ENDOCRINE AND METABOLIC DISORDERS

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Endocrine and Metabolic Disorders

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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, diabetes insipidus, polycystic ovary syndrome, obesity, and disorders of the thyroid, adrenal, and pituitary glands.
2. Review 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 previously mentioned endocrine or metabolic disorders.
4. Recommend appropriate therapeutic management for secondary complications from diabetes or thyroid disorders.

Abbreviations in This Chapter

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
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<tr>
<td>A1C</td>
<td>Hemoglobin A1C</td>
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<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
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<td>ARB</td>
<td>Angiotensin receptor blocker</td>
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<td>BG</td>
<td>Blood glucose</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>DI</td>
<td>Diabetes insipidus</td>
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<td>DKA</td>
<td>Diabetic ketoacidosis</td>
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<td>DM</td>
<td>Diabetes mellitus</td>
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<tr>
<td>DPP</td>
<td>Dipeptidyl peptidase-4</td>
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<tr>
<td>FBG</td>
<td>Fasting blood glucose</td>
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<td>FPG</td>
<td>Fasting plasma glucose</td>
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<td>FSH</td>
<td>Follicle-stimulating hormone</td>
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<td>GH</td>
<td>Growth hormone</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
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<tr>
<td>GLP-1</td>
<td>Glucagon-like peptide-1</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Insulin-like growth factor-1</td>
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<tr>
<td>LH</td>
<td>Luteinizing hormone</td>
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<tr>
<td>NPH</td>
<td>Neutral protamine Hagedorn</td>
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<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<tr>
<td>PCOS</td>
<td>Polycystic ovary syndrome</td>
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<tr>
<td>SGLT-2</td>
<td>Sodium glucose cotransporter-2</td>
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<tr>
<td>T1D</td>
<td>Type 1 diabetes</td>
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<td>T2D</td>
<td>Type 2 diabetes</td>
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<tr>
<td>TDI</td>
<td>Total daily insulin</td>
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<tr>
<td>T3</td>
<td>Triiodothyronine</td>
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<td>T4</td>
<td>Thyroxine</td>
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<tr>
<td>TSH</td>
<td>Thyroid-stimulating hormone</td>
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Self-Assessment Questions

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

1. A 66-year-old Hispanic man (weight 123.8 kg; body mass index [BMI] 42 kg/m²) with a history of myocardial infarction, dyslipidemia, and hypertension received a diagnosis of type 2 diabetes (T2D). After 1 month of exercise and dietary changes and no diabetes medications, his hemoglobin A1C (A1C) and fasting glucose concentration today are 11.5% and 362 mg/dL, respectively. 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 patient weighing 65 kg with symptoms of hyperglycemia and a fasting glucose concentration of 298 mg/dL is given a diagnosis of type 1 diabetes (T1D). The patient’s physician asks for a recommendation of an appropriate starting dose of basal insulin and estimates the total daily insulin (TDI) needs of 0.4 unit/kg/day. Which recommendation is most appropriate?
   A. 13 units of insulin detemir.
   B. 13 units of insulin aspart.
   C. 26 units of insulin glargine.
   D. 26 units of insulin glulisine.

3. A patient with T2D has a blood pressure reading of 152/84 mm Hg, a serum creatinine (SCr) of 1.8 mg/dL, and two recent random 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. Non-dihydropyridine calcium channel blocker.

4. Regarding propylthiouracil and methimazole in the treatment of hyperthyroidism, which statement is most appropriate?
A. Propylthiouracil is clinically superior to methimazole in efficacy.
B. Propylthiouracil may be associated with greater liver toxicity than methimazole.
C. Both agents are equally efficacious in the treatment of Hashimoto disease.
D. Both medications should be administered three times daily.

5. Which medication is most appropriate for a patient with a diagnosis of Cushing syndrome who has had inadequate symptom relief after surgical resection for a pituitary adenoma?
A. Ketoconazole.
B. Spironolactone.
C. Hydrocortisone.
D. Bromocriptine.

6. A physician asks for a recommendation of initial therapy for a patient with T2D. 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/minute/1.73 m². Which agent would be the best recommendation?
A. Canagliflozin.
B. Alogliptin.
C. Glargine.
D. Exenatide.

7. A 76-year-old woman (weight 47 kg) recently given a diagnosis of Hashimoto disease presents with mild symptoms of lethargy, weight gain, and intolerance to cold. Her thyroid-stimulating hormone (TSH) is 12.2 mIU/L and free thyroxine (T₄) is below normal limits. 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?
A. Levothyroxine 25 mcg once daily.
B. Levothyroxine 75 mcg once daily.
C. Liothyronine 25 mcg once daily.
D. Liothyronine 75 mcg once daily.

8. A woman with T2D 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 185–200 mg/dL. Which is the best insulin adjustment to improve her overall glycemic control?
A. Increase prebreakfast aspart to 10 units.
B. Increase predinner aspart to 14 units.
C. Increase bedtime glargine to 65 units.
D. Increase prelunch aspart to 9 units.

9. A 53-year-old woman with a history of Graves disease had ablative therapy 3 years ago, after which she had significant symptom relief and became euthyroid. Her thyroid laboratory values today include TSH 0.12 mIU/L and free T₄ 3.8 g/dL. She states that many of her previous symptoms have returned but are mild. Which would be the most appropriate treatment for her condition?
A. Methimazole.
B. Lugol’s solution.
C. Propylthiouracil.
D. Metoprolol.

10. A 65-year-old man with T2D has received metformin 1000 mg twice daily for the past 2 years. His A1C today is 7.8%. His morning FPG readings are consistently at goal. His after-meal glucose readings average 190–200 mg/dL. Which would be most appropriate for this patient?
A. Increase metformin to 1000 mg three times daily.
B. Add insulin glargine 10 units once daily.
C. Change from metformin to insulin glargine 10 units once daily.
D. 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 0.9 kg (2 lb) in 6 months. She exercises regularly but cannot do more because she has two jobs and young children.
Her medical history is significant for depression, T2D, 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?

A. Continue her diet and exercise routine; additional intervention is unwarranted.
B. Initiate lorcaserin 10 mg twice daily.
C. Initiate phentermine/topiramate 3.75/23 mg once daily.
D. 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 T2D. Two weeks ago, her A1C was 7.4%. Her fasting glucose concentration is 178 mg/dL. She is asymptomatic. Which is the best course of action?

A. Diagnose T2D and begin treatment.
B. Diagnose T1D and begin treatment.
C. Obtain another A1C today.
D. Obtain another glucose concentration another day.

13. A 42-year-old man has a history of T2D. His current therapy includes metformin 1000 mg twice daily, glyburide 10 mg twice daily, and aspirin 81 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) 98 mg/dL, high-density lipoprotein cholesterol (HDL) 45 mg/dL, and triglycerides (TG) 145 mg/dL. Which would be most appropriate for this patient?

A. Add insulin detemir 10 units once daily.
B. Add lisinopril 10 mg once daily.
C. Add atorvastatin 10 mg once daily.
D. Add fenofibrate 145 mg once daily.
BPS Pharmacotherapy Specialty Examination Content Outline
This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-centered pharmacotherapy
   a. Task 1 with knowledge of:
      i. Anatomy, physiology, and pathophysiology
      ii. Disease processes, including drug-induced diseases
      iii. Pharmacology and toxicology
      iv. Evidence-based standards of care and clinical pathways
      v. Allergies and adverse drug reactions
      vi. Interpretation of laboratory tests, diagnostics, and procedures
      vii. Drug interactions
      viii. Nonpharmacologic treatments
      ix. Preventive care (e.g., screening, immunizations)
      x. Patient-specific goals of care and prioritization of needs
   b. Task 4 with knowledge of:
      i. Response to therapy and implications for therapeutic goals
      ii. Interpretation of laboratory tests, diagnostics, and procedures
      iii. Changes in patient clinical status
      iv. Disease progression or resolution
      v. Drug interactions
      vi. Adverse drug reactions
   c. Systems and patient-care problems:
      i. Thyroid disorders
      ii. Diabetes insipidus
      iii. Pituitary gland disorders
      iv. Adrenal gland disorders
      v. Obesity
      vi. Polycystic ovary syndrome
      vii. Diabetes (types 1 and 2)
      viii. Treatment of DM complications

2. Domain 3: System-based standards and population-based pharmacotherapy
   a. Task 1 with knowledge of laws and regulations
I. THYROID DISORDERS

Hypothalamus

\[ \text{TRH} \quad -\text{ve} \]

Pituitary

\[ \text{TSH} \quad -\text{ve} \]

Thyroid

\[ T_3 \quad T_4 \]

Figure 1. Hypothalamus-pituitary-thyroid axis.

\(^{3}T_4\) is converted to \(T_3\) by peripheral tissue. Only unbound (free) thyroid hormone is biologically active.

\(T_3\) = triiodothyronine; \(T_4\) = 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 try oral pharmacotherapy first. Her thyroid laboratory values today include TSH 0.22 mIU/L (normal 0.5–4.5 mIU/L) and free \(T_4\) 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 is best 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 (\(T_3\)) and \(T_4\) production.
   b. Pituitary adenomas: Produce excessive TSH secretion that does not respond to normal \(T_3\) 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
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 dosages, amiodarone therapy)

2. Diagnosis
   a. Elevated free $T_g$ 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 can be used.
      i. Radioactive iodine uptake elevated if thyroid gland is actively and excessively secreting $T_g$ and/or $T_c$; 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 thyrophosphodiase), 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 $T_g$ 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 caused by thyroiditis
      ii. Those who are not ablative or surgical candidates (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
c. Thioureas (i.e., propylthiouracil, methimazole)
   i. Mechanism of action: Inhibits iodination and synthesis of thyroid hormones; propylthiouracil can block T4/T3 conversion in the periphery as well
   ii. Dosing
      (a) Propylthiouracil
         (1) Initial: 100 mg by mouth three times daily
         (2) Maximal: 400 mg three times daily
         (3) Once euthyroid, can 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 propylthiouracil
            (A) American Thyroid Association recommends propylthiouracil in the first trimester because of the risk of embryopathy.
            (B) Change to methimazole in the second trimester.
         (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 dosage titrations as needed (depending on symptoms and free T4 concentrations); TSH may remain low for months after therapy begins
   iii. Adverse effects
      (a) Hepatotoxicity risk with propylthiouracil (boxed warning): AACE recommends baseline liver function tests. Routine evaluation of liver function while receiving antithyroid agents has not been shown to prevent severe hepatotoxicity.
      (b) Rash
      (c) Arthralgia, lupus-like symptoms
      (d) Fever
      (e) Agranulocytosis early in therapy (usually within 3 months): AACE recommends a baseline complete blood cell count; no routine monitoring recommended. Can 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-fold more potent than propylthiouracil.
      (d) Remission rates low: 20%–30%. Remission is defined as normal TSH and T4 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 might not affect remission rate
         (2) Consider trial off oral therapy if TSH is normal; antibody titers can help guide decision.
         (3) Monitor thyroid concentrations every 1–3 months for up to 12 months for relapse (abnormal TSH or T4 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) T4 conversion to (more active) T3
      ii. Propranolol dosing
         (a) Initial: 20–40 mg by mouth three or four times daily
         (b) Maximal: 240–480 mg/day
### Endocrine and Metabolic Disorders

iii. Adverse effects (see Hypertension section in Cardiology 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; consider use in all symptomatic patients. Also recommended for use before ablative iodine therapy in those who are extremely symptomatic or have a free T4 2–3 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 the text that follows).
   
