Type 2 Diabetes Mellitus

(See also *Harrison's Principles of Internal Medicine*, 17th Edition, Chapter 338)

Definition

- Diabetes mellitus (DM)
  - A group of common metabolic disorders that share the phenotype of hyperglycemia
  - Caused by complex interaction of genetics, environmental factors, and lifestyle choices
  - Classified on the basis of a pathogenic process leading to hyperglycemia
- Type 1 DM
  - Results from pancreatic beta-cell destruction, usually leading to absolute insulin deficiency
  - See Type 1 Diabetes Mellitus.
- Type 2 DM
  - A heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production
  - Preceded by a period of abnormal glucose homeostasis, classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)

Epidemiology

- DM
  - Worldwide prevalence: greatly increased over past 2 decades
  - Prevalence
    - By age (in 2000)
      - <20 years: 190 cases per 100,000 persons
      - ≥20 years: 8,600 cases per 100,000 persons
      - >65 years: 20,100 cases per 100,000 persons
    - By sex
      - Most age ranges: equal in men and women
      - >60 years of age: slightly more men than women
    - By race (in the U.S. in 2000)
      - African Americans: 13,000 cases per 100,000 persons
      - Hispanic Americans: 10,200 cases per 100,000 persons
      - Native Americans (American Indians and Alaska natives): 15,500 cases per 100,000 persons
      - Non-Hispanic white persons: 7,800 cases per 100,000 persons
- Type 2 DM
  - Incidence/prevalence varies by geography (likely owing to genetic, behavioral, and environmental factors).
    - Highest: certain Pacific islands
    - Intermediate: India and U.S.
    - Relatively low: Russia and China

- Prevalence is expected to increase more rapidly than type 1 DM because of increasing obesity and reduced activity levels
- Age of onset
  - Can develop at any age
  - Typically develops with increasing age, >30 years of age
  - Age of diagnosis is decreasing in some ethnic groups.
    - Occurs at an earlier average age in ethnic groups other than non-Hispanic whites
  - Marked increase among overweight children and adolescents

Risk Factors

- Family history of type 2 DM (i.e., parent or sibling)
- Obesity (body mass index >25 kg/m^2)
  - Particularly visceral or central (hip/waist ratio)
- Habitual physical inactivity
- Race/ethnicity
  - African American
  - Hispanic American
  - Native American
  - Asian American
  - Pacific Islander
- Previously identified IFG or IGT
  - 40% risk of developing type 2 DM over the next 5 years
- History of gestational diabetes or delivery of baby >4 kg (>9 lb)
- Hypertension (blood pressure >140/90 mmHg)
- High-density lipoprotein cholesterol level < 35 mg/dL (0.90 mmol/L) and/or triglycerides >250 mg/dL (2.82 mmol/L)
- Polycystic ovary syndrome (PCOS)
- Acanthosis nigracans
- History of vascular disease

Etiology

- Type 2 DM is caused by a complex interaction of genetics, environmental factors, and lifestyle choices.
  - Insulin resistance and abnormal insulin secretion are central to the development of type 2 DM.
  - Controversy remains regarding the primary defect; most studies support the view that:
    - Insulin resistance precedes insulin secretory defects.
    - Diabetes develops when insulin secretion becomes inadequate to compensate for insulin resistance.
- Genetic considerations
  - Major genes that predispose have yet to be identified; it is clear that the disease is polygenic.
  - Susceptibility genes or polymorphisms that have been identified that may contribute to the risk of type 2 DM include:
    - Calpain 10
    - Pro12Ala (common) variant of peroxisome proliferator-activated receptor γ
    - Glu23Lys variant of the adenosine triphosphate–sensitive potassium channel Kir6.2

    - Concordance in identical twins: 70–90%
    - 1 parent with disease: increased risk
    - Both parents with disease: risk approaches 40%
    - A genetic defect may not manifest itself unless an environmental event or another genetic defect, such as obesity, is superimposed.
- Environmental factors and lifestyle choices modulate phenotypic expression.
    - Nutrition
    - Physical activity
- Pathophysiologic abnormalities
    - Peripheral insulin resistance (especially muscle and liver)
    - Excessive hepatic glucose production
    - Impaired insulin secretion

Associated Conditions

- Insulin resistance syndromes
- Metabolic syndrome
    - Also referred to as *insulin resistance syndrome* or *syndrome X* (see Metabolic Syndrome)
    - Spectrum of disorders with hyperglycemia as prominent feature
    - Constellation of metabolic derangements includes:
        - Insulin resistance
        - Hypertension
        - Dyslipidemia (low high-density lipoprotein cholesterol level and elevated triglyceride level)
        - Central or visceral obesity
        - Type 2 DM or IGT/IFG
        - Accelerated cardiovascular disease
        - Predisposition to fatty liver
    - Very common; ~20% of U.S. adults
- PCOS
    - Common disorder in premenopausal women that is characterized by chronic anovulation and hyperandrogenism
    - Insulin resistance (independent of obesity) is present in the majority of patients.
    - Associated with a substantially increased risk for type 2 DM
- Rare forms of severe insulin resistance
    - Include features of type 2 DM or IGT
    - Common features
        - Acanthosis nigricans
        - Signs of hyperandrogenism (hirsutism, acne, and oligomenorrhea in women)
    - Type A
        - Affects young women
        - Characterized by severe hyperinsulinemia, obesity, and features of hyperandrogenism
        - Caused by an undefined defect in insulin-signaling pathway
    - Type B
        - Affects middle-aged women
        - Characterized by severe hyperinsulinemia, features of hyperandrogenism, and autoimmune disorders
        - Caused by autoantibodies directed at insulin receptor that may block insulin binding or may stimulate the insulin receptor, leading to intermittent hypoglycemia

- Genetic syndromes sometimes associated with DM
  - Lipodystrophy
  - Leprechaunism
  - Down's syndrome
  - Klinefelter's syndrome
  - Turner's syndrome
  - Wolfram syndrome
  - Friedreich's ataxia
  - Huntington's chorea
  - Laurence-Moon-Biedl syndrome
  - Myotonic dystrophy
  - Porphyria
  - Prader–Willi syndrome
- Periodontal disease
- Psychiatric conditions (occur more frequently in patients with DM than the general population)
  - Depression
  - Eating disorders
    - Binge-eating disorders
    - Bulimia
    - Anorexia nervosa

Symptoms & Signs

- DM and its complications produce a wide range of symptoms and signs.
  - Those secondary to acute hyperglycemia
    - May occur at any stage of the disease
  - Those related to chronic complications
    - Begin to appear during second decade of hyperglycemia
- A long asymptomatic period of hyperglycemia is common in type 2 DM.

