Type 1 Diabetes Mellitus

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

Definition

- Diabetes mellitus (DM) comprises a group of common metabolic disorders that share the phenotype of hyperglycemia.
  - Caused by a 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
  - Type 1A DM results from autoimmune beta-cell destruction, which leads to insulin deficiency.
  - Type 1B DM lacks immunologic markers indicative of an autoimmune destructive process of beta cells, but like type IA DM, it is a ketosis-prone insulin deficiency that develops by unknown mechanisms.
- Type 2 DM
  - A heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production
  - See Type 2 Diabetes Mellitus.

Epidemiology

- DM
  - Worldwide prevalence: dramatic increase over past 2 decades and projected to increase further
  - 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: slightly greater in 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 1 DM
  - Incidence varies by geography.
    - Believed to reflect the frequency of high-risk human leukocyte antigen (HLA) alleles among ethnic groups in different geographic locations
    - Scandinavia: highest incidence (e.g., Finland, 35 cases per 100,000 persons yearly)
    - Northern Europe and U.S.: intermediate rate (8–17 cases per 100,000 persons yearly)
    - Pacific Rim: much lower rate (Japan and China, 1–3 cases per 100,000 persons yearly)
  - Age of onset
    - Can develop at any age, but often in childhood or early teens
    - Usually <30 years of age
    - Of persons who develop DM after 30 years of age, ~5–10% have type 1A DM.

Risk Factors

- Genetic susceptibility to type 1A DM involves multiple genes.
  - The major susceptibility gene is located in HLA region on chromosome 6.
    - Polymorphisms in the HLA complex account for 40–50% of genetic risk.
    - The HLA region contains genes that encode class II major histocompatibility complex molecules that are involved in initiating the immune response.
    - Most persons with type 1A DM have the HLA DR3 and/or DR4 haplotype.
    - Haplotypes most strongly associated
      - DQA1*0301
      - DQB1*0302
      - DQA1*501
      - DQB1*0201
      - These haplotypes are present in 40% of children with type 1A DM versus 2% of the normal U.S. population.
  - At least 17 additional genetic loci contribute to susceptibility.
    - Polymorphisms in the promoter region of the insulin gene account for 10% of the predisposition to type 1A DM.
  - Genes that confer protection against development of type 1A DM
    - Haplotypes
      - DQA1*0102
      - DQB1*0602
      - Present in 20% of U.S. population
      - Extremely rare in type 1A DM (<1%)
  - Risk of type 1A DM is increased 10-fold in relatives of persons with the disease.
    - Most persons with predisposing haplotypes do not develop diabetes.
    - Most persons with type 1A DM do not have an affected first-degree relative.
  - Concordance in identical twins is 30–70%.

Etiology

- Type 1A DM
  - Results from synergistic effects of genetic, environmental, and immunologic factors that ultimately destroy pancreatic beta cells
  - Genetic susceptibility (see Risk Factors)

    - Environmental triggers
        - Putative triggers: viruses (especially coxsackie and rubella), bovine milk proteins, nitrosourea compounds
        - Event may precede onset of DM by several years.
    - Immunologic factors
        - Abnormalities in the humoral and cellular arms of the immune system that have been identified include:
            - Islet-cell autoantibodies
            - Activated lymphocytes in the islets, peripancreatic lymph nodes, and systemic circulation
            - T lymphocytes that proliferate when stimulated with islet proteins
            - Release of cytokines within the islets
        - Precise mechanisms of beta-cell death are not known but may involve formation of nitric oxide metabolites, apoptosis, and direct CD8+ T-cell cytotoxicity.
    - Temporal development of type 1A DM
        - Persons with genetic susceptibility have normal beta-cell mass at birth but begin to lose beta cells through autoimmune destruction over months to years.
        - This autoimmune process is thought to be triggered by infectious or environmental stimulus and sustained by beta-cell–specific antigens.
        - Beta-cell mass begins to decrease, and insulin secretion becomes progressively impaired.
        - The rate of decrease in beta-cell mass varies widely, with some patients progressing rapidly to clinical diabetes and others evolving more slowly.
        - Features of diabetes become evident once the majority (~80%) of beta cells are destroyed.
        - Transition from glucose intolerance to frank diabetes is triggered by events associated with increased insulin requirements (e.g., infections or puberty).
- Type 1B DM
    - Etiology unknown