   (e) Alternatives to β-blockers: Clonidine, non-dihydropyridine calcium channel blocker

e. Iodines and 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 of iodide per drop)
   
   (b) Saturated solution of potassium iodide (38–50 mg of 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 T4

2. Risk
   
   a. Associated with elevated risk of atrial fibrillation in patients older than 60
   
   b. Associated with elevated risk of bone fracture in postmenopausal women
   
   c. Conflicting data about mortality risk

3. Treatment (according to 2011 guidelines) similar to treatment of overt hyperthyroidism
   
   a. Oral antithyroid drug therapy alternative to ablative therapy in young patients with Graves disease
   
   b. β-Blockers may help control cardiovascular morbidity, especially with atrial fibrillation.

4. If untreated, screen regularly for the development of overt hyperthyroidism (elevated free T4 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. Propylthiouracil
      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 propylthiouracil initiation (dosed as stated earlier) to block hormone release
   c. β-Blocker therapy: Propranolol or esmolol commonly used to control symptoms and block conversion of T\(_4\) to T\(_3\)
   d. Acetaminophen as antipyretic therapy, if needed (avoid nonsteroidal anti-inflammatory drugs 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 dosages of, for example, dexamethasone, hydrocortisone). Provides prophylaxis against relative adrenal insufficiency and can block conversion of T\(_4\) to T\(_3\)

Patient Case
2. A 63-year-old woman has Hashimoto disease. Her thyroid laboratory values today include TSH 10.6 mIU/L (normal 0.5–4.5 mIU/L) and free T\(_4\) 0.5 ng/dL (normal 0.8–1.9 ng/dL). She feels consistently rundown and has dry skin that does not respond to the use of hand creams. Which is 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 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 radiiodine ablative therapy for hyperthyroidism
   c. Iodine deficiency most common cause worldwide
   d. Secondary causes
      i. Pituitary insufficiency (failure to produce adequate TSH secretion, called by some a 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 greater than 10 mIU/L (normal or low if central hypothyroidism is the cause)
   c. Thyroid antibodies such as antithyroid peroxidase and antithyroglobulin autoantibodies
   d. Screen patients older than 60, especially women (many different screening recommendations are given 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 T₄ and TSH concentrations

5. Therapeutics
   a. Levothyroxine (drug of choice)
      i. Mechanism of action: Synthetic T₄
      ii. Dosing
         (a) Initial
            (1) In otherwise healthy adults, 1.6 mcg/kg (use ideal body weight) per day
            (2) In patients age 50–60, 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 (particularly calcium or iron supplements and antacids)
         (c) Dosage titration depending on response (control of symptoms, normalization of TSH and free T₄)
         (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 T₄). May take longer for TSH to achieve steady-state concentrations
         (b) Use free T₄ 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 dosages or over-supplementation)
      v. Efficacy: If levothyroxine is properly dosed, most patients will maintain TSH and free T₄ in the normal ranges and experience symptomatic relief.
      vi. Considered drug of choice because of its adverse effect profile, cost, lack of antigenicity, and uniform potency
vii. Bioequivalence
   (a) AACE recommends brand-name levothyroxine (none of the other thyroid preparations
given later in text is 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 obtained; small changes in T₄
between products can significantly change the TSH. Pharmacokinetic studies were con-
ducted in healthy subjects with normal thyroid function.

b. Liothryronine (synthetic T₃), liotrix (synthetic T₄/T₃), 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 T₄. Often the result of early
Hashimoto 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).
   4. Whom to treat
      a. TSH 4.5–10 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 T₄
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, anesthe-
sia, 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. T₄: 100- to 500-mcg loading dose, followed by 75–100 mcg/day, until the patient can tolerate
oral therapy. Lower the initial dose in frail patients or patients with established cardiovascular
disease.
         ii. Some advocate the use of T₃ over T₄, given that T₃ is more biologically active and that T₄/T₃
conversion may be suppressed in myxedema coma. Cost and availability limit intravenous
T₃ use.
      b. Antibiotic therapy: Given common infectious causes, some clinicians 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

<table>
<thead>
<tr>
<th>Anterior Pituitary Hormone</th>
<th>Primary Function(s)</th>
<th>Hypothalamic Stimulator</th>
<th>Primary Secretion Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone (GH)</td>
<td>Promote tissue growth</td>
<td>GH-releasing hormone</td>
<td>Somatostatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Insulin-like growth factor-1</td>
</tr>
<tr>
<td>Adrenocorticotropin hormone (ACTH)</td>
<td>Stimulate adrenal cortisol and androgen release</td>
<td>Corticotropin-releasing hormone</td>
<td>Cortisol</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>Metabolic stability</td>
<td>Thyrotropin-releasing hormone</td>
<td>Triiodothyronine</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Regulate lactation</td>
<td>Thyrotropin-releasing hormone</td>
<td>Dopamine</td>
</tr>
<tr>
<td>Follicle-stimulating hormone</td>
<td>Maturation of ovarian follicles Sperm production</td>
<td>Gonadotropin-releasing hormone</td>
<td>Inhibin</td>
</tr>
<tr>
<td>Luteinizing hormone</td>
<td>Secretion of sex steroids</td>
<td>Gonadotropin-releasing hormone</td>
<td>Estrogens and progestins Testosterone</td>
</tr>
</tbody>
</table>

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 adrenocorticotropin hormone (ACTH) deficiency, GH deficiency, hypo-
      thyroidism, 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 that the disease has a 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. T2D
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 is 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 is adequate, 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) Flulike 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. Her medical history includes hypertension and depression. Her pituitary and thyroid tests results have been negative. Her current medications include atenolol and fluoxetine. Her prolactin concentration today is 112 ng/mL (normal 15–25 ng/mL). Which is the most likely cause of her elevated prolactin concentration?

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 common nontumor cause), renal failure, hypothyroidism, breastfeeding
   c. Potential causative drugs: Typical antipsychotics, opiates, non-dihydropyridine calcium channel blockers, antidepressants
2. Diagnosis and clinical presentation
   a. Elevated serum prolactin concentrations; may be challenging to find specific cause (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. Relieve symptoms
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 according to the Endocrine Society guidelines, long-acting oral agent; adverse effect profile similar to that for bromocriptine but fewer gastrointestinal [GI] adverse effects)
         (a) Initial: 0.5 mg once weekly
         (b) Maximal: 4.5 mg/week
      ii. Bromocriptine (see previous text)
      iii. Efficacy: May restore fertility in more than 90% of women. Cabergoline may be easier for patients to take, given its weekly administration.
      iv. Consider tapering or discontinuing 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. Increase growth velocity
   b. Increase 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. Arthralgia, 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.](image)

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 (172/98 mm Hg today), despite his 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 plasma aldosterone/renin ratio is 125 (normal is less than 25). Which most likely caused this patient’s uncontrolled hypertension?

A. Cushing syndrome.
B. Addison disease.
C. Hyperprolactinemia.
D. Hyperaldosteronism.

A. Hypersecretory Cortisol Diseases (Cushing syndrome)

1. Classification
   a. ACTH-dependent: Result of excessive ACTH secretion
      i. Pituitary corticotroph adenoma (Cushing disease)
      ii. Ectopic ACTH syndrome (extrapituitary tumor)
   b. ACTH-independent: Result of excessive cortisol secretion or exogenous steroids
      i. Unilateral adrenocortical tumors
      ii. Bilateral adrenal hyperplasia or dysplasia
      iii. Exogenous steroid administration

2. Diagnosis and clinical presentation
   a. Presence of hypercortisolism through 24-hour urinary free cortisol concentration
   b. Differentiate etiology (key to treatment options).
      i. Complex and beyond the scope of this chapter
      ii. Plasma ACTH concentrations (normal or elevated in ACTH-dependent)
      iii. Pituitary magnetic resonance imaging (Cushing syndrome vs. ectopic ACTH syndrome)
      iv. Overnight dexamethasone suppression test
      v. Late-night salivary cortisol concentration
      vi. 24-hour urinary free cortisol (low sensitivity)
   c. Clinical presentation
      i. Central obesity and facial rounding quite common
      ii. Peripheral obesity and fat accumulation
      iii. Myopathies
      iv. Osteoporosis, back pain, compression fracture
      v. Abnormal glucose tolerance or diabetes
      vi. Amenorrhea and hirsutism in women
      vii. Lower abdominal pigmented striae (red to purple)
      viii. Hypertension (principal cause of morbidity and mortality)

3. Therapy goals
   a. Reduce morbidity and mortality and eliminate cause
   b. Reverse clinical features
   c. Normalize biochemical changes (when possible)
   d. Achieve long-term control without recurrence (remission when possible)