Symptoms of hyperglycemia

- Polyuria
- Polydipsia
- Weight loss
- Fatigue
- Weakness
- Blurry vision
  - Results from changes in water content of lens
  - Resolves as hyperglycemia is controlled
- Frequent superficial infections (vaginitis, fungal skin infections)
- Slow healing of skin lesions after minor trauma

Historical features to assess

- In persons with newly diagnosed DM
  - Complete medical history with emphasis on DM-relevant aspects
    - Weight
    - Family history of DM and its complications
    - Risk factors for cardiovascular disease
    - Exercise

        - Smoking
        - Ethanol use
    - Assess for symptoms or signs of acute hyperglycemia.
    - Screen for:
        - Chronic complications and conditions associated with DM
        - DM-related comorbid conditions (cardiovascular disease, hypertension, renal disease, retinopathy, dyslipidemia)
- In persons with previously diagnosed DM
    - All of the above **plus**
    - Assessment of prior diabetes care (in established DM)
        - Type of therapy
        - Prior hemoglobin A_{1C} levels
        - Results of self-monitoring of blood glucose (SMBG)
        - Frequency of hypoglycemia
        - Presence of DM-specific complications
        - Assessment of patient's knowledge about diabetes

Complete physical examination

- Pay particular attention to:
    - Weight or body mass index
    - Retinal examination
    - Orthostatic blood pressure
        - Blood pressure > 130/80 mmHg considered hypertension in DM
    - Careful examination of lower extremities to seek evidence of:
        - Sites of potential skin ulceration
        - Peripheral neuropathy
            - Vibratory sensation (128-MHz tuning fork at base of great toe)
            - Ability to sense touch with monofilament (5.07, 10-g monofilament)
        - Calluses
        - Superficial fungal infections
        - Nail disease
        - Foot deformities (e.g., hammer or claw toes and Charcot foot)
    - Peripheral pulses
    - Insulin injection sites
    - Teeth and gums
        - Periodontal disease more frequent in DM

Differential Diagnosis

Type 1 DM

- Common characteristics, see Type 1 Diabetes Mellitus
    - Onset of disease before 30 years of age
    - Lean body habitus
    - Requirement of insulin as the initial therapy
    - Propensity to develop ketoacidosis
    - Increased risk of other autoimmune disorders

- Despite revised classification, difficult to categorize some patients unequivocally
  - Some persons with phenotypic type 2 DM present with diabetic ketoacidosis but lack autoimmune markers.
    - May require insulin initially, but can be transitioned to oral glucose-lowering agents after improving glycemic control
    - Most often of Hispanic or African American descent
  - About 5–10% of patients with phenotypic appearance of type 2 DM:
    - Do not have absolute insulin deficiency at presentation
    - Have autoimmune markers (islet-cell or glutamic acid decarboxylase autoantibodies) suggestive of type 1A DM
    - Are much more likely to require insulin treatment within 5 years
    - This condition is termed *autoimmune diabetes not requiring insulin at diagnosis* or *latent autoimmune diabetes of the adult.*

Other specific types of diabetes

- Maturity-onset diabetes of the young (MODY) and other genetic defects of beta-cell function, characterized by mutations in:
  - Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)
  - Glucokinase (MODY 2)
  - HNF-1α (MODY 3)
  - Insulin promoter factor 1 (MODY 4)
  - HNF-1β (MODY 5)
  - NeuroD1 (MODY 6)
  - Mitochondrial DNA
  - Proinsulin-to-insulin conversion
- Genetic defects in insulin action
  - Type A insulin resistance
  - Leprechaunism
  - Rabson–Mendenhall syndrome
  - Lipodystrophy syndrome
- Uncommon forms of immune-mediated diabetes
  - "Stiff-man" syndrome
  - Anti–insulin receptor antibodies
- Diseases of the exocrine pancreas
  - Pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy
- Endocrinopathies
  - Acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma
- Drug or chemical induced
  - Vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, β-adrenergic agonists, thiazides, phenytoin, interferon α, protease inhibitors, clozapine, beta blockers
- Infections
  - Congenital rubella, cytomegalovirus, coxsackievirus
- Gestational DM
- Other genetic syndromes sometimes associated with diabetes
  - Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader–Willi syndrome

Diagnostic Approach

National Diabetes Data Group and World Health Organization criteria for DM

- Based on following the premises:
  - Fasting plasma glucose (FPG) and response to oral glucose load vary among normal persons.
  - DM is defined as the level of glycemia at which diabetes-specific complications occur rather than by deviations from population-based mean.
    - For example, pthe revalence of retinopathy in Native Americans (Pima Indian population) begins to increase at an FPG >6.4 mmol/L (116 mg/dL).
- Diagnostic criteria for diabetes
  - Symptoms of diabetes **plus** random blood glucose concentration >11.1 mmol/L (200 mg/dL)
    - Random: without regard to time since last meal
  - **Or** FPG level >7.0 mmol/L (126 mg/dL)
    - Fasting: no caloric intake for at least 8 hours
  - **Or** 2-hour plasma glucose level >11.1 mmol/L (200 mg/dL) during oral glucose tolerance test
    - Test should be performed by using a glucose load containing equivalent of 75 g of anhydrous glucose dissolved in water.
    - Not recommended for routine clinical use
  - In the absence of unequivocal hyperglycemia and acute metabolic decompensation, criteria should be confirmed by repeated testing on a different day.
- IFG
  - Glucose level >5.6 mmol/ L (100 mg/dL) but <7.0 mmolL (126 mg/dL)
- IGT
  - Glucose level 7.8–11.1 mmol/L (140–200 mg/dL) 2 hours after a 75-g oral glucose load

Laboratory and additional assessments

- Assess diagnostic criteria for DM (see above).
- Assess degree of glycemic control by measuring hemoglobin A_{1C}.
- Screen for DM-associated conditions (e.g., microalbuminuria, dyslipidemia).
- Perform cardiac stress testing to screen for asymptomatic coronary artery disease if the patient is at high risk for cardiovascular disease.