Associated Conditions

- Celiac sprue
- Autoimmune disorders
    - Autoimmune thyroid disease
    - Adrenal insufficiency
    - Pernicious anemia
    - Vitiligo
- Genetic syndromes sometimes associated with DM
    - 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 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.
  - Symptoms secondary to acute hyperglycemia
    - May occur at any stage of the disease
  - Symptoms related to chronic complications
    - Begin to appear during second decade of hyperglycemia
  - The most common presentation in nonobese young persons is acute hyperglycemia.
  - Older persons may present with more insidious onset of symptoms, or rarely, may be identified by laboratory testing.

Hyperglycemia

- Symptoms
  - Polyuria
  - Polydipsia
  - Weight loss
  - Fatigue
  - Weakness
  - Blurry vision
    - Results from changes in water content of lens
    - Resolves as hyperglycemia is controlled
- Signs
  - 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, 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
  - Funduscopic examination
  - Blood pressure determination, including orthostatic measurement when indicated
    - 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 is more frequent in DM.

Differential Diagnosis

Type 2 DM

- Common characteristics
  - Development of DM after 30 years of age
  - Obese (80%)
    - Elderly persons may be lean.
  - May not require insulin initially
  - May have associated conditions (e.g., hypertension, cardiovascular disease, dyslipidemia, or polycystic ovary syndrome)
  - Insulin resistance often associated with central obesity and hypertriglyceridemia

Patients who may be difficult to categorize unequivocally

- Some persons with phenotypic type 2 DM can 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
- 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 [GAD] 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 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 or insulin conversion
- Genetic defects in insulin action
    - Type A insulin resistance
    - Leprechaunism
    - Rabson–Mendenhall syndrome
    - Lipodystrophy syndromes
- 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 diabetes mellitus
- Other genetic syndromes sometimes associated with diabetes (see Associated Conditions)
    - 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 the following 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 as deviations from the population-based mean.
        - For example, the prevalence 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 the 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 mmol/L (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.
- Assess degree of glycemic control by measuring hemoglobin A_{1C}.
- Screen for DM-associated conditions (e.g., microalbuminuria, dyslipidemia, thyroid dysfunction).
- 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
    - The FPG level will usually range between 300 and 500 mg/dL in acute presentations of type 1 DM.
- 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 h 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 persons with DM during the initial evaluation and as part of comprehensive diabetes care
- Notes on use
  - Hemoglobin A_{1C} measurement 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 the 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.

Immunologic markers

- Primarily used in initial evaluation for possible type 1 DM
- Islet-cell autoantibodies
  - Composite of several different antibodies directed at pancreatic islet molecules (e.g., GAD, insulin, IA-2/ICA-512, and an islet ganglioside)
  - Marker of autoimmune process of type 1A DM
  - Present in:
    - >75% of patients with new-onset type 1A DM
    - 3–4% of first-degree relatives of persons with type 1A DM
  - Presence predicts risk for type 1A DM.
    - Persons with impaired insulin secretion after intravenous glucose tolerance testing: >50% 5-year risk
    - Without impaired insulin secretion: <25% 5-year risk
- Assays for autoantibodies to GAD-65 are commercially available and can be helpful in confirming a diagnosis of type 1A DM.

