SECTION 8
ENDOCRINOLOGIC DISORDERS

CHAPTER 77

Diabetes Mellitus

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KEY CONCEPTS

1. Diabetes mellitus is a group of metabolic disorders of fat, carbohydrate, and protein metabolism that results from defects in insulin secretion, insulin action (sensitivity), or both.
2. The incidence of type 2 diabetes mellitus (DM) is increasing. This has been attributed in part to a Western style diet, increasing obesity, sedentary lifestyle, and an increasing minority population.
3. The two major classifications of DM are type 1 (insulin deficient) and type 2 (combined insulin resistance and relative deficiency in insulin secretion). They differ in clinical presentation, onset, etiology, and progression of disease. Both are associated with microvascular and macrovascular disease complications.
4. Diagnosis of diabetes is made by three criteria: fasting plasma glucose ≥126 mg/dL, a 2-hour value from a 75-g oral glucose tolerance test ≥200 mg/dL, or a casual plasma glucose level of ≥200 mg/dL with symptoms of diabetes; with results confirmed by any of the three criteria on a separate day.
5. Goals of therapy in diabetes mellitus are directed toward attaining normoglycemia, reducing the onset and progression of retinopathy, nephropathy, and neuropathy complications, intensive therapy for associated cardiovascular risk factors, and improving quality and quantity of life.
6. Metformin should be included in the therapy for all type 2 DM patients, if tolerated and not contraindicated, as it is the only oral antihyperglycemic medication proven to reduce the risk of total mortality, according to the United Kingdom Prospective Diabetes Study (UKPDS).
7. Intensive glycemic control is paramount for reduction of microvascular complications (neuropathy, retinopathy, and nephropathy) as evidenced by the Diabetes Control and Complications Trial (DCCT) in type 1 DM and the UKPDS in type 2 DM. The UKPDS also reported that control of hypertension in patients with diabetes will not only reduce the risk of retinopathy and nephropathy but also reduce cardiovascular risk.
8. Knowledge of the patient's quantitative and qualitative meal patterns, activity levels, pharmacokinetics of insulin preparations, and pharmacology of oral and injected antihyperglycemic agents are essential to individualize the treatment plan and optimize blood glucose control while minimizing risks for hypoglycemia and other adverse effects of pharmacologic therapies.
9. Type 1 treatment necessitates insulin therapy. Currently, the basal-bolus insulin therapy or pump therapy in motivated individuals often leads to successful glycemic outcomes. Basal-bolus therapy includes a basal insulin for fasting and postabsorptive control, and rapid-acting bolus insulin for mealtime coverage. Addition of pramlintide in patients with uncontrolled or erratic postprandial glycemia can be warranted, if the patient is willing to inject additional times before each meal.
10. Treatment of type 2 DM often necessitates use of multiple therapeutic agents (combination therapy), including oral and/or injected antihyperglycemics and insulin to obtain glycemic goals.
11. Aggressive management of cardiovascular disease risk factors in type 2 DM is necessary to reduce the risk for adverse cardiovascular events or death. Smoking cessation, use of antiplatelet therapy as a primary prevention strategy, aggressive management of dyslipidemia minimally toward a goal of low-density lipoprotein-cholesterol (LDLC) at <100 mg/dL and secondarily to increase high-density lipoprotein-cholesterol (HDLC) to ≥40 mg/dL, and treatment of hypertension (again often requiring multiple drugs) minimally to attain a blood pressure of <130/80 mm Hg are vital.
12. Prevention strategies for type 1 DM have been unsuccessful. Prevention strategies for type 2 DM are established. Lifestyle changes, dietary restriction of fat, aerobic exercise for 30 minutes five times a week, and weight loss, form the backbone of successful prevention. No medication is currently FDA approved for prevention of diabetes, although several, including metformin and rosiglitazone, have evidence of potential delay of the onset of diabetes.

Learning objectives, review questions, and other resources can be found at **www.pharmacotherapyonline.com.**

13 Patient education and ability to demonstrate self-care and adherence to therapeutic lifestyle and pharmacologic interventions are crucial to successful outcomes. Multidisciplinary teams of healthcare professionals including physicians (primary care, endocrinologists, ophthalmologists, and vascular surgeons), podiatrists, dietitians, nurses, pharmacists, social workers, behavioral health specialists, and certified diabetes educators are needed to optimize these outcomes in persons with diabetes mellitus.

1 DM is a group of metabolic disorders characterized by hyperglycemia. It is associated with abnormalities in carbohydrate, fat, and protein metabolism and results in chronic complications including microvascular, macrovascular, and neuropathic disorders. Nearly 20.8 million Americans have DM, yet only approximately two-thirds of them have been diagnosed.[1] The economic burden of DM approximated $132 billion in 2002, including direct medical and treatment costs as well as indirect costs attributed to disability and mortality.[1] DM is the leading cause of blindness in adults aged 20 to 74 years, and the leading contributor to development of end-stage renal disease. It also accounts for approximately 82,000 lower extremity amputations annually.[1] Finally, a cardiovascular event is responsible for two-thirds of deaths in individuals with type 2 DM.[1]

Although efforts to control hyperglycemia and associated symptoms are important, the major challenges in optimally managing the patient with DM are targeted at reducing or preventing complications, and improving life expectancy and quality of life. Research and drug development efforts over the past several decades have provided valuable information that applies directly to improving outcomes in patients with DM and have expanded the therapeutic armamentarium. Additionally, interventions in an attempt to prevent disease in high-risk populations have been reported for type 1 and 2 DM.