Laboratory Tests

Plasma glucose

- FPG: reliable and convenient for diagnosing DM in asymptomatic persons
- Classification of glucose tolerance
  - Normal: FPG level <5.6 mmol/L (100 mg/dL)
  - IFG: FPG level ≥5.6 mmol/L (100 mg/dL) but <7.0 mmol/L (126 mg/dL)
    - Comparable to IGT (plasma glucose level 7.8–11.1 mmol/L (140–200 mg/dL) 2 hours after a 75-g oral glucose load)
  - Diagnosis of DM: FPG level >7.0 mmol/L (126 mg/dL)
  - In the absence of unequivocal hyperglycemia and acute metabolic decompensation, criteria should be confirmed by repeated testing on a different day.

- A random plasma glucose level >11.1 mmol/L (200 mg/dL) accompanied by classic symptoms of DM is sufficient for diagnosis of DM.

Hemoglobin A_{1C}

- Standard method for assessing long-term glycemic control
- Should be measured in all patients with DM during the initial evaluation and as part of comprehensive diabetes care
- Notes on use
  - Hemoglobin A_{1C} is not currently recommended for diagnosis.
  - In standardized assays, the hemoglobin A_{1C} value approximates the following mean plasma glucose values.
    - 6%: 7.5 mmol/L (135 mg/dL)
    - 7%: 9.5 mmol/L (170 mg/dL)
    - 8%: 11.5 mmol/L (205 mg/dL)
    - A 1% increase in the hemoglobin A_{1C} level translates into a 2.0-mmol/L (35 mg/dL) increase in mean glucose level.
  - Significant interassay variations exist.
    - Assay methods must be similar in order to compare with prior measurements.
  - Hemoglobinopathies, anemias, and uremia may interfere with hemoglobin A_{1C} results.

Other laboratory tests

- C-peptide measurement
  - A low level confirms need for insulin.
  - May help distinguish type 1 DM from type 2 DM in some circumstances
- Screening laboratory tests for DM-associated conditions
  - Microalbuminuria
    - Spot urine microalbumin/creatinine ratio (at the time of initial diagnosis of type 2 DM)
    - Microalbuminuria is defined by a microalbumin/creatinine ratio >30 mg/g creatinine.
  - Dyslipidemia
    - Fasting lipid profile (annual)

Imaging

- Not indicated

Diagnostic Procedures

- Not indicated

Treatment Approach

Goals of therapy

- Eliminate symptoms related to hyperglycemia.
- Achieve sustained euglycemia.
- Avoid hypoglycemia.

- Reduce or eliminate long-term microvascular and macrovascular complications.
- Allow the patient to maintain as normal a lifestyle as possible.

Factors to consider in developing goals of therapy

- Age
- Ability to understand and implement complex treatment regimen
- Presence and severity of complications
- Ability to recognize hypoglycemic symptoms
- Presence of other medical conditions or treatments that might alter response to therapy
- Lifestyle and occupation (e.g., possible consequences of experiencing hypoglycemia on the job)
- Level of support available from family and friends
- Life expectancy at time of diagnosis
- Presence of microvascular complications

Steps needed to reach goals

- Identify target level of glycemic control for each patient.
    - Ideal goals for glycemic control
        - Preprandial plasma glucose level: 5.0–7.2 mmol/L (90–130 mg/dL)
        - Peak postprandial plasma glucose level: <10 mmol/L (<180 mg/dL)
        - Hemoglobin A_{1C} level: <7.0%
- Provide patient with educational and pharmacologic resources necessary to reach goal.
- Monitor/treat DM-related complications.

Comprehensive care

- Best accomplished by a multidisciplinary team approach
    - Primary care provider and/or endocrinologist or diabetologist
    - Certified diabetes educator
    - Nutritionist
    - Subspecialists with experience in DM-related complications
        - Neurologist
        - Nephrologist
        - Vascular surgeon
        - Cardiologist
        - Ophthalmologist
        - Podiatrist

Patient education

- Diabetes educator
    - A health care professional (nurse, dietician, or pharmacist) with specialized patient education skills
    - Certified in diabetes education (e.g., American Association of Diabetes Educators)
- Topics important for optimal care
    - Nutrition
    - SMBG
    - Insulin administration (if needed)
    - Guidelines for diabetes management during illnesses
    - Management of hypoglycemia

  - Foot and skin care
  - Diabetes management before, during, and after exercise (if taking insulin)
  - Risk factor–modifying activities

Treatment approach in a newly diagnosed patient

- Diabetes management should begin with medical nutrition therapy in most persons with mild hyperglycemia (hemoglobin A_{1C} level < ~9%).
- After medical nutrition therapy and increased physical activity have been instituted, glycemic control should be reassesed.
- If the patient's glycemic target is not achieved after 4 weeks of medical nutrition therapy, pharmacologic therapy is indicated.

Pharmacologic management

- Oral glucose-lowering agents
  - Usually are preferred by patients
  - Should not be used in severely ill persons

Insulin therapy

- Insulin, alone or in combination with oral agents, often becomes necessary as type 2 DM progresses.
- Insulin is sometimes used as the initial glucose-lowering agent in patients with moderate to severe hyperglycemia.

Specific Treatments

Medical nutrition therapy

- Nutritional recommendations for all persons with DM
  - Protein
    - ~15–20% of kcal/d
    - ~10% in patients with nephropathy
  - Saturated fat
    - <10% of kcal/d
    - <7% in patients with elevated low-density lipoprotein cholesterol level
  - Polyunsaturated fat
    - ~10% of kcal/d
    - Avoid trans-unsaturated fatty acids.
  - 60–70% of calories divided between carbohydrate and monounsaturated fat
    - Based on medical needs and personal tolerance
  - Use of caloric sweeteners, including sucrose, is acceptable.
  - Fiber
    - 20–35 g/d
    - Increased consumption of soluble dietary fiber may improve glycemic control.
  - Sodium: <3,000 mg/d
  - Cholesterol: <300 mg/d
  - Alcohol
    - Same precautions as in general population
    - May increase risk for hypoglycemia and should be taken with food