Other laboratory tests

- C-peptide measurement
  - 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 (beginning 5 years after onset of type 1 DM)
  - Microalbuminuria is defined by a microalbumin/creatinine ratio >30 mg/g creatinine.
- Dyslipidemia
  - Fasting lipid profile (annual)
- Thyroid dysfunction
  - Serum thyroid-stimulating hormone

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 treating 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
  - Urine ketone monitoring
  - Insulin administration
  - Guidelines for diabetes management during illnesses
  - Management of hypoglycemia
  - Foot and skin care
  - Diabetes management before, during, and after exercise
  - Risk factor–modifying activities

Other steps

- Insulin replacement
- Treatment of cardiovascular risk factors

Specific Treatments

Medical nutrition therapy

- Nutritional recommendations for all persons with DM (see Table 1)
  - Protein
    - ~15–20% of kcal/d
    - ~10% in patients with nephropathy

Table 1: Nutritional Recommendations for All Persons with Diabetes

-Protein to provide ~15–20% of kcal/d (~10% for those with nephropathy)
-Saturated fat to provide <10% of kcal/d (<7% for those with elevated LDL)
-Polyunsaturated fat to provide ~10% of kcal; avoid trans-unsaturated fatty acids
-60–70% of calories to be divided between carbohydrate and monounsaturated fat, based on medical needs and personal tolerance; glycemic index of food not as important
-Use of caloric sweeteners, including sucrose, is acceptable.
-Fiber (20–35 g/d) and sodium (≤3000 mg/d) levels as recommended for the general healthy population
-Cholesterol intake ≤300 mg/d
-The same precautions regarding alcohol use in the general population also apply to individuals with diabetes.

Note : LDL, low-density lipoprotein.
Adapted from R Farkas-Hirsch, *Intensive Diabetes Management*, Alexandria, VA, American Diabetes Association, 1998; and American Diabetes Association: Diabetes Care 25:S1, 2002.

  - 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
    - Glycemic index of food is not as important.
  - Use of caloric sweeteners, including sucrose, is acceptable.
  - Fiber : 20–35 g/d
  - 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

- Avoid exercise-related hyper- or hypoglycemia.
  - Monitor blood glucose before, during, and after exercise.
  - Delay exercise if blood glucose level is >14 mmol/L (250 mg/dL) or <5.5 mmol/L (100 mg/dL), or if ketones are present.
  - Monitor glucose level during exercise and ingest carbohydrate to prevent hypoglycemia.
  - Decrease insulin doses (based on previous experience) before exercise and inject insulin into nonexercising area.
  - Learn individual glucose responses to different types of exercise and increase food intake for up to 24 hours after exercise, depending on intensity and duration of exercise.
- 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 for coronary artery disease
  - Autonomic neuropathy

Insulin preparations

- Current insulin preparations
  - Generated by recombinant DNA technology
    - Amino-acid sequence of human insulin or variations
    - Beef or pork insulins are no longer used.
    - All insulin in the U.S.: U-100 (100 U/mL)
- Short-acting
  - Lispro
    - Onset: <0.25 hour
    - Peak: 0.5–1.5 hours
    - Effective duration: 3–4 hours

    - Insulin aspart
        - Onset: <0.25 hour
        - Peak: 0.5–1.5 hours
        - Effective duration: 3–4 hours
    - Regular
        - Onset: 0.5–1 hour
        - Peak: 2–3 hours
        - Effective duration: 3–6 hours
- 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
- Combinations
    - 75/25 (75% protamine lispro, 25% lispro)
        - Onset: 0.5–1 hour
        - Peak: dual
        - Effective duration: 10–14 hours
    - 70/30 (70% NPH, 30% regular)
        - Onset: 0.5–1 hour
        - Peak: dual
        - Effective duration: 10–16 hours
    - 50/50 (50% NPH, 50% regular)
        - Onset: 0.5–1 hour
        - Peak: dual
        - Effective duration: 10–16 hours

Insulin regimens

General

- Goal: insulin regimens that mimic physiologic insulin secretion (basal requirements and postprandial spikes)
    - Basal requirements: intermediate- or long-acting insulins
    - Prandial insulin: short-acting
        - Lispro and insulin aspart: Inject just before or just after a meal.
        - Regular insulin: Inject 30–45 minutes before a meal.
- The most physiologic regimens entail:
    - More frequent insulin injections

    - Greater reliance on short-acting insulin
    - More frequent capillary plasma glucose measurements
- Daily insulin requirements
    - Patients with type 1 DM require 0.5–1.0 U/kg per day of insulin, divided into multiple doses.
    - ~40–50% should be given as basal insulin.
    - Initial insulin-dosing regimens should be conservative.