4. Therapeutics
   a. If excessive exogenous corticosteroid use is causative, discontinue or minimize use.
   b. Surgical resection of causative area or tumor is usual treatment of choice.
   c. Pharmacotherapy is usually reserved on the basis of the same criteria listed earlier for pituitary adenomas.
d. Inhibit ACTH secretion
   i. Pasireotide
      (a) Mechanism of action: Somatostatin analog blocks ACTH secretion from pituitary, leading to decreased circulating cortisol concentrations (better selectivity to pertinent somatostatin receptors than other analogs such as octreotide). Pasireotide is usually not effective for adrenally caused Cushing syndrome. Pasireotide’s main role is in Cushing disease, but its role according to the guidelines is yet to be determined.
      (b) Dosing: 0.6–0.9 mg twice-daily subcutaneous injection (dose adjustments based on urinary free cortisol and symptom improvements)
      (c) Adverse effects: Hyperglycemia, hypocorticalism, diarrhea, nausea, gallstones, headache, bradycardia
      (d) Obtain an electrocardiogram, FPG, A1C, liver function tests, and gallbladder ultrasonography before initiating therapy.
      (e) Self-monitor BG values every week for first 2–3 months, and 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.
   ii. Cabergoline (see dosing and ADR profile listed earlier)


 e. Inhibit cortisol synthesis
   i. Ketoconazole
      (a) Mechanism of action: In addition to its antifungal activity, it hinders cortisol production by inhibiting 11- and 17-hydroxylase.
      (b) Dosing
         (1) Initial: 200 mg twice daily by mouth
         (2) Maximal: 400 mg three times daily
      (c) Adverse effects
         (1) Gynecomastia
         (2) Abdominal discomfort
         (3) Reversible hepatic transaminase elevations
   ii. Mitotane
      (a) Mechanism of action: Inhibits 11-hydroxylase but also has some direct adrenolytic activity
      (b) Dosing
         (1) Initial: 500–1000 mg/day by mouth (some use much higher daily dosages, but they are not well tolerated)
         (2) Maximal: 9–12 g/day
      (c) Adverse effects
         (1) Adrenocortical atrophy: Can persist on discontinuation and, in severe cases, may necessitate androgen and glucocorticoid replacement
         (2) Anorexia
         (3) Ataxia
         (4) Abdominal discomfort
         (5) Lethargy
   iii. Etomidate
      (a) Mechanism of action: Similar to ketoconazole, inhibits 11-hydroxylase
      (b) Dosing
         (1) Initial: 0.03 mg/kg intravenously, followed by a 0.1-mg/kg/hour infusion
         (2) Maximal: 0.3 mg/kg/hour
(c) Adverse effects
   (1) Pain at injection site
   (2) Nausea and vomiting
   (3) Myoclonus
   (4) Psychoses
(d) Given route of administration is usually reserved for when rapid control of cortisol concentra-
tions is needed and oral therapy is problematic.
iv. Metyrapone (by compassionate use only)
   (a) Mechanism of action: Hinders secretion of cortisol by blocking final step in cortisol syn-
thesis by inhibiting 11-hydroxylase activity
   (b) Dosing
      (1) Initial: 500 mg three times daily by mouth
      (2) Average dose in Cushing syndrome is 2000 mg/day, but dose is about 4000 mg in
          ectopic ACTH syndrome.
   (c) Adverse effects
      (1) Hypoadrenalism
      (2) Hypertension
      (3) Worsening of hirsutism and acne if present before treatment
      (4) Headache
      (5) Abdominal discomfort
f. Efficacy is measured by control of symptoms and normalization of 24-hour urine-free cortisol
concentrations.
g. Glucocorticoid replacement may be necessary if circulating cortisol is reduced to lower than phys-
iologic concentrations.
h. Mifepristone for hyperglycemia associated with endogenous Cushing syndrome; proposed to limit
binding of cortisol; can 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: Hypernatremia, 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 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 (i.e., Addison 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 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

3. Therapy goals (same as earlier for Cushing syndrome)
4. Therapeutics (Table 2)
   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 (use may reduce need for fludrocortisone compared with use of 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: 25–50 mg/day
   e. Efficacy can be measured by symptom improvement.
   f. Note that during times of stress or illness, corticosteroid dosages must be increased. Dose and route of administration depend on level of stress to the body.
### Table 2. Comparative Glucocorticoid Dosing

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Relative Equivalent Dosing (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone</td>
<td>25</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
</tr>
</tbody>
</table>

### IV. OBESITY

A. Recent Guidelines

1. American College of Cardiology/American Heart Association (ACC/AHA) and The Obesity Society 2013 guidelines; first significant guideline since 1998. Most of the therapeutic agents that follow were approved for obesity after the guideline was initiated and are not included.

2. Endocrine Society 2015 guidelines are focused on new obesity agents. No specific recommendations of a particular agent over another, but a good review of the therapeutic options

3. AACE/American College of Endocrinology 2016 guidelines. A comprehensive review of nonpharmacologic and pharmacologic therapy for obesity. Like the Endocrine Society guidelines, there are no specific recommendations regarding one agent over another.

B. Classification

1. Based on BMI

   1. Normal: BMI 18.5–24.9 kg/m²
   2. Overweight: BMI 25.0–29.9 kg/m²
   3. 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., T2D, hypertension, cardiovascular disease)

D. Nonpharmacologic Therapy (aimed at providing an energy deficit)

1. Increased physical activity: 200–300 minutes per week (minimum 150)
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. 1200–1500 kcal/day for women
   c. 1500–1800 kcal/day for men
3. Behavioral intervention: According to ACC/AHA/The Obesity Society guidelines: 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 patients with severe obesity (BMI greater than 40 kg/m²) or BMI of at least 35 kg/m² with at least one obesity-related comorbidity such as diabetes, hypertension, or obstructive sleep apnea
   a. Roux-en-Y gastric bypass
   b. Sleeve gastrectomy
   c. Adjustable gastric banding

Patient Case
5. A patient takes the maximal daily dose of phentermine/topiramate for the treatment of obesity. The patient’s baseline BMI is 36 kg/m² and weight is 115.7 kg (255 lb). Which best represents the minimum weight loss required to consider continuing treatment with this agent?
   A. 3.2 kg (7 lb).
   B. 5.9 kg (13 lb).
   C. 7.7 kg (17 lb).
   D. 11.8 kg (26 lb).

E. Pharmacotherapy
   1. Always in conjunction with diet, physical activity, and behavioral therapy
   2. Medications should be reserved for those not achieving or sustaining weight reduction with adequate lifestyle modifications, in those with obesity, or in those with a BMI of at least 27 kg/m² with significant weight-related comorbidities (e.g., diabetes, hypertension, dyslipidemia).
   3. Medication selected according to risk-benefit profile should be approved by the U.S. Food and Drug Administration (FDA). After 1 year, approved agents should provide at least a statistically significant 5% weight loss difference from placebo, or at least 35% of treated subjects should achieve at least a 5% weight loss from baseline and twice that of placebo-treated subjects.
   4. 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. GI tract: Flatulence, oily stools, loose stools, fecal urgency, or incontinence (highly 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 (FDA warnings)
      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.
   5. Lorcaserin (schedule IV)
      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 (20 mg once daily with extended-release formulation)
      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.

6. Phentermine/extended-release topiramate (schedule IV)
   a. Mechanism of action: Phentermine promotes appetite suppression and decreases food intake secondary to its sympathomimetic activity. Mechanism of topiramate is unknown, but it can 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.

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

7. Bupropion/naltrexone
   a. Mechanism of action: Reuptake inhibitor of dopamine and norepinephrine (bupropion) and opioid antagonist (naltrexone)
   b. Dosing (8 mg naltrexone/90 mg bupropion tablets)
      i. Dosage escalation at weekly intervals by 1 tablet daily
      ii. Initially, 1 tablet once daily
      iii. Target dosage: 2 tablets twice daily
   c. Adverse effects: Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth

d. Precautions and contraindications: Uncontrolled hypertension, seizure disorders, anorexia nervosa or bulimia, drug or alcohol withdrawal. Avoid with chronic use of opioids.

e. Efficacy: 5%–6% weight loss from baseline; 40%–55% attained at least a 5% weight loss after 56 weeks of therapy, 20%–25% attained at least a 10% weight loss

f. Discontinue use if at least a 5% weight loss is not achieved after 12 weeks of use.

8. Liraglutide
   a. Mechanism of action: Glucagon-like peptide-1 (GLP-1) agonist (part of incretin system). Thought to cause satiety and delay gastric emptying. Used in treatment of T2D (see text that follows)
   b. Dosing (administered subcutaneously by pen device)
      i. Target dosage higher in obesity than in treatment of diabetes. Brand-name product for obesity is not approved for diabetes and vice versa.
      ii. Initially, 0.6 mg once daily; increase by 0.6 mg at weekly intervals
      iii. Target dosage for obesity: 3 mg daily
   c. Adverse effects: Nausea, vomiting, diarrhea, constipation, dyspepsia

d. Precautions and contraindications
   i. See the Diabetes Mellitus section.
   ii. Obesity formulation should be avoided in patients receiving insulin (increased risk of hypoglycemia).
   iii. Do not use with other GLP-1 agonists used in the treatment of diabetes mellitus (DM).
Efficacy
i. Patients without diabetes: 8%–9% weight loss from baseline; 60%–65% attained at least a 5% weight loss after 56 weeks of treatment, and about 33% attained at least a 10% weight loss
ii. Patients with diabetes: 6% weight loss from baseline; 54% attained at least a 5% weight loss after 56 weeks of treatment, and 25% attained at least a 10% weight loss. Only minimally more effective at A1C reduction than standard diabetes dosage (see text that follows for diabetes dosing)
f. Discontinue use if the patient does not achieve at least a 4% weight loss after 16 weeks of therapy or if the patient cannot tolerate the target 3-mg daily dosage.

9. Diethylpropion (schedule IV), phentermine (schedule IV), phendimetrazine (schedule III)
a. Should be used only for a limited time, up to 3 months, and avoid in those with abuse potential
b. Clinical guidelines do not recommend their use.
c. Adverse effects: Increased blood pressure, constipation, increased heart rate, dysrhythmias, abuse potential (avoid in patients with hypertension or a history of cardiovascular disease)

10. Other issues
   a. Concurrent use of obesity medications has not been studied.
   b. Comparative studies between agents are lacking (although liraglutide has been shown to reduce weight better than orlistat).
   c. Long-term safety of all agents is unknown.
   d. Consider obesity a chronic medication. Weight loss after continuation of agent is not sustained

11. Off-label medications used but not well studied specifically for obesity: Selective serotonin reuptake inhibitors, zonisamide, metformin, pramlintide

V. POLYCYSTIC OVARY SYNDROME

A. Background and Classification
1. Can be a cause of infertility in up to 20% of infertile couples
2. Mainly considered to be caused by androgen excess or hyperandrogenism
3. Underlying cause appears to be insulin resistance (in patients with and without obesity), with subsequent compensatory insulin hypersecretion or increased insulin action. This increased action stimulates androgen secretion by the ovaries or adrenal cells, leading to increased luteinizing hormone (LH) secretion but normal or low follicle-stimulating hormone (FSH) concentrations, with a subsequent decrease in follicular maturation and anovulation.
4. Has several potential comorbidities with endocrine and cardiovascular implications (e.g., T2D, obesity)
5. Can affect 6%–10% of women (or more depending on diagnostic criteria used), making it one of the most prevalent endocrine disorders in young women
6. No clear consensus on classifying polycystic ovary syndrome (PCOS), although some rate it from mild to severe
7. Endocrine Society has the only recent guideline on PCOS diagnosis and treatment.

