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 mellitus, obesity, polycystic ovary syndrome, and disorders of the thyroid, adrenal, and pituitary glands.
2. Compare and contrast the various therapeutic agents used in treating endocrine and metabolic disorders.
3. Select appropriate treatment and monitoring options for a given patient presenting with one of the above disorders.
4. Recommend appropriate therapeutic management for secondary complications from diabetes or thyroid disorders.

Self-Assessment Questions

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

1. A 66-year-old Hispanic man with a history of myocardial infarction, dyslipidemia, and hypertension received a diagnosis of type 2 diabetes mellitus (DM). After 1 month of exercise and dietary changes and no diabetic medications, his hemoglobin A_{1c} (A_{1c}) and fasting glucose concentration today are 11.5% and 322 mg/dL, respectively. He weighs 273 lb with a body mass index (BMI) of 42 kg/m^2. Which set of drugs is best to initiate?
   A. Metformin and glipizide.
   B. Glipizide and insulin glulisine.
   C. Pioglitazone and acarbose.
   D. Insulin detemir and glulisine.

2. A 21-year-old patient is given a diagnosis of type 1 DM after having been found to have elevated glucose concentrations (average 326 mg/dL) and is showing signs and symptoms of hyperglycemia. Her weight is 80 kg. Which is the most appropriate initial dose of rapid-acting insulin before breakfast for this patient? Assume a total daily insulin (TDI) regimen of 0.5 unit/kg/day.
   A. 2.
   B. 4.
   C. 7.
   D. 14.

3. A patient with type 2 DM has a blood pressure reading of 152/84 mm Hg, a serum creatinine of 1.8 mg/dL, and two recent spot urine albumin/creatinine concentrations of 420 and 395 mg/g. Which class of drugs (barring any contraindications) is best to initiate in this patient?
   A. Thiazide diuretic.
   B. Dihydropyridine calcium channel blocker.
   C. Angiotensin receptor blocker (ARB).
   D. Nondihydropyridine calcium channel blocker.

4. Regarding propylthiouracil (PTU) and methimazole in the treatment of hyperthyroidism, which statement is most appropriate?
   A. PTU is clinically superior in efficacy to methimazole.
   B. PTU may be associated with increased liver toxicity compared with methimazole.
   C. Both agents are equally efficacious in the treatment of Hashimoto's disease.
   D. Both medications should be administered three times/day.

5. Which medication is the most appropriate choice for a patient with a diagnosis of Cushing's syndrome who did not experience adequate symptom relief after surgical resection for a pituitary adenoma?
   A. Ketoconazole.
   B. Spironolactone.
   C. Hydrocortisone.
   D. Bromocriptine.

6. A 26-year-old Hispanic woman with polycystic ovary syndrome (PCOS) has been trying to become pregnant for more than 1 year. She has tried to lose weight during the past 6 months, and she is very concerned about using medications because of the risk of multiple children during the pregnancy. Which is the best drug to improve fertility in this patient?
   A. Clomiphene citrate.
   B. Recombinant follicle-stimulating hormone (FSH).
   C. Metformin.
   D. Spironolactone.

7. A 76-year-old woman recently given a diagnosis of Hashimoto's disease presents with mild symptoms of lethargy, weight gain, and intolerance to cold. Her thyroid-stimulating hormone (TSH) is 12.2 mIU/L, and her free thyroxine (T4) is below normal limits. Her current weight is 47 kg. She has a history of hypertension and 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 type 2 DM has an A_{1c} 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 very consistent in her carbohydrate intake at each meal. Her morning fasting plasma glucose (FPG) and premeal blood glucose (BG) readings have consistently averaged 112 mg/dL. Her bedtime readings are averaging between 185 and 200 mg/dL. Which is the best insulin adjustment to improve her overall glycemic control?
   A. Increase her prebreakfast aspart to 10 units.
   B. Increase her predinner aspart to 14 units.
   C. Increase her bedtime glargine to 65 units.
   D. Increase her prelunch aspart to 9 units.

9. A 53-year-old woman with a history of Graves disease underwent ablative therapy 3 years ago. She experienced significant symptom relief and became euthyroid. Her thyroid laboratory values today include TSH 0.12 mIU/L (normal 0.5–4.5 mIU/L) and a free T4 concentration of 3.8 g/dL (normal 0.8–1.9 ng/dL). She states that many of her previous symptoms have now returned but are mild. Which would be the most appropriate treatment option for her condition?
   A. Methimazole.
   B. Thyroidectomy.
   C. PTU.
   D. Metoprolol.

10. A 65-year-old man with type 2 DM for 6 years has been receiving metformin 1000 mg twice daily for the past 2 years. His A_{1c} today is 7.8%. His fasting morning BG readings are consistently at goal. His after-meal glucose readings average 190–200 mg/dL. Which option would be most appropriate for this patient?
   A. Increase metformin to 1000 mg three times/day.
   B. Add insulin glargine 10 units once daily.
   C. Switch 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/m^2. With dietary changes, she has lost 2 lb in 6 months. She exercises regularly but is unable to do more because she has two jobs and young children. She has a history significant for depression, type 2 DM, and substance abuse. Her current medications include metformin 1000 mg twice daily, aspirin 81 mg once daily, and sertraline 100 mg once daily. She is most concerned about weight loss. Which would be the best recommendation to help her lose weight?
   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/day with meals.

12. A 53-year-old Hispanic woman has a BMI of 44 kg/m^2 and a history of gestational diabetes. Her mother and sister both have type 2 DM. She had an A_{1c} of 7.4% 2 weeks ago. Her fasting glucose concentration today is 178 mg/dL. She is asymptomatic. Which is the best course of action?
   A. Diagnose type 2 DM and begin treatment.
   B. Diagnose type 1 DM and begin treatment.
   C. Obtain another A_{1c} today.
   D. Obtain another glucose concentration another day.

13. A 66-year-old man has a history of type 2 DM. His current therapy includes metformin 1000 mg twice daily, glyburide 10 mg twice daily, aspirin 81 mg once daily, and lisinopril 20 mg once daily. Today, his A_{1c} is 6.9%, blood pressure is 126/78 mm Hg, and fasting lipid panel is as follows: total cholesterol 212 mg/dL, low-density lipoprotein cholesterol (LDL-C) 128 mg/dL, high-density lipoprotein cholesterol (HDL-C) 45 mg/dL, and triglycerides (TG) 145 mg/dL. Which would be the most appropriate choice for this patient?

    A. Add insulin detemir 10 units once daily.
    B. Add hydrochlorothiazide (HCTZ) 25 mg once daily.
    C. Add atorvastatin 10 mg once daily.
    D. Add fenofibrate 145 mg once daily.

I. THYROID DISORDERS

Figure 1. Hypothalamus-pituitary-thyroid axis.[a]
[a]T4 is converted to T3 by peripheral tissue. Only unbound (free) thyroid hormone is biologically active.
T3 = triiodothyronine; T4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; - ve = negative feedback loop.

A. Classification
   1. Hyperthyroid disorders (thyrotoxicosis)
      a. Toxic diffuse goiter (Graves disease): Most common hyperthyroid disorder
         i. Autoimmune disorder
         ii. Thyroid-stimulating antibodies directed at thyrotropin receptors mimic TSH and stimulate triiodothyronine/thyroxine (T3/T4) production.
      b. Pituitary adenomas: Produce excessive TSH secretion that does not respond to normal T3 feedback
      c. Toxic adenoma: Nodule in thyroid, autonomous of pituitary and TSH
      d. Toxic multinodular goiter (Plummer's 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 doses, amiodarone therapy)
   2. Hypothyroid disorders
      a. Hashimoto's disease: Most common hypothyroid disorder in areas with iodine sufficiency
         i. Autoimmune-induced thyroid injury resulting in decreased thyroid secretion
         ii. Disproportionately affects women
      b. Iatrogenic: Thyroid resection or radioiodine ablative therapy for treatment of hyperthyroidism
      c. Iodine deficiency most common cause worldwide
      d. Secondary causes
         i. Pituitary insufficiency (failure to produce adequate TSH secretion, referred to by some as central or secondary hypothyroidism)
         ii. Drug induced (e.g., amiodarone, lithium)

B. Diagnosis
   1. Hyperthyroid disorders
      a. Elevated free T4 serum concentrations
      b. Suppressed TSH concentrations (except in TSH-secreting adenomas)
      c. If examination and history do not provide the exact etiology, radioactive iodine uptake may be employed.
         i. Radioactive iodine uptake elevated if thyroid gland is actively and excessively secreting T4 and/or T3: Graves disease, TSH-secreting adenoma, toxic adenoma, multinodular goiter
         ii. Radioactive iodine uptake is suppressed in disorders caused by thyroiditis or hormone ingestion.
      d. Can also assess for the presence of various thyroid-related antibodies (thyroid stimulating, thyrotropin receptor, or thyroperoxidase), thyroglobulin, and thyroid biopsy
   2. Hypothyroid disorders
      a. Decreased free T4 serum concentrations
      b. Elevated TSH concentrations, usually above 10 mIU/L (normal or low if central hypothyroidism is the etiology)
      c. Thyroid antibodies such as antithyroid peroxidase and antithyroglobulin autoantibodies
      d. Screen patients older than 60.

C. Clinical Presentation
   1. Hyperthyroid disorders
      a. Weight loss/increased appetite
      b. Lid lag
      c. Heat intolerance
      d. Goiter
      e. Fine hair
      f. Heart palpitations/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
   2. Hypothyroid disorders
      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)

D. Therapy Goals for Both Hyperthyroid and Hypothyroid Disorders
   1. Minimize or eliminate symptoms, improve quality of life
   2. Minimize long-term damage to organs.
      a. Hypothyroidism: Myxedema coma, heart disease
      b. Hyperthyroidism: Heart disease, arrhythmias, sudden cardiac death, bone demineralization, and fractures
   3. Normalize free T4 and TSH concentrations.

Patient Cases

1. A 63-year-old woman has Hashimoto's disease. Her thyroid laboratory values today include the following: TSH 10.6 mIU/L (normal 0.5–4.5 mIU/L) and a free T4 concentration of 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 would be considered the best drug for initial treatment of her condition?

