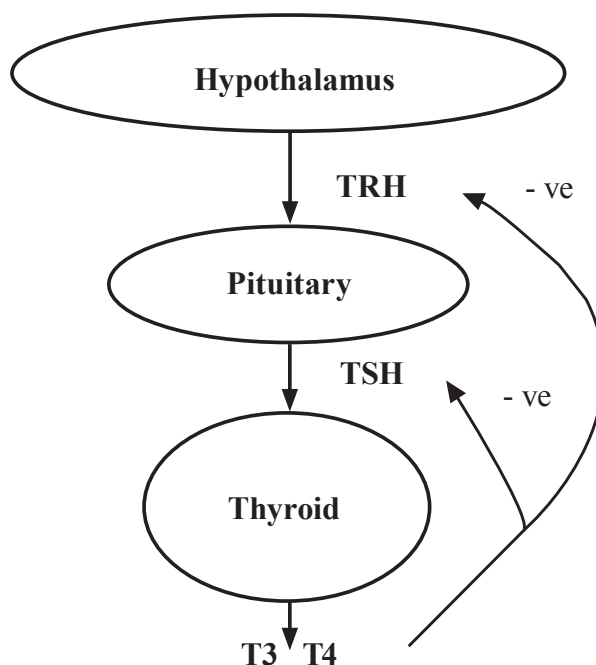


Figure 1. Hypothalamus-pituitary-thyroid axis.^a

^aT₄ is converted to T₃ by peripheral tissue. Only unbound (free) thyroid hormone is biologically active.

T₃ = triiodothyronine; T₄ = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; - ve = negative feedback loop.

Patient Case

1. A 43-year-old woman has received a diagnosis of Graves' disease. She is reluctant to try ablative therapy and wants to attempt oral pharmacotherapy first. Her thyroid laboratory values today include TSH 0.22 mIU/L (normal 0.5–4.5 mIU/L) and a free T₄ concentration of 3.2 ng/dL (normal 0.8–1.9 ng/dL). She is anxious and always feels warm when others say it is too cold. Which would be considered the best drug for initial treatment of her condition?
 - A. Lugol's solution.
 - B. Propylthiouracil.
 - C. Atenolol.
 - D. Methimazole.

A. Hyperthyroid Disorders (Thyrotoxicosis)

1. Classification
 - a. Toxic diffuse goiter (Graves' disease): Most common hyperthyroid disorder
 - i. Autoimmune disorder
 - ii. Thyroid-stimulating antibodies directed at thyrotropin receptors mimic TSH and stimulate triiodothyronine/thyroxine (T₃/T₄) production.
 - b. Pituitary adenomas: Produce excessive TSH secretion that does not respond to normal T₃ negative feedback
 - c. Toxic adenoma: Nodule in thyroid, autonomous of pituitary and TSH
 - d. Toxic multinodular goiter (Plummer disease): Several autonomous follicles that, if large enough, cause excessive thyroid hormone secretion

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- e. Painful subacute thyroiditis: Self-limiting inflammation of the thyroid gland caused by viral invasion of the parenchyma, resulting in the release of stored hormone
 - f. Drug induced (e.g., excessive exogenous thyroid hormone doses, amiodarone therapy)
2. Diagnosis
 - a. Elevated free T_4 serum concentrations
 - b. Suppressed TSH concentrations (except in TSH-secreting adenomas)
 - c. If examination and history do not provide the exact etiology, radioactive iodine uptake may be used.
 - i. Radioactive iodine uptake elevated if thyroid gland is actively and excessively secreting T_4 and/or T_3 ; Graves' disease, TSH-secreting adenoma, toxic adenoma, multinodular goiter
 - ii. Radioactive iodine uptake is suppressed in disorders caused by thyroiditis or hormone ingestion.
 - d. Can also assess for the presence of various thyroid-related antibodies (thyroid stimulating, thyrotropin receptor, or thyroperoxidase), thyroglobulin, and thyroid biopsy
 3. Clinical presentation
 - a. Weight loss or increased appetite
 - b. Lid lag
 - c. Heat intolerance
 - d. Goiter
 - e. Fine hair
 - f. Heart palpitations or tachycardia
 - g. Nervousness, anxiety, insomnia
 - h. Menstrual disturbances (lighter or more infrequent menstruation, amenorrhea) caused by hypermetabolism of estrogen
 - i. Sweating or warm, moist skin
 - j. Exophthalmos, pretibial myxedema in Graves' disease
 4. Therapy goals
 - a. Minimize or eliminate symptoms, improve quality of life.
 - b. Minimize long-term damage to organs (heart disease, arrhythmias, sudden cardiac death, bone demineralization, and fractures).
 - c. Normalize free T_4 and TSH concentrations.
 5. Therapeutics
 - a. Ablative therapy: Treatment of choice for Graves' disease, toxic nodule, multinodular goiter: Radioactive iodine ablative therapy and surgical resection for adenomas according to patient preferences or comorbidities. Ablative therapy often results in hypothyroidism.
 - b. Antithyroid pharmacotherapy usually reserved for:
 - i. Those awaiting ablative therapy or surgical resection
 - (a) Depletes stored hormone
 - (b) Minimizes risk of posttreatment hyperthyroidism because of thyroiditis
 - ii. Those who are not an ablative or surgical candidate (e.g., serious cardiovascular disease, candidate unlikely to be adherent to radiation safety)
 - iii. When ablative therapy or surgical resection fails to normalize thyroid function
 - iv. Those with a high probability of remission with oral therapy for Graves' disease
 - (a) Mild disease
 - (b) Small goiter
 - (c) Low or negative antibody titers
 - v. Those with limited life expectancy
 - vi. Those with moderate to severe active Graves' ophthalmopathy
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- c. Thioureas (i.e., propylthiouracil [PTU], methimazole)
 - i. Mechanism of action: Inhibits iodination and synthesis of thyroid hormones; PTU may block T_4/T_3 conversion in the periphery as well.
 - ii. Dosing
 - (a) PTU
 - (1) Initial: 100 mg by mouth three times daily
 - (2) Maximal: 400 mg three times daily
 - (3) Once euthyroid, may reduce to 50 mg two or three times daily
 - (b) Methimazole
 - (1) Preferred agent for Graves' disease according to the American Association of Clinical Endocrinologists (AACE) for most patients unless in first trimester of pregnancy; then use PTU
 - (2) Initial: 10–20 mg by mouth once daily
 - (3) Maximal: 40 mg three times daily
 - (4) Once euthyroid, may reduce to 5–10 mg/day
 - (c) Monthly dose titrations as needed (based on symptoms and free T_4 concentrations); TSH may remain low months after therapy starts.
 - iii. Adverse effects
 - (a) Hepatotoxicity risk with PTU (boxed warning): AACE recommends baseline liver function tests.
 - (b) Rash
 - (c) Arthralgias, lupus-like symptoms
 - (d) Fever
 - (e) Agranulocytosis early in therapy (usually within 3 months): AACE recommends baseline complete blood cell count (CBC); no routine monitoring recommended. May repeat if patient becomes febrile or develops pharyngitis.
 - iv. Efficacy
 - (a) Slow onset in reducing symptoms (weeks). Maximal effect may take 4–6 months.
 - (b) Neither drug appears superior to the other in efficacy.
 - (c) On a milligram-to-milligram basis, methimazole is 10 times more potent than PTU.
 - (d) Remission rates low: 20%–30%. Remission defined as normal TSH and T_4 for 1 year after discontinuing antithyroid therapy.
 - (e) Therapy duration in Graves' disease (oral agents unlikely to cause remission in those with nodular thyroid disease):
 - (1) Usually 12–18 months; length of trial may not affect remission rate.
 - (2) Consider trial off oral therapy if TSH is normal; antibody titers may help guide decision.
 - (3) Monitor thyroid concentrations every 1–3 months for up to 12 months for relapse (abnormal TSH or T_4 return).
- d. Nonselective β -blockers (primarily propranolol; sometimes nadolol)
 - i. Mechanism of action: Blocks many hyperthyroidism manifestations mediated by β -adrenergic receptors. Also may block (less active) T_4 conversion to (more active) T_3 .
 - ii. Propranolol dosing
 - (a) Initial: 20–40 mg by mouth three or four times daily
 - (b) Maximal: 240–480 mg/day
 - iii. Adverse effects (see Hypertension section in Cardiovascular II chapter)
 - iv. Efficacy
 - (a) Used primarily for symptomatic relief (e.g., palpitations, tachycardia, tremor, anxiety)

- (b) Guidelines recommend use in symptomatic older adults and in others with heart rates greater than 90 beats/minute or existing cardiovascular disease, and consider use in all symptomatic patients. Recommended for use before ablative iodine therapy also in those who are extremely symptomatic or have a free T_4 two to three times the upper limit of normal.
 - (c) Poor remission rates: 20%–35%
 - (d) Primary role is treatment of thyroiditis, which is usually self-limiting, and for acute management of symptoms during thyroid storm (see below).
 - (e) Alternatives to β -blockers: Clonidine, nondihydropyridine calcium channel blocker
 - e. Iodines/iodides (e.g., Lugol's solution, saturated solution of potassium iodide)
 - i. Mechanism of action: Inhibits the release of stored thyroid hormone. Minimal effect on hormone synthesis. Helps decrease vascularity and size of gland before surgery.
 - ii. Dosing
 - (a) Lugol's solution (6.3–8 mg iodide per drop)
 - (b) Saturated solution of potassium iodide (38–50 mg iodide per drop)
 - (c) Potassium iodide tablets: (130-mg tablets contain 100 mg of iodide)
 - (d) Usual daily dose: 120–400 mg mixed with juice or water, split three times daily
 - iii. Adverse effects
 - (a) Hypersensitivity
 - (b) Metallic taste
 - (c) Soreness or burning in mouth or tongue
 - (d) Do not use in the days before ablative iodine therapy (may reduce uptake of radioactive iodine).
 - iv. Efficacy
 - (a) Limited efficacy after 7–14 days of therapy because thyroid hormone release will resume
 - (b) Primary use is temporary before surgery (7–10 days) to shrink the gland.
 - (c) Can be used after ablative therapy (3–7 days) to inhibit thyroiditis-mediated release of stored hormone
 - (d) Used acutely in thyroid storm
- B. Subclinical Hyperthyroidism
- 1. Definition: Low (below lower limit of reference range) or undetectable TSH with normal T_4
 - 2. Risk
 - a. Associated with elevated risk of atrial fibrillation in patients older than 60 years
 - b. Associated with elevated risk of bone fracture in postmenopausal women
 - c. Conflicting data about mortality risk
 - 3. Treatment (based on 2011 guidelines) similar to treating overt hyperthyroidism
 - a. Oral antithyroid drug therapy alternative to ablative therapy in young patients with Graves' disease
 - b. β -Blockers may be of benefit in controlling cardiovascular morbidity, especially with atrial fibrillation.
 - 4. If untreated, screen regularly for the development of overt hyperthyroidism (increased free T_4 concentrations).
- C. Thyroid Storm
- 1. Severe and life-threatening decompensated thyrotoxicosis. Mortality rate may be as high as 20%.
 - 2. Precipitating causes: Trauma, infection, antithyroid agent withdrawal, severe thyroiditis, postablative therapy (especially if inadequate pretreatment)
 - 3. Presentation: Fever, tachycardia, vomiting, dehydration, coma, tachypnea, delirium

4. Pharmacotherapy
 - a. PTU
 - i. 500- to 1000-mg loading dose, then 250 mg every 4 hours
 - ii. Blocks new hormone synthesis
 - iii. Can use methimazole 60–80 mg daily
 - b. Iodide therapy 1 hour after PTU initiation (dosed as above) to block hormone release
 - c. β -Blocker therapy: Propranolol or esmolol commonly used to control symptoms and blocks conversion of T_4 to T_3
 - d. Acetaminophen as antipyretic therapy, if needed (avoid nonsteroidal anti-inflammatory drugs [NSAIDs] because of displacement of protein-bound thyroid hormones)
 - e. Corticosteroid therapy: Prednisone 300 mg intravenous loading dose then 100 mg every 8 hours (or equivalent doses of, e.g., dexamethasone, hydrocortisone). Prophylaxis against relative adrenal insufficiency and may block conversion of T_4 to T_3 .

Patient Case

2. A 63-year-old woman has Hashimoto's disease. Her thyroid laboratory values today include the following: TSH 10.6 mIU/L (normal 0.5–4.5 mIU/L) and a free T_4 concentration of 0.5 ng/dL (normal 0.8–1.9 ng/dL). She feels consistently run down and has dry skin that does not respond to the use of hand creams. Which would be considered the best drug for initial treatment of her condition?
 - A. Levothyroxine.
 - B. Liothyronine.
 - C. Desiccated thyroid.
 - D. Methimazole.