Exercise

- A regular physical activity program, adapted to the presence of complications, is recommended for all patients with diabetes who are capable of participating.
- Regular exercise provides the following benefits in type 2 DM.
    - Improves blood glucose control
    - Reduces cardiovascular risk factors
    - Contributes to weight loss and weight loss maintenance
    - Increases insulin sensitivity
    - Improves well-being
- Exercise-related hypoglycemia occurs less frequently in patients with type 2 DM than in those with type 1 DM, but may develop in those who are treated with insulin or sulfonylureas.
- Strategies to avoid exercise-related hypoglycemia (mainly for persons requiring insulin therapy)
    - Monitor blood glucose before, during, and after exercise as needed.
    - Ingest carbohydrate if needed to prevent hypoglycemia.
    - Learn individual glucose responses to different types of exercise and alter insulin doses in advance of anticipated exercise, if needed (depending on intensity and duration).
- Relative contraindication: untreated proliferative retinopathy
    - May lead to vitreous hemorrhage or retinal detachment
- Consider formal exercise tolerance testing for:
    - Age >35 years
    - DM duration >15 years
    - Microvascular complications
    - Peripheral arterial disease
    - Other risk factors of coronary artery disease
    - Autonomic neuropathy

Oral glucose-lowering agents

Overview

- Indicated if the patient's glyemic target is not achieved after 3–4 weeks therapy with nutrition and exercise
- Insulin secretagogues
    - Sulfonylureas
        - Mechanism of action: enhance insulin secretion
        - Examples: chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, glyburide
        - Anticipated reduction in hemoglobin A_{1C} level: 1–2%
        - Agent-specific advantages: decreases fasting blood glucose level, well tolerated
        - Agent-specific disadvantages: hypoglycemia, weight gain, hyperinsulinemia
        - Contraindications: renal/liver disease
    - Meglitinides
        - Mechanism of action: enhance insulin secretion
        - Examples: repaglinide, nateglinide
        - Anticipated reduction in hemoglobin A_{1C} value: 1–2%
        - Agent-specific advantages: short onset of action, lower postprandial glucose level

        - Agent-specific disadvantage: hypoglycemia (lower risk than observed with sulfonylureas)
        - Contraindications: renal/liver disease
- Biguanides
    - Mechanism of action: reduce hepatic glucose production, weight loss, increase glucose utilization, decrease insulin resistance
    - Examples: metformin
    - Anticipated reduction in hemoglobin A_{1C} level: 1–2%
    - Agent-specific advantages: associated with weight loss, improvement in lipid profile, no hypoglycemia
    - Agent-specific disadvantages: diarrhea, nausea, risk of lactic acidosis
    - Contraindications: serum creatinine level >1.5 mg/dL (men) or >1.4 mg/dL (women); avoid use at time of radiographic contrast studies, in seriously ill patients, in patients at risk for acidosis
- α-Glucosidase inhibitors
    - Mechanism of action: reduce glucose absorption by inhibiting the enzyme that cleaves oligosaccharides into simple sugars in the intestinal lumen
    - Examples: acarbose, miglitol
    - Anticipated reduction in hemoglobin A_{1C} level: 0.5–1.0%
    - Agent-specific advantage: no risk of hypoglycemia
    - Agent-specific disadvantages: GI flatulence, small risk of increased liver function values
    - Contraindications: renal/liver disease
- Thiazolidinediones
    - Mechanism of action: decrease insulin resistance, increase glucose utilization
    - Examples: rosiglitazone, pioglitazone
    - Anticipated reduction in hemoglobin A_{1C} level: 1–2%
    - Agent-specific advantages: decrease insulin and sulfonylurea requirements, decrease triglyceride level
    - Agent-specific disadvantage: weight gain, delayed response, need for frequent hepatic monitoring for idiosyncratic hepatocellular injury, financial cost
    - Contraindications: liver disease, congestive heart failure (class III or IV)

Insulin secretagogues

- Most effective in patients with:
    - Disease of relatively recent onset (<5 years)
    - Tendency to obesity
    - Residual endogenous insulin production
- Sulfonylureas
    - Should be initiated at low doses and increased at 1- to 2-week intervals on the basis of SMBG results
    - Should be taken shortly before a meal
- First-generation sulfonylureas
    - At maximum doses, first-generation sulfonylureas similar in potency to second generation sulfonylureas but have
        - Longer half-life
        - Greater incidence of hypoglycemia
        - More frequent drug interactions
    - Chlorpropamide
        - Approved daily dosage range: 100–500 mg
        - Duration of action: >48 hours
        - Clearance: renal

    - Tolazamide
        - Approved daily dosage range: 100–1,000 mg
        - Duration of action: 12–24 hours
        - Clearance: hepatic, renal
    - Tolbutamide
        - Approved daily dosage range: 500–3,000 mg
        - Duration of action: 6–12 hours
        - Clearance: hepatic
- Second-generation sulfonylureas
    - Generally preferred over first generation drugs
    - Glimepiride
        - Approved daily dosage range: 1–8 mg
        - Duration of action: 24 hours
        - Clearance: hepatic, renal
    - Glipizide
        - Approved daily dosage range: 2.5–40 mg
        - Duration of action: 12–18 hours
        - Clearance: hepatic
    - Glipizide (extended release)
        - Approved daily dosage range: 5–10 mg
        - Duration of action: 24 hours
        - Clearance: hepatic
    - Glyburide
        - Approved daily dosage range: 1.25–20 mg
        - Duration of action: 12–24 hours
        - Clearance: hepatic, renal
    - Glyburide (micronized)
        - Approved daily dosage range: 0.75–12 mg
        - Duration of action: 12–24 hours
        - Clearance: hepatic, renal
- Meglitinides
    - Given with each meal or immediately before to reduce meal-related glucose excursions
    - Repaglinide
        - Approved daily dosage range: 0.5–16 mg
        - Duration of action: 2–6 hours
        - Clearance: hepatic
    - Nateglinide
        - Approved daily dosage range: 180–360 mg
        - Duration of action: 2–4 hours
        - Clearance: renal

Biguanides

- Metformin (representative of this class of agents)
    - Initial dose: 500 mg qd or bid
        - Can be increased to 1,000 mg bid
        - Increase dose every 2–3 weeks, based on SMBG results.
    - Also available
        - Extended-release formulation
        - Combination formulations with glyburide or glipizide
        - Combination formulations with pioglitazone or rosiglitazone