B. Diagnosis
1. Still somewhat under debate; no clear consensus
2. 1990 National Institutes of Health criteria
   a. Hyperandrogenism or hyperandrogenemia
   b. Oligo-ovulation (infrequent or irregular ovulation)
   c. Exclusion of other secondary causes, particularly adrenal hyperplasia, Cushing syndrome, hyperprolactinemia
3. 2003 Rotterdam criteria: Presence of at least two of the following and ruling out secondary causes
   a. Menstrual irregularity (oligo-ovulation or anovulation)
   b. Hyperandrogenism (clinical or biochemical signs)
   c. Polycystic ovaries (by transvaginal ultrasonography)
   d. Recommended by the Endocrine Society guideline
4. 2006 Androgen Excess Society: Follow 1990 National Institutes of Health criteria, but recognize concerns brought about from the Rotterdam criteria.

C. Clinical Presentation
1. Clinical signs of hyperandrogenism: Hirsutism, acne, pattern alopecia (can vary by ethnicity)
2. Biochemical signs of hyperandrogenism (should not be used as the sole criterion because 20%–40% of patients with PCOS may be in the normal range)
   a. Elevated free or total serum testosterone
   b. LH/FSH ratio greater than 2
3. Infrequent, irregular (e.g., late), or no ovulation, leading to irregular menses
4. Infertility despite unprotected and frequent intercourse during the past year
5. In patients with obesity (50%–80% of cases), prediabetes (impaired glucose tolerance) or T2D may be present.

D. Therapy Goals
1. Normalize ovulation and menses
2. Improve fertility in those who want to become pregnant
3. Limit clinical signs
4. Reduce progression to T2D (perhaps cardiovascular disease)

E. Nonpharmacologic Therapy
1. Weight loss (5%–10%) important in patients who are overweight or have obesity
2. Mechanical hair removal for hirsutism

F. Pharmacotherapy
1. Fertility improvement
   a. Clomiphene citrate
      i. Mechanism of action: Induces ovulation as a selective estrogen receptor modulator that improves LH-FSH secretion
      ii. Dosing
         (a) 50 mg/day for 5 days starting on the third or fifth day of the menstrual cycle
         (b) Increase to 100 mg if ovulation does not occur after first cycle of treatment.
         (c) Maximal daily dosage: 150–200 mg/day
      iii. Adverse effects: Flushing, GI discomfort, vision disturbances, vaginal dryness, multiple pregnancies
      iv. Drug of choice for infertility according to the Endocrine Society guideline
      vi. Improved ovulation and pregnancy rates when used in combination with metformin
   b. Gonadotropin (e.g., recombinant FSH) or recombinant gonadotropin-releasing hormone therapy with or without clomiphene
      i. Mechanism of action: Normalizes LH/FSH ratio to stimulate ovulation
      ii. Dosing: Many dosing strategies used
      iii. Adverse effects: Multiple pregnancies, ovarian hypertrophy, miscarriage, mood swings, breast discomfort
c. Letrozole
   i. Mechanism of action: Aromatase inhibitor prevents conversion of androgens to estrogen, which results in an increased secretion of FSH from the anterior pituitary; conflicting meta-analysis data on its effectiveness compared with clomiphene on pregnancy rates
   ii. Dosing: 2.5–5 mg daily
   iii. Adverse effects: Edema, sweating, constipation, nausea, arthralgias, headache

2. Symptomatic improvement
   a. Hormonal contraceptives (estrogen/progestin combination): Endocrine Society first-line therapy for menstrual abnormalities, hirsutism, or acne
   b. Metformin
      i. Effective for metabolic and glycemic abnormalities, if present, but only modestly effective for hirsutism
      ii. Alternative to hormonal contraception for irregular menses when hormonal contraceptives are contraindicated
      iii. Few data to support use for increased fertility (may improve pregnancy rate but not shown to improve rates of live births)
   c. Spironolactone
      i. Often added to hormonal contraceptives
      ii. Can help with hirsutism
   d. Pioglitazone: Questionable whether benefits outweigh risks in PCOS. Not recommended in Endocrine Society guidelines

VI. DIABETES MELLITUS

A. Consensus Recommendations
   2. American College of Endocrinology/AACE
   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. T1D
      a. Attributable to cellular-mediated β-cell destruction leading to insulin deficiency (insulin needed for survival)
      b. Accounts for 5%–10% of DM
      c. Formerly known as insulin-dependent diabetes and juvenile-onset diabetes
      d. Usually presents in childhood or early adulthood but can present in any stage of life
      e. Usually symptomatic with a rapid onset in childhood, but a slower onset can occur in older adults
      f. The ADA now recommends a staging of patients with T1D based on the degree of dysglycemia and symptoms.
         i. Stage 1: Multiple autoantibodies present but glucose concentrations are normal
         ii. Stage 2: Multiple autoantibodies present, glucose concentrations consistent with prediabetes (see criteria in text that follows), and patient is asymptomatic
         iii. Stage 3: Symptomatic and glucose concentrations consistent with diabetes (see criteria in text that follows)
2. T2D  
   a. Results primarily from insulin resistance in muscle and liver, with subsequent defect in pancreatic insulin secretion, though GI, brain, liver, and kidneys are all involved in the pathophysiology  
   b. Accounts for 90%–95% of diabetes mellitus  
   c. Formerly known as non–insulin-dependent diabetes or adult-onset diabetes  
   d. Often asymptomatic, with a slow onset over 5–10 years. Rationale for early, frequent screening of those at risk (see text that follows) and initial assessment for complications at diagnosis  
   e. Disturbing increased trends in T2D 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 can mimic T1D or T2D  
4. Gestational diabetes  
   a. Glucose intolerance occurring during pregnancy  
   b. Prevalence: 1%–14% of pregnancies (complicates about 4% of pregnancies)  
   c. Most common in third trimester  
5. Prediabetes  
   a. Impaired glucose tolerance  
   b. Impaired fasting glucose  
6. Other DM types  
   a. Genetic defects in β-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 T2D. Her fasting glucose concentration today is 212 mg/dL. Which is the best course of action?  
   A. Diagnose T2D and begin treatment.  
   B. Diagnose T1D and begin treatment.  
   C. Obtain another glucose concentration today.  
   D. Obtain another glucose concentration another day.  

C. Screening for DM  
1. T1D  
   a. Symptomatic patients  
   b. Asymptomatic patients at higher risk  
      i. Relatives with T1D  
      ii. Measure islet autoantibodies to assess risk of T1D.  
      iii. If screen is positive for antibodies, counsel on symptoms of hyperglycemia and risk of DM. Consider enrollment in observational study.  
2. T2D  
   a. Age 45 or older, repeat every 3 years if normal  
   b. Screen regardless of age 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. A1C is 5.7% or greater, impaired glucose tolerance, or impaired fasting glucose in previous testing

iii. History of PCOS

iv. HDL less than 35 mg/dL or TG greater than 250 mg/dL

v. Hypertension

vi. Women with a diagnosis of gestational diabetes

vii. High-risk ethnicity: African American, Latino, Native American, Asian American, Pacific Islander

viii. First-degree relative with T2D

ix. Physical inactivity

x. Insulin resistance conditions (e.g., severe obesity, acanthosis nigricans)

3. Gestational DM
   a. Screen at first prenatal visit for undiagnosed T2D in all patients with T2D risk factors present.
   b. Screen at 24–28 weeks’ gestation using OGTT.
   c. If a diagnosis of gestational DM is made, screen for diabetes 4–12 weeks after delivery.
   d. Continue to screen patients who have had gestational DM every 3 years for T2D for life.

D. DM Diagnosis

1. T1D and T2D 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 any of the tests listed earlier can be used 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 anemia, chronic malaria, sickle cell anemia, pregnancy, 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 T1D and normal or elevated early in T2D)
      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. “One-step” approach: 75-g OGTT at 24–28 weeks’ 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
   c. “Two-step” approach: 50-g OGTT (nonfasting) at 24–28 weeks’ gestation
      i. If 1 hour after 50-g OGTT is less than 140 mg/dL, no further workup
      ii. If 140 mg/dL or greater, do additional fasting OGTT using 100 g (see the ADA guidelines for
diagnostic glucose criteria)

3. Prediabetes diagnosis (high-risk population)
   a. Impaired fasting glucose: FPG 100–125 mg/dL
   b. Impaired glucose tolerance: 2-hour plasma glucose after OGTT (75 g) of 140–199 mg/dL
   c. A1C 5.7%–6.4%

Patient Case
7. A 56-year-old man with T2D takes metformin 1000 mg twice daily. He has no other chronic diseases or his-
tory of cardiovascular disease. His current vital signs and laboratory results are as follows: blood pressure
148/78 mm Hg, heart rate 74 beats/minute, and A1C 6.9%. Which agent, if added to the current regimen, has
the most potential to reduce both microvascular and macrovascular complications in this patient?
   A. Insulin glargine.
   B. Lisinopril.
   C. Glyburide.
   D. Niacin.

E. Goals of Diabetes Management in Nonpregnant Adults
   1. Primary goal: 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/AACE 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, longstanding 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.
      c. Peak postprandial glucose (1–2 hours after a meal) less than 180 mg/dL
5. Non-glycemic therapy goals
   a. Blood pressure less than 140/90 mm Hg (according to the 2018 ADA guidelines)
      i. Lower blood pressure goals (e.g., less than 130/80 mm Hg) may be appropriate in patients at high risk of cardiovascular disease.
      ii. ACC/AHA hypertension guidelines recommend less than 130/80 mm Hg.
   b. Lipids
      i. ADA: No specific LDL goal is currently recommended.
      ii. ACC/AHA 2018 guidelines suggest lowering LDL by 30%–49% in patients with diabetes age 40–75 and by at least 50% if at higher risk, e.g. age 50-75 or patient has other risk factors.
      iii. No specific TG or HDL goals are currently recommended.