D. Hypothyroid Disorders

1. Classification
 - a. Hashimoto's disease: Most common hypothyroid disorder in areas with iodine sufficiency
 - i. Autoimmune-induced thyroid injury resulting in decreased thyroid secretion
 - ii. Disproportionately affects women
 - b. Iatrogenic: Thyroid resection or radioiodine ablative therapy for treatment of hyperthyroidism
 - c. Iodine deficiency most common cause worldwide
 - d. Secondary causes
 - i. Pituitary insufficiency (failure to produce adequate TSH secretion, referred to by some as central or secondary hypothyroidism)
 - ii. Drug induced (e.g., amiodarone, lithium)
2. Diagnosis
 - a. Low free T_4 serum concentrations
 - b. Elevated TSH concentrations, usually above 10 mIU/L (normal or low if central hypothyroidism is the etiology)
 - c. Thyroid antibodies such as antithyroid peroxidase and antithyroglobulin autoantibodies
 - d. Screen patients older than 60, especially women (there are many different screening recommendations by various professional groups with little consensus).
3. Clinical presentation
 - a. Cold intolerance
 - b. Dry skin
 - c. Fatigue, lethargy, weakness
 - d. Weight gain

- e. Bradycardia
 - f. Slow reflexes
 - g. Coarse skin and hair
 - h. Periorbital swelling
 - i. Menstrual disturbances (more frequent or longer menstruation, painful menstruation, menorrhagia) caused by hypometabolism of estrogen
 - j. Goiter (primary hypothyroidism)
4. Therapy goals
- a. Minimize or eliminate symptoms; improve quality of life.
 - b. Minimize long-term damage to organs (myxedema coma, heart disease).
 - c. Normalize free T_4 and TSH concentrations.
5. Therapeutics
- a. Levothyroxine (drug of choice)
 - i. Mechanism of action: Synthetic T_4
 - ii. Dosing
 - (a) Initial
 - (1) In otherwise healthy adults, 1.6 mcg/kg (use ideal body weight) per day.
 - (2) In patients 50–60 years of age, consider 50 mcg/day.
 - (3) In those with existing cardiovascular disease, consider 12.5–25 mcg/day.
 - (b) Usually dosed in the morning on an empty stomach 30–60 minutes before breakfast or at bedtime 4 hours after last meal; dosed separately from other medications
 - (c) Dose titration based on response (control of symptoms, normalization of TSH and free T_4)
 - (d) Can increase or decrease in 12.5- to 25-mcg/day increments
 - (e) Daily requirements are higher in pregnancy (separate guidelines available for treating thyroid disorders in pregnancy).
 - iii. Monitoring
 - (a) 4–8 weeks is appropriate to assess patient response in TSH after initiating or changing therapy (about a 7-day half-life for T_4). May take longer for TSH to achieve steady-state concentrations
 - (b) Use free T_4 rather than TSH if central or secondary hypothyroidism; obtain sample before daily dosing of levothyroxine.
 - iv. Adverse effects
 - (a) Hyperthyroidism
 - (b) Cardiac abnormalities (tachyarrhythmias, angina, myocardial infarction)
 - (c) Linked to risk of fractures (usually at higher doses or oversupplementation)
 - v. Efficacy: If levothyroxine is properly dosed, most patients will maintain TSH and free T_4 in the normal ranges and experience symptomatic relief.
 - vi. Considered drug of choice secondary to its adverse effect profile, cost, lack of antigenicity, and uniform potency
 - vii. Bioequivalency
 - (a) AACE recommends brand-name levothyroxine (none of the other thyroid preparations below are supported by AACE).
 - (b) Although legal, guidelines recommend against changing from brand to generic and vice versa. It is recommended to stay with one product throughout therapy.
 - (c) TSH concentrations in bioequivalence testing were never performed; small changes in T_4 between products may result in significant changes in TSH. Pharmacokinetic studies were conducted in normal subjects with normal thyroid function.

- b. Liothyronine (synthetic T_3), liotrix (synthetic T_4/T_3), desiccated thyroid are not recommended by leading professional organizations or clinical guidelines.
- E. Subclinical Hypothyroidism
1. Definition: Elevated TSH (above upper limit of reference range) with normal T_4 . Often the result of early Hashimoto's disease
 2. Risk:
 - a. TSH greater than 7.0 mIU/L in older adults associated with elevated risk of heart failure
 - b. TSH greater than 10 mIU/L associated with elevated risk of coronary heart disease
 3. Treatment of subclinical hypothyroidism is controversial because benefits in identified patients are inconclusive. An association between the use of levothyroxine and a reduction in heart disease in younger patients (40–70 years of age) does appear to exist, but not in older patients (older than 70 years).
 4. Whom to treat
 - a. TSH between 4.5 and 10 mIU/L and
 - i. Symptoms of hypothyroidism
 - ii. Antithyroid peroxidase antibodies present
 - iii. History of cardiovascular disease, heart failure, or risk factors for such
 - b. Initial daily doses of 25–75 mcg recommended
 5. If untreated, screen regularly for the development of overt hypothyroidism (decreased free T_4 concentrations).
- F. Myxedema Coma
1. Severe and life-threatening decompensated hypothyroidism. Mortality rate 30%–60%
 2. Precipitating causes: Trauma, infections, heart failure, medications (e.g., sedatives, narcotics, anesthesia, lithium, amiodarone)
 3. Presentation: Coma is not required and is uncommon, despite terminology; altered mental state (very common); diastolic hypertension; hypothermia; hypoventilation
 4. Pharmacotherapy
 - a. Intravenous thyroid hormone replacement
 - i. T_4 : 100- to 500-mcg loading dose, followed by 75–100 mcg/day, until patient can tolerate oral therapy. Lower the initial dose in frailer patients or in patients with established cardiovascular disease.
 - ii. Some advocate the use of T_3 over T_4 , given that T_3 is more biologically active and that T_4/T_3 conversion may be suppressed in myxedema coma. Cost and availability limit intravenous T_3 use.
 - b. Antibiotic therapy: Given common infectious causes, some advocate empiric therapy with broad-spectrum antibiotics.
 - c. Corticosteroid therapy
 - i. Hydrocortisone 100 mg every 8 hours (or equivalent steroid)
 - ii. Can be discontinued if random cortisol concentration not depressed

II. PITUITARY GLAND DISORDERS

Table 1. Basic Pituitary Gland (Anterior) Hormone Physiology

Anterior Pituitary Hormone	Primary Functions	Hypothalamic Stimulator	Primary Secretion Inhibitor
Growth hormone (GH)	Promote tissue growth	GH-releasing hormone	Somatostatin Increased IGF-1
Adrenocorticotrophic hormone (ACTH)	Stimulate adrenal cortisol and androgen release	Corticotropin-releasing hormone	Cortisol
Thyroid-stimulating hormone (TSH)	Metabolic stability	Thyrotropin-releasing hormone	T ₃
Prolactin	Regulate lactation	Thyrotropin-releasing hormone	Dopamine
Follicle-stimulating hormone	Maturation of ovarian follicles Sperm production	Gonadotropin-releasing hormone	Inhibin Estrogens
Luteinizing hormone	Secretion of sex steroids	Gonadotropin-releasing hormone	Estrogens and progestins Testosterone

IGF-1 = insulin-like growth factor-I; T₃ = triiodothyronine.

- A. Classification (focus on the common anterior pituitary disorders)
 1. Hypersecretory diseases
 - a. Acromegaly and gigantism: Usually caused by growth hormone (GH)-secreting pituitary adenoma
 - b. Hyperprolactinemia:
 - i. Most common cause is prolactinomas (prolactin-secreting pituitary tumor).
 - ii. Drug induced (e.g., serotonin reuptake inhibitors and some antipsychotics)
 - iii. Central nervous system lesions
 2. Hyposecretory disease
 - a. GH deficiency:
 - i. Congenital abnormality caused by GH gene deletion, GH-releasing hormone deficiency
 - ii. Other causes are pituitary aplasia, head trauma, and central nervous system infection.
 - iii. Idiopathic
 - b. Panhypopituitarism: Result of partial or complete loss of anterior and posterior pituitary function. Can be caused by primary pituitary tumor, ischemic necrosis of the pituitary, trauma from surgery, or irradiation. Results in adrenocorticotrophic hormone (ACTH) deficiency, GH deficiency, hypothyroidism, gonadotropin deficiency
- B. Acromegaly
 1. Diagnosis and clinical presentation
 - a. Failure of an oral glucose tolerance test (OGTT) to suppress GH serum concentrations but with elevated insulin-like growth factor-1 (IGF-1). (GH serum concentrations alone are unreliable, given the pulsatile pattern of release in the body.)
 - b. Clinical presentation (Note: Disease has a very slow onset, and many symptoms do not appear for years.)
 - i. Excessive sweating

- ii. Osteoarthritis, joint pain, paresthesias, or neuropathies
 - iii. Coarsening of facial features
 - iv. Increased hand volume or ring size, increased shoe size
 - v. Hypertension, heart disease, cardiomyopathy
 - vi. Sleep apnea
 - vii. Type 2 DM
2. Therapy goals
- a. Reduce GH and IGF-1 concentrations.
 - b. Decrease mortality.
 - c. Improve clinical symptoms.
 - d. Normalize IGF-1 concentrations and suppressed GH concentrations after OGTT.
3. Therapeutics
- a. Treatment of choice is surgical resection of tumor, if causative.
 - b. Pharmacotherapy usually reserved for:
 - i. Control before surgery or irradiation
 - ii. When surgery is not possible (usually requires lifelong pharmacotherapy)
 - iii. Surgical failures or relapses after period of remission after surgery
 - c. Dopamine agonists (e.g., bromocriptine, cabergoline)
 - i. Mechanism of action: Dopamine agonist that, in acromegaly, causes paradoxical decrease in GH production
 - ii. Dosing (bromocriptine, most commonly used agent)
 - (a) Initial: 1.25 mg/day by mouth
 - (b) Maximal: 20–30 mg/day (can titrate once or twice weekly as needed)
 - iii. Adverse effects
 - (a) Fatigue, dizziness, nervousness
 - (b) Diarrhea, abdominal pain
 - iv. Efficacy: Normalization of IGF-1 concentrations in about 10% of patients. More than 50% of patients experience symptomatic relief.
 - d. Somatostatin analog (e.g., octreotide)
 - i. Mechanism of action: Blocks GH secretion; 40 times more potent than endogenous somatostatin
 - ii. Dosing
 - (a) Initial: 50–100 mcg subcutaneously every 8 hours
 - (b) Maximal: Little benefit greater than 600 mcg/day
 - (c) If response to above, can be changed to long-acting octreotide formulation administered once monthly
 - iii. Adverse effects
 - (a) Diarrhea, nausea, cramps, flatulence, fat malabsorption
 - (b) Arrhythmias
 - (c) Hypothyroidism
 - (d) Biliary tract disorders
 - (e) Changes in serum glucose concentrations (usually reduces)
 - iv. Efficacy: 50%–60% of patients experience normalization of IGF-1 concentrations with good symptomatic relief as well. May shrink tumor mass in some patients
 - e. GH receptor antagonist (e.g., pegvisomant)
 - i. Mechanism of action: GH derivative binds to liver GH receptors and inhibits IGF-1.
 - ii. Dosing:
 - (a) Initial: 40 mg once-daily subcutaneous injection loading dose and then 10 mg once daily
 - (b) Maximal: 30 mg/day

- iii. Adverse effects
 - (a) Nausea, vomiting
 - (b) Flu-like symptoms
 - (c) Reversible elevations in hepatic transaminase
- iv. Efficacy: More than 95% of patients attain normal IGF-1 concentrations, and most have improved symptoms.

Patient Case

3. A 28-year-old woman presents with acne, facial hair growth, and irregular menses that have lasted for 6–7 months. She has diagnoses of hypertension and depression. Her pituitary and thyroid tests have all come back negative. Her current medications include atenolol and fluoxetine. Her prolactin level today is 112 ng/mL (normal 15–25 ng/mL). Which is the most likely cause of her elevated prolactin level?
- A. Atenolol.
 - B. Prolactin-secreting adenoma.
 - C. Pregnancy.
 - D. Fluoxetine.

C. Hyperprolactinemia

1. Causes
 - a. Direct: Pituitary tumor (lactotroph adenoma)
 - b. Indirect: Drug induced (most frequent nontumor cause), renal failure, hypothyroidism, breastfeeding
 - c. Potential causative drugs: Typical antipsychotics, opiates, nondihydropyridine calcium channel blocker, antidepressants
2. Diagnosis and clinical presentation
 - a. Elevated serum prolactin concentrations. May be challenging to find specific etiology (unless drug induced)
 - b. Clinical presentation
 - i. Amenorrhea, anovulation, infertility, hirsutism, and acne in women
 - ii. Erectile dysfunction, decreased libido, gynecomastia, and reduced muscle mass in men
 - iii. Headache, visual disturbances, bone loss
3. Therapy goals
 - a. Normalize prolactin concentrations
 - b. Normalize gonadotropin secretion
 - c. Symptomatic relief
4. Therapeutics
 - a. Treatment of choice is surgical resection of tumor, if causative.
 - b. Pharmacotherapy usually reserved for:
 - i. Control before surgery or irradiation
 - ii. When surgery is not possible (usually requires lifelong pharmacotherapy)
 - iii. Surgical failures or relapses after period of remission after surgery
 - c. Discontinue causative agent if drug induced.
 - i. Recheck prolactin concentration 3 days after discontinuation.
 - ii. Select agent with similar action but no known effect on prolactin concentrations.
 - iii. If discontinuation of causative agent not feasible, consider dopamine agonist.
 - d. Dopamine agonists
 - i. Cabergoline (preferred agent per Endocrine Society guidelines, long-acting oral agent; adverse effect profile similar to that of bromocriptine)

- (a) Initial: 0.5 mg once weekly
 - (b) Maximal: 4.5 mg/week
 - ii. Bromocriptine (see above)
 - iii. Efficacy: May restore fertility in more than 90% of women. Cabergoline may be easier for patients to take, given weekly administration.
 - iv. Consider taper or discontinuation after 2 years of therapy if asymptomatic, prolactin concentrations normalized, and no tumor remnant by imagery.
5. GH deficiency: Diagnosis and clinical presentation
 - a. Decreased GH concentrations after provocative pharmacologic challenge (e.g., insulin, clonidine, GH-releasing hormone)
 - b. Clinical presentation
 - i. Delayed growth velocity or short stature
 - ii. Central obesity
 - iii. Immaturity of the face or prominence of the forehead
 6. Therapy goals
 - a. Increased growth velocity
 - b. Increased final adult height when treating children
 7. Therapeutics: Recombinant GH (somatropin)
 - a. Dosing
 - i. Depends on which of the various products are selected (dosed subcutaneously or intramuscularly once daily)
 - ii. When to discontinue therapy on the basis of growth velocity is controversial.
 - iii. Once- or twice-monthly long-acting depot formulation is also available.
 - b. Adverse effects
 - i. Arthralgias, injection site pain
 - ii. Rare but serious cases of idiopathic intracranial hypertension have been reported.
 - c. Efficacy: All products are considered equally efficacious.