α-Glucosidase inhibitors

- Acarbose and miglitol
  - Initiate at a low dose (25 mg) with evening meal.
  - May titrate to maximal dose over weeks to months
    - Acarbose, 50–100 mg with each meal
    - Miglitol, 50 mg with each meal
- Avoid using in the following situations.
  - Simultaneous treatment with bile acid resins and antacids
  - Inflammatory bowel disease
  - Gastroparesis
  - Serum creatinine concentration >177 μmol/L (2.0 mg/dL)

Thiazolidinediones

- Pioglitazone and rosiglitazone
  - Appear to exhibit similar efficacy
  - Appear to have less risk of liver abnormalities than troglitazone (withdrawn in U.S.)
  - Effects on lipids: slight increase in low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels, 10-15% reduction in triglyceride level
- Pioglitazone
  - Initial dose: 15–30 mg/d in a single daily dose
  - May increase dose in 15 mg increments to 45 mg once daily
- Rosiglitazone
  - Initial dose: 2–4 mg once daily
  - May increase dose to 4–8 mg/d either once daily or bid in divided doses
- Side effects
  - Minor weight increase (1–2 kg)
  - Small decrease in hematocrit
  - Mild increase in plasma volume
  - May precipitate peripheral edema and/or congestive heart failure, particularly in persons treated with insulin
  - Induces ovulation in premenopausal women with PCOS
    - Women should be warned about risk of pregnancy.
    - Safety in pregnancy has not been established.

Insulin

- Overview
  - Current insulin preparations are generated by recombinant DNA technology.
    - Amino-acid sequence of human insulin or variations
    - Beef or pork insulins are no longer used.
    - All insulin in U.S.: U-100 (100 U/mL)
- Specific preparations
  - Intermediate-acting
    - NPH
      - Onset: 2–4 hours
      - Peak: 6–10 hours
      - Effective duration: 10–16 hours

        - Lente
            - Onset: 3–4 hours
            - Peak: 6–12 hours
            - Effective duration: 12–18 hours
    - Long-acting
        - Ultralente
            - Onset: 6–10 hours
            - Peak: 10–16 hours
            - Effective duration: 18–20 hours
        - Glargine
            - Onset: 4 hours
            - Peak: minimal
            - Effective duration: 24 hours
- Insulin should be considered as initial therapy, particularly in the following subsets of patients.
    - Patients with a lean body habitus or those with severe weight loss
    - Patients with underlying renal or hepatic disease that precludes oral glucose-lowering agents
    - Patients who are hospitalized or acutely ill
- Insulin is ultimately required by a substantial proportion of patients with type 2 DM.
    - Usually initiated in a single dose of intermediate- or long-acting insulin (0.3–0.4 U/kg per day)
        - A single dose may be administered either before breakfast (NPH, lente, or ultralente) or just before bedtime (NPH, lente, ultralente, or glargine).
        - A single dose of insulin at bedtime is more effective than a single dose of morning insulin (except with the use of insulin glargine).
    - Some physicians prefer a relatively low, fixed starting dose to avoid hypoglycemia.
        - Intermediate-acting insulin (~15–20 U in the morning and 5–10 U at bedtime)
    - Dose may then be adjusted in 10% increments every 2–3 days as dictated by SMBG results.
    - Intermediate- or long-acting insulin may be used with oral glucose-lowering agents (biguanides, α-glucosidase inhibitors, or thiazolidinediones).
    - Eventually, regimens identical to those used in the treatment of type 1 DM (combinations of intermediate-, long-acting, and short-acting insulins) may be required.

Incretin mimetics

- Glucagon-like peptide 1 (GLP-1) agonist
    - GLP-1 is an endogenous hormone secreted from the distal small bowel and metabolized by dipeptidyl peptidase-IV (DPP-IV).
    - GLP-1 stimulates beta-cell insulin secretion, inhibits glucagon secretion, and slows gastric emptying.
    - Exenatide is a 39–amino acid peptide that stimulates the GLP-1 receptor.
        - A glycine for alanine substitution at position 2 of the GLP-1 peptide renders it relatively resistant to DPP-IV–mediated inactivation, and prolongs its half life.
    - Exenatide has the following physiologic effects.
        - Enhances glucose-dependent pancreatic secretion of insulin in response to nutrient intake
        - Inhibits glucagon secretion
        - Delays gastric emptying
        - Promotes early satiety

    - Exenatide is currently approved as adjunctive therapy for use in combination with a sulfonylurea, metformin, or both.
        - Exenatide does not cause hypoglycemia on its own, but may increase the risk for hypoglycemia in patients treated concomitantly with sulfonylureas.
        - Exenatide advantage: associated with weight loss (~1.5–2.5 kg).
    - Efficacy: 0.4–1.0% reduction in hemoglobin A_{1C} level
    - Initial dosing: 5 μg SC bid, given within the 60 minutes before the morning and evening meal
        - May increase dose up to a maximum of 10 μg SC bid after 1 month
    - Side effects: nausea, vomiting, diarrhea
    - Contraindications: severe renal impairment, severe GI disease

Amylin analogue

- Amylin is a 37–amino acid peptide that is expressed almost exclusively within pancreatic beta cells and is co-secreted with insulin in response to a glucose load.
- Patients with type 2 DM have a relative deficiency of amylin.
- Amylin has the following effects on glucose homeostasis.
    - Complements the actions of insulin in postprandial glucose homeostasis via suppression of postprandial glucagon secretion and inhibition of gastric emptying
    - Mitigates the influx of endogenous (liver-derived) and exogenous (meal-derived) glucose into the circulation
- Pramlintide
    - A human amylin analogue that may be used as an adjunct to insulin in type 2 DM.
    - Primary benefit may be improved control of postprandial glucose excursions
    - Pramlintide advantage: associated with weight loss (~1.5 kg).
    - Dosing: Initiate with 15 μg SC, then increase in 15-μg increments to a maintenance dose of 30–60 μg SC before meals, separate from insulin.
    - Efficacy: ~0.6% reduction in hemoglobin A_{1C} level
    - Side effects: transient mild to moderate nausea and anorexia
    - Contraindications: gastroparesis or inability to monitor for hypoglycemia

Choice of initial glucose-lowering agent

- The level of hyperglycemia should influence the initial choice of therapy.
    - Mild to moderate hyperglycemia
        - FPG level <11.1–13.9 mmol/L (200–250 mg/dL)
        - Often responds well to single agent
    - More severe hyperglycemia:
        - FPG level >13.9 mmol/L (250 mg/dL)
        - Unlikely to achieve normoglycemia with oral monotherapy
        - A stepwise approach can be used starting with single agent; add a second or third agent to achieve glycemic target.
    - Severe hyperglycemia
        - FPG level >13.9–16.7 mmol/L (250–300 mg/dL)
        - Can use insulin as initial therapy for more rapid glycemic control to:
            - Reduce "glucose toxicity" to islet cells
            - Improve endogenous insulin secretion
            - Allow oral glucose-lowering agents to be more effective
            - Insulin therapy may be discontinued if glycemic control improves with this strategy.