   A. Levothyroxine.
   B. Liothyronine.
   C. Desiccated thyroid.
   D. Methimazole.

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

   A. Lugol's solution.
   B. Propylthiouracil.
   C. Atenolol.
   D. Methimazole.

E. Pharmacotherapy
   1. Hyperthyroidism
      a. Ablative therapy: Treatment of choice for Graves disease, toxic nodule, multinodular goiter: Radioactive iodine ablative therapy and surgical resection for adenomas based on patient preferences or comorbidities. Ablative therapy often results in hypothyroidism.
      b. Antithyroid pharmacotherapy usually reserved for:
         i. Awaiting ablative therapy or surgical resection
            (a) Depletes stored hormone
            (b) Minimizes risk of posttreatment hyperthyroidism because of thyroiditis
         ii. Not an ablative or surgical candidate (e.g., serious cardiovascular disease, candidate unlikely to be adherent to radiation safety)
         iii. When ablative therapy or surgical resection fails to normalize thyroid function
         iv. High probability of remission with oral therapy with Graves disease
            (a) Mild disease
            (b) Small goiter
            (c) Low or negative antibody titers
         v. Limited life expectancy
         vi. Moderate to severe active Graves ophthalmopathy
      c. Thioureas (i.e., PTU, methimazole)
         i. Mechanism of action: Inhibits iodination and synthesis of thyroid hormones; PTU may block T4/T3 conversion in the periphery as well
         ii. Dosing
            (a) PTU
               (1) Initial: 100 mg by mouth three times/day
               (2) Maximal: 400 mg three times/day
               (3) Once euthyroid, may reduce to 50 mg two or three times/day

(b) Methimazole
(1) Preferred agent for Graves disease according to the American Association of Clinical Endocrinologists (AACE) for most patients unless in first trimester of pregnancy; then use PTU
(2) Initial: 10–20 mg by mouth once daily
(3) Maximal: 40 mg three times/day
(4) Once euthyroid, may reduce to 5–10 mg/day
(c) Monthly dose titrations as needed (based on symptoms and free T4 concentrations); TSH may remain low months after starting therapy

iii. Adverse effects
(a) Hepatotoxicity issue with PTU (black box warning): AACE recommends baseline liver function tests.
(b) Rash
(c) Arthralgias, lupus-like symptoms
(d) Fever
(e) Agranulocytosis early in therapy (rare): AACE recommends baseline CBC (complete blood cell count); no routine monitoring recommended. May repeat if patient becomes febrile or develops pharyngitis

iv. Efficacy
(a) Slow onset in reducing symptoms (weeks). Maximal effect may take 4–6 months.
(b) Neither drug appears superior to the other in efficacy.
(c) On a milligram-to-milligram basis, methimazole is 10 times more potent than PTU.
(d) Remission rates low: 20%–30%. Remission defined as normal TSH and T4 for 1 year after discontinuing antithyroid therapy
(e) Therapy duration in Graves disease (oral agents not likely to cause remission in those with nodular thyroid disease):
(1) Usually 12–18 months, length of trial may not affect remission rate
(2) Consider trial off oral therapy if TSH is normal, antibody titers may help guide decision
(3) Monitor thyroid concentrations every 1–3 months for up to 6–12 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/day
(b) Maximal: 240–480 mg/day
iii. Adverse effects (see Hypertension section in Cardiovascular chapter)
iv. Efficacy
(a) Primarily used for symptomatic relief (e.g., palpitations, tachycardia, tremor, anxiety)
(b) Guidelines recommend use in elderly, symptomatic patients, and others with heart rates greater than 90 beats/minute. Consider using in all symptomatic patients.
(c) Poor remission rates: 20%–35%
(d) Primary role is treatment of thyroiditis, which is usually self-limiting, and for acute management of symptoms during thyroid storm (see below).
(e) Alternatives to β-blockers: Clonidine, nondihydropyridine calcium channel blocker

e. Iodines (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) Usual daily dose: 120–400 mg mixed with juice or water, split three times/day

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 surgery (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 size of the gland.
(c) Used postablative therapy (3–7 days) to inhibit thyroiditis-mediated release of stored hormone
(d) Used acutely in thyroid storm

2. Hypothyroidism
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 50–60 years of age, consider 50 mcg/day.
(3) In those with existing cardiovascular disease, consider 12.5–25 mcg/day.
(b) Usually dosed in the morning on an empty stomach 30–60 minutes before breakfast or at bedtime 4 hours after last meal; separate from other medications.
(c) Dose titration based 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 will be higher in pregnancy (separate guidelines available for treating thyroid disorders in pregnancy, if interested).
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/secondary hypothyroidism; obtain sample before daily dosing of levothyroxine
iv. Adverse effects
(a) Hyperthyroidism
(b) Cardiac abnormalities (tachyarrhythmias, angina, myocardial infarction)
(c) Linked to risk of fractures (usually at higher doses or oversupplementation)
v. Efficacy: If levothyroxine is properly dosed, most patients will maintain TSH and free T4 in the normal ranges and experience symptomatic relief.
vi. Considered drug of choice secondary to its adverse effect profile, cost, lack of antigenicity, and uniform potency
vii. Bioequivalency
(a) AACE recommends brand-name levothyroxine (none of the other thyroid preparations below are supported by AACE).
(b) Although legal, guidelines recommend against changing from brand to generic and vice versa. It is recommended to stay with one product throughout therapy.
(c) TSH concentrations in bioequivalence testing were never performed; small changes in T4 between products may result in significant changes in TSH. Pharmacokinetic studies were in normal subjects with normal thyroid function.
b. Liothyronine (synthetic T3), liotrix (synthetic T4/T3), desiccated thyroid are not recommended by leading professional organizations or clinical guidelines

F. Subclinical Hypothyroidism
   1. Definition: Elevated TSH (above upper limit of reference range) with normal T4. Often the result of early Hashimoto's disease
   2. Risk?
      a. TSH greater than 7.0 mIU/L in the elderly associated with increased risk of heart failure
      b. TSH greater than 10 mIU/L associated with increased risk of coronary heart disease
   3. Treatment of subclinical hypothyroidism is controversial because benefits in identified patients are inconclusive. There does appear to be an association between the use of levothyroxine and a reduction in heart disease in younger patients (40–70 years of age) but not in older patients (older than 70 years).
   4. Whom to treat
      a. TSH between 4.5 and 10 mIU/L and
         i. Symptoms of hypothyroidism
         ii. Antithyroid peroxidase antibodies present
         iii. History of cardiovascular disease, heart failure, or risk factors for such
      b. Initial daily doses of 25–75 mcg recommended
   5. If untreated, screen regularly for the development of overt hypothyroidism (decreased free T4 concentrations).

G. Subclinical Hyperthyroidism
   1. Definition: Low (below lower limit of reference range) or undetectable TSH with normal T4
   2. Risk?
      a. Associated with increased risk of atrial fibrillation in patients older than 60 years
      b. Associated with increased risk of bone fracture in postmenopausal women
      c. Conflicting data regarding mortality risk
   3. Treatment (based on 2011 guidelines) similar to treating overt hyperthyroidism
      a. Oral antithyroid drug-therapy alternative to ablative therapy in young patients with Graves disease
      b. β-Blockers may be of benefit to control cardiovascular morbidity, especially with atrial fibrillation.
   4. If untreated, screen regularly for the development of overt hyperthyroidism (increased free T4 concentrations).

H. 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 not adequate pretreatment)
   3. Presentation: Fever, tachycardia, vomiting, dehydration, coma, tachypnea, delirium
   4. Pharmacotherapy
      a. PTU
         i. Dose 500- to 1000-mg loading dose; then 250 mg every 4 hours
         ii. Blocks new hormone synthesis
      b. Iodide therapy 1 hour after PTU initiation (dosed as above) to block hormone release
      c. β-Blocker therapy: Esmolol commonly used (can use other agents [e.g., propranolol]) to control symptoms and blocks conversion of T4 to T3
      d. Acetaminophen as antipyretic therapy, if needed (avoid NSAIDs [nonsteroidal anti-inflammatory inhibitors] because of displacement of protein-bound thyroid hormones)
      e. Corticosteroid therapy: Prednisone 25–100 mg/day in divided doses (or equivalent doses of dexamethasone, hydrocortisone, etc.). Prophylaxis against relative adrenal insufficiency

I. Myxedema Coma
   1. Severe and life-threatening decompensated hypothyroidism. Mortality rate 30%–60%
   2. Precipitating causes: Trauma, infections, heart failure, medications (e.g., sedatives, narcotics, anesthesia, lithium, amiodarone)
   3. Presentation: Coma is not required and is uncommon despite terminology, altered mental state (very common), diastolic hypertension, hypothermia, hypoventilation

4. Pharmacotherapy
    a. Intravenous thyroid hormone replacement
        i. T4: 100- to 500-mcg loading dose, followed by 75–100 mcg/day, until patient can tolerate oral therapy. Lower the initial dose in frailer patients or in patients with established cardiovascular disease.
        ii. Some advocate the use of T3 over T4 given that T3 is more biologically active and T4/T3 conversion may be suppressed in myxedema coma. Cost and availability limit intravenous T3 use.
    b. Antibiotic therapy: Given common infectious causes, some advocate empiric therapy with broad-spectrum antibiotics.
    c. Corticosteroid therapy
        i. Hydrocortisone 100 mg every 8 hours (or equivalent steroid)
        ii. Can be discontinued if random cortisol concentration not found to be depressed

II. PITUITARY GLAND DISORDERS

Table 1. Basic Pituitary Gland (Anterior) Hormone Physiology

Anterior Pituitary Hormone	Primary Function(s)	Hypothalamic Stimulator	Primary Secretion Inhibitor
Growth hormone (GH)	Promote tissue growth	GH-releasing hormone	Somatostatin Increased IGF-1
Adrenocorticotropic hormone (ACTH)	Stimulate adrenal cortisol/ androgen release	Corticotropin-releasing hormone	Cortisol
Thyroid-stimulating hormone (TSH)	Metabolic stability	Thyrotropin-releasing hormone	T3
Prolactin	Regulate lactation	Thyrotropin-releasing hormone	Dopamine
Follicle-stimulating hormone	Maturation of ovarian follicles Sperm production	Gonadotropin-releasing hormone	Inhibin Estrogens
Luteinizing hormone	Secretion of sex steroids	Gonadotropin-releasing hormone	Estrogens/progestins Testosterone

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

A. Classification (focus on the common anterior pituitary disorders)
    1. Hypersecretory diseases
        a. Acromegaly and gigantism: Usually caused by growth hormone (GH)-secreting pituitary adenoma
        b. Hyperprolactinemia:
            i. Most common cause is prolactinomas (prolactin-secreting pituitary tumor).
            ii. Drug induced (e.g., serotonin reuptake inhibitors and some antipsychotics)
            iii. Central nervous system lesions
    2. Hyposecretory disease
        a. GH deficiency:
            i. Congenital abnormality caused by GH gene deletion, GH-releasing hormone deficiency
            ii. Other causes are pituitary aplasia, head trauma, and central nervous system infection.
            iii. Idiopathic
        b. Panhypopituitarism: Result of partial or complete loss of anterior and posterior pituitary function. Can be caused by primary pituitary tumor, ischemic necrosis of the pituitary, trauma from surgery, or irradiation. Results in adrenocorticotropic hormone (ACTH) deficiency, GH deficiency, hypothyroidism, gonadotropin deficiency