EPIDEMIOLOGY

Typical type 1 DM is an autoimmune disorder developing in childhood or early adulthood, although some latent forms do occur. Type 1 DM accounts for 5% to 10% of all cases of DM and is likely initiated by the exposure of a genetically susceptible individual to an environmental agent.[2] Candidate genes and environmental factors are reportedly prevalent in the general population, but development of β-cell autoimmunity occurs in less than 10% of the genetically susceptible population and progresses to type 1 DM in less than 1% of the population.[3]

The prevalence of β-cell autoimmunity appears proportional to the incidence of type 1 DM in various populations. For instance, the countries of Sweden, Sardinia, and Finland have the highest prevalence of islet cell antibody (3% to 4.5%) and are associated with the highest incidence of type 1 DM, 22 to 35 per 100,000.[4]

Markers of autoimmunity have been detected in 14% to 33% of persons with type 2 DM in some populations and manifest with early failure of oral agents and insulin dependence. This type of DM has also been referred to as latent autoimmune diabetes of adults (LADA).[4]

Type 1 DM idiopathic is a nonimmune form of diabetes frequently seen in minorities with intermittent insulin requirements.[5] The prevalence of type 1 DM has been increasing over the last 100 years.[6] Maturity-onset diabetes of youth (MODY), which can be caused by one of at least six genetic defects, and endocrine disorders such as acromegaly and Cushing syndrome, can be secondary causes of DM.[7] These unusual etiologies, however, only account for 1% to 2% of the total cases of type 2 DM. See the section on Other Specific Types of Diabetes later in this chapter for further discussion.

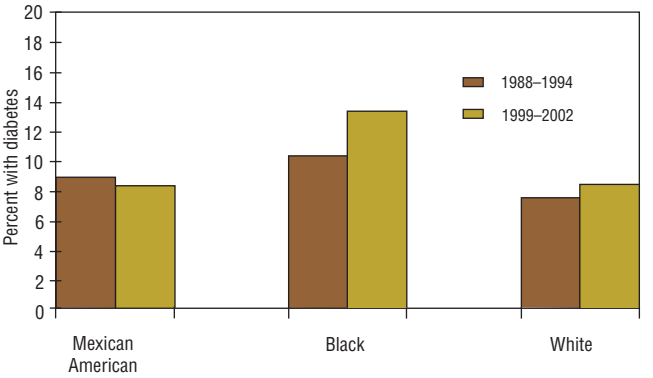


FIGURE 77-1. National Health and Nutrition Evaluation Survey (NHANES) prevalence of diabetes by race among adults ≥20 years of age: United States, 1988–1994 and 1999–2002. *(Adapted from Cowie et al.[9])*

2 The prevalence of type 2 DM is increasing. Type 2 DM accounts for as much as 90% of all cases of DM, and the overall the prevalence of type 2 DM in the United States is approximately 9.6% in persons age 20 years or older. However, there is likely one person undiagnosed for every three persons currently diagnosed with the disease.[1] Multiple risk factors for the development of type 2 DM have been identified, including family history (i.e., parents or siblings with diabetes); obesity (i.e., ≥20% over ideal body weight, or body mass index [BMI] ≥25 kg/m^2); habitual physical inactivity; race or ethnicity; previously identified impaired glucose tolerance or impaired fasting glucose (see Diagnosis of Diabetes section); hypertension (≥140/90 mm Hg in adults); high-density lipoprotein (HDL) cholesterol ≤35 mg/dL and/or a triglyceride level ≥250 mg/dL; history of gestational DM (see Classification of Diabetes section) or delivery of a baby weighing >4 kg (9 lb); history of vascular disease; presence of acanthosis nigricans; and polycystic ovary disease.[8] The prevalence of type 2 DM increases with age, it is more common in women than in men in the United States, and varies widely among various racial and ethnic populations, being especially increased in some groups of Native Americans, Hispanic American, Asian American, African American, and Pacific Island people[9] (Fig. 77–1). Although the prevalence of type 2 DM increases with age (Fig. 77–2),[9] the disorder is increasingly being recognized in adolescence. Much of the increase in adolescent type 2 DM is related to an increase in adiposity and sedentary lifestyle, in addition to an inheritable predisposition.[10] Most cases of type 2 DM do not have a well-known cause; therefore it is uncertain whether it represents a few or many independent disorders manifesting as hyperglycemia.[11]

Gestational diabetes mellitus (GDM) complicates roughly 7% of all pregnancies in the United States.[12] Most women will return to

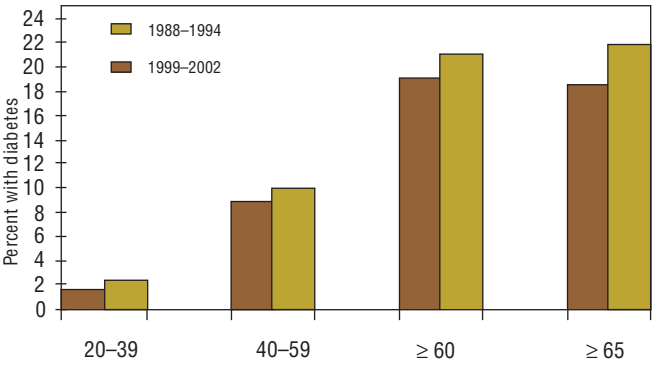


FIGURE 77-2. National Health and Nutrition Evaluation Survey (NHANES) prevalence of diabetes mellitus in United States by age (≥20 years of age) 1988–1994 and 1999–2002. *(Adapted from Cowie et al.[9])*

normoglycemia postpartum, but 30% to 50% will develop type 2 DM or glucose intolerance later in life.

PATHOGENESIS, DIAGNOSIS, AND CLASSIFICATION

CLASSIFICATION OF DIABETES

Diabetes is a metabolic disorder characterized by resistance to the action of insulin, insufficient insulin secretion, or both.[13] The clinical manifestation of these disorders is hyperglycemia. The vast majority of diabetic patients are classified into one of two broad categories: type 1 diabetes caused by an absolute deficiency of insulin, or type 2 diabetes defined by the presence of insulin resistance with an inadequate compensatory increase in insulin secretion. Women who develop diabetes because of the stress of pregnancy are classified as having gestational diabetes. Finally, uncommon types of diabetes caused by infections, drugs, endocrinopathies, pancreatic destruction, and known genetic defects are classified separately (Table 77–1).