- Medications approved for monotherapy
  - Insulin secretagogues
  - Biguanides
  - α-Glucosidase inhibitors
  - Thiazolidinediones
  - Insulin
- Each class has unique advantages and disadvantages.
- Not all agents are effective in all persons (primary failure).
- Assuming a similar degree of glycemic improvement, no clinical advantage to 1 class of drugs has been demonstrated and any therapy that improves glycemic control is likely to be beneficial.
- Certain generalizations apply.
  - Insulin secretagogues, biguanides, and thiazolidinediones
    - Improve glycemic control to similar degree (1–2% reduction in hemoglobin A_{1C} level)
    - More effective than α-glucosidase inhibitors
  - Insulin secretagogues and α-glucosidase inhibitors
    - Begin to decrease plasma glucose level immediately
    - Effects of biguanides and thiazolidinediones are usually delayed by several weeks to months.
  - Biguanides, α-glucosidase inhibitors, and thiazolidinediones do not directly cause hypoglycemia.
  - Most persons will eventually require treatment with > 1 class of oral glucose-lowering agents or insulin.
- Treatment algorithm for initial therapy
  - Sulfonylurea or metformin is often chosen as the initial drug because of efficacy, known side-effect profile, and relatively low cost.
  - A comparison of sulfonylrurea versus metformin in randomized, prospective clinical trials shows no difference in
    - Response rate
    - Degree of glycemic control
  - Dose of either the sulfonylurea or metformin should be increased until glycemic target is achieved.
    - Response is based on analysis of SMBG results and hemoglobin A_{1C} level.
    - One-third will reach target glycemic goal.
    - 25% will not respond; the drug usually should be discontinued.
  - Combination therapy can be considered for those who show improvement in glycemic control but do not achieve glycemic target.
  - Metformin
    - Often initial choice for obese patient
    - Promotes mild weight loss
    - Lowers insulin levels
    - Improves lipid profile slightly
    - May have lower secondary failure rate
  - Thiazolidinediones
    - Alternative initial agents
    - Disadvantage: more expensive
  - α-Glucosidase inhibitors
    - Least potent agents
    - Not as desirable for monotherapy

Combination therapy

- Dosing in combination is the same as when agents used alone.
- Effect on glycemic control is usually additive because of different mechanisms of action.
- Commonly used regimens include:
  - Insulin secretagogue with metformin or thiazolidinedione
  - Sulfonylurea with α-glucosidase inhibitor
  - Insulin with metformin or thiazolidinedione
  - Metformin with a thiazolidinedione
- If adequate control is not achieved with 2 oral agents, bedtime insulin or a third oral agent may be added.

Intensive diabetes management

- Treatment option in type 2 DM when patients:
  - Cannot achieve optimal glycemic control
  - Are capable of implementing such regimens
- Intensive management
  - Goal: euglycemia or near-normal glycemia
  - Approach requires:
    - Thorough and continuing patient education
    - Comprehensive recording of plasma glucose measurements and nutrition intake by patient
    - Variable insulin regimen that matches glucose intake and insulin dose
      - Insulin regimens usually include multiple-component insulin regimens, multiple daily injections, or insulin infusion devices.
  - Benefits
    - Reduction in microvascular complications
    - Possible delay or reduction in macrovascular complications
    - Patient experiences greater control over diabetes
    - Improved sense of well-being, greater flexibility in timing and content of meals, and capability to alter insulin dosing with exercise
    - In pregnancy, reduces risk of fetal malformations and morbidity
  - Complications
    - Increased economic costs
    - Greater demands on patient
    - Risk of hypoglycemia, though less than patients with type 1 DM

Emerging therapies

- Inhaled insulin and additional insulin analogues are in advanced stages of clinical trials.
- Aminoguanidine, an inhibitor of formation of advanced glycosylation end products, and inhibitors of protein kinase C may reduce DM complications.
- Closed-loop pumps that infuse appropriate amount of insulin in response to changing glucose levels are potentially feasible.
- New continuous glucose-monitoring technology is emerging.

The hospitalized patient

- Goals of diabetes management during hospitalization
  - Avoid hypoglycemia.
  - Optimize glycemic control.

    - Maintain a near-normal glucose level with insulin.
    - Transition back to outpatient diabetes treatment regimen.
- Optimal glycemic control in hospitalized patient
    - Preprandial: <6.1 mmol/L (100 mg/dL)
    - Postprandial: <10 mmol/L (180 mg/dL)
- Perioperative management
    - Assessment
        - Hemoglobin A_{1C} measurement, to assess glycemic control; optimize prior to surgery, if possible
        - Monitor electrolytes, renal function, and intravascular volume.
        - Consider preoperative cardiovascular evaluation, even in asymptomatic persons.
    - Oral glucose-lowering agents should be discontinued on admission.
    - Metformin should be withheld when radiographic contrast media will be given or if severe congestive heart failure, acidosis, or declining renal function is present.
    - Treatment regimens
        - Insulin infusion
            - Initial infusion rate: 0.5–5 U/h; depends on degree of insulin resistance and clinical situation
            - Adjustment of infusion rate, based on algorithm or in consultation with physician
            - Rate adjusted to maintain plasma glucose within optimal range; based on hourly capillary glucose measurements
            - Can be temporarily discontinued if hypoglycemic; can resume at lower infusion rate once plasma glucose level >5.6 mmol/L (100 mg/dL)
        - Subcutaneous insulin regimens
            - Intermediate- or long-acting insulin can be supplemented with short-acting insulin on the basis of capillary glucose measurements.
            - Glucose may be infused to prevent hypoglycemia.
- Total parenteral nutrition (TPN)
    - Greatly increases insulin requirements
        - Intravenous insulin infusion (rather than subcutaneous) is the preferred mode of insulin administration.
            - Use separate insulin infusion for rapid titration to required dose.
            - After determination of the total insulin dose, continue to administer insulin as separate infusion (preferred) or add insulin directly to TPN solution.
        - Subcutaneous insulin regimens
            - Doses must be adjusted because TPN or enteral nutrition is most often given continuously.