B. Diagnosis/Clinical Presentation
   1. Acromegaly
      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 not reliable given the pulsatile pattern of release in the body.)
      b. Clinical presentation (Note: Disease has a very slow onset, and many symptoms do not appear for years.)
         i. Excessive sweating
         ii. Osteoarthritis, joint pain, paresthesias, or neuropathies
         iii. Coarsening of facial features
         iv. Increased hand volume/ring size, increased shoe size
         v. Hypertension, heart disease, cardiomyopathy
         vi. Sleep apnea
         vii. Type 2 DM
   2. Hyperprolactinemia
      a. Elevated serum prolactin concentrations. May be challenging to find specific etiology (unless drug induced)
      b. Clinical presentation
         i. Amenorrhea, anovulation, infertility, hirsutism, and acne in women
         ii. Erectile dysfunction, decreased libido, gynecomastia, and reduced muscle mass in men
         iii. Headache, visual disturbances
   3. GH deficiency
      a. Decreased GH concentrations after provocative pharmacologic challenge (e.g., insulin, clonidine, GH-releasing hormone)
      b. Clinical presentation
         i. Delayed growth velocity/short stature
         ii. Central obesity
         iii. Immaturity of the face or prominence of the forehead

C. Therapy Goals
   1. Acromegaly: Reduce GH and IGF-1 concentrations, decrease mortality, improve clinical symptoms. Normal IGF-1 concentrations and suppressed GH concentrations post-OGTT
   2. Hyperprolactinemia: Normalize prolactin concentrations, normal gonadotropin secretion, and symptom relief
   3. GH deficiency: Increased growth velocity, increased final adult height when treating children

Patient Case

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

   A. Atenolol.
   B. Prolactin-secreting adenoma.
   C. Pregnancy.
   D. Fluoxetine.

D. Pharmacotherapy
   1. Treatment of choice is surgical resection of tumor if causative.
   2. Pharmacotherapy usually reserved for:
      a. Control before surgery or irradiation
      b. When surgery is not possible (usually requires lifelong pharmacotherapy)
      c. Surgical failures or relapses after period of remission postsurgery
   3. Acromegaly
      a. Dopamine agonists (e.g., bromocriptine, cabergoline)
         i. Mechanism of action: Dopamine agonist that, in acromegaly, causes paradoxical decrease in GH production
         ii. Dosing (bromocriptine, most commonly used agent)
            (a) Initial: 1.25 mg/day by mouth
            (b) Maximal: 20–30 mg/day (can titrate once or twice weekly as needed)
         iii. Adverse effects
            (a) Fatigue, dizziness, nervousness
            (b) Diarrhea, abdominal pain
         iv. Efficacy: Normalization of IGF-1 concentrations in about 10% of patients. More than 50% of patients will experience symptomatic relief.
      b. Somatostatin analog (e.g., octreotide)
         i. Mechanism of action: Blocks GH secretion, 40 times more potent than endogenous somatostatin
         ii. Dosing:
            (a) Initial: 50–100 mcg subcutaneously every 8 hours
            (b) Maximal: Little benefit greater than 600 mcg/day
            (c) If response to above, can be changed to long-acting octreotide formulation administered once monthly
         iii. Adverse effects
            (a) Diarrhea, nausea, cramps, flatulence, fat malabsorption
            (b) Arrhythmias
            (c) Hypothyroidism
            (d) Biliary tract disorders
            (e) Changes in serum glucose concentrations (usually reduces)
         iv. Efficacy: 50%–60% of patients experience normalization of IGF-1 concentrations with good symptomatic relief as well. May shrink tumor mass in some patients
      c. 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.
   4. Hyperprolactinemia
      a. Discontinue causative agent if drug induced.
      b. Dopamine agonists
         i. Cabergoline (long-acting oral agent, adverse effect profile similar to that of bromocriptine)
            (a) Initial: 0.5 mg once weekly
            (b) Maximal: 4.5 mg/week
         ii. Bromocriptine (see above)

iii. Efficacy: May restore fertility in greater than 90% of women. Cabergoline may be easier for patients to take, given weekly administration.

5. GH deficiency: Recombinant GH (somatropin)
   a. Dosing
      i. Depends on which of the various products are selected (dosed subcutaneously or intramuscularly once daily)
      ii. When to discontinue therapy on the basis of growth velocity is controversial
      iii. Once- or twice-monthly long-acting depot formulation is also available.
   b. Adverse effects
      i. Arthralgias, injection site pain
      ii. Rare but serious cases of idiopathic intracranial hypertension have been reported.
   c. Efficacy: All products are considered equally efficacious.

III. ADRENAL GLAND DISORDERS

A. Classification
   1. Hypersecretory cortisol diseases (a.k.a. Cushing's syndrome)
      a. ACTH-dependent: Result of excessive ACTH secretion (80% of cases)
         i. Pituitary corticotroph adenoma (Cushing's syndrome)
         ii. Ectopic ACTH syndrome (extrapituitary tumor)
      b. ACTH-independent: Result of excessive cortisol secretion or exogenous steroids (20% of cases)
         i. Unilateral adrenocortical tumors
         ii. Bilateral adrenal hyperplasia or dysplasia
         iii. Endogenous steroid administration
   2. Hyperaldosteronism – Primary aldosteronism
      a. Bilateral adrenal hyperplasia (70% of cases)
      b. Aldosterone-producing adenoma (30% of cases)
   3. Hyposecretory
      a. Primary adrenal insufficiency (a.k.a. Addison's disease)
         i. Caused by autoimmune disorder, infection, or infarction
         ii. Results in cortisol, aldosterone, and androgen deficiencies
      b. Secondary adrenal insufficiency
         i. Exogenous steroid use (from chronic suppression). Oral, inhaled, intranasal, and topical administration
         ii. Surgery, trauma, infection, infarction
         iii. Results in impaired androgen and cortisol production

Figure 2. Basic adrenal cortex hormone physiology.
ACTH = adrenocorticotropic hormone; RAS = renin-angiotensin system; + ve = positive stimulation; - ve = negative feedback.

Patient Case

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

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

B. Diagnosis/Clinical Presentation
   1. Cushing's syndrome
      a. Presence of hypercortisolism through 24-hour urine-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 MRI (magnetic resonance imaging) (Cushing's syndrome vs. ectopic ACTH syndrome)
         iv. Overnight dexamethasone suppression test

c. Clinical presentation
    i. Central obesity and facial rounding quite common
    ii. Peripheral obesity and fat accumulation
    iii. Myopathies
    iv. Osteoporosis, back pain, compression facture
    v. Abnormal glucose tolerance/diabetes
    vi. Amenorrhea and hirsutism in women
    vii. Lower abdominal pigmented striae (red to purple)
    viii. Hypertension (principal cause of morbidity/mortality)

2. Hyperaldosteronism
    a. Elevated plasma aldosterone-to-renin ratio
    b. Other features: Hypernatremia, hypokalemia, hypomagnesemia, glucose intolerance
    c. Clinical presentation (can be asymptomatic)
        i. Hypertension
        ii. Muscle weakness/fatigue
        iii. Headache
        iv. Polydipsia
        v. Nocturnal polyuria
3. Addison's disease: Primary failure of the adrenal gland
    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 BUN (blood urea nitrogen)

C. Therapy Goals – For all, reduce morbidity and mortality and eliminate cause.
1. Reversal of clinical features
2. Normalization of biochemical changes (when possible)
3. Long-term control without recurrence (remission when possible)

D. Pharmacotherapy
1. Cushing's syndrome: Surgical resection of causative area/tumor is usual treatment of choice. Pharmacotherapy usually reserved for the same criteria listed earlier for pituitary adenomas
    a. Pasireotide
        i. Mechanism of action: Somatostatin analog blocks ACTH secretion from pituitary, leading to decreased circulating cortisol levels.
        ii. Dosing: 0.6–0.9 two times/day subcutaneous injection (dose adjustments based on urinary free cortisol and symptom improvements)
        iii. Adverse effects: Hyperglycemia, hypocorticalism, diarrhea, nausea, gallstones, headache, bradycardia
        iv. Obtain electrocardiogram, FPG, A_{1c}, liver function tests, gallbladder ultrasonography before initiating therapy.
        v. Self-monitor BG values every week for first 2–3 months; then periodically obtain liver function tests 1–2 weeks after starting therapy; then obtain them monthly for 2–3 months and then every 6 months. Repeat gallbladder ultrasonography at 6- to 12-month intervals.
    b. Ketoconazole
        i. Mechanism of action: In addition to its antifungal activity, it hinders cortisol production by inhibition of 11- and 17-hydroxylase.
        ii. Dosing
            (a) Initial: 200 mg two times/day by mouth
            (b) Maximal: 400 mg three times/day

iii. Adverse effects
(a) Gynecomastia
(b) Abdominal discomfort
(c) Reversible hepatic transaminase elevations

c. Mitotane
i. Mechanism of action: Inhibits 11-hydroxylase but also has some direct adrenolytic activity
ii. Dosing
(a) Initial: 500–1000 mg/day by mouth (some use much higher daily doses, but they are not well tolerated)
(b) Maximal: 9–12 g/day
iii. Adverse effects
(a) Anorexia
(b) Ataxia
(c) Abdominal discomfort
(d) Lethargy

d. Etomidate
i. Mechanism of action: Similar to ketoconazole, inhibits 11-hydroxylase
ii. Dosing
(a) Initial: 0.03 mg/kg intravenously, followed by a 0.1-mg/kg/hour infusion
(b) Maximal: 0.3 mg/kg/hour
iii. Given route of administration is usually reserved for situations in which rapid control of cortisol levels is required and oral therapy is problematic.

e. Metyrapone (by compassionate use only)
i. Mechanism of action: Hinders secretion of cortisol by blocking final step in cortisol synthesis through inhibition of 11-hydroxylase activity
ii. Dosing
(a) Initial: 500 mg three times/day by mouth
(b) Average dose in Cushing's syndrome is 2000 mg/day, but it is about 4000 mg in ectopic ACTH syndrome.
iii. Adverse effects
(a) Hypoadrenalism
(b) Hypertension
(c) Worsening of hirsutism and acne if present before treatment
(d) Headache
(e) Abdominal discomfort

f. Efficacy is measured by control of symptoms and normalization of 24-hour urine-free cortisol concentrations.

g. Mifepristone approved in 2012 for hyperglycemia associated with endogenous Cushing's syndrome. Proposed to limit binding of cortisol. May reduce insulin requirements and improve clinical symptoms associated with hyperglycemia

2. Hyperaldosteronism
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.

3. Addison's disease
    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 and/or variable serum concentrations in some patients.
            (b) Daily cortisol production in average patient: 5–10 mg/m^2
    b. Hydrocortisone: 15 mg/day (may negate need for fludrocortisone compared with using cortisone or prednisone)
        i. Cortisone acetate: 20 mg/day
        ii. Prednisone: 2.5 mg/day
        iii. Dexamethasone: 0.25–0.75 mg/day
    c. Fludrocortisone (replaces loss of mineralocorticoid): 0.05–0.2 mg/day by mouth
    d. For women with decreased libido or low energy levels because of androgen deficiency: DHEA (dehydroepiandrosterone): 25–50 mg/day
    e. Efficacy can be measured by symptom improvement.
    f. Note that, during times of stress/illness, corticosteroid doses will need to be increased. Dosage and route of administration depend on level of stress to the body.