III. ADRENAL GLAND DISORDERS

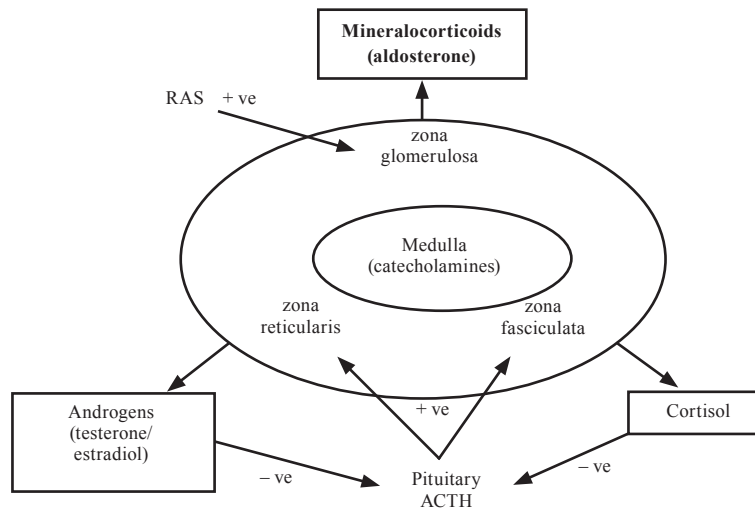


Figure 2. Basic adrenal cortex hormone physiology.

ACTH = adrenocorticotropic hormone; RAS = renin-angiotensin system; + ve = positive stimulation; - ve = negative feedback.

Patient Case

4. A 44-year-old man has consistently high blood pressure (e.g., 172/98 mm Hg today) despite documented adherence to two maximal-dose blood pressure medications. He has frequent headaches, increased thirst, and fatigue. His urine-free cortisol is 45 mcg/24 hours (normal range 20–90), and his plasma aldosterone/renin ratio is 125 (normal is less than 25). Which condition is the most likely cause of this patient's uncontrolled hypertension?
- Cushing's syndrome.
 - Addison's disease.
 - Hyperprolactinemia.
 - Hyperaldosteronism.

A. Hypersecretory Cortisol Diseases (a.k.a. Cushing's syndrome)

- Classification
 - ACTH-dependent: Result of excessive ACTH secretion
 - Pituitary corticotroph adenoma (Cushing's disease)
 - Ectopic ACTH syndrome (extrapituitary tumor)
 - ACTH-independent: Result of excessive cortisol secretion or exogenous steroids
 - Unilateral adrenocortical tumors
 - Bilateral adrenal hyperplasia or dysplasia
 - Exogenous steroid administration
- Diagnosis and clinical presentation
 - Presence of hypercortisolism through 24-hour urine-free cortisol concentration
 - Differentiate etiology (key to treatment options).
 - Complex and beyond the scope of this chapter
 - Plasma ACTH concentrations (normal or elevated in ACTH-dependent)
 - Pituitary magnetic resonance imaging (MRI) (Cushing's syndrome vs. ectopic ACTH syndrome)
 - Overnight dexamethasone suppression test
 - 24-hour urinary-free cortisol
 - Clinical presentation
 - Central obesity and facial rounding quite common
 - Peripheral obesity and fat accumulation
 - Myopathies
 - Osteoporosis, back pain, compression fracture
 - Abnormal glucose tolerance or diabetes
 - Amenorrhea and hirsutism in women
 - Lower abdominal pigmented striae (red to purple)
 - Hypertension (principal cause of morbidity and mortality)
- Therapy goals
 - Reduce morbidity and mortality and eliminate cause.
 - Reverse clinical features.
 - Normalize biochemical changes (when possible).
 - Achieve long-term control without recurrence (remission when possible).
- Therapeutics
 - If excessive exogenous corticosteroid use is causative, discontinue or minimize use.

- b. Cushing's disease: Surgical resection of causative area or tumor is usual treatment of choice (70%–90% cure rate). Pharmacotherapy is usually reserved on the basis of the same criteria listed earlier for pituitary adenomas.
- c. Pasireotide
 - i. Mechanism of action: Somatostatin analog blocks ACTH secretion from pituitary, leading to decreased circulating cortisol levels (better selectivity to pertinent somatostatin receptors than other analogs such as octreotide).
 - ii. Dosing: 0.6–0.9 mg twice-daily subcutaneous injection (dose adjustments based on urinary-free cortisol and symptom improvements)
 - iii. Adverse effects: Hyperglycemia, hypocorticalism, diarrhea, nausea, gallstones, headache, bradycardia
 - iv. Obtain an electrocardiogram, an FPG, an A1C, liver function tests, and a gallbladder ultrasound before initiating therapy.
 - v. Self-monitor BG values every week for first 2–3 months, then periodically obtain liver function tests 1–2 weeks after starting therapy, then obtain them monthly for 2–3 months and then every 6 months. Repeat gallbladder ultrasonography at 6- to 12-month intervals.
- d. Ketoconazole
 - i. Mechanism of action: In addition to its antifungal activity, it hinders cortisol production by inhibiting 11- and 17-hydroxylase.
 - ii. Dosing
 - (a) Initial: 200 mg twice daily by mouth
 - (b) Maximal: 400 mg three times daily
 - iii. Adverse effects
 - (a) Gynecomastia
 - (b) Abdominal discomfort
 - (c) Reversible hepatic transaminase elevations
- e. Mitotane
 - i. Mechanism of action: Inhibits 11-hydroxylase but also has some direct adrenolytic activity
 - ii. Dosing
 - (a) Initial: 500–1000 mg/day by mouth (some use much higher daily doses, but they are not well tolerated)
 - (b) Maximal: 9–12 g/day
 - iii. Adverse effects
 - (a) Adrenocortical atrophy: Can persist upon discontinuation and, in severe cases, may necessitate androgen and glucocorticoid replacement
 - (b) Anorexia
 - (c) Ataxia
 - (d) Abdominal discomfort
 - (e) Lethargy
- f. Etomidate
 - i. Mechanism of action: Similar to ketoconazole, inhibits 11-hydroxylase
 - ii. Dosing
 - (a) Initial: 0.03 mg/kg intravenously, followed by a 0.1-mg/kg/hour infusion
 - (b) Maximal: 0.3 mg/kg/hour
 - iii. Given route of administration is usually reserved for when rapid control of cortisol levels is needed and oral therapy is problematic.

- g. Metyrapone (by compassionate use only)
 - i. Mechanism of action: Hinders secretion of cortisol by blocking final step in cortisol synthesis by inhibiting 11-hydroxylase activity
 - ii. Dosing
 - (a) Initial: 500 mg three times daily by mouth
 - (b) Average dose in Cushing's syndrome is 2000 mg/day, but it is about 4000 mg in ectopic ACTH syndrome.
 - iii. Adverse effects
 - (a) Hypoadrenalism
 - (b) Hypertension
 - (c) Worsening of hirsutism and acne if present before treatment
 - (d) Headache
 - (e) Abdominal discomfort
 - h. Efficacy is measured by control of symptoms and normalization of 24-hour urine-free cortisol concentrations.
 - i. Mifepristone approved in 2012 for hyperglycemia associated with endogenous Cushing's syndrome. Proposed to limit binding of cortisol. May reduce insulin requirements and improve clinical symptoms associated with hyperglycemia
- B. Hyperaldosteronism: Primary Aldosteronism
1. Classification
 - a. Bilateral adrenal hyperplasia (70% of cases)
 - b. Aldosterone-producing adenoma (30% of cases)
 2. Diagnosis and clinical presentation
 - a. Elevated plasma aldosterone/renin ratio
 - b. Other features: Hyponatremia, hypokalemia, hypomagnesemia, glucose intolerance
 - c. Clinical presentation (can be asymptomatic)
 - i. Hypertension
 - ii. Muscle weakness or fatigue
 - iii. Headache
 - iv. Polydipsia
 - v. Nocturnal polyuria
 3. Therapy goals (same as earlier for Cushing's syndrome)
 4. Therapeutics
 - a. Spironolactone (drug of choice)
 - i. Mechanism of action: Competitively inhibits aldosterone biosynthesis
 - ii. Dosing
 - (a) Initial: 25–50 mg/day by mouth
 - (b) Maximal: 400 mg/day
 - iii. Adverse effects
 - (a) Hyperkalemia
 - (b) Gynecomastia
 - (c) Abdominal discomfort
 - b. Eplerenone and amiloride are alternatives to spironolactone.

C. Hyposecretory Adrenal Disorders

1. Classification
 - a. Primary adrenal insufficiency (a.k.a. Addison’s disease)
 - i. Caused by autoimmune disorder, infection, or infarction
 - ii. Results in cortisol, aldosterone, and androgen deficiencies
 - b. Secondary adrenal insufficiency
 - i. Exogenous steroid use (from chronic suppression). Oral, inhaled, intranasal, and topical administration
 - ii. Surgery, trauma, infection, infarction
 - iii. Results in impaired androgen and cortisol production
2. Diagnosis and clinical presentation (focus on Addison’s disease)
 - a. Abnormal rapid cosyntropin (synthetic ACTH) stimulation test (blunted increase in cortisol concentrations) suggests adrenal insufficiency.
 - b. Clinical presentation
 - i. Hyperpigmentation (caused by elevated ACTH concentrations)
 - ii. Weight loss
 - iii. Dehydration
 - iv. Hyponatremia, hyperkalemia, elevated blood urea nitrogen (BUN)
3. Therapy goals (same as above for Cushing’s syndrome)
4. Therapeutics
 - a. Steroid replacement (replace cortisol loss)
 - i. Oral administration is commonly dosed to mimic normal cortisol production circadian rhythm.
 - ii. Two-thirds administered in the morning and one-third in the evening
 - (a) This may cause periods of transient adrenal insufficiency or variable serum concentrations in some patients.
 - (b) Daily cortisol production in average patient: 5–10 mg/m²
 - b. Hydrocortisone: 15 mg/day (may reduce need for fludrocortisone compared with using cortisone or prednisone)
 - i. Cortisone acetate: 20 mg/day
 - ii. Prednisone: 2.5 mg/day
 - iii. Dexamethasone: 0.25–0.75 mg/day
 - c. Fludrocortisone (replaces loss of mineralocorticoid): 0.05–0.2 mg/day by mouth
 - d. For women with decreased libido or low energy levels because of androgen deficiency, dehydroepiandrosterone (DHEA): 25–50 mg/day
 - e. Efficacy can be measured by symptom improvement.
 - f. Note that during times of stress or illness, corticosteroid doses will need to be increased. Dosage and route of administration depend on level of stress to the body.

Table 2. Comparative Glucocorticosteroid Dosing

Glucocorticosteroid	Relative Equivalent Dosing (mg)
Cortisone	25
Hydrocortisone	20
Prednisone	5
Prednisolone	5
Triamcinolone	4
Methylprednisolone	4
Dexamethasone	0.75

IV. OBESITY

- A. American College of Cardiology/American Heart Association (ACC/AHA) and the Obesity Society 2013 guidelines. First significant guidelines since 1998
- B. Classification
 1. Based on BMI
 2. Normal: BMI 18.5–24.9 kg/m²
 3. Overweight: BMI 25.0–29.9 kg/m²
 4. Obesity
 - a. Class I: BMI 30.0–34.9 kg/m²
 - b. Class II: BMI 35.0–39.9 kg/m²
 - c. Class III: BMI 40 kg/m² or greater
- C. Therapy Goals
 1. Weight loss: Initial goal 5%–10% decrease from baseline weight over 6 months
 2. Maintain lower weight in the long term.
 3. Limit weight-induced comorbidities (e.g., type 2 DM, hypertension, cardiovascular disease).
- D. Nonpharmacologic Therapy (aimed at providing an energy deficit)
 1. Increased physical activity: 200–300 minutes per week
 2. Dietary options: Any diet that has proven weight reduction data available is appropriate. No specific recommendations of one diet over another. Individualize according to patient preferences.
 - a. Strive for at least a 500-kcal/day deficit.
 - b. 1200–1800 kcal/day for women
 - c. 1500–1800 kcal/day for men
 3. Behavioral intervention: Preferably in-person, high-intensity (at least 14 sessions in 6 months) comprehensive weight loss intervention through group or individual sessions with a professional (e.g., dietitian, exercise specialist, health counselor)
 4. Surgery: Usually reserved for severely obese (BMI greater than 40) or lower BMIs with existing comorbidities
 - a. Gastric bypass
 - b. Gastric banding

Patient Case

5. A patient is taking the maximal daily dose of phentermine/topiramate for treatment of obesity. The patient's baseline BMI is 36 kg/m² and weight is 255 lb. Which would be the most accurate minimal weight loss expected to consider continuing treatment with this agent?
 - A. 7 lb.
 - B. 13 lb.
 - C. 17 lb.
 - D. 26 lb.