Monitoring

Guidelines for ongoing medical care

- Monitor the level of glycemic control with:
    - SMBG (individualized frequency)
    - Hemoglobin A_{1C} testing (2–4 times yearly)
- Patient education in diabetes management (annual)
- Medical nutrition therapy and education (annual)

- Surveillance for complications
    - Retinopathy
        - Eye examination (annual)
        - The American Diabetes Association (ADA) recommends the following ophthalmologic examination schedule.
            - Onset of DM at ≤29 years: initial examination within 3–5 years of diagnosis
            - Onset of DM at ≥30 years: initial examination at time of diabetes diagnosis
            - Women with DM contemplating pregnancy: examination before conception and during first trimester
    - Neuropathy
        - Foot examination (1–2 times yearly by physician; daily by patient)
        - The ADA advises visual foot inspection for potential problems at each outpatient visit.
    - Nephropathy (annually)
        - If no protein on routine urinalysis: Measure microalbuminuria with microalbumin/creatinine ratio in spot urine.
        - If proteinuria on urinalysis: Quantify the amount of protein by standard urine protein measurements.
        - Screening should commence 5 years after onset of DM.
- Blood pressure measurement (quarterly)
- Lipid profile (annually)
- Influenza vaccine (annually)
- Pneumococcal and tetanus immunizations (at recommended intervals)
- Consider antiplatelet therapy (aspirin, 75–162 mg/d) for the following.
    - Secondary prevention of macrovascular disease in patients with diabetes with a history of myocardial infarction, vascular bypass, cerebrovascular disease, peripheral vascular disease, claudication, or angina
    - Primary prevention of macrovascular disease in patients with DM at increased cardiovascular risk (age >40 years, smoking, hypertension, dyslipidemia, albuminuria, or family history of coronary artery disease)
- Screening or diagnostic cardiac stress testing should be performed in the following situations.
    - Symptoms of cardiac disease
    - History of peripheral or cerebrovascular disease
    - Sedentary lifestyle
    - Age > 35 years
    - Plans to begin a vigorous exercise program
    - Abnormal resting electrocardiogram

SMBG

- The standard of care in diabetes management
- Provides an assessment of short-term glycemic control
- Performed by measurement of fingerstick capillary plasma glucose
    - Frequency of SMBG measurements should be individualized and adapted to goals of diabetes care.
    - Optimal frequency is not clearly defined in type 2 DM.
        - Once or twice daily may be sufficient.
        - SMBG should be performed more frequently in patients using insulin.

- Continuous blood glucose monitoring
  - 2 recently approved by U.S. Food and Drug Administration
    - Glucowatch: uses iontophoresis to assess glucose in interstitial fluid
    - Minimed continuous glucose monitoring system: an indwelling subcutaneous catheter to monitor interstitial fluid glucose
  - Not yet routinely used

Assessment of long-term glycemic control

- Measurement of glycosylated hemoglobin (hemoglobin A_{1C})
  - Standard method for assessing long-term glycemic control
  - Reflects glycemic history over previous 2–3 months
  - Measure during initial evaluation and as part of comprehensive diabetes care.
- The ADA recommends measurement of hemoglobin A_{1C}:
  - Every 3 months in most patients
  - Twice yearly in patients achieving glycemic goal
- Alternative indicator of glycemic control
  - Fructosamine assay: degree of glycation of albumin
    - Used when hemoglobin A_{1C} is inaccurate (hemolytic anemia, hemoglobinopathies)
    - Reflects glycemic status over prior 2 weeks
  - Current consensus statements do not favor use.
    - Not known whether accurately predicts complications of DM

Complications

Acute complications

- Diabetic ketoacidosis
  - Once considered the hallmark of type 1 DM
  - May occur in patients who lack immunologic features of type 1 DM and who can subsequently be treated with oral agents
    - Most often of Hispanic or African American descent
  - See Diabetic Ketoacidosis for details.
- Hyperglycemic hyperosmolar state
  - See Hyperglycemic Hyperosmolar State for details.

Chronic complications

General

- Responsible for majority of morbidity and mortality associated with DM
- Leading cause of adult blindness, nontraumatic lower extremity amputation, and end-stage renal disease in U.S.
- Risk increases with duration of hyperglycemia.
  - Usually become apparent in second decade of hyperglycemia

Microvascular

- Eye disease
  - Retinopathy (nonproliferative/proliferative)
    - See Diabetic Retinopathy for details.
  - Macular edema
  - Other nonvascular eye disease (cataracts, glaucoma)
- Neuropathy
  - Sensory and motor (mononeuropathy and polyneuropathy)
  - Autonomic
  - See Diabetic Neuropathy for details.
- Nephropathy
  - See Diabetic Nephropathy for details.

Macrovascular

- See Cardiovascular Complications of Diabetes Mellitus for details.
  - Coronary artery disease
  - Peripheral vascular disease
  - Cerebrovascular disease

GI

- Gastroparesis
- Diarrhea
- See Diabetic Neuropathy for details.

Genitourinary

- See Diabetic Neuropathy for details.