Table 2. Comparative Glucocorticosteroid Dosing

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

IV. OBESITY

A. Classification
    1. Based on BMI in kilograms per square meter
    2. Normal: BMI 18.5–24.9
    3. Overweight: BMI 25.0–29.9
    4. Obesity
        a. Class I: BMI 30.0–34.9
        b. Class II: BMI 35.0–39.9
        c. Class III: BMI of 40 or greater

B. Therapy Goals
    1. Weight loss
    2. Maintain lower weight long term.
    3. Limit weight-induced comorbidities (e.g., type 2 DM, hypertension, cardiovascular disease).

C. Nonpharmacologic Therapy
    1. Increased physical activity
        a. Initially, moderate activity for 30–45 minutes, 3–5 times a week
        b. Institute of Medicine recommends 1 hour/day of moderately intensive exercise.

2. Dietary options
    a. Reduced-caloric intake/low-fat diet
        i. 1200–1800 kcal/day
        ii. Less than 30% of calories from fat
    b. Low-carbohydrate diet
        i. Increased fat and protein at the expense of carbohydrates
        ii. Faster reduction in weight compared with low-fat diets, but overall weight reduction is similar after 1–2 years
        iii. Has beneficial effect on lipids compared with low-fat diets
        iv. Vegetable-based fat source associated with lower mortality compared with animal-based fat source
3. Surgery: Usually reserved for severely obese (BMI greater than 40) or lower BMIs with existing co-morbidities
    a. Gastric bypass
    b. Gastric banding

Patient Case

5. A patient recently started lorcaserin for treatment of his or her obesity. The patient's baseline BMI is 32 kg/m^2 and weight is 298 lb. Which would be the minimal weight loss expected to consider continuing treatment with this agent?

    A. 10 lb.
    B. 15 lb.
    C. 20 lb.
    D. 25 lb.

D. Pharmacotherapy
1. In conjunction with diet, physical activity, and behavior therapy
2. Should be reserved for those not achieving adequate lifestyle modifications, those who are obese (consider in overweight patients with significant weight-related comorbidities [e.g., diabetes, hypertension])
3. Orlistat
    a. Mechanism of action: Reduced absorption of fat by inhibition of gastric and pancreatic lipases
    b. Dosing
        i. Prescription (Xenical): 120 mg three times/day during or up to 1 hour after meals
        ii. Over the counter (Alli): 60 mg three times/day during or up to 1 hour after meals
    c. Adverse effects
        i. GI tract: Flatulence, oily stool, loose stool, fecal urgency/incontinence (very dependent on fat content of meal)
        ii. Reduced absorption of fat-soluble vitamins (A, D, E, and K): Use vitamin supplement before or well after use.
        iii. Hepatotoxicity, kidney stones
    d. Efficacy: 35%–54% of patients taking a prescription-strength product attained at least a 5% weight loss after 1 year of therapy, and 16%–25% attained at least a 10% weight loss.
4. Lorcaserin
    a. Mechanism of action: Reduced hunger by stimulating serotonin 2C receptors in the brain. Previous serotonin agonists used for obesity (e.g. fenfluramine) were nonselective and caused unwanted cardiac and pulmonary issues.
    b. Dosing: 10 mg twice daily

c. Adverse effects: Headache, dizziness, nausea, dry mouth, constipation, memory or attention disturbances, hypoglycemia in patients with diabetes
d. Efficacy: 4.5%–6% weight loss from baseline, 47% attained at least a 5% loss, 23% attained at least a 10% weight loss. In overweight patients with diabetes, up to a 1% reduction in A_{1c}
e. Discontinue use if at least a 5% weight loss not achieved after 12 weeks of use.
f. Avoid concurrent use with serotonergic drugs, including selective serotonin reuptake inhibitors.
g. Long-term cardiac risk or benefit unknown

5. Phentermine/extended-release topiramate
   a. Mechanism of action: Phentermine promotes appetite suppression and decreased food intake secondary to its sympathomimetic activity. Mechanism of topiramate is unknown but may cause appetite suppression and satiety through increased γ-aminobutyrate activity.
   b. Dosing (phentermine/topiramate): Should be taken in the morning to avoid insomnia
      i. Initial: 3.75/23 mg daily for 2 weeks; then increase to 7.5/46 mg daily
      ii. If at least a 3% weight loss not achieved after 12 weeks, can discontinue or increase to 11.25/69 mg daily for 2 weeks; then increase to 15/92 mg daily if tolerated
      iii. If at least a 5% weight loss not achieved with 15/92 mg daily, discontinue use. Taper when discontinuing to avoid seizures.
      iv. Dosing in moderate hepatic or renal impairment: Do not exceed 7.5/46 mg daily.
      v. Availability is restricted by the FDA to specific certified pharmacies.
   c. Adverse effects: Dry mouth, paresthesia, constipation, dysgeusia, insomnia, attention/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 use of adequate contraception during use.
   e. Efficacy: 9%–10% weight loss from baseline, 60%–70% attained at least a 5% weight loss after 1 year of treatment, and 37%–48% attained at least a 10% weight loss
   f. Long-term cardiac risk or benefit unknown
6. Diethylpropion or phentermine monotherapy
   a. Both are controlled substances, schedule IV
   b. Should only be used for limited duration, up to 3 months, and avoid in those with abuse potential
   c. Adverse effects: Increased blood pressure, constipation, increased heart rate, dysrhythmias, abuse potential (avoid in patients with hypertension or history of cardiovascular disease)
7. Concurrent use of obesity medications has not been studied, nor are comparative studies between agents available.
8. Off-label medications used, although not well studied specifically for obesity: Exenatide, selective serotonin reuptake inhibitors, bupropion with or without naltrexone, zonisamide, metformin, pramlintide

V. POLYCYSTIC OVARY SYNDROME

A. Background/Classification
   1. May be a cause of infertility in up to 20% of infertile couples
   2. Mainly considered a condition caused by androgen excess or hyperandrogenism
   3. Underlying cause appears to be insulin resistance (in obese and nonobese patients) with subsequent compensatory insulin hypersecretion or increased insulin action. This increased action stimulates androgen secretion by the ovaries and/or adrenal cells, leading to increased luteinizing hormone (LH) secretion but normal or low FSH levels with a subsequent decrease in follicular maturation and anovulation.
   4. Has several potential comorbidities with endocrine and cardiovascular implications (e.g., type 2 DM, obesity)
   5. May affect 6%–10% of women, making it one of the most prevalent endocrine disorders in young women
   6. No clear consensus on classifying PCOS, although some rate it from mild to severe

B. Diagnosis
   1. Still somewhat under debate, no clear consensus
   2. 1990 National Institutes of Health (NIH) criteria
      a. Hyperandrogenism and/or hyperandrogenemia
      b. Oligoovulation (infrequent or irregular ovulation)
      c. Exclusion of other secondary causes, particularly adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia
   3. 2003 Rotterdam criteria: Presence of at least two of the following and ruling out secondary causes:
      a. Menstrual irregularity (oligo- and/or anovulation)
      b. Hyperandrogenism (clinical or biochemical signs)
      c. Polycystic ovaries (by transvaginal ultrasonography)
   4. 2006 Androgen Excess Society: Follow 1990 NIH 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 sole criteria because 20%–40% of patients with PCOS may be in the normal range):
      a. Elevated free or total serum testosterone
      b. Increased 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 obese patients, prediabetes (impaired glucose tolerance [IGT]) or type 2 DM may be present.

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

E. Nonpharmacologic Therapy: Weight loss (5%–10%) is the therapy of choice in overweight/obese patients.

F. Pharmacotherapy
   1. If goal is to improve fertility
      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 dose 150–200 mg/day
         iii. Adverse effects: Flushing, gastrointestinal (GI) discomfort, vision disturbances, vaginal dryness, multiple pregnancies
      b. Gonadotropin (e.g., recombinant FSH) or recombinant gonadotropin-releasing hormone therapy with or without clomiphene
         i. Mechanism of action: Normalize 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. Metformin
         i. Mechanism of action: Improves insulin sensitivity, which may lower insulin concentrations or insulin activity with subsequent reduction in adrenal or ovarian androgen secretion. Can be monotherapy or is commonly used with clomiphene

ii. Dosing: Similar to dosing strategy for type 2 DM listed below
iii. Adverse effects: See Type 2 DM section earlier.