E. Pharmacotherapy

1. Updated 2013 guidelines do not address pharmacotherapy. Future updates will address this issue in more detail.
2. In conjunction with diet, physical activity, and behavioral therapy
3. Medications should be reserved for those not achieving or sustaining weight reduction with adequate lifestyle modifications or in those who are obese or have BMI at least 27 kg/m² with significant weight-related comorbidities (e.g., diabetes, hypertension).
4. Medication selected according to risk-benefit profile should be Food and Drug Administration (FDA) approved. Approved agents should provide after 1 year at least a statistically significant 5% weight loss difference from placebo, and at least 35% of treated subjects should achieve at least a 5% weight loss from baseline and twice that of placebo-treated subjects.
5. Orlistat
 - a. Mechanism of action: Reduced absorption of fat by inhibition of gastric and pancreatic lipases
 - b. Dosing
 - i. Prescription: 120 mg three times daily during or up to 1 hour after meals
 - ii. Over the counter: 60 mg three times daily during or up to 1 hour after meals
 - c. Adverse effects
 - i. Gastrointestinal (GI) tract: Flatulence, oily stools, loose stools, fecal urgency or incontinence (very dependent on fat content of meal)
 - ii. Reduced absorption of fat-soluble vitamins (A, D, E, and K): Use vitamin supplement before or well after use.
 - iii. Hepatotoxicity, kidney stones
 - d. Efficacy: 35%–54% of patients taking a prescription-strength product attained at least a 5% weight loss after 1 year of therapy, and 16%–25% attained at least a 10% weight loss.
6. Lorcaserin
 - a. Mechanism of action: Reduced hunger by stimulating serotonin 2C receptors in the brain. Previous serotonin agonists used for obesity (e.g., fenfluramine) were nonselective and caused cardiac and pulmonary problems.
 - b. Dosing: 10 mg twice daily
 - c. Adverse effects: Headache, dizziness, nausea, dry mouth, constipation, memory or attention disturbances, hypoglycemia in patients with diabetes
 - d. Efficacy: 4.5%–6% weight loss from baseline; 47% attained at least a 5% loss, and 23% attained at least a 10% weight loss. In overweight patients with diabetes, up to a 1% reduction in A1C
 - e. Discontinue use if at least a 5% weight loss is not achieved after 12 weeks of use.
 - f. Avoid concurrent use with serotonergic drugs, including selective serotonin reuptake inhibitors.
 - g. Long-term cardiac risk or benefit unknown
7. Phentermine/extended-release topiramate
 - a. Mechanism of action: Phentermine promotes appetite suppression and decreased food intake secondary to its sympathomimetic activity. Mechanism of topiramate is unknown but may cause appetite suppression and satiety through increased γ -aminobutyrate activity.
 - b. Dosing (phentermine/topiramate): Should be taken in the morning to avoid insomnia
 - i. Initial: 3.75/23 mg daily for 2 weeks; then increase to 7.5/46 mg daily
 - ii. If at least a 3% weight loss not achieved after 12 weeks, can discontinue or increase to 11.25/69 mg daily for 2 weeks; then increase to 15/92 mg daily if tolerated
 - iii. If at least a 5% weight loss not achieved with 15/92 mg daily, discontinue use. Taper when discontinuing to avoid seizures.
 - iv. Dosing in moderate hepatic or renal impairment: Do not exceed 7.5/46 mg daily.
 - v. Availability is restricted by the FDA to specific certified pharmacies.

- c. Adverse effects: Dry mouth, paresthesia, constipation, dysgeusia, insomnia, attention and memory disturbances, increased heart rate
 - d. In women of childbearing age, obtain a negative pregnancy test before initiating and monthly thereafter because of fetal toxicity. Stress the importance of adequate contraception during use.
 - e. Efficacy: 9%–10% weight loss from baseline; 60%–70% attained at least a 5% weight loss after 1 year of treatment, and 37%–48% attained at least a 10% weight loss.
 - f. Long-term cardiac risk or benefit unknown
8. Diethylpropion or phentermine monotherapy
 - a. Both are controlled substances, schedule IV.
 - b. Should be used only for a limited time, up to 3 months, and avoid in those with abuse potential.
 - c. Adverse effects: Increased blood pressure, constipation, increased heart rate, dysrhythmias, abuse potential (avoid in patients with hypertension or history of cardiovascular disease)
 9. Concurrent use of obesity medications has not been studied, nor are comparative studies between agents available.
 10. Off-label medications used, although not well studied specifically for obesity: Exenatide, selective serotonin reuptake inhibitors, bupropion with or without naltrexone, zonisamide, metformin, pramlintide

V. DIABETES MELLITUS

A. Consensus Recommendations

1. American Diabetes Association (ADA). Updated yearly in the January supplement of Diabetes Care (www.diabetes.org)
2. American College of Endocrinology/American Association of Clinical Endocrinologists
3. Canadian Diabetes Association
4. Various European groups
5. For the remainder of this section, unless otherwise noted, the ADA recommendations will be followed.

B. Classification

1. Type 1 DM
 - a. Attributable to cellular-mediated beta-cell destruction leading to insulin deficiency (insulin needed for survival)
 - b. Accounts for 5%–10% of DM
 - c. Formerly known as insulin-dependent diabetes, juvenile-onset diabetes
 - d. Prevalence in the United States: 0.12% (about 340,000)
 - e. Usually presents in childhood or early adulthood but can present in any stage of life
 - f. Usually symptomatic with a rapid onset in childhood, but a slower onset can occur in older adults
2. Type 2 DM
 - a. Results primarily from insulin resistance in muscle and liver, with subsequent defect in pancreatic insulin secretion, although GI, brain, liver, and kidneys are all involved in the pathophysiology
 - b. Accounts for 90%–95% of DM
 - c. Formerly known as non–insulin-dependent diabetes, adult-onset diabetes
 - d. Prevalence in the United States: 7.8% (about 23.6 million and growing)
 - e. Often asymptomatic, with a slow onset over 5–10 years. Rationale for early, frequent screening of those at risk (below) and initial assessment for complications at diagnosis
 - f. Disturbing increased trends in type 2 DM in children and adolescents attributed to rise in obesity

3. Maturity-onset diabetes of the young
 - a. Result of genetic disorder leading to impaired secretion of insulin with little or no impairment in insulin action
 - b. Onset usually before age 25 and may mimic type 1 or 2 DM
4. Gestational diabetes
 - a. Glucose intolerance occurring during pregnancy
 - b. Prevalence: 1%–14% of pregnancies (complicates about 4% of pregnancies)
 - c. New diagnostic criteria (see below) will probably improve the diagnosis and change the prevalence.
 - d. Most common in third trimester
5. Prediabetes
 - a. Impaired glucose tolerance (IGT)
 - b. Impaired fasting glucose (IFG)
6. Other DM types
 - a. Genetic defects in beta-cell function or insulin action
 - b. Diseases of the pancreas (e.g., pancreatitis, neoplasia, cystic fibrosis)
 - c. Drug or chemical induced (e.g., glucocorticoids, nicotinic acid, protease inhibitors, atypical antipsychotics)

Patient Case

6. A 64-year-old African American woman has had a 12-kg (27-lb) weight increase during the past year, primarily because of inactivity and a poor diet. Her BMI is 44 kg/m². Her mother and sister both have type 2 DM. Her fasting glucose concentration today is 212 mg/dL. Which is the best course of action?
 - A. Diagnose type 2 DM and begin treatment.
 - B. Diagnose type 1 DM and begin treatment.
 - C. Obtain another glucose concentration today.
 - D. Obtain another glucose concentration another day.

- C. Screening for DM
 1. Type 1 DM
 - a. Symptomatic patients
 - b. Asymptomatic patients at higher risk
 - i. Relatives with type 1 DM
 - ii. Measure islet autoantibodies to assess risk of type 1 DM
 - iii. If screen is positive for antibodies, counsel on symptoms of hyperglycemia and risk of DM. Consider enrollment in observational study.
 2. Type 2 DM
 - a. Age 45 or older, repeat every 3 years if normal
 - b. Start younger if BMI is 25 kg/m² or greater (23 kg/m² or greater in Asian Americans) and at least one of the following risk factors:
 - i. History of cardiovascular disease
 - ii. IGT or IFG
 - iii. History of polycystic ovary syndrome
 - iv. HDL-C less than 35 mg/dL or TG greater than 250 mg/dL
 - v. Hypertension
 - vi. Women with a diagnosis of gestational diabetes or women who delivered a baby weighing more than 4.1 kg (9 lb)

- vii. High-risk ethnicity: African American, Latino, Native American, Asian American, Pacific Islander
 - viii. First-degree relative with type 2 DM
 - ix. Physical inactivity
3. Gestational DM
- a. Screen at first prenatal visit for undiagnosed type 2 DM in all patients with type 2 DM risk factors present.
 - b. Screen at 24–28 weeks' gestation using a 75-g OGTT.
 - c. If a diagnosis of gestational DM is made, screen for diabetes 6–12 weeks after delivery.
 - d. Continue to screen patients who have had gestational DM every 3 years for type 2 DM for life.
- D. DM Diagnosis
1. Type 1 and type 2 DM diagnosis
- a. Glycemic values in nonpregnant patients
 - i. FPG
 - (a) Easy and preferred method
 - (b) 126 mg/dL or greater
 - ii. Random plasma glucose
 - (a) 200 mg/dL or greater with symptoms of hyperglycemia
 - (b) Common hyperglycemia symptoms include polyuria, polydipsia, and unexplained weight loss.
 - (c) Prudent to verify with A1C concentration
 - iii. OGTT
 - (a) Plasma glucose concentration obtained 2 hours after a 75-g oral glucose ingestion
 - (b) 200 mg/dL or greater
 - (c) More sensitive and specific than FPG but more cumbersome to perform
 - iv. With an abnormal test result, the patient should be retested (preferably with the same test, but it can be any of the above on a subsequent day or by obtaining an A1C unless unequivocal hyperglycemia is noted).
 - v. A1C (glycated hemoglobin)
 - (a) 6.5% or greater
 - (b) Confirmed by repeating (unless unequivocal hyperglycemia is noted), although interval for repeating test is not provided
 - (c) May be less sensitive than FPG in identifying mild diabetes but does not require fasting and has less variability from day to day
 - (d) A1C values may be inaccurate in patients with hemolytic anemia, chronic malaria, sickle cell anemia, or significant blood loss or recent blood transfusion.
 - b. Other useful diagnostic tests if type of DM is in question
 - i. C-peptide (measure of endogenous insulin secretion, usually negligible in type 1 DM and normal or elevated early in type 2 DM)
 - ii. Presence of islet cell autoantibodies, autoantibodies to insulin, glutamic acid decarboxylase, or tyrosine phosphatase (all suggest autoimmune activity)
2. Gestational diabetes diagnosis: Glycemic values in pregnancy
- a. Updated and simplified diagnostic criteria
 - b. 75-g OGTT at weeks 24–28 of gestation
 - i. Fasting: 92 mg/dL or greater
 - ii. 1 hour after OGTT: 180 mg/dL or greater
 - iii. 2 hours after OGTT: 153 mg/dL or greater

3. Prediabetes diagnosis (high-risk population)
 - a. IFG: FPG between 100 and 125 mg/dL
 - b. IGT: 2-hour plasma glucose after OGTT (75 g) between 140 and 199 mg/dL
 - c. A1C between 5.7% and 6.4%

Patient Case

7. A 56-year-old man was recently given a diagnosis of type 2 DM. He has no other chronic diseases or history of cardiovascular disease. His current vital signs and laboratory results are as follows: blood pressure 148/78 mm Hg, A1C 6.9%, LDL-C 112 mg/dL, and TG 174 mg/dL. Which is considered under good control or meet current general recommendations?
 - A. Blood pressure.
 - B. A1C.
 - C. LDL-C.
 - D. TG.

E. Goals of Diabetes Management in Nonpregnant Adults

1. Primary goal is to prevent the onset of acute or chronic complications.
2. Acute complications: Hypoglycemia, diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar non-ketotic syndrome
3. Chronic complications
 - a. Microvascular: Retinopathy, nephropathy, and neuropathy
 - b. Macrovascular: Cardiovascular, cerebrovascular, and peripheral vascular diseases
4. Glycemic therapy goals
 - a. A1C less than 7.0% (Note: The American College of Endocrinology/American Association of Clinical Endocrinologists guidelines recommend 6.5% or less.)
 - i. Obtain every 6 months in patients at goal A1C and every 3 months in those over goal.
 - ii. Less stringent A1C targets may be appropriate in those with a short life expectancy (e.g., terminal cancer), advanced diabetic complications, long-standing diabetes that is difficult to control (e.g., frail older adults with a history of hypoglycemia at risk of falls), or extensive other comorbidities. (In such situations, a higher A1C [e.g., less than 8%] may be sufficient to limit the risk of acute complications of hyperglycemia such as dehydration and electrolyte deficiencies.)
 - b. FPG or premeal 80–130 mg/dL. Frequency of monitoring depends on regimen, type of DM, and current glycemic control. This is a change in 2015 by the ADA.
 - c. Peak postprandial glucose (1–2 hours after a meal) less than 180 mg/dL
5. Nonglycemic therapy goals
 - a. Blood pressure less than 140/90 mm Hg (updated in 2015 ADA guidelines to be more consistent with JNC-8 recommendations)
 - i. Lower blood pressure goals may be appropriate in younger patients with long life expectancy to reduce nephropathy risk and in those with higher risk of stroke.
 - ii. Suggested lower blood pressure goal is less than 130/80 mm Hg
 - b. Lipids
 - i. ADA: No specific LDL-C goal are currently recommended (updated by ADA in 2015 to be consistent with ACC/AHA recommendations)
 - ii. ACC/AHA 2013 guidelines suggest lowering LDL-C by 30%–49% in patients with diabetes 40–75 years of age and by at least 50% if 10-year risk of cardiovascular event is at least 7.5%.
 - iii. No specific TG or HDL-C goals are currently recommended.