F. Goals for Gestational Diabetes
   1. Primary goal: 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, T2D after pregnancy
      b. Fetus/child: Macrosomia, hypoglycemia, jaundice, respiratory distress syndrome

G. Benefits of Optimizing Diabetes Management in Nonpregnant Adults
   1. Glycemic control
      a. Reduces the risk of developing retinopathy, nephropathy, and neuropathy in T1D and T2D
      b. Prospective studies, specifically designed to assess optimizing glycemic control and effect on cardiovascular events, have shown little or no reduction in cardiovascular outcomes.
      c. However, the “legacy” effect in the Diabetes Control and Complications Trial of T1D and the UK Prospective Diabetes Study of T2D suggests early control has future cardiovascular benefit.
      d. No profound benefit of aggressive glycemic control in T2D (A1C less than 6.5%)  
   2. Blood pressure control: Reduction in both macrovascular and microvascular complications

Patient Case
8. A 21-year-old patient (weight 80 kg) is given a diagnosis of T1D after the discovery of elevated glucose concentrations (average 326 mg/dL), and the patient has signs and symptoms of hyperglycemia. Which is the most appropriate initial dose of rapid-acting insulin before breakfast for this patient? (Assume a TDI regimen of 0.5 unit/kg/day.)
   A. 2 units.
   B. 4 units.
   C. 7 units.
   D. 14 units.

H. Therapeutic Management of T1D (Table 3)
   1. Insulin agents
      a. Categorized on the basis of duration after injection
         i. Rapid acting: Insulin aspart (two formulations), lispro, glulisine, and inhaled insulin
ii. Short acting: Regular human insulin
iii. Intermediate acting: Neutral protamine Hagedorn (NPH)
iv. Long acting: Insulin glargine, degludec and detemir

b. Combination insulin products (intermediate or long acting, regular or rapid acting): 70/30, 75/25, insulin degludec and glargine available in combination with GLP-1 agonist

c. Higher-concentration insulin products
i. More commonly used in patients with T2D needing significant daily insulin doses
ii. U-300 glargine (300 units/mL), U-200 degludec (200 units/mL), U-200 lispro (200 units/mL), U-500 regular insulin (500 units/mL)

Table 3. Characteristics of U-100 (100 units/mL) Insulins

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug Name</th>
<th>Clarity</th>
<th>Onset (min)</th>
<th>Administration Time Before Meal</th>
<th>Peak (hr)</th>
<th>Duration (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid acting</td>
<td>Aspart</td>
<td>Clear</td>
<td>15–30</td>
<td>15 (inhaled insulin at beginning of meal)</td>
<td>1–3</td>
<td>2–5</td>
</tr>
<tr>
<td></td>
<td>Lispro</td>
<td></td>
<td></td>
<td>(shorter with inhaled)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glulisine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhaled insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short acting</td>
<td>Regular</td>
<td>Clear</td>
<td>30–60</td>
<td></td>
<td>2–3</td>
<td>4–6</td>
</tr>
<tr>
<td>Intermediate acting</td>
<td>Neutral protamine Hagedorn</td>
<td>Cloudy</td>
<td>1–2</td>
<td>N/A</td>
<td>4–8</td>
<td>10–20</td>
</tr>
<tr>
<td>Long acting</td>
<td>Detemir</td>
<td>Clear</td>
<td>2–4</td>
<td></td>
<td>6–8</td>
<td>6–24</td>
</tr>
<tr>
<td></td>
<td>Glargine</td>
<td></td>
<td>1–2 hr</td>
<td>“Peakless”</td>
<td>“Peakless”</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Degludec</td>
<td></td>
<td>1–2 hr</td>
<td></td>
<td></td>
<td>24–42</td>
</tr>
</tbody>
</table>

*The times given depend on the source of data and intersubject variability. N/A = not applicable.

d. Glycemic target
i. Regular- and short-acting insulins target postprandial glucose concentrations.
ii. Intermediate- and long-acting insulins target fasting glucose concentrations.

e. 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 is given before the morning meal. Two-thirds of this is given as NPH, and one-third is given as regular insulin.
ii. One-third of TDI is given before the evening meal. Again, two-thirds of this is given as NPH, and one-third is given as regular insulin. Alternative is regular given before evening meal and NPH at bedtime.

iii. Advantages: Daily insulin injection frequency two or three times daily and less expensive than newer insulins
iv. Disadvantages: Does not mimic natural insulin secretion pattern; prone to hypoglycemic events
d. Basal-bolus insulin therapy (i.e., physiologic insulin therapy)
   i. Use insulin analogs to better mimic natural insulin secretion patterns
   ii. Use long-acting basal insulin to prevent ketosis and control FPG
   iii. Use bolus insulin to control postprandial hyperglycemia
   iv. Basal insulins: Insulin glargine or degludec once daily or insulin detemir once or twice daily
   v. Bolus insulins: Rapid-acting insulin (can use short-acting insulin)
   vi. Basal requirements are typically 50% of estimated TDI.
   vii. Bolus requirements are typically 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. Requires significant patient education in food carbohydrate estimates
      (c) Alternative bolus requirement (Rule of 500): Dividing 500 by TDI will estimate the amount of carbohydrates (in grams) that 1 unit of a rapid-acting insulin will cover.
   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 that the same process of basal-bolus insulin therapy can apply to a patient with T2D 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/TDI = milligrams per deciliter of glucose lowering per 1 unit of rapid-acting insulin
      (a) For example, if TDI is 60 units, 1800/60 = 30, suggesting that 1 unit of rapid-acting insulin will reduce BG concentrations by 30 mg/dL.
      (b) Also called insulin sensitivity factor
      (c) Alternative: “1500 rule” when using regular human insulin (i.e., 1500/TDI)
   iii. More patient-specific than traditional sliding-scale insulin

f. Continuous subcutaneous insulin infusion (insulin pump)
   i. Device allows patient-specific hourly basal dosing and bolus insulin dosing.
   ii. Uses rapid-acting insulins
   iii. Requires patient education and carbohydrate counting
   iv. Used in conjunction with continuous glucose monitoring devices. Technology is rapidly advancing.

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 dosage or patient behavior accordingly.
   v. Same process for treating T2D applies (see text that follows)

3. Amylin analog
   a. Mechanism of action: Amylin is cosecreted with insulin and has effects similar to those of GLP-1 described in the text that follows.
   b. Pramlintide is currently the only agent in this class available in the United States. Pramlintide can be used in either T1D or T2D as adjunctive therapy in patients receiving insulin.
   c. Dosing
i. T1D
   (a) Initial: 15 mcg subcutaneously immediately before main meals
   (b) Must reduce dosage of preprandial rapid-acting, short-acting, or combination insulin
       products by 50%
   (c) Maximal daily dosage is 60 mcg with each meal.
   (d) Dosage should be titrated in 15-mcg increments, as tolerated, but no more rapidly than
       every 3 days.
ii. T2D
   (a) Initial: 60 mcg subcutaneously immediately before main meals
   (b) Must reduce preprandial insulins by 50%
   (c) Maximal daily dosage: 120 mcg with each meal
   (d) Dosage 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 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. Boxed warning for severe hypoglycemia, especially in patients with T1D
   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. Effective at controlling postprandial glucose excursions

Patient Cases
9. A 55-year-old man with T2D for 6 months has been receiving metformin 1000 mg twice daily since his diag-
nosis. His A1C today is 8.2%. His morning fasting blood glucose (FBG) readings are consistently at goal. His
after-meal glucose readings average 210–230 mg/dL. The patient states that he is worried about his weight and
does not want to add a medication that might increase it. Which would be most appropriate for this patient?
   A. Glyburide.
   B. Liraglutide.
   C. Pioglitazone.
   D. Insulin glargine.

10. A 66-year-old man has had T2D for 4 years. His A1C today is 7.7%. He has altered his diet and states that he
    has been exercising regularly for months. He takes metformin 1000 mg twice daily. Which would best 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 T2D

1. Given the progressive nature of T2D, a stepwise approach is usually needed.

2. ADA treatment 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 contraindicated or adverse effects preclude its use or if improvements in exercise and diet early after diagnosis fail to control hyperglycemia. (Consider combination therapy of metformin with the medications listed in the text that follows if baseline A1C is 1.5% or greater above personal goal A1C.)

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. Existing comorbidities
      i. Cardiovascular disease: Consider GLP-1 agonist or SGLT-2 inhibitor
      ii. Heart failure or chronic kidney disease: Consider SGLT-2 inhibitor
   c. Risk of hypoglycemia
   d. Effects on weight
   e. Adverse effect profile
   f. Cost
   g. Oral or injection patient preference

5. Sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose cotransporter-2 (SGLT-2) inhibitors, GLP-1 agonists, and basal insulin are preferred to less efficacious options or agents with a higher adverse risk profile.

6. Adding injectable medications to existing oral DM agents
   a. 2018 ADA updated report recommends GLP-1 agonists as preferred to insulin unless extreme or symptomatic hyperglycemia is present.
      i. Similar A1C reduction between GLP-1 agonists and insulin therapies
      ii. GLP-1 agonists have a lower risk of hypoglycemia and are associated with weight loss.
   b. Consider addition of a basal insulin / GLP-1 agonist combination or basal/bolus insulin regimen when significant hyperglycemia exists. 2018 ADA updated report suggests adding either early in therapy if:
      i. A1C greater than 10% or
      ii. A1C is greater than 2% above goal
   c. Weight-based dosing: For example, 0.1–0.2 unit/kg/day of basal insulin (higher dosages if significant hyperglycemia exists)
   d. Can increase basal insulin according to fasting glucose concentrations
   e. Can add GLP-1 agonist or SGLT-2 inhibitor if weight gain is a concern or bolus insulin to one or more meals if postprandial glucose is a concern after initiating basal insulin
   f. Insulin secretagogues should be lowered in dosage or discontinued altogether when bolus insulin added to reduce risk of hypoglycemia
   g. Thiazolidinediones should be lowered or discontinued when basal or bolus insulin is added to the regimen because of the increased risk of edema.