Type 1 Diabetes

3 This form of diabetes results from autoimmune destruction of the β cells of the pancreas. Markers of immune destruction of the β cell are present at the time of diagnosis in 90% of individuals and include islet cell antibodies, antibodies to glutamic acid decarboxylase, and antibodies to insulin. Although this form of diabetes usually occurs in children and adolescents, it can occur at any age. Younger individuals typically have a rapid rate of β-cell destruction and present with ketoacidosis, whereas adults often maintain sufficient insulin secretion to prevent ketoacidosis for many years, which is often referred to as LADA.[4]

Type 2 Diabetes

3 This form of diabetes is characterized by insulin resistance and a relative lack of insulin secretion, with progressively lower insulin secretion over time. Most individuals with type 2 diabetes exhibit abdominal obesity, which itself causes insulin resistance. In addition, hypertension, dyslipidemia (high triglyceride levels and low HDL-cholesterol levels), and elevated plasminogen activator inhibitor type 1 (PAI-1) levels are often present in these individuals. This clustering of abnormalities is referred to as the *insulin resistance syndrome* or the *metabolic syndrome*. Because of these abnormalities, patients with type 2 diabetes are at increased risk of developing macrovascular complications. Type 2 diabetes has a strong genetic predisposition and is more common in all ethnic groups other than those of European ancestry. At this point the genetic cause of most cases of type 2 diabetes is not well defined.[14]

TABLE 77-1 Etiologic Classification of Diabetes Mellitus

- **1. Type 1 diabetes**[a] (β-cell destruction, usually leading to absolute insulin deficiency)
  - Immune mediated
  - Idiopathic
- **2. Type 2 diabetes**[a] (can range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
- **3. Other specific types**
  - Genetic defects of β-cell function
    - Chromosome 20q, HNF-4α (MODY1)
    - Chromosome 7p, glucokinase (MODY2)
    - Chromosome 12q, HNF-1β (MODY3)
    - Chromosome 13q, insulin promoter factor (MODY4)
    - Chromosome 17q, HNF-1β (MODY5)
    - Chromosome 2q, neurogenic differentiation 1/b-cell e-box transactivator 2 (MODY6)
    - Mitochondrial DNA
    - Others
  - Genetic defects in insulin action
    - Type 1 insulin resistance
    - Leprechaunism
    - Rabson-Mendenhall syndrome
    - Lipoatrophic diabetes
    - Others
  - Diseases of the exocrine pancreas
    - Pancreatitis
    - Trauma/pancreatectomy
    - Neoplasia
    - Cystic fibrosis
    - Hemochromatosis
    - Fibrocalculous pancreatopathy
    - Others
  - Endocrinopathies
    - Acromegaly
    - Cushing's syndrome
    - Glucagonoma
    - Pheochromocytoma
    - Hyperthyroidism
    - Somatostatinoma
    - Aldosteronoma
    - Others
  - Drug- or chemical-induced
    - Vacor (pyriminil)
    - Pentamidine
    - Nicotinic acid
    - Glucocorticoids
    - Thyroid hormone
    - Diazoxide
    - β-Adrenergic agonists
    - Thiazides
    - Phenytoin
    - Interferon alpha
    - Others
  - Infections
    - Congenital rubella
    - Cytomegalovirus
    - Others
  - Uncommon forms of immune-mediated diabetes
    - "Stiff-man" syndrome
    - Anti-insulin receptor antibodies
    - Others
  - Other genetic syndromes sometimes associated with diabetes
    - Down's syndrome
    - Klinefelter's syndrome
    - Turner's syndrome
    - Wolfram's syndrome
    - Friedreich's ataxia
    - Huntington's chorea
    - Laurence-Moon-Biedel syndrome
    - Myotonic dystrophy
    - Porphyria
    - Prader-Willi syndrome
    - Others
- **4. Gestational diabetes mellitus (GDM)**

[a]Patients with any form of diabetes can require insulin treatment at some stage of their disease. Such use of insulin does not in itself classify the patient.

Adapted with permission from Report of the Expert Committee.[13]

Gestational Diabetes Mellitus

GDM is defined as glucose intolerance that is first recognized during pregnancy. Gestational diabetes complicates approximately 7% of all pregnancies. Clinical detection is important, as therapy will reduce perinatal morbidity and mortality.

Other Specific Types of Diabetes

Genetic Defects MODY is characterized by impaired insulin secretion with minimal or no insulin resistance. Patients typically exhibit mild hyperglycemia at an early age. The disease is inherited in an autosomal dominant pattern with at least six different loci identified to date. Genetic inability to convert proinsulin to insulin results in mild hyperglycemia and is inherited in an autosomal dominant pattern. Similarly, the production of mutant insulin molecules has been identified in a few families and results in mild glucose intolerance.

Several genetic mutations have been described in the insulin receptor and are associated with insulin resistance. Type A insulin resistance refers to the clinical syndrome of acanthosis nigricans, virilization in women, polycystic ovaries, and hyperinsulinemia. In contrast, type B insulin resistance is caused by autoantibodies to the insulin receptor. Leprechaunism is a pediatric syndrome with specific facial features and severe insulin resistance because of a defect in the insulin receptor gene. Lipoatrophic diabetes probably results from postreceptor defects in insulin signaling.