Lower extremity

- Amputation
  - DM is the leading cause of nontraumatic lower-extremity amputation in the U.S.
- Foot ulcers
  - Interaction of several pathogenic factors
    - Neuropathy
    - Abnormal foot biomechanics
    - Peripheral arterial disease
    - Poor wound healing
  - Approximately 15% of patients with DM develop a foot ulcer.
    - A significant subset undergo amputation; risk is 14–24% with first ulcer and subsequent ulcers.
- Risk factors for foot ulcers or amputations
  - Male sex
  - DM >10 years
  - Peripheral neuropathy
  - Abnormal structure of foot (bony abnormalities, callus, thickened nails)
  - Peripheral arterial disease
  - Smoking

  - History of previous ulcer or amputation
  - Poor glycemic control

Infectious

- Persons with diabetes have a greater frequency and severity of infection.
  - Osteomyelitis
  - Pneumonia
  - Urinary tract infections
  - Skin and soft-tissue infections
- Several rare infections occur almost exclusively in DM.
  - Rhinocerebral mucormycosis
  - Emphysematous infections of gall bladder and urinary tract
  - "Malignant" or invasive otitis externa
  - Fournier's syndrome, a necrotizing fasciitis most commonly confined to the groin

Dermatologic

- Common features
  - Protracted wound healing
  - Skin ulcerations
  - Xerosis and pruritus
- Diabetic dermopathy (pigmented pretibial papules or "diabetic skin spots")
- Bullous diseases (shallow pretibial ulcerations or erosions)
- Necrobiosis lipoidica diabeticorum (primarily observed in type 1 DM)
- Granuloma annulare
- Scleredema
- Lipoatrophy and lipohypertrophy
  - Can occur at insulin injection sites
  - Unusual with human insulin

Prognosis

- Prognosis is variable.
  - Overall, the risk for death is about 2 times that of people without diabetes.
  - Heart disease is the leading cause of death.
    - Death rates due to heart disease are 2–4 times higher in adults with diabetes than adults without diabetes.
    - Prognosis if coronary artery disease or myocardial infarction is present is worse than for nondiabetic persons.
      - Coronary artery disease is more likely to involve multiple vessels.
      - After controlling for all known cardiovascular risk factors, type 2 DM increases the cardiovascular death rate 2-fold in men and 4-fold in women.
  - Stroke
    - Risk of stroke is 2–4 times higher in adults with diabetes.
    - Approximately 65% of deaths are due to heart disease and stroke (macrovascular complications).
    - Diabetic persons are 25 times more likely to become legally blind than are persons without DM.
  - Diabetic nephropathy is the leading cause of DM-related morbidity and mortality.
    - Proteinuria/nephropathy in DM is associated with:

        - Markedly reduced survival
        - Increased risk of cardiovascular disease
        - Atherosclerosis is the leading cause of death in diabetic persons receiving dialysis.
- United Kingdom Prospective Diabetes Study (UKPDS) findings
    - Intensive diabetes management and improved glycemic control can improve prognosis.
        - Reduced microvascular complications (each percentage point reduction in hemoglobin A_{1C} is associated with 35% reduction in microvascular complications)
            - Retinopathy
            - Neuropathy
            - Nephropathy
        - Possibly reduces or delays macrovascular complications
    - Strict blood pressure control significantly reduces both macrovascular and microvascular complications.
        - Beneficial effects of blood pressure control were greater than the beneficial effects of glycemic control in the UKPDS.
        - Lowering blood pressure to moderate goals (144/82 mmHg) reduced the risk of:
            - DM-related death
            - Stroke
            - Microvascular end points
            - Retinopathy
            - Heart failure

Prevention

Screening

- Rationale for the widespread use of the FPG as a screening test
    - A large number of persons who meet current criteria are asymptomatic and unaware that they have the disorder.
    - Type 2 DM may be present for up to a decade before diagnosis.
    - As many as 50% with type 2 DM have ≥1 diabetes-specific complications at diagnosis.
    - Treatment may favorably alter natural history of DM.
- The ADA recommends screening in:
    - All persons >45 years every 3 years
    - Persons with additional risk factors should be screened at an earlier age.

Prevention

- Efforts to prevent type 2 DM should be encouraged in:
    - Those with a strong family history of DM
    - Others at high risk for DM
    - Persons wiith IFG or IGT
- Recommendations
    - Strongly encourage patients to maintain normal body mass index.
    - Encourage patients to engage in regular physical activity.
- Supportive data
    - Type 2 DM is preceded by a period of IGT.

    - Lifestyle modifications and pharmacologic agents can prevent or delay onset of DM during IGT.
    - Diabetes Prevention Program
        - Trial demonstrated that changes in lifestyle (diet and exercise for 30 min/d 5 times weekly) were beneficial.
            - Prevented or delayed DM by 58% compared to placebo
            - Effect was seen regardless of age, sex, or ethnic group.
        - Metformin
            - Prevented or delayed DM by 31% compared to placebo
    - Studies in Finland and China
        - Similar efficacy of diet and exercise in preventing or delaying DM
- Additional data
    - Acarbose, metformin, and the thiazolidinediones
        - May prevent or delay type 2 DM
        - Not approved for this purpose
    - Ramipril, pravastatin
        - Reduced number of new cases of DM
        - Administered to nondiabetic persons for other reasons (e.g., cardiac, cholesterol lowering)

ICD-9-CM

- 250._0 Diabetes mellitus, (specific complication specified by fourth digit), type II or unspecified, not stated as uncontrolled
- 250._2 Diabetes mellitus, (specific complication specified by fourth digit), type II or unspecified, uncontrolled
- 250.00 Diabetes mellitus without mention of complication, type II or unspecified, not stated as uncontrolled
- 250.02 Diabetes mellitus without mention of complication, type II or unspecified, uncontrolled

See Also

- Cardiovascular Complications of Diabetes Mellitus
- Carpal Tunnel Syndrome and Other Entrapment Neuropathies
- Diabetic Ketoacidosis
- Diabetic Nephropathy
- Diabetic Neuropathy
- Diabetic Retinopathy
- Health Care Screening and Disease Prevention
- Hyperuricemia
- Metabolic Syndrome
- Silent Ischemia
- Type 1 Diabetes Mellitus

Internet Sites

- Professionals
    - Clinical Practice Recommendations
      American Diabetes Association

- Patients
  - Diabetes
    MedlinePlus
  - Homepage
    American Diabetes Association

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PEARLS

- Persons with IFG or IGT are at substantial risk for type 2 DM (40% risk over the next 5 years) and cardiovascular disease.
- Glycemic control and blood pressure control are equally important in the prevention of long-term complications of type 2 DM.

- Most of the oral agents available for the treatment of type 2 DM (insulin secretagogues, biguanides, and thiazolidinediones) improve glycemic control by a similar degree (1–2% reduction in hemoglobin A_{1C} level).
- Meticulous attention to lifestyle factors can reduce the risk for type 2 DM in persons with IFG or IGT.
- The oral glucose tolerance test is not routinely used to screen for type 2 DM but may be indicated in the evaluation of patients with IFG or in the postpartum evaluation of women with gestational DM.
- DM-specific complications may be present in up to 20–50% of persons with newly diagnosed type 2 DM.