F. Goals for Gestational Diabetes

1. Primary goal is to prevent complications to mother and child.
2. Glycemic therapy goals (more stringent)
 - a. FPG of 95 mg/dL or less
 - b. 1-hour postprandial glucose 140 mg/dL or less
 - c. 2-hour postprandial glucose 120 mg/dL or less
3. Potential complications of hyperglycemia during pregnancy
 - a. Mother: Hypertension, preeclampsia, type 2 DM after pregnancy
 - b. Fetus/child: Macrosomia, hypoglycemia, jaundice, respiratory distress syndrome

G. Benefits of Optimizing Diabetes Management in Nonpregnant Adults

1. Glycemic control
 - a. Reduce the risk of developing retinopathy, nephropathy, and neuropathy in type 1 and type 2 DM.
 - b. Prospective studies, specifically designed to assess optimizing glycemic control and effect on cardiovascular events, have not shown significantly improved cardiovascular outcomes.
 - c. However, the “legacy” effect seen in the Diabetes Control and Complications Trial in type 1 DM and the UK Prospective Diabetes Study in type 2 DM suggests early control has future cardiovascular benefit.
 - d. No profound benefit of very aggressive glycemic control in type 2 DM (A1C less than 6.5%)
2. Blood pressure control: Reduction in both macrovascular and microvascular complications
3. Lipid control: Reduction in LDL-C with moderate intensity statin therapy reduces cardiovascular complications.

Patient Case

8. A patient weighing 110 lb has been given a diagnosis of type 1 DM. The physician wants to start at a TDI of 0.4 unit/kg/day with a combination of long- and rapid-acting insulin. The patient is unwilling to estimate his or her carbohydrate intake at this time. Which would be the most appropriate initial basal insulin regimen?
- A. 30 units of insulin glargine once daily.
 - B. 20 units of insulin detemir once daily.
 - C. 10 units of insulin aspart once daily.
 - D. 10 units of insulin glargine once daily.

H. Therapeutic Insulin Management of Type 1 DM

1. Insulin agents
 - a. Categorized on the basis of duration after injection
 - i. Short acting: Regular human insulin
 - ii. Rapid acting: Insulin aspart, lispro, glulisine, and inhaled insulin
 - iii. Intermediate acting: Neutral protamine Hagedorn (NPH)
 - iv. Long acting: Insulin glargine and detemir; cannot be mixed with other insulins

- b. Combination products (NPH/either regular or rapid-acting insulin): 70/30, 75/25

Table 3. Insulin Characteristics^a

Category	Drug Name	Clarity	Onset	Injection Time Before Meal (minutes)	Peak (hours)	Duration (hours)
Short acting	Regular	Clear	30–60 minutes	30	2–3	4–6
Rapid acting	Aspart Lispro Glulisine Inhaled insulin	Clear	5–20 minutes	15 (inhaled insulin at beginning of meal)	1–3	2–5
Intermediate acting	NPH	Cloudy	1–2 hours	N/A	4–8	10–20
Long acting	Detemir Glargine	Clear	2–4 hours 1–2 hours	N/A	6–8 “Peakless”	6–24 ~24

^aNote: The above times are dependent on the source of data and intersubject variability.
N/A = not applicable; NPH = neutral protamine Hagedorn.

- c. Glycemic target
 - i. Regular- and short-acting insulins target postprandial glucose concentrations.
 - ii. Intermediate- and long-acting insulins target fasting glucose concentrations.
 - d. Inhaled insulin may cause bronchospasm and is contraindicated in patients with asthma, chronic obstructive pulmonary disease, or lung cancer. Requires spirometry testing at baseline, at 6 months of therapy, and annually thereafter.
2. Management of insulin therapy
- a. First step is to estimate TDI requirements.
 - b. Weight-based estimate if insulin naive
 - i. 0.3–0.6 unit/kg/day
 - ii. Requirements higher if treating DKA near initial diagnosis of DM
 - iii. Honeymoon phase shortly after treatment initiation often requires lower daily insulin needs.
 - c. One common approach is to use older insulin formulations (NPH and regular insulin).
 - i. Two-thirds of TDI given before morning meal. Two-thirds of this is given as NPH and one-third as regular insulin.
 - ii. One-third of TDI given before the evening meal (or regular given before a meal and NPH at bedtime). Again, two-thirds of this is given as NPH and one-third as regular insulin.
 - iii. Advantages: Daily insulin injection frequency two or three times daily and inexpensive
 - iv. Disadvantages: Does not mimic natural insulin secretion pattern; prone to hypoglycemic events
 - d. Another approach is basal/bolus insulin therapy (a.k.a. physiologic insulin therapy).
 - i. Use of newer insulin analogs to better mimic natural insulin secretion patterns
 - ii. Provides daylong basal insulin to prevent ketosis and control FPG
 - iii. Provides bolus insulin to control postprandial hyperglycemia
 - iv. Basal insulins: Insulin glargine once daily or insulin detemir once or twice daily
 - v. Bolus insulins: Rapid-acting insulin
 - vi. Basal requirements are 50% of estimated TDI.

- vii. Bolus requirements are 50% of estimated TDI split three ways before meals.
 - (a) Provides initial estimate of prandial insulin needs
 - (b) Typically, patients begin to estimate bolus requirements given the amount of carbohydrates to be ingested.
- viii. Advantages over NPH plus regular approach: More physiologic, less hypoglycemia, more flexible to patient mealtimes
- ix. Disadvantages: Cost and increased frequency and number of daily injections (rapid-acting and basal insulin must be injected separately). Note: The same process of basal/bolus insulin therapy can apply to a patient with type 2 DM who is receiving intensive insulin therapy with or without oral DM medications.
- e. Correctional insulin needs
 - i. Always a need to correct for hyperglycemic excursions, despite optimal basal/bolus therapy
 - ii. “1800 rule”: $1800/\text{TDI} = \# \text{ mg/dL of glucose lowering per 1 unit of rapid-acting insulin.}$
 - (a) For example, if TDI is 60 units, $1800/60 = 30$, suggesting 1 unit of rapid-acting insulin will reduce BG concentrations by 30 mg/dL.
 - (b) Also referred to as insulin sensitivity
 - (c) Some advocate the “1500 rule” when using regular human insulin (i.e., $1500/\text{TDI}$).
 - iii. More patient-specific than traditional sliding-scale insulin
- f. Continuous subcutaneous insulin infusion (insulin pump)
 - i. Device allows very patient-specific hourly basal dosing and bolus insulin dosing.
 - ii. Uses rapid-acting insulins
 - iii. Requires considerable patient education and carbohydrate counting
- g. Assessing therapy and dosage adjustment
 - i. Know the goals for fasting and postprandial glucose concentrations.
 - ii. Identify when patient is at goal and not at goal (hypoglycemia or hyperglycemia). Look for consistent trends rather than isolated events.
 - iii. Identify which insulin affects problematic glucose concentrations.
 - iv. Adjust insulin dose or patient behavior accordingly.
 - v. Same process for treating type 2 DM applies (see below).
- 3. Amylin analog
 - a. Mechanism of action: Amylin is cosecreted with insulin and has effects similar to those of glucagon-like peptide-1 (GLP) described below.
 - b. Pramlintide is currently the only agent in this class available in the United States. Can be used in either type 1 or type 2 DM as adjunctive therapy in patients receiving insulin
 - c. Dosing
 - i. Type 1 DM
 - (a) Initial: 15 mcg subcutaneously immediately before main meals
 - (b) Must reduce dose of preprandial rapid-acting, short-acting, or combination insulin products by 50%
 - (c) Maximal daily dose: 60 mcg with each meal
 - (d) Dose should be titrated in 15-mcg increments, as tolerated, but no more rapidly than every 3 days.
 - ii. Type 2 DM
 - (a) Initial: 60 mcg subcutaneously immediately before main meals
 - (b) As above, must reduce preprandial insulins by 50%
 - (c) Maximal daily dose: 120 mcg with each meal
 - (d) Dose should be titrated in 60-mcg increments, as tolerated, but no more rapidly than every 3–7 days.

- iii. Use of prefilled pens is strongly recommended, when possible, rather than using a syringe and vial, to reduce the risk of dosing errors (dosing instructions with U-100 syringes and vial in package insert).
- iv. Cannot be mixed with insulin products; requires increased frequency of daily injections
- d. Adverse effects
 - i. Black box warning for severe hypoglycemia, especially in patients with type 1 DM
 - ii. Nausea, vomiting, anorexia, headache
- e. Contraindications and precautions
 - i. Substantial gastroparesis
 - ii. History of poor adherence or monitoring of BG
 - iii. A1C greater than 9%
 - iv. Hypoglycemia unawareness or frequent bouts of hypoglycemia
- f. Efficacy
 - i. A 0.5%–1% reduction in A1C
 - ii. Very effective at controlling postprandial glucose excursions

Patient Cases

9. A 52-year-old woman received a diagnosis today of type 2 DM. Her A1C is 7.8%, and her FBG is 186 mg/dL. She has no other chronic disease states or history of cardiovascular disease. According to the current ADA guidelines, which would be considered the best initial treatment of choice for this patient?
- A. Implement changes in lifestyle (diet and exercise), and initiate metformin 500 mg once daily.
 - B. Implement changes in lifestyle (diet and exercise).
 - C. Implement changes in lifestyle (diet and exercise), and initiate sitagliptin 100 mg once daily.
 - D. Implement changes in lifestyle (diet and exercise), and initiate insulin glargine 10 units once daily.
10. A 66-year-old man has had type 2 DM for 4 years. His A1C today is 7.7%. He has altered his diet, and he states that he has been exercising regularly for months now. He is taking metformin 1000 mg twice daily. Which would be the best choice to help optimize his glycemic control?
- A. Continue current medications and counsel to improve his diet and exercise.
 - B. Discontinue metformin and initiate exenatide 5 mcg twice daily.
 - C. Add bromocriptine 0.8 mg at bedtime.
 - D. Add sitagliptin 100 mg once daily to his metformin therapy.

I. Therapeutic Management of Type 2 DM

- 1. Given the progressive nature of type 2 DM, a stepwise approach is usually needed.
- 2. 2012 ADA treatment recommendations and recent 2015 updates to these 2012 recommendations for hyperglycemia emphasize a patient-centered approach to care, considering patient preferences, needs, and values.
- 3. Metformin remains the initial drug of choice, unless it is contraindicated or adverse effects preclude its use, if improvements in exercise and diet early after diagnosis fail to control hyperglycemia.
- 4. If metformin monotherapy fails to allow the patient to attain or maintain glycemic control, adding other agents is based on several criteria and weighs the advantages and disadvantages of the various oral and injectable agents:
 - a. Efficacy in lowering A1C (also focus on ability to lower fasting or postprandial glucose concentrations or both)

- b. Risk of hypoglycemia
 - c. Effects on weight
 - d. Adverse effect profile
 - e. Cost
5. Sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose cotransporter-2 (SGLT-2) inhibitors, GLP-1 agonists, and basal insulin are preferred over less efficacious or agents with a higher adverse risk profile.
 6. Initial insulin therapy: Use insulin early with any of the following baseline characteristics:
 - a. A1C greater than 10%
 - b. Glucose greater than 300-350 mg/dL
 - c. Hyperglycemic symptoms
 - d. Presence of urine ketones
 7. Adding insulin to existing oral DM agents
 - a. Common to add a basal insulin regimen to existing oral agents when hyperglycemia still not controlled but do not want to switch to all-insulin regimen
 - b. Weight-based dosing: For example, 0.1–0.2 unit/kg/day (higher doses if significant hyperglycemia exists)
 - c. Can increase basal insulin based on fasting glucose concentrations
 - d. Can add bolus insulin to one or more meals if postprandial glucose is of concern
 - e. Insulin secretagogues should be lowered in dose or discontinued altogether when bolus insulin added to reduce risk of hypoglycemia.
 - f. Thiazolidinediones (TZDs) should be lowered or discontinued when basal or bolus insulin added to regimen because of increased risk of edema.
 8. Changing from oral DM medications to insulin-only management (e.g., because of adverse effects, contraindications, lack of efficacy of oral medications)
 - a. Can follow NPH/regular insulin or basal/bolus approach similar to that in type 1 DM described earlier
 - b. The TDI requirements in type 2 DM are usually much higher than in type 1 DM because of insulin resistance.
 9. Changing from NPH to long-acting insulin (either insulin glargine or detemir)
 - a. If adequate glycemic control already attained, initiate insulin glargine at 80% of total daily NPH dose
 - b. Detemir may be initiated by a unit-to-unit conversion and may require higher daily insulin dosages after conversion, but this is determined by glycemic response.
- J. Therapeutic Agents in Type 2 DM
1. Metformin (biguanide)
 - a. Mechanism of action: Reduces hepatic gluconeogenesis. Also favorably affects insulin sensitivity and, to a lesser extent, intestinal absorption of glucose
 - b. Dosing
 - i. Initial: 500 mg once or twice daily (once daily with extended-release formulation)
 - ii. Maximal daily dose: 2550 mg (more commonly, 2000 mg/day)
 - iii. Can increase at weekly intervals as necessary
 - iv. Small initial dosage and slow titration secondary to GI disturbances
 - c. Adverse effects
 - i. Common: Nausea, vomiting, diarrhea, epigastric pain
 - ii. Less common: Decrease in vitamin B₁₂ levels, lactic acidosis (rare)
 - iii. Signs or symptoms of lactic acidosis include acidosis, nausea, vomiting, increased respiratory rate, abdominal pain, shock, and tachycardia.