SCREENING

Type 1 Diabetes Mellitus

There is still a low prevalence of type 1 DM in the general population and because of the acuteness of symptoms, screening for type 1 DM is not recommended.[8]

Type 2 Diabetes Mellitus

Based on expert opinion, and not uniformly accepted by all guidance organizations, the American Diabetes Association (ADA) recommends screening for type 2 DM every 3 years in all adults beginning at age 45 years.[8] Testing should be considered at an earlier age and more frequently in individuals with risk factors. The recommended screening test is the fasting plasma glucose (FPG). An oral glucose tolerance test (OGTT) (more costly, less convenient, less reproducible) can be performed alternatively or in addition to FPG when a high index of suspicion for the disease is present.[5]

Children and Adolescents

Despite a lack of clinical evidence to support widespread testing of children for type 2 DM, it is clear that more children and adolescents are developing type 2 DM. The ADA, by expert opinion, recommends that overweight (defined as BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal [50th percentile] for height) youths with at least two of the following risk factors: a family history of type 2 diabetes in first- and second-degree relatives; Native Americans, African Americans, Hispanic Americans, and Asians/South Pacific Islanders; and those with signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome) be screened. Testing should be done every 2 years starting at 10 years of age or at the onset of puberty if it occurs at a younger age.[8]

Gestational Diabetes

Risk assessment for GDM should occur at the first prenatal visit. Women at high risk (positive family history, history of GDM, marked obesity, or member of a high-risk ethnic group) should be screened as soon as feasible. If the initial screening is negative, they should undergo retesting at 24 to 28 weeks of gestation, as should all other pregnant women with the possible exception of low-risk primigravidas. Evaluation for GDM can be done in one of two ways. The one-step approach involves a 3-hour, 100 gram-OGTT and can be cost-effective in high-risk patient populations. The two-step approach uses a screening test to measure plasma or serum glucose concentration 1 hour after a 50 gram oral glucose load (glucose challenge test), followed by a diagnostic 3-hour OGTT on the subset of women exceeding a glucose threshold of either ≥140 mg/dL (80% sensitive) or ≥130 mg/dL (90% sensitive). The diagnosis of GDM is based on a 75-gram (not as well validated) or 100-gram OGTT. Criteria for diagnosis of GDM based on the OGTT are summarized in Table 77–2.

TABLE 77-2 Diagnosis of Gestational Diabetes Mellitus with a 100-g or 75-g Glucose Load

Time	Plasma Glucose
100-g Glucose load	
Fasting	≥95 mg/dL (5.3 mmol/L)
1 hour	≥180 mg/dL (10.0 mmol/L)
2 hours	≥155 mg/dL (8.6 mmol/L)
3 hours	≥140 mg/dL (7.8 mmol/L)
75-g Glucose load	
Fasting	≥95 mg/dL (5.3 mmol/L)
1 hour	≥180 mg/dL (10.0 mmol/L)
2 hours	≥155 mg/dL (8.6 mmol/L)

Two or more values must be met or exceeded for a diagnosis of diabetes to be made. The test should be done in the morning after an 8- to 14-hour fast.

DIAGNOSIS OF DIABETES

4 The diagnosis of diabetes requires the identification of a glycemic cut point, which discriminates normal persons from diabetic patients (Table 77–3). The present cut points reflect the level of glucose above which microvascular complications have been shown to increase. Cross-sectional studies from Egypt, in Pima Indians, and in a representative sample from the United States have shown a consistent increase in the risk of developing retinopathy at a fasting glucose level above 99 to 116 mg/dL (5.5 to 6.4 mmol/L), at a 2-hour postprandial level above 125 to 185 mg/dL (6.9 to 10.3 mmol/L), and a hemoglobin A_{1c} (HbA_{1c}) above 5.9 to 6.0% (Fig. 77–3).[13,15,16]

The ADA recommends using the fasting glucose test as the principal tool for the diagnosis of DM in nonpregnant adults. In addition, as shown in Table 77–4, they defined a new category of glycemia, impaired fasting glucose (IFG). IFG is a plasma glucose of at least 100 mg/dL (5.6 mmol/L) but less than 126 mg/dL (7.0

TABLE 77-3 Criteria for the Diagnosis of Diabetes Mellitus[a]

Symptoms of diabetes plus casual[b] plasma glucose concentration ≥200 mg/dL (11.1 mmol/L)
or
Fasting[c] plasma glucose ≥126 mg/dL (7.0 mmol/L)
or
2-hour postload glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT[d]

OGTT, oral glucose tolerance test.

[a]In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The third measure is not recommended for routine clinical use.

[b]Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

[c]Fasting is defined as no caloric intake for at least 8 hours.