2. For symptomatic improvement and fertility not desired:
   a. Estrogen-progesterone contraceptive
   b. Spironolactone
   c. Pioglitazone

VI. DIABETES MELLITUS

A. Consensus Recommendations
   1. American Diabetes Association (ADA). Updated yearly in the January supplement of *Diabetes Care* (www.diabetes.org)
   2. American College of Endocrinology/American Association of Clinical Endocrinologists (ACE/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. Type 1 DM
      a. Attributable to cellular-mediated beta-cell destruction leading to insulin deficiency (insulin required for survival)
      b. Accounts for 5%–10% of DM
      c. Formerly known as insulin-dependent diabetes, juvenile-onset diabetes
      d. Prevalence in the United States: 0.12% (about 340,000)
      e. Usually presents in childhood or early adulthood but can present in any stage of life
      f. Usually symptomatic with a rapid onset in childhood, but a slower onset can present in older adults
   2. Type 2 DM
      a. Result of insulin resistance with subsequent defect in insulin secretion
      b. Accounts for 90%–95% of DM
      c. Formerly known as non–insulin-dependent diabetes, adult-onset diabetes
      d. Prevalence in the United States: 7.8% (about 23.6 million and growing!)
      e. Often, relatively asymptomatic with a slow onset over 5–10 years. Rationale for early, frequent screening of those at risk (below) and initial assessment for complications at diagnosis
      f. Disturbing increased trends in type 2 DM in children and adolescents attributed to rise in obesity
   3. Maturity-onset diabetes of the young
      a. Result of genetic disorder leading to impaired secretion of insulin with little or no impairment in insulin action
      b. Onset usually before age 25 and may mimic either type 1 or 2 DM
   4. Gestational diabetes
      a. Glucose intolerance occurring during pregnancy
      b. Prevalence: 1%–14% of pregnancies (complicates about 4% of pregnancies)
      c. New diagnostic criteria (see below) will likely improve the diagnosis and change the prevalence.
      d. Most common in third trimester
   5. Prediabetes
      a. IGT
      b. Impaired fasting glucose (IFG)
   6. Other DM types
      a. Genetic defects in beta-cell function or insulin action
      b. Diseases of the pancreas (e.g., pancreatitis, neoplasia, cystic fibrosis)
      c. Drug or chemical induced (e.g., glucocorticoids, nicotinic acid, protease inhibitors, atypical antipsychotics)

Patient Case

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

C. Screening for DM
   1. Type 1 DM:
      a. Symptomatic patients
      b. Asymptomatic patients at higher risk
         i. Relatives with type 1 DM
         ii. Measure islet autoantibodies to assess risk of type 1 DM
         iii. If screen is positive for antibodies counsel on symptoms of hyperglycemia and risk of DM. Consider enrollment in observational study
   2. Type 2 DM:
      a. Age 45 or older, repeat every 3 years if normal
      b. Start younger if BMI is 25 kg/m^2 or greater and at least one of the following risk factors:
         i. History of cardiovascular disease
         ii. IGT or IFG
         iii. History of PCOS
         iv. HDL-C less than 35 mg/dL and/or TG greater than 250 mg/dL
         v. Hypertension
         vi. Women with a diagnosis of gestational diabetes or women who delivered a baby weighing more than 4.1 kg (9 lb)
         vii. High-risk ethnicity: African American, Latino, Native American, Asian American, Pacific Islander
         viii. First-degree relative with type 2 DM
         ix. Physical inactivity
   3. Gestational DM:
      a. Screen at first prenatal visit for undiagnosed type 2 DM in all patients with type 2 DM risk factors present.
      b. Screen at 24–28 weeks of gestation using a 75-g OGTT.
      c. If a diagnosis of gestational DM is made, screen for diabetes 6–12 weeks after delivery.

D. DM Diagnosis
   1. Type 1 and type 2 DM diagnosis
      a. Glycemic parameters 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 A_{1c} 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 re-tested (preferably with the same test, but it can be any of the above on a subsequent day or by obtaining an A_{1c} unless unequivocal hyperglycemia is noted).
v. A_{1c} (glycated hemoglobin)
(a) 6.5% or greater
(b) Confirmed by repeating (unless unequivocal hyperglycemia is noted), though 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) A_{1c} values may be inaccurate in patients with hemolytic anemia, chronic malaria, sickle cell anemia, or significant blood loss and/or recent blood transfusion.

b. Other useful diagnostic tests if type of DM present is in question
i. C-peptide (measure of endogenous insulin secretion, usually negligible in type 1 DM and normal or elevated in type 2 DM)
ii. Presence of islet cell autoantibodies, autoantibodies to insulin, glutamic acid decarboxylase, or tyrosine phosphatase (all suggest autoimmune activity)

2. Gestational diabetes diagnosis: Glycemic parameters in pregnancy
a. Updated and simplified diagnostic criteria
b. 75-g OGTT at weeks 24–28 of gestation
i. Fasting: 92 mg/dL or greater
ii. 1 hour post-OGTT: 180 mg/dL or greater
iii. 2 hours post-OGTT: 153 mg/dL or greater

3. Prediabetes diagnosis (high-risk population)
a. IFG: FPG between 100 and 125 mg/dL
b. IGT: 2-hour plasma glucose post-OGTT (75 g) between 140 and 199 mg/dL
c. A_{1c} between 5.7% and 6.4%

Patient Case

7. A 56-year-old man was recently given a diagnosis of type 2 DM. He has no other chronic diseases or history of cardiovascular disease. Which set of values is the best selection of goals for his A_{1c}, blood pressure, and LDL-C?

A. A_{1c} less than 6.0%, blood pressure less than 120/80 mm Hg, LDL-C less than 70 mg/dL.
B. A_{1c} less than 7.0%, blood pressure less than 140/80 mm Hg, LDL less than 100 mg/dL.
C. A_{1c} less than 6.5%, blood pressure less than 140/90 mm Hg, LDL less than 130 mg/dL.
D. A_{1c} less than 8.0%, blood pressure less than 130/85 mm Hg, LDL-C less than 160 mg/dL.

E. Goals of Diabetes Management in Nonpregnant Adults
1. Primary goal is to prevent the onset of acute or chronic complications.
2. Acute complications: Hypoglycemia, diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar non-ketotic syndrome
3. Chronic complications
a. Microvascular: Retinopathy, nephropathy, and neuropathy
b. Macrovascular: Cardiovascular, cerebrovascular, and peripheral vascular diseases

4. Glycemic therapy goals
    a. A_{1c} less than 7.0% (Note: The ACE/AACE guidelines recommend 6.5% or less.)
        i. Obtain every 6 months in patients at goal A_{1c} and quarterly in those over goal.
        ii. Less-stringent A_{1c} targets may be appropriate in those with a short life expectancy (e.g., terminal cancer), advanced diabetic complications, long-standing diabetes that is difficult to control (e.g., frail elderly with history of hypoglycemia at risk of falls), or extensive other comorbidities. (In such situations, a higher A_{1c} (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 70–130 mg/dL. Frequency of monitoring very dependent 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. Nonglycemic therapy goals
    a. Blood pressure less than 140/80 mm Hg (ADA guidelines suggest lower systolic blood pressure goals are appropriate in younger patients to reduce nephropathy risk and in those with higher risk of stroke
    b. Lipids
        i. LDL-C less than 100 mg/dL; less than 70 mg/dL an option in those with existing cardiovascular disease
        ii. TG less than 150 mg/dL

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

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

Patient Cases

8. A 52-year-old woman received a diagnosis today of type 2 DM. Her A_{1c} is 7.8%, and her FBG is 186 mg/dL. She has no other chronic disease states or history of cardiovascular disease. According to the current ADA guidelines, which would be considered the best initial treatment of choice for this patient?
   A. Implement changes in lifestyle (diet and exercise).
   B. Implement changes in lifestyle (diet and exercise) plus metformin 500 mg once daily.
   C. Implement changes in lifestyle (diet and exercise) plus sitagliptin 100 mg once daily.
   D. Implement changes in lifestyle (diet and exercise) plus insulin glargine 10 units once daily.

9. A 66-year-old man has had type 2 DM for 4 years and has a history of pancreatitis. His A_{1c} today is 7.7%. He has altered his diet, and he states that he has been exercising regularly for months now. His currently is receiving metformin 1000 mg twice daily. Which would be the best choice to help optimize his glycemic control?
   A. Continue current medications and counsel to improve his diet and exercise.
   B. Discontinue metformin and initiate exenatide 5 mcg twice daily.
   C. Add sitagliptin 100 mg once daily to his metformin therapy.
   D. Add glyburide 5 mg twice daily to his metformin therapy.

H. Oral Diabetic Agents in Type 2 DM
   1. Sulfonylureas
      a. Mechanism of action: Bind to receptors on pancreatic beta-cells, leading to membrane depolarization with subsequent stimulation of insulin secretion (insulin secretagogue)
      b. First-generation agents seldom used today (e.g., chlorpropamide, tolbutamide)
      c. Second-generation agents (e.g., glyburide, glipizide, glimepiride). Dose titration: Can increase at weekly intervals as necessary
      d. Adverse effects
         i. Common: Hypoglycemia, weight gain
         ii. Less common: Rash, headache, nausea, vomiting, photosensitivity
      e. Contraindications/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 elderly patients or in those with renal impairment because drug or active metabolites are not renally eliminated)
      f. Efficacy
         i. 1%–2% A_{1c} reduction
         ii. Note: For this and all medications used to treat hyperglycemia, the absolute decrease in A_{1c} is larger for higher baseline A_{1c} values and smaller for lower A_{1c} values.

Table 3. Second-Generation Sulfonylurea Dosing Strategies

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

2. 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 B_{12} levels, lactic acidosis (rare)
        iii. Signs or symptoms of lactic acidosis include acidosis, nausea, vomiting, increased respiratory rate, abdominal pain, shock, and tachycardia.
    d. Contraindications/precautions (because of risk of lactic acidosis)
        i. Renal impairment: Serum creatinine 1.5 mg/dL or greater in men and 1.4 mg/dL or greater in women or reduced creatinine clearance (CrCl; CrCl cutoff is not well established, but it may be as low as 30 mL/minute). Renal insufficiency increases the risk of lactic acidosis.
        ii. Age 80 years or older
        iii. High risk of cardiovascular event or hypoxic state
        iv. Hepatic impairment
        v. Congestive heart failure (especially if prone to exacerbations)
        vi. Interrupt therapy if undergoing procedures using iodinated contrast dye because of risk of nephrotoxicity. Reinitiate after 48 hours and after normal serum creatinine concentrations are achieved.
    e. Efficacy
        i. 1%–2% A_{1c} 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 A_{1c}, cost, and limited data that it reduces cardiovascular events in overweight patients
3. Meglitinides
    a. Mechanism of action: Very similar to that of sulfonylureas in increasing insulin secretion from the pancreas but with a more rapid onset and shorter duration of activity
    b. Glucose-dependent activity
    c. Two currently available: Repaglinide and nateglinide
    d. Dosing
        i. Repaglinide
            (a) Initial: 0.5–1 mg 15 minutes before meals
            (b) Maximal daily dose: 16 mg
        ii. Nateglinide
            (a) 120 mg before meals
            (b) 60 mg if A_{1c} 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/precautions
        i. Hypersensitivity
        ii. Caution in concomitant use of repaglinide and gemfibrozil, can lead to greatly increased repaglinide levels
    g. Efficacy
        i. 0.5%–1.5% A_{1c} reduction (repaglinide shown to reduce A_{1c} more than nateglinide)
        ii. Most effective on postprandial glucose excursions