- d. Contraindications and precautions (because of risk of lactic acidosis)
 - i. Renal impairment (contraindicated because of increased risk of lactic acidosis)
 - (a) U.S. package insert: Serum creatinine 1.5 mg/dL or greater in men and 1.4 mg/dL or greater in women or reduced creatinine clearance (CrCl)
 - (b) CrCl and eGFR cutoffs are not well established; differ depending on guideline or package insert. Would discontinue or not initiate if CrCl less than 30 mL/minute).
 - ii. Age 80 years or older (use caution and carefully assess renal function)
 - iii. High risk of cardiovascular event or hypoxic state
 - iv. Hepatic impairment
 - v. Congestive heart failure (especially if prone to exacerbations)
 - vi. Interrupt therapy if undergoing procedures using iodinated contrast dye because of risk of nephrotoxicity. Reinitiate after 48 hours and after normal serum creatinine concentrations are achieved.
 - e. Efficacy
 - i. 1%–2% A1C reduction
 - ii. Some benefit in TG reduction and weight loss
 - iii. Considered first-line therapy unless contraindicated on the basis of adverse effect profile, reduction in A1C, cost, and limited data that it reduces cardiovascular events in overweight patients
2. Sulfonylureas
- a. Mechanism of action: Bind to receptors on pancreatic beta-cells, leading to membrane depolarization, with subsequent stimulation of insulin secretion (insulin secretagogue)
 - b. First-generation agents seldom used today (e.g., chlorpropamide, tolbutamide)
 - c. Second-generation agents (e.g., glyburide, glipizide, glimepiride). Dose titration: Can increase at weekly intervals as necessary
 - d. Adverse effects
 - i. Common: Hypoglycemia, weight gain
 - ii. Less common: Rash, headache, nausea, vomiting, photosensitivity
 - e. Contraindications and precautions
 - i. Hypersensitivity to sulfonamides
 - ii. Patients with hypoglycemic unawareness
 - iii. Poor renal function (glipizide may be a better option than glyburide or glimepiride in older adults or in those with renal impairment because drug or active metabolites are not renally eliminated)
 - f. Efficacy
 - i. 1%–2% A1C reduction
 - ii. Note: For this and all medications used to treat hyperglycemia, the absolute decrease in A1C is larger for higher baseline A1C values and smaller for lower A1C values.

Table 4. Second-Generation Sulfonylurea Dosing Strategies

Drug	Initial Dose	Maximal Daily Dose (mg)
Glyburide (nonmicronized)	2.5–5.0 mg once or twice daily	20
Glyburide (micronized)	1.5–3 mg once or twice daily	12
Glipizide	5 mg once or twice daily (once daily with extended release)	40 (little improved efficacy above 20 mg/day)
Glimepiride	1–2 mg once daily	8

3. Meglitinides
 - a. Mechanism of action: Very similar to that of sulfonylureas in increasing insulin secretion from the pancreas but with a more rapid onset and shorter duration of activity
 - b. Glucose-dependent activity
 - c. Two currently available: Repaglinide and nateglinide
 - d. Dosing
 - i. Repaglinide
 - (a) Initial: 0.5–1 mg 15 minutes before meals
 - (b) Maximal daily dose: 16 mg
 - ii. Nateglinide
 - (a) 120 mg before meals
 - (b) 60 mg if A1C near goal
 - iii. Repaglinide can be increased in weekly intervals if needed.
 - e. Adverse effects: Hypoglycemia (though less than with sulfonylureas), weight gain, upper respiratory infection
 - f. Contraindications and precautions
 - i. Hypersensitivity
 - ii. Caution in concomitant use of repaglinide and gemfibrozil: Can lead to greatly increased repaglinide levels
 - g. Efficacy
 - i. 0.5%–1.5% A1C reduction (repaglinide reduces A1C more than nateglinide)
 - ii. Most effective on postprandial glucose excursions
4. TZDs (often called glitazones)
 - a. Mechanism of action
 - i. Peroxisome proliferator–activated receptor γ -agonist
 - ii. Increases expression of genes responsible for glucose metabolism, resulting in improved insulin sensitivity
 - b. Two agents available: Pioglitazone and rosiglitazone
 - i. In September 2010, the FDA initiated restricted access to rosiglitazone because of continued concerns about its cardiovascular safety. Rosiglitazone was restricted to patients unable to attain glycemic control with other agents and when pioglitazone is not used for medical reasons.
 - ii. In November 2013, the FDA removed some prescribing and dispensing restrictions for rosiglitazone after evaluating clinical trial data. The impact of this change and the availability of the agent is unknown.
 - c. Dosing
 - i. Pioglitazone
 - (a) Initial: 15 mg once daily
 - (b) Maximal daily dose: 45 mg
 - ii. Dose titration is slow, and the maximal effect of a dose change may not be observed for 8–12 weeks.
 - d. Adverse effects
 - i. Weight gain
 - ii. Fluid retention (particularly peripheral edema), worse with insulin use and dose dependent. Edema less responsive to diuretic therapy. May cause macular edema
 - iii. Risk of proximal bone fractures; use caution in patients with existing osteopenia or osteoporosis
 - iv. Possible small risk of bladder cancer with pioglitazone (dose and duration of use dependent). Data is contradictory.

- v. Increased risk of heart failure
 - (a) Boxed warning.
 - (b) More than 2-fold higher relative risk, although absolute risk is quite small
- vi. Both agents have been withdrawn from some countries in Europe.
- e. Contraindications and precautions
 - i. Hepatic impairment
 - ii. Class III/IV heart failure (symptomatic heart failure)
 - iii. Existing fluid retention
- f. Efficacy
 - i. 0.5%–1.4% A1C reduction
 - ii. Both drugs increase HDL-C, but pioglitazone has a more favorable effect in reducing LDL-C and TG compared with rosiglitazone.
- 5. α -Glucosidase inhibitors
 - a. Mechanism of action: Slows the absorption of glucose from the intestine to the bloodstream by slowing the breakdown of large carbohydrates into smaller absorbable sugars
 - b. Two agents available: Acarbose and miglitol
 - c. Dosing (both agents dosed similarly)
 - i. Initial: 25 mg three times daily at each meal
 - ii. Maximal daily dose: 300 mg
 - iii. Slow titration, increasing as tolerated every 4–8 weeks to minimize GI adverse effects
 - d. Adverse effects
 - i. Flatulence, diarrhea, abdominal pain
 - ii. Increased liver enzymes observed with high doses of acarbose
 - e. Contraindications and precautions: Inflammatory bowel disease, colonic ulcerations, intestinal obstruction
 - f. Efficacy
 - i. 0.5%–0.8% reduction in A1C, also shown to decrease body weight
 - ii. Targets postprandial glucose excursions
 - iii. May not be as effective in patients using low-carbohydrate diets
- 6. DPP-4 inhibitors
 - a. Mechanism of action: Inhibits the breakdown of GLP-1 secreted during meals, which in turn increases pancreatic insulin secretion, limits glucagon secretion, slows gastric emptying, and promotes satiety
 - b. Dosing
 - i. Sitagliptin: 100 mg once daily
 - (a) Reduce dose with CrCl between 30 and 50 mL/minute to 50 mg once daily.
 - (b) Reduce dose with CrCl less than 30 mL/minute to 25 mg once daily.
 - ii. Saxagliptin: 5 mg once daily.
 - (a) Reduce with CrCl of 50 mL/minute or less to 2.5 mg once daily.
 - (b) Reduce dose when coadministered with strong CYP3A4/5 inhibitor (e.g., ketoconazole) to 2.5 mg once daily.
 - iii. Linagliptin: 5 mg once daily (no dosage adjustment for renal impairment)
 - iv. Alogliptin: 25 mg once daily
 - (a) Reduce dose with CrCl between 30 and 60 mL/minute to 12.5 mg once daily.
 - (b) Reduce dose with CrCl less than 30 mL/minute to 6.25 mg once daily.
 - c. Adverse effects
 - i. Upper respiratory and urinary tract infections, headache

- ii. Hypoglycemia with monotherapy is minimal, but frequency is increased with concurrent sulfonylurea therapy (can lower dose of sulfonylurea when initiating)
 - iii. Sitagliptin has had some postmarketing reports of acute pancreatitis, angioedema, Stevens–Johnson syndrome, and anaphylaxis.
 - d. Contraindications and precautions
 - i. Previous hypersensitivity to the agents
 - ii. History of pancreatitis
 - e. Efficacy: 0.5%–0.8% reduction in A1C, considered weight neutral
- 7. Bile acid sequestrant: Colesevelam is the only studied drug in this class.
 - a. Mechanism of action
 - i. Bile acid sequestrant used primarily for cholesterol management. Its mechanism to reduce serum glucose concentrations is not clearly understood. Thought to be an antagonist to the farnesoid X receptor (FXR), which subsequently reduces hepatic gluconeogenesis. By reducing bile acid absorption, colesevelam reduces FXR activity.
 - ii. Used in conjunction with insulin or oral DM medications
 - b. Colesevelam is the only studied and approved drug in this class.
 - c. Dosing: Six 625-mg tablets once daily or three 625-mg tablets twice daily
 - d. Adverse effects: Constipation, dyspepsia, nausea, myalgia
 - e. Contraindications and precautions
 - i. Contraindicated in patients with a history of bowel obstruction, serum TG concentration greater than 500 mg/dL
 - ii. Caution in patients with swallowing disorders (large pill), dysphasia, gastric mobility disorders, and serum TG concentrations greater than 300 mg/dL
 - f. Efficacy: A 0.3%–0.5% reduction in A1C
- 8. Bromocriptine
 - a. Mechanism of action: Not clearly understood. Agonist for dopamine receptor D₂ is thought to reset circadian rhythm that may reduce caloric intake and storage. Other effects may be through α_1 antagonism, α_2 -agonistic properties, and modulation of serotonin and prolactin.
 - b. Dosing
 - i. Initial: 0.8 mg once daily on waking; take with food (increases bioavailability)
 - ii. Maximal daily dose: 4.8 mg
 - iii. Titrate weekly by 0.8 mg/day as tolerated and according to response.
 - iv. Tablet strength is different from that of generic formulations currently on the market.
 - c. Adverse effects: Nausea, somnolence, fatigue, dizziness, vomiting, headache, orthostatic hypotension, syncope
 - d. Contraindications and precautions
 - i. Can limit the effectiveness of agents used to treat psychosis or exacerbate psychotic disorders
 - ii. Should not be used in nursing mothers or patients with syncopal migraines
 - iii. Concomitant use with dopamine antagonists (e.g., neuroleptic agents) may limit the efficacy of both agents.
 - e. Efficacy
 - i. 0.1%–0.6% reduction in A1C
 - ii. Possible cardiovascular benefit
- 9. SGLT-2 inhibitor
 - a. Mechanism of action: Increases urinary glucose excretion by blocking normal reabsorption in the proximal convoluted tubule. Has some effect on delaying GI glucose absorption as well

- b. Dosing
 - i. Canagliflozin
 - (a) 100 mg once daily before the first meal of the day
 - (b) Maximal daily dose: 300 mg
 - (c) Reduce dose with CrCl between 45 and 59 mL/minute to 100 mg daily.
 - (d) Discontinue or do not initiate if eGFR < 45 mL/min/1.73 m².
 - ii. Dapagliflozin
 - (a) 5 mg once daily in the morning (with or without food)
 - (b) Maximal daily dose: 10 mg
 - (c) Discontinue or do not initiate if eGFR < 60 mL/min/1.73 m².
 - iii. Empagliflozin
 - (a) 10 mg once daily in the morning (with or without food)
 - (b) Maximal daily dose 25 mg
 - (c) Discontinue or do not initiate if eGFR < 45 mL/min/1.73 m².
- c. Adverse effects
 - i. Increased urination
 - ii. Urinary tract infections
 - iii. Genital mycotic infections
 - iv. Hypotension
 - v. Increased hypoglycemia risk with concomitant insulin or insulin secretagogue
- d. Contraindications and precautions
 - i. Significant renal impairment (varies as above by agent)
 - ii. Suggested to ensure euvolemia before initiating agent, given its diuretic effect especially in older adults, patients with existing renal impairment or already low blood pressure, or patients receiving diuretics
- e. Efficacy
 - i. 0.3%–1.0% reduction in A1C
 - ii. Effect on both fasting and postprandial glucose concentrations
 - iii. Mild weight loss

Patient Case

11. A 66-year-old man is given a diagnosis today of type 2 DM. Two weeks ago, his A1C was 7.5%, and his serum creatinine was 1.8 mg/dL (estimated CrCl 25 mL/minute). He has a history of hypertension, dyslipidemia, and systolic heart failure (New York Heart Association class III, ejection fraction 33%). He has 2+ pitting edema bilaterally. In addition to improvements in diet and exercise, which is the best drug to initiate?
- A. Linagliptin.
 - B. Pioglitazone.
 - C. Exenatide.
 - D. Metformin.