[d]The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

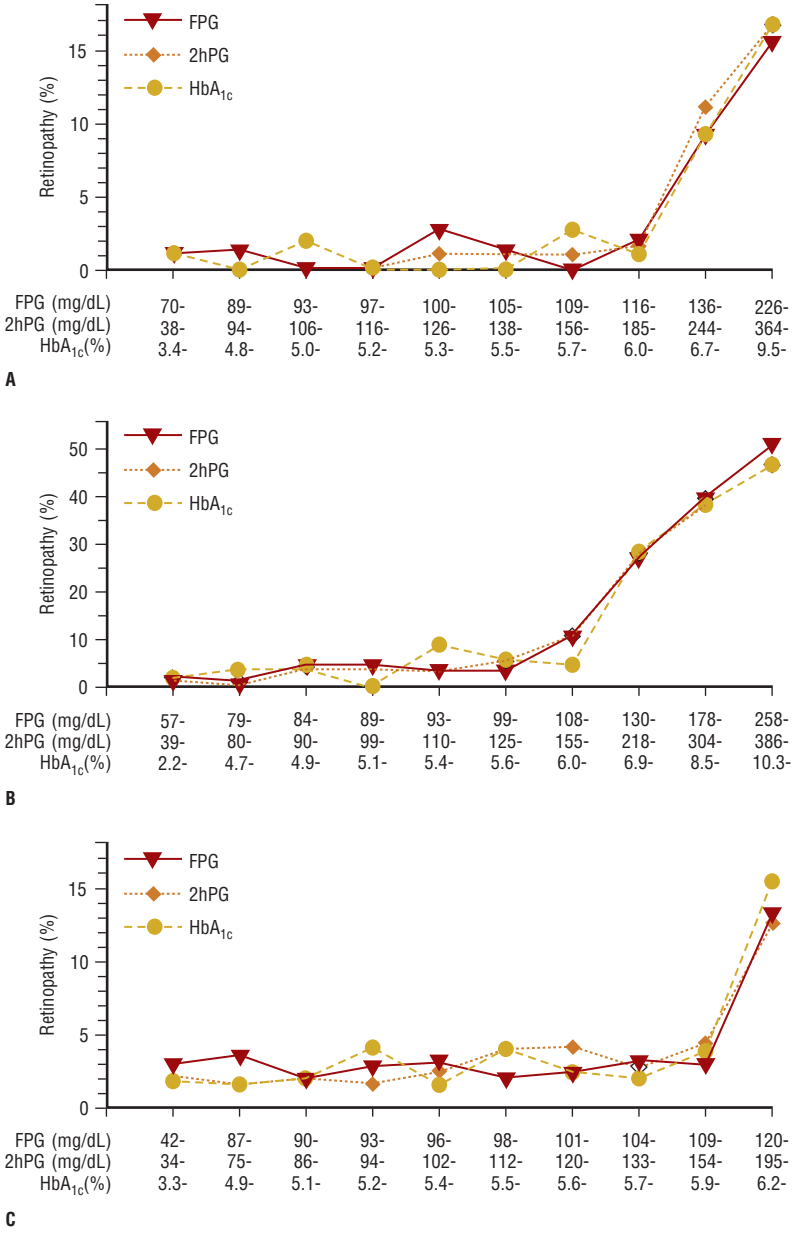


FIGURE 77-3. Prevalence of retinopathy by deciles of the distribution of fasting plasma glucose (FPG), 2-hour postprandial glucose (2-h PG), and hemoglobin A_{Ic} (HbA_{Ic}) in *(A)* Pima Indians,[12] *(B)* Egyptians,[11] and *(C)* in 40- to 74-year old participants in National Health and Nutrition Examination Survey (NHANES) III.[13] The *X*-axis labels indicate the lower limit of each decile group. Note that these deciles and the prevalence rates of retinopathy differ considerably among the studies, especially the Egyptian study, in which diabetic subjects were oversampled. Retinopathy was ascertained by different methods in each study; therefore the absolute prevalence rates are not comparable between studies, but their relationships with FPG, 2-h PG, and HbA_{Ic} are very similar within each population.

mmol/L). Impaired glucose tolerance (IGT), is defined as a 2-hour glucose value ≥140 mg/dL (7.8 mmol/L), but less than 200 mg/dL (11.0 mmol/L) during an OGTT. Patients with either IFG or IGT are now commonly referred to as having "prediabetes" because of a higher risk of developing diabetes in the future.

TABLE 77-4 Categorization of Glucose Status

Fasting plasma glucose (FPG)
Normal
- FPG <100 mg/dL (5.6 mmol/L)

Impaired fasting glucose (IFG)
- 100–125 mg/dL (5.6–6.9 mmol/L)

Diabetes mellitus[a]
- FPG ≥126 mg/dL (7.0 mmol/L)

2-Hour postload plasma glucose (oral glucose tolerance test)
Normal
- Postload glucose <140 mg/dL (7.8 mmol/L)

Impaired glucose tolerance (IGT)
- 2-hour postload glucose 140–199 mg/dL (7.8–11.1 mmol/L)

Diabetes mellitus[a]
- 2-hour postload glucose ≥200 mg/dL (11.1 mmol/L)

[a]Provisional diagnosis of diabetes (diagnosis to be confirmed; see Table 77–3).

The fasting and postprandial glucose levels do not measure the same physiologic processes and do not identify the same individuals as having diabetes. The fasting glucose reflects hepatic glucose production, which depends on insulin secretory capacity of the pancreas. The postprandial glucose reflects uptake of glucose in peripheral tissues (muscle and fat) and depends on insulin sensitivity of these tissues.

The ADA recommends use of HbA_{1c} determinations to monitor glycemic control in known diabetic patients. Because there is no gold standard assay and several countries do not have ready access to the test, a HbA_{1c} determination is not recommended to diagnose diabetes at the present time.

PATHOGENESIS

Type 1 Diabetes Mellitus

Type 1 DM is characterized by an absolute deficiency of pancreatic β-cell function. Most often this is the result of an immune-mediated destruction of pancreatic β cells, but rare unknown or idiopathic processes can contribute. What is evident are four main features: (1) a long preclinical period marked by the presence of immune markers when β-cell destruction is thought to occur; (2) hypergly-

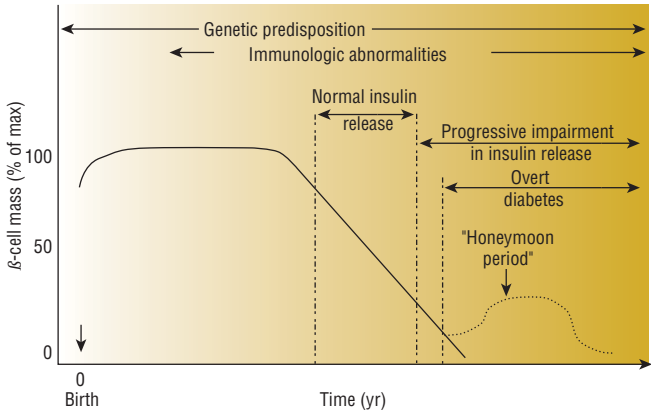


FIGURE 77-4. Scheme of the natural history of the β-cell defect in type 1 diabetes mellitus. *(From ADA Medical Management of Type 1 Diabetes, 3rd ed. American Diabetes Association, Alexandria, VA, 1998.)*

cemia when 80% to 90% of β cells are destroyed; (3) transient remission (the so-called *honeymoon* phase); and (4) established disease with associated risks for complications and death. Unknown is whether there is one or more inciting factors (e.g., cow's milk, or viral, dietary, or other environmental exposure) that initiate the autoimmune process (Fig. 77–4).[2]