4. Thiazolidinediones (often called TZDs or glitazones)
    a. Mechanism of action
        i. Peroxisome proliferator-activated receptor γ-agonist
        ii. Increases expression of genes responsible for glucose metabolism, resulting in improved insulin sensitivity
    b. Two agents available: Pioglitazone and rosiglitazone
        i. In September 2010, the FDA initiated restricted access to rosiglitazone secondary to continued concerns about its cardiovascular safety.
        ii. Rosiglitazone is restricted to patients unable to attain glycemic control with other agents and when pioglitazone is not used for medical reasons.
    c. Dosing
        i. Pioglitazone
            (a) Initial: 15 mg once daily
            (b) Maximal daily dose: 45 mg
        ii. Dose titration is slow, and the maximal effect of a dose change may not be observed for 8–12 weeks.
    d. Adverse effects
        i. Weight gain
        ii. Fluid retention (particularly peripheral edema), worse with insulin use (manufacturer of rosiglitazone states to use it no longer with insulin). Edema less responsive to diuretic therapy
        iii. Risk of bone fractures, use caution in patients with existing osteopenia or osteoporosis
        iv. Small risk of bladder cancer (recent updated label information)
        v. Increased risk of heart failure
            (a) Boxed warning.
            (b) More than 2-fold higher relative risk, though absolute risk is quite small
        vi. Both agents have been withdrawn from European Union.
        vii. Risk Evaluation and Mitigation Strategies (REMS) in the United States with rosiglitazone
            (a) Although not taken off the U.S. market, REMS drastically reduces those who will be able to obtain it.
            (b) See end of chapter for more detail on REMS.
    e. Contraindications/precautions
        i. Hepatic impairment
        ii. Class III/IV heart failure
        iii. Existing fluid retention
    f. Efficacy
        i. 0.5%–1.4% A_{1c} reduction
        ii. Both drugs increase HDL-C, but pioglitazone has a more favorable effect in reducing LDL-C and TG compared with rosiglitazone.
5. α-Glucosidase inhibitors
    a. Mechanism of action: Slows the absorption of glucose from the intestine into 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/day at each meal
        ii. Maximal daily dose: 300 mg
        iii. Slow titration, increasing as tolerated every 4–8 weeks to minimize GI adverse effects
    d. Adverse effects
        i. Flatulence, diarrhea, abdominal pain
        ii. Increased liver enzymes observed with high doses of acarbose
    e. Contraindications/precautions: Inflammatory bowel disease, colonic ulcerations, intestinal obstruction

f. Efficacy
   i. 0.5%–0.8% reduction in A_{1c}
   ii. Targets postprandial glucose excursions
   iii. May not be as effective in patients using low-carbohydrate diets

6. Dipeptidyl peptidase-4 (DPP-4) inhibitors
   a. Mechanism of action: Inhibits the breakdown of glucagon-like peptide-1 (GLP-1) secreted during meals, which in turn increases pancreatic insulin secretion, limits glucagon secretion, slows gastric emptying, and promotes satiety
   b. Dosing
      i. Sitagliptin: 100 mg once daily
         (a) Reduce dose with CrCl between 30 and 50 mL/minute to 50 mg once daily.
         (b) Reduce dose with CrCl less than 30 mL/minute to 25 mg once daily.
      ii. Saxagliptin: 5 mg once daily (Reduce with CrCl of 50 mL/minute or less to 2.5 mg once daily.)
      iii. Linagliptin: 5 mg once daily (no dosage adjustment for renal impairment)
   c. Adverse effects
      i. Upper respiratory and urinary tract infections, headache
      ii. Hypoglycemia with monotherapy is minimal, but increased frequency with concurrent sulfonylurea therapy (can lower dose of sulfonylurea when initiating)
      iii. Sitagliptin has had some postmarketing reports of acute pancreatitis, angioedema, Stevens-Johnson syndrome, and anaphylaxis.
   d. Contraindications/precautions
      i. Previous hypersensitivity to the agents
      ii. History of pancreatitis
   e. Efficacy: 0.5%–0.8% reduction in A_{1c}

7. Bile acid sequestrant—Colesevelam only studied drug in this class
   a. Mechanism of action
      i. Bile acid sequestrant used primarily for cholesterol management. Its mechanism to reduce serum glucose concentrations is not clearly understood. Suspected to be an antagonist to the farnesoid X receptor (FXR), which subsequently reduces hepatic gluconeogenesis. By reducing bile acid absorption, colesevelam reduces FXR activity.
      ii. Used in conjunction with insulin or oral DM medications
   b. Colesevelam 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/precautions
      i. Contraindicated in patients with a history of bowel obstruction, serum TG concentration greater than 500 mg/dL
      ii. Caution in patients with swallowing disorders (large pill), dysphasia, gastric mobility disorders, and serum TG concentrations greater than 300 mg/dL
   f. Efficacy: A 0.3%–0.5% reduction in A_{1c}

8. Bromocriptine
   a. Mechanism of action: Not clearly understood. Agonist for dopamine D_2 receptor thought to "reset" circadian rhythm that may reduce caloric intake and storage. Other effects may be through α_1 antagonism, α_2-agonistic properties, and modulation of serotonin and prolactin.
   b. Dosing
      i. Initial: 0.8 mg once daily on waking, take with food (increases bioavailability)
      ii. Maximal daily dose: 4.8 mg
      iii. Titrate weekly by 0.8 mg/day as tolerated and based on response.
      iv. Tablet strength is different from generic formulations currently on the market.
   c. Adverse effects: Nausea, somnolence, fatigue, dizziness, vomiting, headache, orthostatic hypotension, syncope

d. Contraindications/precautions
   i. Can limit the effectiveness of agents used to treat psychosis or exacerbate psychotic disorders
   ii. Should not be used in nursing mothers or patients with syncopal migraines
   iii. Concomitant use with dopamine antagonists (e.g., neuroleptic agents) may limit the efficacy of both agents.
e. Efficacy: 0.1%–0.6% reduction in A_{1c}

Patient Case

10. A 66-year-old man is given a diagnosis today of type 2 DM. Two weeks ago, his A_{1c} was 7.5%, and his serum creatinine was 1.8 mg/dL (estimated CrCl 25 mL/minute). He has a history of hypertension, dyslipidemia, and systolic heart failure (New York Heart Association class III, ejection fraction 33%). He has 2+ pitting edema bilaterally. In addition to improvements in diet and exercise, which is the best drug to initiate?

A. Linagliptin.
B. Pioglitazone.
C. Exenatide.
D. Metformin.

I. Incretin Analogs
   1. GLP-1 analog
      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. Two agents available (exenatide and liraglutide)
      c. Dosing
         i. Exenatide
            (a) Twice-daily formulation
               (1) Initial: 5 mcg subcutaneously twice daily, administered no more than 60 minutes before morning and evening meals
               (2) Maximal dose: 10 mcg twice daily
               (3) Dose titration from 5 to 10 mcg twice daily after 1 month if tolerated
            (d) Once-weekly formulation
               (1) 2 mg once weekly
               (2) Current formulation must be reconstituted by patient immediately before injection.
         ii. Liraglutide
            (a) 0.6 mg subcutaneously once daily for 1 week (regardless of mealtime)
            (b) Dose titration from 0.6 to 1.2 mg/day if tolerated
            (c) Maximal daily dose: 1.8 mg/day
      d. Adverse effects
         i. Nausea, vomiting, diarrhea very common
         ii. Hypoglycemia common with concurrent sulfonylurea (consider reduction in sulfonylurea dose if adding exenatide)
         iii. Postmarketing reports of pancreatitis and acute renal failure or impairment
      e. Contraindications/precautions
         i. Impaired renal function: CrCl less than 30 mL/minute for either exenatide formulation, less specific for liraglutide
         ii. History of severe GI tract disorder, particularly gastroparesis
         iii. History of pancreatitis
         iv. For liraglutide: Contraindicated in patients with a personal or family history of medullary thyroid carcinoma (adverse effect found in rodent studies but not in humans)

f. Efficacy
   i. A 0.5%–1.1% reduction in A_{1c}
   ii. Effects on postprandial hyperglycemia better than on fasting glucose concentrations with once- or twice-daily formulations
   iii. Improved A_{1c}, fasting glucose reduction, and nausea/vomiting with once-weekly compared with twice-daily exenatide formulation
   iv. Modest weight loss

2. Amylin analog
   a. Mechanism of action: Amylin is cosecreted with insulin and has effects similar to GLP-1 described earlier.
   b. Pramlintide is currently the only agent in this class available in the United States. Can be used in either type 1 or type 2 DM as adjunctive therapy in patients receiving insulin
   c. Dosing
      i. Type 1 DM
         (a) Initial: 15 mcg subcutaneously immediately before main meals
         (b) Must reduce dose of preprandial rapid-acting, short-acting, or combination insulin products by 50%
         (c) Maximal daily dose: 60 mcg with each meal
         (d) Dose should be titrated in 15-mcg increments, as tolerated, no more rapidly than every 3 days.
      ii. Type 2 DM
         (a) Initial: 60 mcg subcutaneously immediately before main meals
         (b) As above, must reduce preprandial insulins by 50%
         (c) Maximal daily dose: 120 mcg with each meal
         (d) Dose should be titrated in 60-mcg increments, as tolerated, no more rapidly than every 3–7 days.
      iii. Use of prefilled pens is strongly recommended, when possible, versus using a syringe and vial to reduce risk of dosing errors (dosing instructions with U-100 syringes and vial in package insert).
      iv. Cannot be mixed with insulin products, requires increased frequency of daily injections
   d. Adverse effects
      i. Black box warning for severe hypoglycemia, especially in patients with type 1 DM
      ii. Nausea, vomiting, anorexia, headache
   e. Contraindications/precautions
      i. Substantial gastroparesis
      ii. History of poor adherence or monitoring of BG
      iii. A_{1c} greater than 9%
      iv. Hypoglycemia unawareness or frequent bouts of hypoglycemia
   f. Efficacy
      i. A 0.5%–1% reduction in A_{1c}
      ii. Very effective at controlling postprandial glucose excursions

J. Insulin
   1. Categorized on the basis of duration after injection
      a. Short acting: Regular human insulin
      b. Rapid acting: Insulin aspart, lispro, and glulisine
      c. Intermediate acting: Neutral protamine Hagedorn (NPH)
      d. Long acting: Insulin glargine and detemir; cannot be mixed with other insulins

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

Table 4. Insulin Characteristics[a]

Category	Drug Name	Clarity	Onset	Injection Time Before Meal (minutes)	Peak (hours)	Duration (hours)
Short acting	Regular	Clear	30–60 minutes	30	2–3	4–6
Rapid acting	Aspart/lispro/ glulisine	Clear	5–20 minutes	15	1–3	3–5
Intermediate acting	NPH	Cloudy	1–2 hours	N/A	4–8	10–20
Long acting	Detemir Glargine	Clear	2–4 hours 1–2 hours	N/A	6–8 "peakless"	6–24 ~24

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

3. Glycemic target
   a. Regular- and short-acting insulins target postprandial glucose concentrations.
   b. Intermediate- and long-acting insulins target fasting glucose concentrations.