Multiple-component insulin regimens (multiple daily injections)

- Combination of basal insulin, preprandial short-acting insulin, and changes in short-acting insulin doses to accommodate results of frequent SMBG, anticipated food intake, and physical activity
- Numerous variations of these regimens exist that can be optimized for individual patients.
    - SMBG 4–8 times per day is absolutely essential for this type of regimen.
- Numerous variations exist; optimize for individual patients.
- Example 1
    - Basal insulin using glargine at bedtime
    - Preprandial lispro or insulin aspart
        - Preprandial dose based on individualized algorithms that integrate preprandial glucose level and anticipated carbohydrate intake
- Example 2
    - Basal insulin using 2 equal doses of ultralente (breakfast and evening; 10–12 hours apart)
    - Preprandial lispro or insulin aspart
- Example 3
    - Basal insulin using intermediate insulin at bedtime, a small dose of intermediate insulin at breakfast (20–30% of bedtime dose)
    - Preprandial short-acting insulin

Intermediate-acting insulin mixed with short-acting insulin

- Twice-daily injections of intermediate-acting insulin (NPH or lente) mixed with a short-acting insulin before morning and evening meal
    - Two-thirds of total daily insulin dose in morning
        - About two-thirds given as intermediate-acting insulin
        - One-third as short-acting
    - One-third before evening meal
        - About one-half as intermediate-acting insulin
        - One-half as short-acting
    - Moving intermediate insulin from before the evening meal to bedtime may:
        - Avoid nocturnal hypoglycemia
        - Provide more insulin as glucose levels increase in early morning (dawn phenomenon)
    - Adjust insulin dose on the basis of SMBG results, with the following assumptions.
        - FPG level is primarily determined by the prior evening intermediate-acting insulin dose.
        - Pre-lunch glucose level is a function of the morning short-acting insulin dose.
        - Pre-supper glucose level is a function of the morning intermediate-acting insulin dose.
        - Bedtime glucose level is a function of the pre-supper short-acting insulin dose.

Continuous subcutaneous insulin infusion (CSII)

- Also referred to as insulin pump
- Sophisticated insulin infusion devices that can accurately deliver small doses of insulin (microliters per hour)
    - Lispro or insulin aspart is most often used in CSII.
- Multiple basal infusion rates can be programmed to:
    - Accommodate nocturnal versus daytime basal insulin requirement
    - Alter infusion rate during exercise
    - Select different waveforms of insulin infusion
- Preprandial insulin ("bolus") is delivered on the basis of instructions from the patient, who follows individualized algorithms that account for the preprandial plasma glucose level and anticipated carbohydrate intake.
    - Requires a health professional with considerable experience with insulin infusion devices and frequent patient interactions with diabetes management team
- Unique complications of CSII
    - Infection at infusion site
    - Unexplained hyperglycemia due to obstruction of infusion set
    - Diabetic ketoacidosis if pump becomes disconnected

Intensive management

- Requires multiple resources, including:
    - Thorough and continuing patient education
    - Comprehensive recording of plasma glucose measurements and nutrition intake by the 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
- Goal: achieve euglycemia or near-normal glycemia
- Indications
    - Otherwise healthy adults with type 1 DM (selected adolescents and older children)
    - Purposeful, therapeutic attempt to avoid or lessen microvascular complications
    - All pregnant women with DM
    - All women with DM who are planning pregnancy
    - Management of labile DM
    - Availability of health care professionals with appropriate expertise
    - Patients who have had kidney transplantation for diabetic nephropathy
    - Strongly encouraged in patients with newly diagnosed type 1 DM
- Benefits
    - Reduction in microvascular complications
    - Possible delay or reduction in macrovascular complications
    - The patient experiences greater control over his or her 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
    - Not associated with greater degree of side effects, such as hypoglycemia or weight gain
- Complications
    - Increased economic costs
    - Greater demands on patient