7. 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/regulat insulin or basal-bolus approach similar to that in T1D described earlier
   b. The TDI requirements in T2D are usually much higher than in T1D because of insulin resistance.
8. Changing from NPH to long-acting insulin
   a. If adequate glycemic control is already attained, initiate insulin glargine at 80% of total daily NPH dose.
   b. Detemir and degludec can be initiated by a unit-to-unit conversion. Some patients may require higher daily insulin dosages after conversion, but this is determined by glycemic response.

J. Therapeutic Agents in T2D
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 concentrations (monitor periodically), 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) Historically contraindicated if SCr 1.5 mg/dL or greater in men and 1.4 mg/dL or greater in women or reduced creatinine clearance (CrCl)
         b) In 2016, the FDA suggested that eGFR be used as a measure of kidney function rather than creatinine alone. Discontinue if eGFR is less than 30 mL/minute/1.73 m², and initiating if eGFR is 30–45 mL/minute/1.73 m² is not recommended. Assess benefit of continuing use in patients already prescribed metformin if eGFR is 30–45 mL/minute/1.73 m² and consider a 50% dose reduction.
      c) Monitor renal function every 3–6 months in patients with eGFR of 45–60 mL/minute/1.73 m² and every 3 months if 30–45 mL/minute/1.73 m²
      ii. Age 80 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 in patients with eGFR of 30–60 mL/minute/1.73 m² if undergoing procedures using iodinated contrast dye because of risk of nephrotoxicity. Reinitiate after 48 hours and after normal SCr 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 β-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). Dosage titration: Can increase at weekly intervals, as necessary

d. Adverse effects
   i. Common: Hypoglycemia, weight gain
   ii. Less common: Rash, headache, nausea, vomiting, photosensitivity
   iii. Rare: Lactic acidosis

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 (Table 4)
   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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dosage</th>
<th>Maximum Daily Dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide (not micronized)</td>
<td>2.5–5.0 mg once or twice daily</td>
<td>20</td>
</tr>
<tr>
<td>Glyburide (micronized)</td>
<td>1.5–3 mg once or twice daily</td>
<td>12</td>
</tr>
<tr>
<td>Glipizide</td>
<td>5 mg once or twice daily (once daily with extended release)</td>
<td>40 (little improved efficacy &gt; 20 mg/day)</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>1–2 mg once daily</td>
<td>8</td>
</tr>
</tbody>
</table>

3. Meglitinides
   a. Mechanism of action: 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 dosage: 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 concentrations
   g. Efficacy
      i. 0.5%–1.5% A1C reduction (repaglinide reduces A1C more than nateglinide)
      ii. Most effective on postprandial glucose excursions
4. Thiazolidinediones (often called glitazones or TZDs)
   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 who are 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.
   c. Dosing
      i. Pioglitazone
         (a) Initial: 15 mg once daily
         (b) Maximal daily dosage: 45 mg
      ii. Dosage titration is slow, and the maximal effect of a dosage change may not be observed for 8–12 weeks.
   d. Adverse effects
      i. Weight gain
      ii. Fluid retention (particularly peripheral edema) is worse with insulin use and is dose-dependent. Edema is less responsive to diuretic therapy. Macular edema can result.
      iii. Risk of proximal bone fractures; use caution in patients with existing osteopenia or osteoporosis (discontinuation reduces risk)
      iv. Possible risk of bladder cancer with pioglitazone (dosage and duration of use dependent). Data are contradictory.
      v. Increased risk of heart failure
         (a) Boxed warning
         (b) More than a 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, but pioglitazone has a more favorable effect in reducing LDL and TG than does rosiglitazone.

5. DPP-4 inhibitors
   a. Mechanism of action: Inhibit 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 dosage with CrCl of 30–50 mL/minute/1.73 m² to 50 mg once daily.
         (b) Reduce dosage with CrCl less than 30 mL/minute/1.73 m² to 25 mg once daily.
      ii. Saxagliptin: 5 mg once daily
         (a) Reduce dosage with CrCl of 50 mL/minute/1.73 m² or less to 2.5 mg once daily.
         (b) Reduce dosage 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 dosage with CrCl of 30–60 mL/minute/1.73 m² to 12.5 mg once daily.
   (b) Reduce dosage with CrCl less than 30 mL/minute/1.73 m² to 6.25 mg once daily.

c. Adverse effects
   i. Upper respiratory and urinary tract infections, headache, severe joint pain
   ii. Hypoglycemia with monotherapy is minimal, but frequency is increased with concurrent sulfonylurea therapy (can lower dosage of sulfonylurea when initiating).
   iii. Sitagliptin has had some postmarketing reports of acute pancreatitis, angioedema, Stevens-Johnson syndrome, and anaphylaxis.
   iv. Safety studies of saxagliptin and, to a lesser extent, alogliptin (but not sitagliptin) have shown an increased risk of heart failure hospitalization (studies still pending on linagliptin). In 2017, the FDA recommended warnings to package labeling of all DPP-4 inhibitors.

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

6. 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
   b. Dosing
      i. Canagliflozin
         (a) 100 mg once daily before the first meal of the day
         (b) Maximal daily dosage: 300 mg
         (c) Reduce dosage with CrCl of 45–59 mL/minute/1.73 m² to 100 mg daily.
         (d) Discontinue or do not initiate if eGFR is less than 45 mL/minute/1.73 m².
      ii. Dapagliflozin
         (a) 5 mg once daily in the morning (with or without food)
         (b) Maximal daily dosage: 10 mg
         (c) Discontinue or do not initiate if eGFR is less than 60 mL/minute/1.73 m².
      iii. Empagliflozin
         (a) 10 mg once daily in the morning (with or without food)
         (b) Maximal daily dosage: 25 mg
         (c) Discontinue or do not initiate if eGFR is less than 45 mL/minute/1.73 m².
      iv. Ertugliflozin
         (a) 5 mg once daily in the morning (with or without food)
         (b) Maximal daily dosage: 15 mg
         (c) Discontinue or do not initiate if eGFR is less than 60 mL/minute/1.73 m².

c. Adverse effects
   i. Increased urination
   ii. Urinary tract infections (in 2016, the FDA strengthened warning in product labeling for dapagliflozin and canagliflozin)
   iii. Genital mycotic infections (more common in females)
   iv. Hypotension
   v. Increased hypoglycemia risk with concomitant insulin or insulin secretagogue
   vi. Class is linked with rare cases of euglycemic DKA.
   vii. Possible increased bone fracture risk, decreased bone mineral density, and foot or leg amputation with canagliflozin
d. Contraindications and precautions
   i. Significant renal impairment (varies by agent, as stated earlier)
   ii. Suggested to ensure euvoemia 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
   iii. Consider factors that could predispose the patient to acute kidney injury (e.g., low blood volume, chronic kidney insufficiency, heart failure, or medications that could alter kidney function).

e. Efficacy
   i. 0.3%–1.0% reduction in A1C
   ii. Effect on both fasting and postprandial glucose concentrations
   iii. Mild weight loss
   iv. Empagliflozin and canagliflozin can reduce cardiovascular morbidity in patients with T2D and established cardiovascular disease (FDA-approved label) and may improve renal outcomes.

Patient Case
11. A 66-year-old man is given a diagnosis today of T2D. Two weeks ago, his A1C was 7.5% and SCr was 1.8 mg/dL (estimated GFR 25 mL/minute/1.73 m²). 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 best to initiate?
   A. Linagliptin.
   B. Pioglitazone.
   C. Exenatide.
   D. Metformin.

7. 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, lixisenatide, and semaglutide
   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 dosage: 10 mcg twice daily
            (3) Dosage titration from 5 mcg 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) Dosage titration from 0.6 to 1.2 mg/day, if tolerated
         (c) Maximal daily dosage: 1.8 mg/day
iii. Lixisenatide (pen)
   (a) Initial dose: 10 mcg once daily for 14 days
   (b) Maintenance dose: 20 mcg once daily
iv. Dulaglutide (pen and single-dose syringe)
   (a) 0.75 mg subcutaneously once weekly
   (b) Dosage titration to 1.5 mg once weekly for additional glycemic control
v. Semaglutide (pen and single-dose syringe)
   (a) 0.25 mg subcutaneously once weekly
   (b) Dosage titration to 1 mg once weekly at monthly intervals for additional glycemic control
d. Adverse effects
   i. Nausea, vomiting, diarrhea 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/1.73 m² for either exenatide formulation; less specific for liraglutide. No dose adjustment necessary with semaglutide
   ii. History of severe GI tract disorder, particularly gastroparesis
   iii. History of pancreatitis
   iv. For liraglutide, semaglutide, dulaglutide, once-weekly exenatide: 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%–1.5% 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 than with twice-daily exenatide formulation
   iv. Modest weight loss
   v. Liraglutide, dulaglutide, and semaglutide shown to reduce some cardiovascular outcomes in high-risk patients, whereas exenatide and lixisenatide have not, question whether class effect
8. 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. Maximum daily dosage: 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 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. Might not be as effective in patients using low-carbohydrate diets

9. **Bile acid sequestrant:** Colesevelam is the only studied and approved 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. Colesevelam is thought to be an antagonist to the farnesoid X receptor, which subsequently reduces hepatic gluconeogenesis. By reducing bile acid absorption, colesevelam reduces farnesoid X receptor 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 or serum triglyceride concentrations greater than 500 mg/dL
      ii. Caution in patients with swallowing disorders (large pill), dysphasia, gastric mobility disorders, and serum triglyceride concentrations greater than 300 mg/dL
   f. **Efficacy:** 0.3%–0.5% reduction in A1C

10. **Bromocriptine**
    a. **Mechanism of action:** Not clearly understood. Agonist for dopamine receptor D₂ is thought to reset circadian rhythm, which can reduce caloric intake and storage. Other effects may be through α₁-antagonism, α₂-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 dosage: 4.8 mg
       iii. Titrate weekly by 0.8 mg/day as tolerated and according to response.
       iv. Tablet strength differs from 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) can limit the efficacy of both agents.
    e. **Efficacy (Table 5)**
       i. 0.1%–0.6% reduction in A1C
       ii. Possible cardiovascular benefit
Table 5. Comparison of Therapies for Type 2 Diabetes Hyperglycemia Added to Metformin