Patient Cases

11. A male patient with an A_{1c} of 7.6% is receiving insulin detemir (60 units once daily at bedtime) and insulin lispro (6 units before breakfast, 5 units before lunch, and 8 units before dinner). His morning FPG concentrations have consistently been high for the past 3 weeks, averaging 160 mg/dL. He reports no daytime or nighttime hypoglycemia. Which is the best insulin adjustment to improve his overall glycemic control?
    A. Increase his dinnertime lispro to 10 units.
    B. Decrease his dinnertime lispro to 6 units.
    C. Increase his bedtime detemir to 65 units.
    D. Decrease his bedtime detemir to 55 units.

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

K. Therapeutic Insulin Management of Type 1 DM
   1. First step is to estimate TDI requirements.
   2. Weight-based estimate if insulin naive
      a. 0.3–0.6 unit/kg/day
      b. Requirements higher if treating DKA near initial diagnosis of DM
      c. Honeymoon phase shortly after treatment initiation often requires lower daily insulin needs.

3. One common approach is to use older insulin formulations (NPH and regular insulin).
    a. Two-thirds of TDI given before morning meal. Two-thirds of this given as NPH and one-third as regular insulin
    b. One-third of TDI given before the evening meal (or regular given before a meal and NPH at bedtime). Again, two-thirds of this given as NPH and one-third as regular insulin
    c. Advantages: Daily insulin injection frequency two or three times/day and inexpensive
    d. Disadvantages: Does not mimic natural insulin secretion pattern, prone to hypoglycemic events
4. Another approach is basal/bolus insulin therapy (a.k.a. physiologic insulin therapy).
    a. Use of newer insulin analogs to better mimic natural insulin secretion patterns
    b. Provides daylong basal insulin to prevent ketosis and control FPG
    c. Provides bolus insulin to control postprandial hyperglycemia
    d. Basal insulins: Insulin glargine once daily or insulin detemir once or twice daily
    e. Bolus insulins: Rapid-acting insulin
    f. Basal requirements are 50% of estimated TDI.
    g. Bolus requirements are 50% of estimated TDI split three ways before meals.
        i. Provides initial estimate about prandial insulin needs
        ii. Typically, patients will begin to estimate bolus requirements given the amount of carbohydrates to be ingested.
    h. Advantages over NPH plus regular approach: More physiologic, less hypoglycemia, more flexible to patient mealtimes
    i. Disadvantages: Cost and increased frequency and number of daily injections (rapid-acting and basal insulin must be injected separately). Note: The same process of basal/bolus insulin therapy can apply to a patient with type 2 DM who is receiving intensive insulin therapy with or without oral DM medications.
5. Correctional insulin needs
    a. Always a need to correct for hyperglycemic excursions despite optimal basal/bolus therapy
    b. "1800 Rule": 1800/TDI = # mg/dL of glucose lowering per 1 unit of rapid-acting insulin
        i. For example: If TDI is 60 units, 1800/60 = 30, suggesting 1 unit of rapid-acting insulin will reduce BG concentrations by 30 mg/dL.
        ii. Also referred to as "insulin sensitivity"
        iii. Some advocate the "1500 Rule" when using regular human insulin (i.e., 1500/TDI).
    c. More patient-specific than traditional sliding-scale insulin
6. Continuous subcutaneous insulin infusion (insulin pump)
    a. Device allows very patient-specific hourly basal dosing and bolus insulin dosing.
    b. Uses rapid-acting insulins
    c. Requires considerable patient education and carbohydrate counting
7. Assessing therapy and dosage adjustment
    a. Know the goals for fasting and postprandial glucose concentrations.
    b. Identify when patient is at goal and not at goal (hypo- or hyperglycemia). Look for consistent trends rather than isolated events.
    c. Identify which insulin affects problematic glucose concentrations.
    d. Adjust insulin dose or patient behavior accordingly.
    e. Same process for treating type 2 DM applies (see below)

L. Therapeutic Management of Type 2 DM
1. Given the progressive nature of type 2 DM, a stepwise approach is usually required.
2. Updated 2012 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, in addition to improvements in exercise and diet.
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 A_{1c} (also focus on ability to lower fasting or postprandial glucose concentrations or both)
b. Risk of hypoglycemia
c. Effects on weight
d. Adverse effect profile
e. Cost

5. Initial insulin therapy: Use insulin early with any of the following baseline characteristics:
   a. A_{1c} greater than 10%
   b. Random glucose greater than 300 mg/dL or fasting glucose greater than 250 mg/dL
   c. Hyperglycemic symptoms
   d. Presence of urine ketones
6. Changing from oral DM medications to insulin-only management (e.g., because of adverse effects, contraindications, lack of efficacy of oral medications)
   a. Can follow NPH/regular insulin or basal/bolus approach similar to that in type 1 DM described earlier
   b. The TDI requirements in type 2 DM are usually higher than in type 1 DM because of insulin resistance.
7. Changing from NPH to long-acting insulin (either insulin glargine or detemir)
   a. If adequate glycemic control already attained, initiate insulin glargine at 80% of total daily NPH dose
   b. Detemir may be initiated by a unit-to-unit conversion and may require higher daily insulin dosages after conversion, but this is determined by glycemic response.

Table 5. Comparison of Therapies for T2DM Hyperglycemia Added to Metformin

Agent or Class	Primary Glycemic Effect	Benefits	Limitations/Precautions
Sulfonylurea	Fasting and prandial	Efficacy Cost	Weight gain Hypoglycemia risk Hastens beta-cell dysfunction
Meglitinide	Prandial	Prandial focus Use in kidney impairment	Hypoglycemia risk Weight gain Mealtime dosing
Pioglitazone	Fasting and prandial	Improves insulin sensitivity Low risk of hypoglycemia Possible cardiovascular benefit Cost	Weight gain and edema Risk of heart failure Risk of osteoporosis Possible bladder cancer risk
α-Glucosidase inhibitor	Prandial	No systemic absorption Prandial focus	GI adverse effect profile Mealtime dosing Modest A_{1c} effect
DPP-4 inhibitor	Prandial	Well tolerated Weight neutral	Possible pancreatitis risk Modest A_{1c} effect Cost
GLP-1 agonist	Fasting and prandial (once-weekly exenatide greater fasting effect)	Greater effect on prandial glucose Weight loss Efficacy	Nausea/vomiting Injection site effects Questionable pancreatitis or thyroid cancer risk Cost

Table 5. Comparison of Therapies for T2DM Hyperglycemia Added to Metformin (continued)

Agent or Class	Primary Glycemic Effect	Benefits	Limitations/Precautions
Colesevelam	Prandial	Lipid benefits No systemic absorption	Large pill size/burden GI adverse effect profile Small decrease in A_{1c} Avoid with high triglycerides
Bromocriptine	Fasting and prandial	Low risk of hypoglycemia	Small decrease in A_{1c} CNS adverse effects
Amylin agonist	Prandial	Modest weight loss Efficacy on postprandial glucose	High risk of hypoglycemia Must be taken with insulin Frequent injections Injection site effects GI adverse effects
Insulin	Basal – Fasting Bolus – Prandial	Significant A_{1c} reduction Flexibility in dosing strategies and titration	Hypoglycemia Weight gain Injection site effects

CNS = central nervous system; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP = glucagon-like peptide; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione.

Information adapted from: Inzucchi S, Bergenstal R, Buse J. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Diabetes Care 2012;35:1364-79; and Rodbard H, Jellinger P, Davidson J, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract 2009;15:540-59.

VII. TREATMENT OF DM COMPLICATIONS

A. Hypoglycemia
   1. Degree of intervention depends on glucose concentrations and presence of symptoms.
   2. Symptoms are very patient-specific.
   3. Definition: Plasma glucose less than 70 mg/dL with or without symptoms
   4. Mild to moderate hypoglycemia
      a. Oral ingestion of 15–20 g of glucose or equivalent
      b. Repeat glucose concentration in 15 minutes and, if still less than 70 mg/dL, repeat ingestion of glucose.
   5. Severe hypoglycemia (altered consciousness, requires assistance from others)
      a. Glucagon 1 mg intramuscularly
      b. Intravenous dextrose if patient does not respond to glucagon
      c. Raise glucose targets for several weeks.

B. Diabetic Ketoacidosis
   1. More common in type 1 DM but can occur in type 2 DM
   2. Usually occurs because of a precipitating factor that considerably stresses the body, resulting in increased counterregulatory 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/symptoms: Polyuria, polydipsia, vomiting, dehydration, weakness, altered mental status, coma, abdominal pain, Kussmaul respirations, tachycardia, hyponatremia, hyperkalemia
   5. Treatment
      a. Treat underlying cause if known.

b. Fluid replacement
    i. 0.45%–0.9% sodium chloride depending on baseline serum sodium concentrations
    ii. Change to 5% dextrose with 0.45% sodium chloride when serum glucose is less than 200 mg/dL.
c. Insulin
    i. Goal is to stop ketosis, not to normalize glucose concentrations.
    ii. Intravenous bolus: 0.1 unit/kg
    iii. Intravenous infusion:
        (a) 0.1 unit/kg/hour (increase if not a 50- to 75-mg/dL drop in serum glucose in the first hour)
        (b) Alternatively, 0.14 unit/kg/hour if no insulin bolus is given
        (c) If not at least a 10% decrease in serum glucose attained in first hour, give 0.14 unit/kg intravenous bolus
        (d) Reduce infusion rate to 0.02–0.05 unit/kg/hour when serum glucose reaches 200 mg/dL, and keep glucose between 150 and 200 mg/dL until DKA resolves.
    iv. Interrupt insulin treatment if baseline serum potassium is less than 3.3 mEq/L and until corrected.
d. Potassium
    i. 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. 20–30 mEq potassium per 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 is greater than 7.3.
    ii. Serum bicarbonate is 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-to-creatinine ratio starting at diagnosis in type 2 DM and after 5 or more years in type 1 DM.
    a. Normal: Less than 30 mg/g (or micrograms per milligram)
    b. Increased urinary albumin excretion 30 mg/g or greater
    c. ADA in 2013 no longer uses terms of microalbuminuria or macroalbuminuria
2. Estimated CrCl yearly as well.
3. With either increased albumin excretion, use of angiotensin-converting enzyme (ACE) inhibitors or ARBs is recommended.
4. Dietary protein restriction as renal function declines

D. Retinopathy
1. Screen annually with dilated and comprehensive eye examinations starting at diagnosis in type 2 DM and after 5 or more years in type 1 DM.
2. Frequency can be reduced to every 2–3 years after one or more normal examinations.
3. No specific pharmacotherapy recommended except to adequately control glucose concentrations and blood pressure

E. DM Neuropathies
1. Can have nerve damage in any area of the body
2. Screen for distal polyneuropathy using monofilament once yearly.
    a. Screen after 5 years of type 1 DM and at diagnosis with type 2 DM.
    b. Diminished sensitivity is a significant risk factor for diabetes-related foot ulcer and increases the need for frequent visual inspection by patients if it exists.