Amylin analogue therapy

- 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 1 DM have an absolute deficiency of amylin (and insulin).
- 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 1 DM
    - Primary benefit may be improved control of postprandial glucose excursions.
    - Dosing: Initiate at 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}
    - Side effects: transient mild to moderate nausea and anorexia
    - Contraindications: gastroparesis or inability to monitor for hypoglycemia

Emerging therapies

- Whole-pancreas transplantation
    - Conventionally performed concomitantly with renal transplantation
    - May normalize glucose tolerance in type 1 DM
    - ~80% of simultaneous pancreas and kidney transplants remain functioning at 1 year.
    - Major disadvantage is immunosuppression.
- Pancreatic islet beta-cell transplantation
    - Less invasive alternative to whole-pancreas transplantation
    - Rates of long-term insulin independence has improved in some centers recently.
    - Current barriers to more widespread use of this approach include poor islet beta-cell yield and tissue availability.
- 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.

The hospitalized patient

Goals of diabetes management during hospitalization

- Avoid hypoglycemia.
- Optimize glycemic control.
- Maintain near-normal glucose levels with insulin.
- Transition the patient back to outpatient diabetes treatment regimen.
- Optimal glycemic control in hospitalized patient
    - Preprandial glucose level: <6.1 mmol/L (100 mg/dL)
    - Postprandial glucose level: <10 mmol/L (180 mg/dL)

Perioperative management

- Assessment
  - Measure hemoglobin A_{1C}, to assess glycemic control; optimize before surgery, if possible.
  - Monitor electrolytes, renal function, and intravascular volume.
  - Consider preoperative cardiovascular evaluation, even in asymptomatic persons.
- Treatment regimens
  - Insulin infusion
    - Preferred method for managing type 1 DM in the perioperative period, especially if patient is receiving nil by mouth
    - Initial infusion rate: 0.5–5 U/h; dependent on degree of insulin resistance and clinical situation
    - Adjustment of infusion rate by staff, 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 exceeds 5.6 mmol/L (100 mg/dL)
  - Subcutaneous insulin regimens
    - Reduced dose of subcutaneous, long-acting insulin may suffice if:
      - Brief diagnostic or surgical procedure
      - Local or regional anesthesia
    - Dose of long-acting insulin should be reduced by 30–40%.
    - Short-acting insulin is either held or reduced by 30–40%.
    - 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 a 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 amount of protein by standard urine protein measurements.
        - Screening should commence 5 years after onset of type 1 DM.
- Blood pressure measurement (quarterly)
- Lipid profile (annually)
- Influenza vaccine (annually)
- Pneumococcal and tetanus immunizations (at recommended intervals)
- Surveillance for comorbid conditions
    - Periodic screening for thyroid disease, depression, and sexual dysfunction
- 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 diabetes and an additional cardiovascular risk factor (age >40 years, smoking, hypertension, obesity, hyperlipidemia, albuminuria, or family history of coronary artery disease)
- Screening cardiac stress test 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 the goals of diabetes care.
        - Standard: 4–8 times per day, to estimate and select mealtime boluses of short-acting insulin and to modify long-acting insulin doses
- Data obtained from SMBG is used for the following purposes.
    - To estimate appropriate doses of preprandial insulin, based on current level of glycemia
    - To identify glycemic patterns to adjust daily insulin regimen
    - To identify or prevent hypoglycemia

- Continuous blood glucose monitoring
  - 2 recently approved by the U.S. Food and Drug Administration
    - Glucowatch: uses iontophoresis to assess glucose in interstitial fluid
    - Minimed continuous glucose monitoring system: an indwelling subcutaneous catheter used to monitor interstitial fluid glucose
  - Not yet routinely used
- Ketones
  - Indicator of early diabetic ketoacidosis
  - Patients should measure urine ketones at home in the following situations.
    - Plasma glucose level consistently >16.7 mmol/L (300 mg/dL)
    - During a concurrent illness
    - Such symptoms as nausea, vomiting, or abdominal pain
  - Blood measurement of β-hydroxybutyrate is preferred over urine testing in the clinical setting.