<table>
<thead>
<tr>
<th>Agent or Class</th>
<th>Primary Glycemic Effect</th>
<th>Benefits</th>
<th>Limitations and Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Fasting and prandial</td>
<td>Efficacy</td>
<td>Weight gain&lt;br&gt;Hypoglycemia risk&lt;br&gt;Hastens β cell dysfunction</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>Prandial</td>
<td>Prandial focus&lt;br&gt;Use in kidney impairment</td>
<td>Hypoglycemia risk&lt;br&gt;Weight gain&lt;br&gt;Mealtime dosing</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Fasting and prandial</td>
<td>Improved insulin sensitivity and pancreatic function&lt;br&gt;Low risk of hypoglycemia&lt;br&gt;Possible cardiovascular benefit Cost</td>
<td>Weight gain and edema&lt;br&gt;Risk of heart failure&lt;br&gt;Risk of osteoporosis&lt;br&gt;Possible bladder cancer risk?</td>
</tr>
<tr>
<td>α-Glucosidase inhibitor</td>
<td>Prandial</td>
<td>No systemic absorption&lt;br&gt;Prandial focus&lt;br&gt;Weight loss</td>
<td>GI adverse effect profile&lt;br&gt;Mealtime dosing&lt;br&gt;Modest A1C effect</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>Prandial</td>
<td>Well tolerated&lt;br&gt;Weight neutral</td>
<td>Possible pancreatitis risk?&lt;br&gt;Modest A1C effect&lt;br&gt;Possible increased heart failure risk (saxagliptin) Cost</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>Once- or twice-daily formulations have prandial focus&lt;br&gt;Once-weekly formulations affect both fasting and prandial</td>
<td>Greater effect on prandial glucose&lt;br&gt;Weight loss&lt;br&gt;Efficacy&lt;br&gt;Improves pancreatic function?&lt;br&gt;Cardiovascular benefit (liraglutide, semaglutide, dulaglutide)</td>
<td>Nausea and vomiting&lt;br&gt;Injection-site effects&lt;br&gt;Questionable pancreatitis or thyroid cancer risk?&lt;br&gt;Cost</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Prandial</td>
<td>Lipid benefits&lt;br&gt;No systemic absorption</td>
<td>Large pill size and burden&lt;br&gt;GI adverse effect profile&lt;br&gt;Small decrease in A1C&lt;br&gt;Avoid with high TG</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Fasting and prandial</td>
<td>Low risk of hypoglycemia&lt;br&gt;Possible cardiovascular benefit</td>
<td>Small decrease in A1C&lt;br&gt;Central nervous system adverse effects</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Fasting and prandial</td>
<td>Low risk of hypoglycemia&lt;br&gt;Efficacy&lt;br&gt;Weight loss&lt;br&gt;Possible heart failure and renal benefit</td>
<td>Urinary tract and genital infections&lt;br&gt;Diuresis&lt;br&gt;Euglycemic DKA?</td>
</tr>
<tr>
<td>Amylin agonist</td>
<td>Prandial</td>
<td>Modest weight loss&lt;br&gt;Efficacy on postprandial glucose</td>
<td>High risk of hypoglycemia&lt;br&gt;Must be taken with insulin&lt;br&gt;Frequent injections&lt;br&gt;Injection-site effects&lt;br&gt;GI adverse effects</td>
</tr>
<tr>
<td>Insulin</td>
<td>Basal: Fasting&lt;br&gt;Bolus: Prandial</td>
<td>Significant A1C reduction&lt;br&gt;Flexibility in dosing strategies and titration</td>
<td>Hypoglycemia&lt;br&gt;Weight gain&lt;br&gt;Injection-site effects</td>
</tr>
</tbody>
</table>

DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP = glucagon-like peptide; SGLT = sodium glucose cotransporter.

K. Treatment of Inpatient DM (non–critically ill population)
   1. Joint guidelines from the ADA and AACE. The Endocrine Society also has guidelines (2016 ADA recommendations added new subsection dedicated to the issue).
   2. Strong association between admission hyperglycemia and worse inpatient outcomes and length of stay. Outcomes are worse in those who have stress-related hyperglycemia or are not known to have diabetes previously.
   3. Glycemic goals
      a. Less than 140 mg/dL fasting or premeal
      b. Less than 180 mg/dL random glucose
   4. Treatment
      a. Assess glucose concentrations before meals and at bedtime, if eating (every 4–6 hours if taking nothing by mouth [NPO]).
      b. Threshold for initiating therapy is 180 mg/dL or greater.
      c. According to the guidelines, subcutaneous insulin administration is the most practical way to improve hyperglycemia.
      d. Oral diabetes agents are generally not recommended unless the patient is clinically stable and eating regularly, and no significant precautions or contraindications for their use exist.
      e. Use of sliding-scale insulin alone is not recommended.
      f. Basal-bolus insulin therapy as described earlier in the treatment of T1D is recommended unless the patient is NPO. If NPO, use basal insulin alone

VII. TREATMENT OF DIABETES MELLITUS COMPLICATIONS

Patient Case
12. A patient with newly diagnosed T2D 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/1.73 m². 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 patient-specific but can include anxiousness, sweating, nausea, tachycardia, hunger, and clammy skin.
   3. Consequences of significant hypoglycemia are most worrisome in the very young, older adults, and those with established heart disease.
   4. Classification (according to the updated ADA recommendations)
      a. Level 1: Plasma glucose of 70 mg/dL or less with or without symptoms
      b. Level 2: Clinically significant hypoglycemia: Plasma glucose less than 54 mg/dL
      c. Level 3: A severe event characterized by altered mental and/or physical status requiring assistance
5. Treatment
   a. Mild to moderate hypoglycemia
      i. Oral ingestion of 15–20 g of glucose or equivalent
      ii. Repeat glucose concentration in 15 minutes and, if still less than 70 mg/dL, repeat ingestion of glucose.
      iii. Once glucose is normalized, ingest snack or meal.
   b. Clinically significant hypoglycemia (altered consciousness, needs assistance from others)
      i. Glucagon 1 mg intramuscularly
      ii. Intravenous dextrose if patient does not respond to glucagon
      iii. Raise glucose targets for several weeks.

B. Diabetic Ketoacidosis
   1. More common in T1D but can occur in T2D
   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 decrease 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 of 150–200 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 T2D and after 5 or more years in T1D.
   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 3–6 months is consistent with a diagnosis of albuminuria
   d. The ADA in 2013 no longer uses the terms microalbuminuria and macroalbuminuria.
2. Estimated CrCl yearly
3. ACE inhibitors or ARBs are considered the initial treatment of choice if urine albumin/creatinine concentrations are greater than 30 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 T2D and after 5 or more years in T1D.
2. Frequency can be reduced to every 2–3 years after one or more normal examinations.
3. Appropriately control glucose concentrations, cholesterol, and blood pressure.
4. Severe forms of retinopathy (e.g., proliferative retinopathy, macular edema) can be treated with intravitreal steroids or antivascular endothelial growth factor with or without photocoagulation.

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
   a. Screen after 5 years in T1D and at diagnosis in T2D, then yearly thereafter
   b. Diminished sensitivity is a significant risk factor for diabetes-related foot ulcers and increases the need for frequent visual inspection by patients, if it exists.
3. Symptoms are patient-specific but can include numbness, burning, tingling sensation, or pain.
4. Treatment of neuropathies should focus on glycemic control to minimize disease progression. Therapies for symptomatic improvement do not prevent progression.
5. Neuropathic pain therapy
   a. New ADA recommendations in 2017
      i. Consider duloxetine or pregabalin as first-line agents (according to clinical trial data, and both agents are approved for the indication).
      ii. Gabapentin is an acceptable alternative if cost is an issue to the patient.
   b. Tricyclic antidepressants (amitriptyline, desipramine)
      i. Effective but limited because of anticholinergic effects; some recommend using secondary amine tricyclic antidepressants (e.g., desipramine, nortriptyline) because they may have less anticholinergic effect than tertiary amines (e.g., amitriptyline, imipramine)
      ii. Daily dose is less than doses used for depression.
   c. Anticonvulsants (gabapentin, lamotrigine, pregabalin)
      i. Comparative data on gabapentin and pregabalin against tricyclic antidepressants show similar efficacy with fewer adverse effects. Adverse effect profile is still significant (e.g., fatigue, dizziness).
      ii. Pregabalin is the only anticonvulsant approved for use in DM neuropathic pain.
   d. Selective serotonin reuptake inhibitor/selective serotonin and norepinephrine reuptake inhibitor (duloxetine, paroxetine, citalopram)
      i. Duloxetine is the only approved agent in this category.
ii. Duloxetine data compared with amitriptyline data show similar efficacy and expected higher anticholinergic adverse effects with amitriptyline.
iii. Duloxetine may provide better pain reduction, with tolerability similar to that of pregabalin.

e. Tramadol/acetaminophen: As effective as gabapentin; different adverse effect profile
f. Opioids: Tapentadol extended release is the only approved agent in this class; no head-to-head efficacy studies

6. Gastroparesis therapy
   a. Autonomic neuropathy causes nausea and vomiting after meals because of delayed gastric emptying.
   b. Nonpharmacologic strategies
      i. More frequent but smaller meals
      ii. Homogenize food
      iii. Decrease fat and fiber in diet
   c. Pharmacologic treatment
      i. Metoclopramide: 10 mg before meals; risk of tardive dyskinesia or extrapyramidal reactions, chronic use should assess the benefit-risk of continued therapy
      ii. Erythromycin: 40–250 mg before meals for up to 1 month

F. Cardiovascular Disease
1. Most common cause of morbidity and mortality and health care expenditures in DM complications
2. Proper DM management should always focus on cardiovascular disease risk reduction (review cardiovascular chapters).
3. Stress and continually assess the blood pressure and lipid goals described earlier.
4. Blood pressure management
   a. Often requires more antihypertensive medications
   b. Hypertensive regimen should include an ACE inhibitor, ARB, dihydropyridine calcium channel blocker, or thiazide-like diuretic.
   c. If both hypertension and increased urine albumin excretion are present, first-line therapy is an ACE inhibitor or an ARB.
   d. Administration of at least one antihypertensive in the evening may improve blood pressure and reduce cardiovascular outcomes.
5. Lipid management (according to the ADA)
   a. Assess fasting lipid profile annually or as needed to monitor adherence.
   b. Statin therapy recommendations are based on age and cardiovascular risk.
      i. Moderate-dose statin therapy is recommended for all patients age 40 and older without cardiovascular risk factors (e.g., LDL of 100 mg/dL or greater, high blood pressure, smoker, overweight or obese).
      ii. High-dose statin therapy is recommended for those age 40–75 with existing cardiovascular risk factors (moderate- or high-dose statin if older than 75).
      iii. High-dose statin therapy is recommended for all patients with existing cardiovascular disease (e.g., previous cardiovascular event or acute coronary syndrome). Consider adding non-statin therapy if LDL remains elevated.
      iv. For patients with acute coronary syndrome and LDL greater than 50 mg/dL who cannot tolerate a high-dose statin, consider a moderate-dose statin plus ezetimibe.
      v. Statin doses are consistent with the ACC/AHA lipid guidelines.
6. Antiplatelet therapy
   a. Low-dose aspirin (75–162 mg/day)
      i. With existing cardiovascular disease
      ii. For primary prevention if at an increased cardiovascular risk (historically includes most patients, regardless of sex, 50 and older 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

VIII. OTHER DIABETES MEDICATION ISSUES

A. Former FDA Risk Evaluation and Mitigation Strategy for Rosiglitazone (removed November 2013)
   1. The strategy limited the use and distribution of rosiglitazone because of concerns for increased myocardial events.
   2. Subsequent review of clinical trial data suggests no increased risk of myocardial infarction, resulting in removal of strategy.
   3. Despite the removal of the strategy, rosiglitazone remains unavailable.