The autoimmune process is mediated by macrophages and T lymphocytes with circulating autoantibodies to various β-cell antigens. The most commonly detected antibody associated with type 1 DM is the islet cell antibody. The test for islet cell antibody, however, is difficult to standardize across laboratories. Other more readily measured circulating antibodies include insulin autoantibodies, antibodies directed against glutamic acid decarboxylase, insulin antibodies against islet tyrosine phosphatase, and several others. More than 90% of newly diagnosed persons with type 1 DM have one or another of these antibodies, as will 3.5% to 4% of unaffected first-degree relatives. Preclinical β-cell autoimmunity precedes the diagnosis of type 1 DM by up to 9 to 13 years. Autoimmunity can remit in some perhaps less-susceptible persons, or can progress to β-cell failure in others. These antibodies are generally considered markers of disease rather than mediators of β-cell destruction. They have been used to identify individuals at risk for type 1 DM in evaluating disease-prevention strategies. Other nonpancreatic autoimmune disorders are associated with type 1 DM, most commonly Hashimoto thyroiditis, but the extent of organ involvement can range from no other organs to polyglandular failure.[17]

There are strong genetic linkages to the DQA and B genes, and certain human leukocyte antigens (HLAs) can be predisposing (DR3 and DR4) or protective (DRB1*04008-DQB1*0302 and DRB1*0411-DQB1*0302) on chromosome 6.[17] Other candidate gene regions have been identified on several other chromosomes as well. Because twin studies do not show 100% concordance, environmental factors such as infectious agents, chemical agents, and dietary agents are likely contributing factors in the expression of the disease.

Destruction of pancreatic β-cell function causes hyperglycemia because of an absolute deficiency of both insulin and amylin.[18] Insulin lowers blood glucose by a variety of mechanisms including: stimulation of tissue glucose uptake, suppression of glucose production by the liver, and suppression of free fatty acid release from fat cells.[19] The suppression of free fatty acids plays an important role in glucose homeostasis. Increased levels of free fatty acids inhibit the uptake of glucose by muscle and stimulate hepatic gluconeogenesis.[20] Amylin, a glucoregulatory peptide hormone cosecreted with insulin, plays a role in lowering blood glucose by slowing gastric emptying, suppressing glucagon output from pancreatic α cells, and increasing satiety.[21] In type 1 DM amylin production, caused by β-cell destruction, is very low.

Type 2 Diabetes Mellitus

Normal Insulin Action In the fasting state 75% of total body glucose disposal takes place in non–insulin-dependent tissues: the brain and splanchnic tissues (liver and gastrointestinal [GI] tissues).[22] In fact, brain glucose uptake occurs at the same rate during fed and fasting periods and is not altered in type 2 diabetes.

The remaining 25% of glucose metabolism takes place in muscle, which is dependent on insulin.[23] In the fasting state approximately 85% of glucose production is derived from the liver, and the remaining amount is produced by the kidney.[22–24] Glucagon, produced by pancreatic α cells, is secreted in the fasting state to oppose the action of insulin and stimulate hepatic glucose production. Thus, glucagon prevents hypoglycemia or restores normoglycemia if hypoglycemia has occurred.[25] In the fed state, carbohydrate ingestion increases the plasma glucose concentration and stimulates insulin release from the pancreatic β cells. The resultant hyperinsulinemia (1) suppresses hepatic glucose production and (2) stimulates glucose uptake by peripheral tissues.[22,26] The majority (~80%–85%) of glucose that is taken up by peripheral tissues is disposed of in muscle,[22,26] with only a small amount (~4%–5%) being metabolized by adipocytes. In the fed state, glucagon is suppressed.[25]

Although fat tissue is responsible for only a small amount of total body glucose disposal, it plays a very important role in the maintenance of total body glucose homeostasis. Small increments in the plasma insulin concentration exert a potent antilipolytic effect, leading to a marked reduction in the plasma free fatty acid (FFA) level. The decline in plasma FFA concentration results in increased glucose uptake in muscle[27] and reduces hepatic glucose production.[28] Thus a decrease in the plasma FFA concentration lowers plasma glucose by both decreasing its production and enhancing the uptake in muscle.[20,29]

Type 2 diabetic individuals are characterized by (1) defects in insulin secretion; and (2) insulin resistance involving muscle, liver, and the adipocyte. Insulin resistance is present even in *lean* type 2 diabetic individuals (Fig. 77–5).

Impaired Insulin Secretion The pancreas in people with a normal-functioning β cell is able to adjust its secretion of insulin to maintain normal glucose tolerance. Thus in nondiabetic individuals, insulin is increased in proportion to the severity of the insulin resistance, and glucose tolerance remains normal. Impaired insulin secretion is a uniform finding in type 2 diabetic patients and the evolution of β-cell dysfunction has been well characterized in diverse ethnic populations.

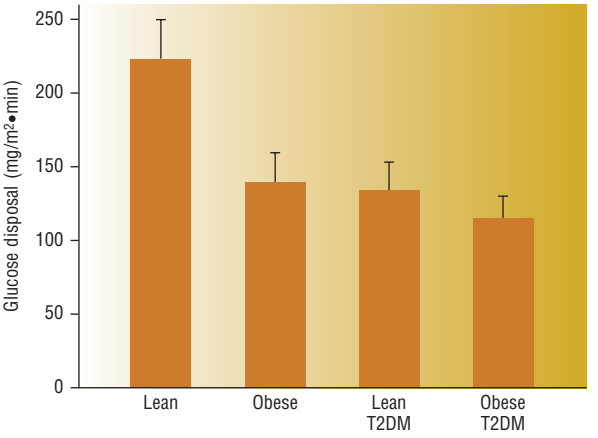


FIGURE 77-5. Whole body glucose disposal, a measure of insulin resistance, is reduced 40% to 50% in obese nondiabetic and lean type 2 diabetic individuals. Obese diabetic individuals are slightly more resistant than lean diabetic patients. (T2DM, type 2 diabetes mellitus.) *(Copyright © 1988 American Diabetes Association. From Diabetes, Vol. 37, 1988;667–687. Reprinted with permission from The American Diabetes Association.)*