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 (i.e., those whose therapy has changed, or who are not meeting glycemic goals)
  - Twice per year in patients who are meeting treatment goals and have stable glycemic control
- Alternative indicator of glycemic control
  - Fructosamine assay: degree of glycation of albumin
    - Used when hemoglobin A_{1C} measurement 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
  - See Diabetic Ketoacidosis for details.
- Hyperglycemic hyperosmolar state
  - Primarily seen in patients with type 2 DM
  - See Hyperosmolar Hyperglycemic State for details.

Chronic complications

- 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 the U.S.
- Risk increases with duration of hyperglycemia.
  - Usually becomes apparent in second decade of hyperglycemia

Microvascular

- Eye disease
  - Retinopathy (nonproliferative or 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 and infections
  - The interaction of several pathogenic factors promote development.
    - Neuropathy
    - Disordered proprioception
    - 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 that ulcer or 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
  - Rare disorder that predominantly affects young women with type 1 DM, neuropathy, and retinopathy
  - Begins in the pretibial region as an erythematous plaque or papules that gradually enlarge, darken, and develop irregular margins, with atrophic centers and central ulceration
  - May be painful
- 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 among diabetic persons is ~2 times that of people without diabetes.
  - Heart disease: leading cause of death (see Cardiovascular Complications of Diabetes Mellitus)
    - 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 than adults without diabetes.
    - Approximately 65% of deaths in diabetic persons 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 (see Diabetic Retinopathy).
    - 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 patients receiving dialysis.
- Intensive diabetes management and improved glycemic control (Diabetes Control and Complications Trial) can improve prognosis by:
    - Reducing microvascular complications
    - Possibly reducing or delaying macrovascular complications

Prevention

- No known prevention of type 1A DM in humans
    - Diabetes Prevention Trial—Type 1 concluded that administering insulin to high-risk persons did not prevent type 1A DM.
- Screening
    - A number of immunologic markers for type 1 DM are becoming available.
    - Their routine use is discouraged pending identification of clinically beneficial interventions for persons at high risk for type 1 DM.

ICD-9-CM

- 250._1 Diabetes mellitus, (specific complication specified by fourth digit), type I [juvenile type], not stated as uncontrolled
- 250._3 Diabetes mellitus, (specific complication specified by fourth digit), type I [juvenile type], uncontrolled
- 250.01 Diabetes mellitus without mention of complication, type I [juvenile type], not stated as uncontrolled
- 250.03 Diabetes mellitus without mention of complication, type I [juvenile type], uncontrolled

See Also

- Cardiovascular Complications of Diabetes Mellitus
- Carpal Tunnel Syndrome and Other Entrapment Neuropathies
- Diabetic Ketoacidosis
- Diabetic Nephropathy
- Diabetic Neuropathy
- Diabetic Retinopathy
- Metabolic Syndrome

- Polyglandular Failure Syndromes
- Type 2 Diabetes Mellitus

Internet Sites

- Professionals
  - Clinical Practice Recommendations
    American Diabetes Association
- Patients
  - Diabetes Type 1
    MedlinePlus
  - Homepage
    American Diabetes Association

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PEARLS

- Type 1 DM is most common in children, but approximately 10% of patients with type 1 DM are diagnosed after 30 years of age.
- Discrepancies between SMBG results and hemoglobin A_{1C} values may be due to glycemic excursions at unmonitored times of the day.
- Falsely decreased hemoglobin A_{1C} values may be observed in hemoglobinopathies, hemolytic anemias, and pregnancy.
- Falsely elevated hemoglobin A_{1C} values may be observed in uremia, alcohol abuse, or iron deficiency.
- A low C-peptide level measured 1 year after the onset of diabetes likely indicates type 1 DM.
- Intensive management of DM, combined with optimal risk factor reduction, can greatly reduce the risk of diabetic complications.
- Comparable levels of glycemic control are achievable with CSII devices or multiple daily injections of insulin.
- MODY should be considered in young nonobese patients (<25 years) who present with mild hyperglycemia and autosomal dominant inheritance pattern of DM.