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
   3. Cardiovascular safety data for many of the newer DPP-4 inhibitors, GLP-1 agonists, insulins, and SGLT-2 inhibitors are still pending.

IX. DIABETES INSIPIDUS

A. Diabetes insipidus (DI) is usually a result of decreased production of antidiuretic hormone, also known as vasopressin, in central DI, or a lack of antidiuretic hormone effect in the kidneys (nephrogenic DI).

B. Classification
   1. Central or neurogenic
      a. Idiopathic
      b. Trauma (brain injury)
      c. Neoplasm
      d. Hypodipsia
      e. Genetic abnormality
2. Nephrogenic
   a. Genetic abnormality
   b. Acquired (more common)
      i. Drug induced (e.g., lithium, amphotericin B, foscarnet, cidofovir)
      ii. Kidney disease (e.g., polycystic kidney disease, obstruction)
      iii. Electrolyte disorder (hypercalcemia, hypokalemia)

C. Diagnosis
   1. Elevated urine volume (greater than 3 L/day)
   2. Decreased urine osmolarity (less than 200 mOsm/kg)
   3. Response to water deprivation (may help differentiate between nephrogenic and central etiology in non–critically ill patients)

D. Signs and Symptoms
   1. Polydipsia
   2. Polyuria or nocturia
   3. Weakness or lethargy
   4. Confusion or delirium (if severe)

E. Treatment
   1. Treat underlying cause, if known.
   2. Central DI
      a. Desmopressin: 5–20 mcg intranasally once or twice daily
      b. Adjunctive therapies: Chlorpropamide, carbamazepine
   3. Nephrogenic DI
      a. Thiazide diuretic
      b. Dietary sodium restriction
      c. Indomethacin
REFERENCES

Thyroid Disorders

Pituitary Gland Disorders

Adrenal Gland Disorders

Obesity


Polycystic Ovary Syndrome


Diabetes Mellitus and Insipidus


ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: D**

Given this patient’s reluctance to undergo ablative therapy, the most common treatment for Graves disease, oral therapy is warranted. Methimazole (Answer D) is recommended over propylthiouracil (Answer B) because it is associated with a lower risk of hepatotoxicity, though 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; although β-blockers might provide some symptomatic relief, they would do little to stabilize this patient’s thyroid concentrations.

2. **Answer: A**

This patient has hypothyroidism, given her elevated TSH and low free T₄, caused by Hashimoto disease. Levothyroxine (Answer A) 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 used to treat hyperthyroidism.

3. **Answer: D**

Fluoxetine (Answer D), a selective serotonin reuptake inhibitor, can cause drug-induced hyperprolactinemia. Answer A is incorrect because β-blockers are not associated with an elevated risk of this condition. Given the patient’s normal pituitary and thyroid tests, Answer B, prolactin-secreting adenoma, is probably incorrect. Answer C is incorrect because pregnancy is not associated with an elevated risk of this condition.

4. **Answer: D**

Because the patient’s aldosterone/renin ratio and blood pressure are high, hyperaldosteronism (Answer D) is the most likely disease listed. Cushing syndrome and hyperaldosteronism can be secondary causes of hypertension. In this case, the patient’s free 24-hour urine cortisol is normal but would be elevated if he had Cushing syndrome, making Answer A incorrect. Answer B is incorrect because Addisons 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, at least 5.9 kg (13 lb), Answer B, is necessary to continue therapy. The other answers provided are too low (Answer A) or exceed the 5% minimal expectation (Answers C and D).

6. **Answer: D**

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

7. **Answer: B**

Improved blood pressure control has been associated with a decrease in both microvascular (e.g., nephropathy) and macrovascular (e.g., myocardial infarction) complications. Answer B is the only option that directly affects blood pressure. Answers A and C address only hyperglycemia, which may improve microvascular complications but not macrovascular complications. Answer D, niacin, has not been shown to reduce either complication in patients with diabetes.

8. **Answer: C**

This patient’s TDI requirement is 40 units (80 kg × 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), making Answer C correct. The other three answers would provide either too much (Answer D is incorrect) or too little (Answers A and B are incorrect) estimated insulin at each meal.
9. **Answer: B**
The GLP-1 agonists mildly reduce weight when used to treat hyperglycemia in patients with T2D. Answer B, liraglutide, is the only GLP-1 provided. Each of the other options, a sulfonylurea (Answer A), a thiazolidinedione (Answer C), and insulin (Answer D), is associated with weight gain.

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 D adds to the existing metformin therapy and provides for a sufficient A1C reduction. 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 were having adverse effects from the original agent. Answer C, bromocriptine, would probably not provide sufficient glycemic control, given this patient’s current A1C.

11. **Answer: A**
In this case, initiation of medications for 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 patient’s A1C is not markedly elevated, and renal function does not need to be considered.

12. **Answer: A**
Current recommendations call for an ACE inhibitor or an ARB if a patient has elevated urinary albumin excretion. This patient’s blood pressure is at goal (less than 140/90 mm Hg), and urine albumin/creatinine is normal (less than 30 mg/g), making Answer A correct. No additional therapy is necessary. Answers B and C are incorrect because the patient’s blood pressure is well controlled and 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 and bolus insulin combination. This patient’s A1C is greater than 10%, and his fasting glucose is greater than 300–350 mg/dL. Answers A and C are not optimal because dual therapy with oral agents would probably not bring this patient to his glycemic goal. Answer B is also not optimal because the combination of a sulfonylurea and rapid-acting insulin would increase the risk of hypoglycemia and would probably not sufficiently reduce the A1C.

2. **Answer: A**  
The weight-based initial estimate of total basal insulin needs is 50% of the calculated TDI. The TDI for this patient is 26 units (0.4 unit/kg/day \( \times \) 65 kg). Half of that is 13 units. Answer C is incorrect; although insulin glargine is a basal insulin, the calculated dose would provide too much insulin and would likely cause significant hypoglycemia. Answers B and D are incorrect because they both use a type of insulin reserved for bolus and correctional insulin dosing. Answer A is correct because the estimated dose and type of insulin are appropriate.

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 and ACE inhibitors, making Answer C correct. Answer A (thiazide diuretic) is inappropriate because this class of medications is not as beneficial as agents that block the renin-angiotensin system. Answer B, a dihydropyridine calcium channel blocker, is incorrect for the same reason. Answer D, a non-dihydropyridine calcium channel blocker, is an alternative to agents that block the renin-angiotensin system but should not be used instead of these agents unless a patient has a contraindication.

4. **Answer: B**  
Unlike methimazole, propylthiouracil (Answer B) 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 disease is a result of hypothyroidism, not hyperthyroidism. Methimazole is dosed once daily, whereas propylthiouracil is usually dosed up to three times daily, making Answer D incorrect.

5. **Answer: A**  
Ketoconazole (Answer A) is used in patients with Cushing syndrome because it reduces cortisol synthesis. Answer B, spironolactone, is used in patients with hyperaldosteronism. Answer C is inappropriate because Cushing 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 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 dosage, it would probably not sufficiently reduce the A1C. Initiating insulin is the best option in this case because insulin can be used in patients with renal impairment and can be titrated to attain significant reductions in A1C (Answer C is correct).

7. **Answer: A**  
An older woman with heart disease should be initiated on a lower initial dose (Answer A) of levothyroxine. Answer B is the normal starting dose (i.e., 1.6 mcg/kg) but is probably too high an initial dose for an older adult with established heart disease. Answers C and 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 are not. For BG readings consistently not at goal, determine which insulin is most affecting the readings. In this case, the patient’s BG readings are consistently elevated at bedtime, which is probably caused by insufficient predinner prandial (i.e.,
bolus) insulin. Increasing the predinner rapid-acting insulin, Answer B, should effectively lower the bedtime concentrations. Changing the rapid-acting insulin at other times of the day would not help, making Answers A and D incorrect. Changing the patient’s basal insulin (glargine) would probably not help her bedtime BG and, because her FBG readings have been well controlled, 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 concentrations. Methimazole (Answer A) would be the preferred oral agent, given its dosing frequency and lower risk of hepatotoxicity compared with propylthiouracil (Answer C). Lugol’s solution is used only temporarily and not chronically, making Answer B incorrect. Answer D is not optimal; β-blockers, which may provide symptomatic relief, would not significantly affect her thyroid concentrations.

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

11. **Answer: D**
This patient has tried dieting and exercise, but these have failed to control her weight; thus, her current routine alone is inappropriate, 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 substance abuse, would not be the most favorable selection. Orlistat, Answer D, is the only agent listed to which this patient does not have a specific precaution or contraindication for its use.

12. **Answer: A**
This patient has now had two laboratory glycemic indicators (A1C and FBG) consistent with the diagnosis of diabetes, making Answer A correct. Answer B is probably incorrect because this patient has several risk factors for developing T2D, 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 (Answer C) is recommended for patients older than 40 with diabetes but without established cardiovascular disease. 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) would not be necessary. Answer D is incorrect because this patient does not need fibrate therapy; his HDL and TG are under control.