3. Treatment of neuropathies is for symptomatic improvement and does not prevent progression.
4. Symptoms are patient-specific but may include numbness, burning, and tingling sensation.
5. Neuropathic pain
    a. 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.
    b. Anticonvulsants (gabapentin, lamotrigine, pregabalin)
        i. Comparative data of 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 and is recommended by the American Academy of Neurology in its 2011 guideline.
    c. 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 comparative data with amitriptyline 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.
    d. Tramadol/acetaminophen: As effective as gabapentin, different adverse effect profile
    e. Opioids: Tapentadol extended release only approved agent in this class, no head-to-head efficacy studies
6. Gastroparesis
    a. Autonomic neuropathy causes considerable nausea/vomiting after meals because of delayed gastric emptying.
    b. Nonpharmacologic strategies
        i. More frequent but smaller meals
        ii. Homogenize food.
    c. Pharmacologic treatment
        i. Metoclopramide: 10 mg before meals: Risk of tardive dyskinesia or extrapyramidal reactions
        ii. Erythromycin: 40–250 mg before meals

F. Cardiovascular Disease
1. Most common cause of morbidity and mortality as well as 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 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 or ARB.
    c. Give at least one antihypertensive in the evening (possible reduced blood pressure and improved outcomes).
5. Lipid management
    a. Assess fasting lipid profile annually.
    b. Statin therapy recommended regardless of baseline lipid levels for:
        i. Established cardiovascular disease
        ii. No history of cardiovascular event but older than 40 years with at least one cardiovascular risk factor other than DM
    c. A 30%–40% reduction in LDL-C can be an alternative goal in those who do not attain an LDL-C less than 100 mg/dL.

d. TG goal: Less than 150 mg/dL
e. HDL-C goal: Greater than 40 mg/dL for men, greater than 50 mg/dL for women

6. Antiplatelet therapy
   a. Low-dose aspirin (75–162 mg/day)
      i. With existing cardiovascular disease
      ii. For primary prevention if 10-year risk is greater than 10% (includes most men older than 50 and women older than 60 who have at least one cardiovascular risk factor)
   b. Clopidogrel for those intolerant of aspirin therapy

G. Preventive Immunizations
   1. Annual influenza vaccine
   2. Pneumococcal polysaccharide vaccine
   3. Hepatitis B vaccine

VIII. OTHER DIABETIC MEDICATION ISSUES

A. FDA's REMS for Rosiglitazone
   1. Limits use to
      a. Patients already being successfully treated with these medicines
      b. Patients whose BG cannot be controlled with other antidiabetic medicines and who, after consulting with their health care providers, do not wish to use pioglitazone-containing medicines
   2. Providers and patients must enroll in Avandia-Rosiglitazone Medicines Access Program.
      a. No longer available in retail pharmacies
      b. Available by mail order only through certified pharmacies

B. In the wake of the rosiglitazone safety issue, the FDA now requires all newly approved diabetic 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 elderly patients, as well as in those with some degree of renal impairment and those with more advanced diabetes

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A
This patient has hypothyroidism on the basis of her elevated TSH and low free T4 caused by Hashimoto's disease. Levothyroxine is the drug of choice for this condition given its adverse effect profile, cost, antigenicity profile, and uniform potency. Although liothyronine can be used for hypothyroidism, its potential for increasing the risk of cardiovascular complications makes it second line (Answer B). Answer C is also incorrect given its increased antigenicity compared with levothyroxine. Answer D is incorrect because it is an agent used to treat hyperthyroidism.

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

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

4. Answer: D
Because the aldosterone-to-renin ratio and blood pressure are high, hyperaldosteronism is the most likely disease listed. Cushing's syndrome and hyperaldosteronism can be secondary causes of hypertension. In this case, the patient's free 24-hour urine cortisol is normal but would be elevated if he had Cushing's syndrome; thus, Answer A is incorrect. Answer B is incorrect because Addison's disease is a result of cortisol deficiency and is not associated with hypertension. Answer C, hyperprolactinemia, is unlikely, given the patient's presentation and his abnormal aldosterone-to-renin ratio.

5. Answer: B
The minimal weight loss after 12 weeks of therapy with lorcaserin should be 5%; otherwise, the medication should be discontinued. Given this patient's baseline weight, a minimum of 15 lb is necessary to continue therapy. The other answers provided are either too low (Answer A), or they exceed the 5% minimal expectation (Answer C and Answer D).

6. Answer: D
Unless the patient has significant symptoms of hyperglycemia (none noted in this case), a subsequent evaluation for hyperglycemia by a fasting glucose concentration, a random glucose concentration, an OGTT, or an A_{1c} is warranted; hence, Answer A and Answer B are incorrect. Answer C is incorrect because a subsequent test for hyperglycemia should not be performed on the same day according to ADA guidelines.

7. Answer: B
The goal A_{1c} according to the ADA is less than 7.0%. The goal blood pressure is less than 130/80 mm Hg, and the goal LDL-C is less than 100 mg/dL. The other answers deviate from these goals in one fashion or another.

8. Answer: B
Changes in lifestyle modification, in addition to metformin therapy, are preferred. Changes in lifestyle alone, Answer A, although important, are no longer recommended by the ADA. Answer C and Answer D are incorrect because sitagliptin or insulin therapy as initial monotherapy is not recommended, though both would be effective in controlling BG levels. Metformin is preferred given its safety profile, reduction in A_{1c}, cost, and potential for weight loss.

9. Answer: D
The usual course of therapy for a patient no longer able to maintain adequate glycemic control with monotherapy is to add additional agents. Answer A is incorrect because the patient is already exercising and still has uncontrolled hyperglycemia. Answer B is incorrect because one agent would not normally be changed to an-

other unless a patient was experiencing adverse effects of the original agent. In addition, GLP-1 analogs and DPP-4 inhibitors should not be used in patients with a history of pancreatitis; thus, both Answer B and Answer C are incorrect.

10. Answer: A

In this case, the initiation of medications to treat a patient with newly diagnosed hyperglycemia is complicated by several 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 recommended. 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 A_{1c} is not markedly elevated, and renal function does not need to be considered.

11. Answer: C

This patient is experiencing sustained increases in fasting glucose concentrations in the morning. The insulin most likely to affect the morning glucose concentrations is insulin glargine. Answer A and Answer B are incorrect because the insulin lispro dose at dinnertime will not likely affect the next morning's glucose concentrations according to the information provided in the case. Answer D is incorrect on the basis of the information provided because it would more than likely increase the next morning's glucose concentrations, not reduce them.

12. Answer: D

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

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

According to the ADA guidelines, individuals with this degree of hyperglycemia should be initiated on insulin therapy, and Answer D provides an appropriate basal/bolus insulin combination. This patient's A_{1c} is greater than 10%, and his fasting glucose is greater than 250 mg/dL. Answer A and Answer C are not optimal because dual therapy with oral agents is unlikely to bring this patient to his glycemic goal. Answer B is also not optimal because the combination of a sulfonylurea and rapid-acting insulin would increase the risk of hypoglycemia and would be unlikely to bring about a sufficient reduction in A_{1c}.

2. Answer: C

This patient's TDI requirements equal 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). The other three answers would provide either too much or too little estimated insulin at each meal.

3. Answer: C

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

4. Answer: B

Unlike methimazole, PTU has a k boxed warning regarding the risk of hepatoxicity. Answer A is incorrect because neither agent is considered more efficacious than the other. Answer C is incorrect because Hashimoto's disease is a result of hypothyroidism, not hyperthyroidism. Methimazole is dosed once daily, whereas PTU is usually dosed up to three times/day, so Answer D is incorrect.

5. Answer: A

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

6. Answer: C

Metformin improves fertility in patients with PCOS, but unlike clomiphene and gonadotropin therapy (Answer A and Answer B), it does not significantly increase the risk of multiple pregnancies. Although spironolactone (Answer D) may improve some of the hyperandrogenic signs of PCOS (e.g., hirsutism), it has not been adequately studied for its effects on infertility.

7. Answer: A

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

8. Answer: B

For insulin adjustments, determine which BG readings are at goal and which ones are not. For those consistently not at goal, determine which insulin is most affecting the BG readings. In this case, the patient's BG readings are consistently elevated at bedtime, which is most likely caused by insufficient predinner prandial (a.k.a. bolus) insulin. Changing the rapid-acting insulin at other times of the day would not help; hence, Answer A and Answer D are incorrect. Changing her basal insulin (glargine in this case) would not likely 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 relatively mild symptoms, and her ablative therapy worked initially but now no longer controls her thyroid levels. Methimazole (Answer A) would be the oral agent of preference given its dosing frequency and its lower risk of hepatotoxicity than PTU (Answer C). Thyroidectomy is an option, but it is likely too aggressive for mild Graves disease; thus, Answer B is incorrect. Answer D is not optimal, whereas β-blockers, which may provide symptomatic relief, will not significantly affect her thyroid levels.

10. Answer: D

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

11. Answer: D

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

12. Answer: A

This patient has now had two laboratory glycemic indicators (A_{1c} and FBG) consistent with the diagnosis of diabetes. Answer B is likely incorrect because this patient has several risk factors for developing type 2 DM including obesity, ethnicity, age, a history of gestational diabetes, and a strong family history of the disease. Answer C is incorrect because there is no need to obtain another A_{1c} this soon after the one just 2 weeks ago, and the A_{1c} can be used in the diagnosis of diabetes. Obtaining another glucose reading on another day (Answer D) is also incorrect, again because there are two abnormal glycemic indicators already; thus, another is not necessary to confirm the diagnosis.

13. Answer: C

The LDL-C goal is less than 100 mg/dL. Statin therapy is recommended, regardless of baseline LDL-C, for patients with diabetes, and this patient's LDL-C is elevated. In this case, the patient's glycemic and blood pressure readings are at their goals, less than 7.0% and less than 130/80 mm Hg, respectively. Adding insulin (Answer A) and adding a blood pressure medication (Answer B) are not necessary. Answer D is incorrect because there is no need for fibrate therapy in this patient; the HDL-C and TG are under control.