10. GLP-1 analogs
- a. Mechanism of action: Synthetic analog of human GLP-1 that binds to GLP-1 receptors, resulting in glucose-dependent insulin secretion, reduction in glucagon secretion, and reduced gastric emptying; promotes satiety
 - b. Approved agents: Exenatide, liraglutide, dulaglutide, and albiglutide

- c. Dosing
 - i. Exenatide
 - (a) Twice-daily formulation (pen)
 - (1) Initial: 5 mcg subcutaneously twice daily, administered no more than 60 minutes before morning and evening meals
 - (2) Maximal dose: 10 mcg twice daily
 - (3) Dose titration from 5 to 10 mcg twice daily after 1 month if tolerated
 - (b) Once-weekly formulation (single-dose tray or pen, each containing lyophilized powder and diluent)
 - (1) 2 mg subcutaneously once weekly
 - (2) Powder must be reconstituted by patient immediately before injection.
 - ii. Liraglutide (pen)
 - (a) 0.6 mg subcutaneously once daily for 1 week (regardless of mealtime)
 - (b) Dose titration from 0.6 to 1.2 mg/day if tolerated
 - (c) Maximal daily dose: 1.8 mg/day
 - iii. Albiglutide (pen containing lyophilized powder and diluent)
 - (a) 30 mg subcutaneously once weekly
 - (b) Dose titration to 50 mg once weekly if tolerated and requires improved glycemic control
 - (c) Patient must reconstitute powder via diluent in pen delivery device. Must be injected within 8 hours of reconstituting.
 - iv. Dulaglutide (pen and single dose syringe)
 - (a) 0.75 mg subcutaneously once weekly
 - (b) Dose titration to 1.5 mg once weekly for additional glycemic control
 - v. For each of the once-weekly formulations: Can administer a missed dose if within 3 days of the missed dose; if longer time period, wait until the next regularly scheduled weekly dose.
- d. Adverse effects
 - i. Nausea, vomiting, diarrhea very common but can subside or cease over time
 - ii. Hypoglycemia common with concurrent sulfonylurea (consider reduction in sulfonylurea dose)
 - iii. Postmarketing reports of pancreatitis and acute renal failure or impairment
- e. Contraindications and precautions
 - i. Impaired renal function: CrCl less than 30 mL/minute for either exenatide formulation; less than 15 mL/minute for albiglutide, less specific for liraglutide
 - ii. History of severe GI tract disorder, particularly gastroparesis
 - iii. History of pancreatitis
 - iv. For liraglutide, albiglutide, once-weekly exenatide, dulaglutide: Contraindicated in patients with a personal or family history of medullary thyroid carcinoma (adverse effect found in rodent studies but not in humans)
- f. Efficacy
 - i. A 0.5%–1.1% reduction in A1C
 - ii. Effects on postprandial hyperglycemia better than on fasting glucose concentrations with once- or twice-daily formulations
 - iii. Improved A1C, fasting glucose reduction, and nausea or vomiting with once-weekly compared with twice-daily exenatide formulation
 - iv. Modest weight loss

Table 5. Comparison of Therapies for Type 2 DM Hyperglycemia Added to Metformin

Agent or Class	Primary Glycemic Effect	Benefits	Limitations and Precautions
Sulfonylurea	Fasting and prandial	Efficacy Cost	Weight gain Hypoglycemia risk Hastens beta-cell dysfunction
Meglitinide	Prandial	Prandial focus Use in kidney impairment	Hypoglycemia risk Weight gain Mealtime dosing
Pioglitazone	Fasting and prandial	Improves insulin sensitivity and pancreatic function Low risk of hypoglycemia Possible cardiovascular benefit Cost	Weight gain and edema Risk of heart failure Risk of osteoporosis Possible bladder cancer risk
α -Glucosidase inhibitor	Prandial	No systemic absorption Prandial focus Weight loss	GI adverse effect profile Mealtime dosing Modest A1C effect
DPP-4 inhibitor	Prandial	Well tolerated Weight neutral	Possible pancreatitis risk Modest A1C effect Cost
GLP-1 agonist	Once- or twice-daily formulations have prandial focus Once-weekly formulations affect both fasting and prandial	Greater effect on prandial glucose Weight loss Efficacy Improves pancreatic function	Nausea and vomiting Injection site effects Questionable pancreatitis or thyroid cancer risk Cost
Colesevelam	Prandial	Lipid benefits No systemic absorption	Large pill size and burden GI adverse effect profile Small decrease in A1C Avoid with high triglycerides
Bromocriptine	Fasting and prandial	Low risk of hypoglycemia Possible cardiovascular benefit	Small decrease in A1C CNS adverse effects
SGLT-2 inhibitors	Fasting and prandial	Low risk of hypoglycemia Efficacy Weight loss	Urinary tract and genital infections Diuresis
Amylin agonist	Prandial	Modest weight loss Efficacy on postprandial glucose	High risk of hypoglycemia Must be taken with insulin Frequent injections Injection site effects GI adverse effects
Insulin	Basal: fasting Bolus: prandial	Significant A1C reduction Flexibility in dosing strategies and titration	Hypoglycemia Weight gain Injection site effects

CNS = central nervous system; DPP-4 = dipeptidyl peptidase type-4; GI = gastrointestinal; GLP = glucagon-like peptide; SGLT = sodium glucose cotransporter.

Information adapted from Inzucchi S, Bergenstal R, Buse J. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. *Diabetes Care* 2012;35:1364-79; and Garber A, Aghajam M, Barzilay J, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement. *Endocr Pract* 2013;19(suppl 2):1-48.

VI. TREATMENT OF DM COMPLICATIONS**Patient Case**

12. A patient with newly diagnosed type 2 DM is screened for diabetic nephropathy. The following laboratory values are obtained today: blood pressure 129/78 mm Hg, heart rate 78 beats/minute, urine albumin/creatinine 27 mg/g, and estimated CrCl 94 mL/minute. Which would be the most appropriate treatment strategy?

- A. No change in therapy is warranted.
- B. Add an angiotensin-converting enzyme (ACE) inhibitor.
- C. Add an ARB.
- D. Reduce daily protein intake.

A. Hypoglycemia

1. Degree of intervention depends on glucose concentrations and presence of symptoms.
2. Symptoms are very patient-specific but may include anxiousness, sweating, nausea, tachycardia, hunger, clammy skin, and many others.
3. Consequences of significant hypoglycemia are most worrisome in the very young, older adults, and those with established heart disease.
4. Definition
 - a. Plasma glucose less than 70 mg/dL with or without symptoms
 - b. Hypoglycemic unawareness: Low glucose without symptoms
5. Mild to moderate hypoglycemia
 - a. Oral ingestion of 15–20 g of glucose or equivalent
 - b. Repeat glucose concentration in 15 minutes and, if still less than 70 mg/dL, repeat ingestion of glucose.
 - c. Once glucose is normalized, ingest snack or meal.
6. Severe hypoglycemia (altered consciousness, needs assistance from others)
 - a. Glucagon 1 mg intramuscularly
 - b. Intravenous dextrose if patient does not respond to glucagon
 - c. Raise glucose targets for several weeks.

B. Diabetic Ketoacidosis

1. More common in type 1 DM but can occur in type 2 DM
2. Usually occurs because of a precipitating factor that stresses the body, resulting in increased counter-regulatory hormones
 - a. Inappropriate (including nonadherence) or inadequate insulin therapy and infection are the two most common causes.
 - b. Other causes: Myocardial infarction, pancreatitis, stroke, drugs (e.g., corticosteroids)
3. Results in significant hyperglycemia, dehydration, and ketoacidosis
4. Common signs and symptoms: Polyuria, polydipsia, vomiting, dehydration, weakness, altered mental status, coma, abdominal pain, Kussmaul respirations, tachycardia, hyponatremia, hyperkalemia
5. Treatment
 - a. Treat underlying cause if known.
 - b. Fluid replacement
 - i. 0.45%–0.9% sodium chloride, depending on baseline serum sodium concentrations
 - ii. Change to 5% dextrose with 0.45% sodium chloride when serum glucose is less than 200 mg/dL.

- c. Insulin
 - i. Goal is to stop ketosis, not to normalize glucose concentrations.
 - ii. Intravenous bolus: 0.1 unit/kg
 - iii. Intravenous infusion
 - (a) 0.1 unit/kg/hour (increase if not a 50- to 75-mg/dL drop in serum glucose in the first hour)
 - (b) Alternatively, 0.14 unit/kg/hour if no insulin bolus is given
 - (c) If not at least a 10% decrease in serum glucose attained in first hour, give 0.14 unit/kg intravenous bolus
 - (d) Reduce infusion rate to 0.02–0.05 unit/kg/hour when serum glucose reaches 200 mg/dL and keep glucose between 150 and 200 mg/dL until DKA resolves.
 - iv. Interrupt insulin treatment if baseline serum potassium is less than 3.3 mEq/L and until corrected.
 - d. Potassium
 - i. Potassium 20–30 mEq/L of intravenous fluid if baseline serum potassium greater than 3.3 but less than 5.3 mEq/L
 - ii. Hold if 5.3 mEq/L or greater initially. Monitor and replace as needed.
 - iii. Potassium 20–30 mEq/hour if baseline less than 3.3 mEq/L (while holding insulin)
 - e. Intravenous bicarbonate if serum pH less than 6.9
 - f. DKA considered resolved and can be converted to subcutaneous insulin when serum glucose is less than 200 mg/dL and at least two of the following:
 - i. Venous pH greater than 7.3
 - ii. Serum bicarbonate of 15 mEq/L or greater
 - iii. Calculated anion gap of 12 mEq/L or less
- C. Nephropathy
1. Screen annually with random spot collection of urine albumin/creatinine ratio, starting at diagnosis in type 2 DM and after 5 or more years in type 1 DM.
 - a. Normal: Less than 30 mg/g (or micrograms per milligram)
 - b. Increased urinary albumin excretion (albuminuria) 30 mg/g or greater
 - c. Two of three specimens greater than 30 mg/g obtained over a 3–6 month period is consistent with diagnosis of albuminuria
 - d. ADA in 2013 no longer uses terms microalbuminuria or macroalbuminuria.
 2. Estimated CrCl yearly as well
 3. With increased albumin excretion, use of ACE inhibitors or ARBs is suggested if levels between 30–299 mg/g and recommended if greater than 300 mg/g.
 4. Dietary protein restriction as renal function declines
- D. Retinopathy
1. Screen annually with dilated and comprehensive eye examinations, starting at diagnosis in type 2 DM and after 5 or more years in type 1 DM.
 2. Frequency can be reduced to every 2–3 years after one or more normal examinations.
 3. No specific pharmacotherapy recommended except to adequately control glucose concentrations and blood pressure
- E. DM Neuropathies
1. Can have nerve damage in any area of the body but commonly affects the lower extremities.
 2. Screen for distal polyneuropathy using monofilament once yearly.
 - a. Screen after 5 years of type 1 DM and at diagnosis with type 2 DM.

- b. Statin therapy recommendations based on age and cardiovascular risk
 - i. Moderate dose statin therapy recommended for all patients age 40 or older without cardiovascular risk factors (e.g. LDL-C greater than or equal to 100 mg/dL, high blood pressure, smoker, overweight, or obese).
 - ii. High dose statin therapy recommended for those age 40-75 with existing cardiovascular risk factors (moderate or high dose statin if greater than 75 years of age)
 - iii. High dose statin therapy recommended for all patients with existing cardiovascular disease (e.g. previous cardiovascular event or acute coronary syndrome)
- 6. Antiplatelet therapy
 - a. Low-dose aspirin (75–162 mg/day)
 - i. With existing cardiovascular disease
 - ii. For primary prevention if 10-year risk is greater than 10% (includes most men older than 50 and women older than 60 who have at least one cardiovascular risk factor)
 - b. Clopidogrel for those intolerant of aspirin therapy
- G. Preventive Immunizations
 - 1. Annual influenza vaccine
 - 2. Pneumococcal polysaccharide vaccine
 - 3. Hepatitis B vaccine

VII. OTHER DIABETES MEDICATION ISSUES

- A. Former FDA Risk Evaluation and Mitigation Strategy for Rosiglitazone (removed November 2013)
 - 1. Limits use to:
 - a. Patients already being successfully treated with these medicines
 - b. Patients whose BG cannot be controlled with other antidiabetes medicines and who, after consulting with their health care providers, do not want to use pioglitazone-containing medicines
 - 2. Providers and patients must enroll in the Avandia-Rosiglitazone Medicines Access Program.
 - a. No longer available in retail pharmacies
 - b. Available by mail order only through certified pharmacies
- B. In the wake of the rosiglitazone safety issue, the FDA now requires all newly approved diabetes medications to prove cardiovascular safety.
 - 1. At least 2 years of safety data that include cardiovascular events as an end point and independent adjudication of events
 - 2. Necessary to study in older adults and in those with some degree of renal impairment and those with more advanced diabetes

REFERENCES

Thyroid

1. Garber J, Cobin R, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: co-sponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid* 2012;22:1200-35.
2. Jonklaas J, Talbert RL. Thyroid disorders. In: Talbert RL, DiPiro JT, Matzke GR, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 8th ed. New York: McGraw-Hill, 2011:chap 84. Available at www.accesspharmacy.com/content.aspx?aID=7991868. Accessed October 11, 2012.
3. Pearce E, Farwell A, Braverman L. Thyroiditis. *N Engl J Med* 2005;348:2646-55.
4. Rahn R, Burch H, Cooper D, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract* 2011;17:e1-e65.
5. Razvi S, Weaver J, Butler T, et al. Levothyroxine treatment of subclinical hypothyroidism, fatal and nonfatal cardiovascular events, and mortality. *Arch Intern Med* 2012;172:811-7.
6. Rodondi N, Newman A, Vittinghoff E, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med* 2005;165:2460-6.
7. Surks M, Ortiz E, Daniels G, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004;291:228-38.
8. Wall C. Myxedema coma: diagnosis and treatment. *Am Fam Physician* 2000;62:2485-90.
9. Walsh J, Bremner A, Bulsara M, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch Intern Med* 2005;165:2467-72.

Pituitary

1. Melmed S, Casanueva F, Hoffman A, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;96:273-88.

2. Thorogood N, Baldeweg S. Pituitary disorders: an overview for the general physician. *Br J Hosp Med* 2008;69:198-204.
3. Yanovski JA. Pituitary gland disorders. In: Talbert RL, DiPiro JT, Matzke GR, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 8th ed. New York: McGraw-Hill, 2011:chap 86. Available at www.accesspharmacy.com/content.aspx?aID=7992629. Accessed October 11, 2012.

Adrenal

1. Biller B, Grossman A, Stewart P, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2008;93:2454-62.
2. Shalet S, Mukherjee A. Pharmacological treatment of hypercortisolism. *Curr Opin Endocrinol Diabetes Obes* 2008;15:234-8.
3. Smith SM. Adrenal gland disorders. In: Talbert RL, DiPiro JT, Matzke GR, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 8th ed. New York: McGraw-Hill, 2011:chap 85. Available at www.accesspharmacy.com/content.aspx?aID=7992321. Accessed October 11, 2012.
4. Vaughan E. Diseases of the adrenal gland. *Med Clin North Am* 2004;88:443-66.

Obesity

1. Fidler M, Sanchez M, Raether B, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab* 2011;96:3067-77.
2. Foster G, Wyatt H, Hill J, et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet. *Ann Intern Med* 2010;153:147-57.
3. Jensen M, Ryan D, Apovian C, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society. *J Am Coll Cardiol* 2014;63:2985-3023.