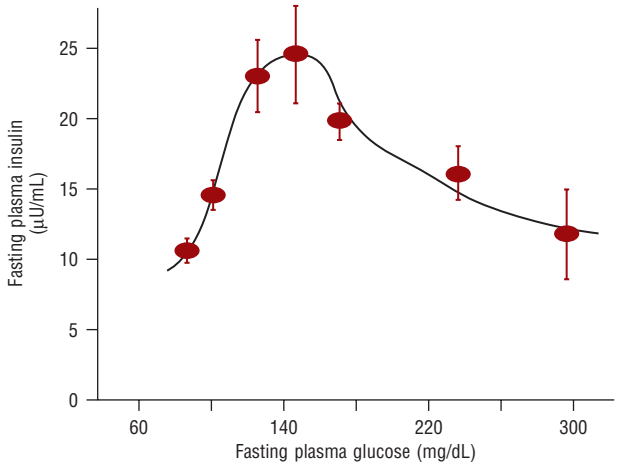


FIGURE 77-6. The relationship between fasting plasma insulin and fasting plasma glucose in 177 normal weight individuals. Plasma insulin and glucose increase together up to a fasting glucose of 140 mg/dL. When the fasting glucose exceeds 140 mg/dL, the β cell makes progressively less insulin, which leads to an overproduction of glucose by the liver and results in a progressive increase in fasting glucose. *(Adapted from DeFronzo,[30] with permission.)*

DeFronzo and colleagues[30] measured the fasting plasma insulin concentration and performed OGTTs in 77 normal-weight type 2 diabetic patients and more than 100 lean subjects with normal or impaired glucose tolerance (Fig. 77–6). The relationship between the FPG concentration and the fasting plasma insulin concentration resembles an inverted U or horseshoe. As the FPG concentration increases from 80 to 140 mg/dL, the fasting plasma insulin concentration increases progressively, peaking at a value that is 2- to 2.5-fold greater than in normal weight nondiabetic controls. When the FPG concentration exceeds 140 mg/dL, the β cell is unable to maintain its elevated rate of insulin secretion, and the fasting insulin concentration declines precipitously. This decrease in fasting insulin leads to an increase in hepatic glucose production overnight, which results in an elevated FPG concentration.[30]

In the type 2 diabetic patient, decreased postprandial insulin secretion is caused by both impaired pancreatic β-cell function and a reduced stimulus for insulin secretion from gut hormones. The role gut hormones play in insulin secretion is best shown by comparing the insulin response to an oral glucose load versus an isoglycemic intravenous glucose infusion.[31] In nondiabetic control individuals 73% more insulin is released in response to an oral glucose load compared to the same amount of glucose given intravenously (Fig. 77–7, left panel). This increased insulin secretion in response to an oral glucose stimulus is referred to as *the incretin effect* and suggests that gut derived hormones when stimulated by glucose lead to an increase in pancreatic insulin secretion. In type 2 diabetic patients this incretin effect is blunted, with the increase in insulin secretion to only 50% of that seen in nondiabetic control individuals (Fig. 77–7).[31] It is now known that two hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin-releasing peptide (GIP), are responsible for more than 90% of the increased insulin secretion seen in response to an oral glucose load. In patients with type 2 diabetes GLP-1 levels are reduced whereas GIP levels are increased.[32]

GLP-1 is secreted from the L-cells in the distal intestinal mucosa in response to mixed meals. Because GLP-1 levels increase within minutes of food ingestion, neural signals initiated by food entry in the proximal gastrointestinal tract must simulate GLP-1 secretion.[33] The insulinotropic action of GLP-1 is glucose-dependent, and for GLP-1 to enhance insulin secretion, glucose concentrations must be higher than 90 mg/dL.[32] In addition to stimulating insulin secretion, GLP-1 suppresses glucagon secretion, slows gastric emptying and reduces food intake by increasing satiety. These effects of GLP-1 combine to limit postprandial glucose excursions. GIP is secreted by K-cells in the intestine and like GLP, increase insulin secretion.[34] However, GIP has no effect on glucagon secretion, gastric motility, or satiety.[35] The half-life of GLP-1 and GIP are short (<10 minutes). Both hormones are rapidly inactivated by removal of two N-terminal amino acids by the enzyme, dipeptidyl peptidase IV (DPP-IV).[36]

Site of Insulin Resistance in Type 2 Diabetes

Liver In type 2 diabetic subjects with mild to moderate fasting hyperglycemia (140 to 200 mg/dL, 7.8 to 11.1 mmol/L), basal hepatic glucose production is increased by ~0.5 mg/kg per minute. Consequently, during the overnight sleeping hours the liver of an 80-kg diabetic individual with modest fasting hyperglycemia adds an additional 35 g of glucose to the systemic circulation. This increase in fasting hepatic glucose production is the cause of fasting hyperglycemia.[22]

Following glucose ingestion, insulin is secreted into the portal vein and carried to the liver, where it suppresses glucagon secretion and reduces hepatic glucose output. Type 2 diabetic patients fail to suppress glucagon in response to a meal and can even have a paradoxical rise in glucagon levels.[36,37] Thus, hepatic insulin resistance and hyperglucagonemia result in continued production of glucose by the liver. Therefore, type 2 diabetic patients have two sources of glucose in the postprandial state, one from the diet and one from continued glucose production from the liver. These sources of glucose in combination with a shortened gastric emptying time can result in marked hyperglycemia.