Diabetes

1. American Diabetes Association (ADA). Standards of Medical Care in Diabetes – 2015: Classification and diagnosis of diabetes. *Diabetes Care* 2015;38(suppl 1):S8-16.
2. American Diabetes Association (ADA). Standards of Medical Care in Diabetes – 2015: Glycemic targets. *Diabetes Care* 2015;38(suppl 1):S33-40.
3. American Diabetes Association (ADA). Standards of Medical Care in Diabetes – 2015: Approaches to glycemic treatment. *Diabetes Care* 2015;38(suppl 1):S41-48.
4. American Diabetes Association (ADA). Standards of Medical Care in Diabetes – 2015: Cardiovascular disease and risk management. *Diabetes Care* 2015;38(suppl 1):S49-57.
5. American Diabetes Association (ADA). Standards of Medical Care in Diabetes – 2015: Microvascular complications and foot care. *Diabetes Care* 2015;38(suppl 1):S58-66.
6. Inzucchi S, Buse J, Ferrannini E, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach. *Diabetes Care* 2015;38:140-149.
7. Boulton A, Vinik A, Arezzo J, et al. Diabetic neuropathies. A statement by the American Diabetes Association. *Diabetes Care* 2005;28:956-62.
8. Bril V, England J, Franklin G, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 2011;76:1-8.
9. Calhoun H, Betteridge D, Durrington P, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multi-centre randomized placebo-controlled trial. *Lancet* 2004;364:685–96.
10. Camilleri M. Diabetic gastroparesis. *N Engl J Med* 2007;356:820-9.
11. The Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643-53.
12. Garber A, Agrahamson M, Barzilay J, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement. *Endocr Pract* 2013;19(suppl 2):1-48.
13. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. *Lancet* 2003;361:2005-16.
14. Holman R, Paul S, Bethel M, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.
15. Inzucchi S, Bergenstal R, Buse J, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. *Diabetes Care* 2012;35:1364-79.
16. Kitabchi A, Umpierrez G, Miles J, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32:1335-43.
17. Seaquist E, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36:1384-95.
18. Skyler J, Bergenstal R, Bonow R, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials. *Diabetes Care* 2009;32:187-92.
19. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317:703-13.
20. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D

Given this patient's reluctance to undergo ablative therapy, usually the most common treatment, oral therapy is warranted. Methimazole is recommended over PTU (Answer B) because it is associated with a lower risk of hepatotoxicity, although it may not be more efficacious. Answer A is incorrect because iodine therapy is indicated in this type of case only before surgery or during an acute case of thyroid storm. Answer C is incorrect because although β -blockers might provide some symptomatic relief, they would do little to stabilize this patient's thyroid levels.

2. Answer: A

This patient has hypothyroidism on the basis of her elevated TSH and low free T_4 , caused by Hashimoto's disease. Levothyroxine is the drug of choice for this condition, given its adverse effect profile, cost, antigenicity profile, and uniform potency. Although liothyronine can be used for hypothyroidism, its potential for increasing the risk of cardiovascular complications makes it second line (Answer B). Answer C is also incorrect, given its increased antigenicity compared with levothyroxine. Answer D is incorrect because it is an agent used to treat hyperthyroidism.

3. Answer: D

Fluoxetine, a selective serotonin reuptake inhibitor, may cause drug-induced hyperprolactinemia. Answer A is incorrect because β -blockers are not associated with an elevated risk of the condition. Given the patient's normal pituitary and thyroid tests, it is unlikely that Answer B, prolactin-secreting adenoma, is correct. Answer C is incorrect because pregnancy is not associated with an elevated risk of the condition.

4. Answer: D

Because the aldosterone/renin ratio and blood pressure are high, hyperaldosteronism is the most likely disease listed. Cushing's syndrome and hyperaldosteronism can be secondary causes of hypertension. In this case, the patient's free 24-hour urine cortisol is normal, but it would be elevated if he had Cushing's syndrome; therefore, Answer A is incorrect. Answer B is incorrect because Addison's disease is a result of cortisol deficiency and is not associated with hypertension. Answer

C, hyperprolactinemia, is unlikely, given the patient's presentation and his abnormal aldosterone/renin ratio.

5. Answer: B

The minimal weight loss after 12 weeks of therapy with phentermine/topiramate should be 5%; otherwise, the medication should be discontinued. Given this patient's baseline weight, a minimum of 13 lb is necessary to continue therapy. The other answers provided are too low (Answer A), or they exceed the 5% minimal expectation (Answer C and Answer D).

6. Answer: D

Unless the patient has significant symptoms of hyperglycemia (none noted in this case), a subsequent evaluation for hyperglycemia by a fasting glucose concentration, a random glucose concentration, an OGTT, or an A1C is warranted; therefore, Answer A and Answer B are incorrect. Answer C is incorrect because a subsequent test for hyperglycemia should not be performed on the same day according to ADA guidelines.

7. Answer: B

In general, the goal A1C, according to the ADA, is less than 7.0% and the goal blood pressure is less than 140/90 mm Hg. Recent updates from both the ADA and ACC/AHA do not promote a specific goal for either LDL-C or TG. Answer A, Answer C, and Answer D deviate from these goals or recommendations.

8. Answer: D

This patient weighs 50 kg (110 lb). $0.4 \text{ unit/kg/day} \times 50 \text{ kg} = 20 \text{ units}$ of TDI. When using insulin analogs, 50% of the TDI dose should be used as an initial estimate of the patient's basal insulin needs; therefore, 10 units is needed. Glargine is a once-daily, long-acting basal insulin. Although they use basal insulin, Answer A and Answer B are incorrect because of the higher-than-estimated dosage. Answer C is incorrect because insulin aspart is used for bolus insulin dosing, not for basal therapy, unless the patient is using an insulin pump.

9. Answer: B

Changes in lifestyle modification are initially preferred. Answer A, changes in lifestyle combined with

metformin, is unwarranted at this time because the A1C is not significantly elevated and patient may be able to control hyperglycemia with lifestyle changes alone. Answer C and Answer D are incorrect because sitagliptin or insulin therapy as initial monotherapy is not recommended unless metformin cannot be used, although both would be effective in controlling BG levels.

10. Answer: D

The usual next step in therapy for a patient no longer able to maintain adequate glycemic control with monotherapy is to add agents. Answer A is incorrect because the patient is already exercising and still has uncontrolled hyperglycemia. Answer B is incorrect because one agent, particularly metformin, would not normally be changed to another unless a patient was experiencing adverse effects of the original agent. Answer C, bromocriptine, is not likely to provide sufficient glycemic control given this patient's current A1C.

11. Answer: A

In this case, the initiation of medications to treat a patient with newly diagnosed hyperglycemia is complicated by the patient's many comorbidities. Normally, metformin, Answer D, would be the initial treatment of choice, but the patient's renal function is poor, and metformin should not be used. Answer C, exenatide, is also incorrect because it, too, should not be used in patients with significant renal impairment. Given the patient's existing edema and history of heart failure, pioglitazone (Answer B) is contraindicated because it can aggravate the conditions. Answer A, linagliptin, is the most appropriate choice because the A1C is not markedly elevated, and renal function does not need to be considered.

12. Answer: A

Current recommendations call for the use of an ACE inhibitor or ARB if a patient has elevated urinary albumin excretion. This patient's blood pressure and urine albumin/creatinine is normal (less than 30 mg/g). No additional therapy is necessary. Answer B and Answer C are incorrect because the patient's blood pressure is well controlled, and the urine albumin/creatinine is normal. Answer D is incorrect because protein restriction is used only after a significant decrease in CrCl, and this patient has normal renal function.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

According to the ADA guidelines, patients with this degree of hyperglycemia should be initiated on insulin therapy, and Answer D provides an appropriate basal/bolus insulin combination. This patient's A1C is greater than 10%, and his fasting glucose is greater than 300 mg/dL. Answer A and Answer C are not optimal because dual therapy with oral agents is unlikely to bring this patient to his glycemic goal. Answer B is also not optimal because the combination of a sulfonurea and rapid-acting insulin would increase the risk of hypoglycemia and would be unlikely to bring about a sufficient reduction in A1C.

2. Answer: C

This patient's TDI requirement is 40 units (80 kg x 0.5 unit/kg/day). Half of this is initially used for basal insulin requirements and half for bolus insulin requirements before meals. The 20 units for bolus requirements should initially be divided equally between three meals (i.e., 6–7 units). The other three answers would provide either too much or too little estimated insulin at each meal.

3. Answer: C

This patient has an elevated blood pressure, poor renal function, and two urine albumin/creatinine concentrations above 30 mg/g. According to the ADA and the clinical literature, the best classes of medications for patients with this condition are ARBs or ACE inhibitors. Answer A (thiazide diuretic) is not appropriate because this class of medications is not more beneficial than agents that block the renin-angiotensin system. Answer B, a dihydropyridine calcium channel blocker, is not best because this class has not been shown to be beneficial in type 1 and type 2 DM and proteinuria. Answer D, a nondihydropyridine calcium channel blocker, is an alternative to agents that block the renin-angiotensin system, but it should not be used instead of these agents unless a patient has contraindications to them.

4. Answer: B

Unlike methimazole, PTU has a boxed warning about the risk of hepatotoxicity. Answer A is incorrect because neither agent is considered more efficacious than the

other. Answer C is incorrect because Hashimoto's disease is a result of hypothyroidism, not hyperthyroidism. Methimazole is dosed once daily, whereas PTU is usually dosed up to three times daily, making Answer D incorrect.

5. Answer: A

Ketoconazole is used in patients with Cushing's syndrome because it reduces cortisol synthesis. Answer B, spironolactone, is used in patients with hyperaldosteronism. Answer C is inappropriate because Cushing's syndrome results in cortisol concentrations that are too high, and adding a corticosteroid to treat its symptoms could make the problem worse. Bromocriptine, Answer D, is used to treat acromegaly, not Cushing's syndrome.

6. Answer: C

This patient has both significant renal impairment and a markedly elevated A1C. Answers A and D are incorrect because they are both contraindicated in patients with significant renal impairment. Answer B is also incorrect. Although alogliptin can be used in patients with renal impairment at a reduced dose, it is not likely to provide a sufficient reduction in A1C. Initiating insulin is the best option in this case because it can be used in patients with renal impairment and can be titrated to attain significant reductions in A1C.

7. Answer: A

An older woman with heart disease should be initiated on a lower initial dose of levothyroxine. Answer B is the normal starting dose (i.e., 1.6 mcg/kg), but it is probably too high an initial dose for an older adult with established heart disease. Answer C and Answer D are incorrect because the drug of choice is levothyroxine, and liothyronine is no longer recommended for this condition.

8. Answer: B

For insulin adjustments, determine which BG readings are at goal and which ones are not. For those consistently not at goal, determine which insulin is most affecting the BG readings. In this case, the patient's BG readings are consistently elevated at bedtime, which is probably caused by insufficient predinner prandial (a.k.a. bolus) insulin. Changing the rapid-acting insulin

at other times of the day would not help; therefore, Answer A and Answer D are incorrect. Changing her basal insulin (glargine in this case) would probably not help her bedtime BG, and because her FBG readings have been well controlled, it could lead to hypoglycemia (Answer C).

9. Answer: A

This patient has mild symptoms, and her ablative therapy worked initially but now no longer controls her thyroid levels. Methimazole (Answer A) would be the preferred oral agent, given its dosing frequency and lower risk of hepatotoxicity compared with PTU (Answer C). Thyroidectomy is an option, but it is probably too aggressive for mild Graves' disease; therefore, Answer B is incorrect. Answer D is not optimal; β -blockers, which may provide symptomatic relief, will not significantly affect her thyroid levels.

10. Answer: D

This patient has good control of his fasting glucose but is experiencing postprandial hyperglycemia. An agent that targets postprandial glucose (e.g., a DPP-4 inhibitor) would be most appropriate. Answer A is incorrect because this would exceed the maximal daily dose for metformin. Answer B is incorrect because insulin glargine is a basal insulin that has an effect on FPG but little effect on postprandial glucose. Answer C is incorrect, again because it is a basal insulin and also because it is more appropriate to add medications than to switch to another agent unless the patient is experiencing adverse effects with the first agent.

11. Answer: D

This patient has tried dieting and some exercise, but these are failing to control her weight; thus, her current routine alone is not appropriate, making Answer A incorrect. Answer B, lorcaserin, is approved for the treatment of obesity but should be avoided in patients taking serotonergic agents, in this case sertraline. Answer C is a federally scheduled medication because of its abuse potential with phentermine, and given this patient's history of abuse, it is not the most favorable selection. Orlistat, Answer D, is the only agent listed to which this patient does not have a specific precaution or contraindication with its use.

12. Answer: A

This patient has now had two laboratory glycemic indicators (A1C and FBG) consistent with the diagnosis of diabetes. Answer B is probably incorrect because this patient has several risk factors for developing type 2 DM, including obesity, ethnicity, age, a history of gestational diabetes, and a strong family history of the disease. Answer C is incorrect because there is no need to obtain another A1C reading this soon after the reading just 2 weeks ago, and the A1C can be used in the diagnosis of diabetes. Obtaining another glucose reading on another day (Answer D) is also incorrect, again because there are already two abnormal glycemic indicators; therefore, another is not necessary to confirm the diagnosis.

13. Answer: C

According to the ADA, moderate dose statin therapy is recommended for patients with diabetes older than 40 years of age but without other cardiovascular risk factors. The updated 2015 ADA guideline are similar to newer guidelines from the ACC/AHA who also advocate moderate intensity statin therapy. In this case, the patient's glycemic and blood pressure readings are at goal (less than 7.0% and less than 140/90 mm Hg, respectively). Adding insulin (Answer A) and adding a blood pressure medication (Answer B) are not necessary. Answer D is incorrect because there is no need for fibrate therapy in this patient; the HDL-C and TG are under control.