Peripheral (Muscle) Muscle is the major site of glucose disposal in man, and approximately 80% of total body glucose uptake occurs

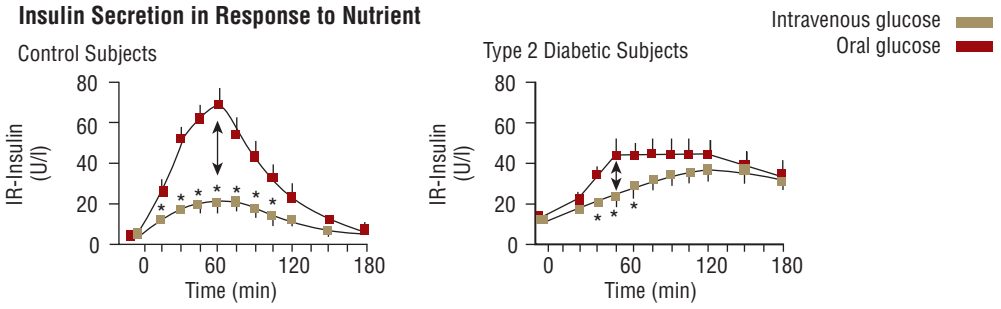


FIGURE 77-7. The loss of the incretin effect in type 2 diabetes mellitus. The plasma insulin responses to oral and intravenous glucose in nondiabetic subjects *(left figure)*, compared to patients with diabetes *(right figure)*. *(Adapted from Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 [non-insulin dependent] diabetes. Diabetologia 1986;29:46–52.)*

in skeletal muscle.[22] In response to a physiologic increase in plasma insulin concentration, muscle glucose uptake increases linearly, reaching a plateau value of 10 mg/kg per minute. In contrast, in lean type 2 diabetic subjects, the onset of insulin action is delayed for ~40 minutes, and the ability of insulin to stimulate leg glucose uptake is reduced by 50%. Therefore the primary site of insulin resistance in type 2 diabetic subjects resides in muscle tissue.

Peripheral (Adipocyte) In obese nondiabetic and diabetic humans, basal plasma FFA levels are increased and fail to suppress normally after glucose ingestion. FFAs are stored as triglycerides in adipocytes and serve as an important energy source during conditions of fasting. Insulin is a potent inhibitor of lipolysis, and restrains the release of FFAs from the adipocyte by inhibiting the hormone-sensitive lipase enzyme. It is now recognized that chronically elevated plasma FFA concentrations can lead to insulin resistance in muscle and liver,[20,22,27,38] and impair insulin secretion.[29,39,40] In addition to FFAs that circulate in plasma in increased amounts, type 2 diabetic and obese nondiabetic individuals have increased stores of triglycerides in muscle[41,42] and liver,[43,44] and the increased fat content correlates closely with the presence of insulin resistance in these tissues.

In summary, insulin resistance involving both muscle and liver are characteristic features of the glucose intolerance in type 2 diabetic individuals. In the basal state, the liver represents a major site of insulin resistance, and this is reflected by overproduction of glucose. This accelerated rate of hepatic glucose output is the primary determinant of the elevated FPG concentration in type 2 diabetic individuals. In the fed state, both decreased muscle glucose uptake and impaired suppression of hepatic glucose production contribute to the insulin resistance. In obese individuals and in the majority (>80%) of type 2 diabetic subjects, there is an expanded fat cell mass, and the adipocytes are resistant to the antilipolytic effects of insulin. Most obese and diabetic individuals are characterized by expanded visceral adiposity, discussed in detail later in the chapter, which is especially refractory to insulin effects and results in a high lipolytic rate. Not surprisingly, both type 2 diabetes and obesity are characterized by an elevation in the mean 24-hour plasma FFA concentration. Elevated plasma FFA levels, as well as increased triglyceride/fatty acyl coenzyme A (CoA) content in muscle, liver, and β cells, lead to the development of muscle/hepatic insulin resistance and impaired insulin secretion.

Cellular Mechanisms of Insulin Resistance

Insulin resistance and the components of the insulin resistance syndrome are described below.

Obesity and Insulin Resistance Weight gain leads to insulin resistance, and obese nondiabetic individuals have the same degree of insulin resistance as lean type 2 diabetic patients.[45] In 1,146 nondiabetic, normotensive individuals, Ferrannini and associates showed a progressive loss of insulin sensitivity when the BMI increased from 18 kg/m^2 to 38 kg/m^2.[46] The increase in insulin resistance with weight gain is directly related to the amount of visceral adipose tissue.[47,48]

The term *visceral adipose tissue* (VAT) refers to fat cells located within the abdominal cavity and includes omental, mesenteric, retroperitoneal, and perinephric adipose tissue. VAT has been shown to correlate with insulin resistance and explain much of the variation in insulin resistance seen in a population of African Americans.[49] Visceral adipose tissue represents 20% of fat in men and 6% of fat in women. This fat tissue has been shown to have a higher rate of lipolysis than subcutaneous fat, resulting in an increase in FFA production. These fatty acids are released into the portal circulation and drain into the liver, where they stimulate the production of very-low-density lipoproteins and decrease insulin sensitivity in peripheral tissues.[47] VAT also produces a number of cytokines that cause insulin resistance. These factors drain into the portal circulation and reduce insulin sensitivity in peripheral tissues.[50]

The fat cell also has the capability of producing at least one hormone that improves insulin sensitivity: adiponectin. This factor is made in decreasing amounts as an individual becomes more obese.[51,52] In animal models, adiponectin decreases hepatic glucose production and increases fatty acid oxidation in muscle.[53,54]

The Metabolic Syndrome The association of insulin resistance with a clustering of cardiovascular risk factors including hyperinsulinemia, hypertension, abdominal obesity, dyslipidemia, and coagulation abnormalities has been referred to by a variety of names including "the insulin resistance syndrome," "the metabolic syndrome," "the dysmetabolic syndrome," and "the deadly quartet," to name a few. Since the description of the "insulin resistance syndrome" by Reaven in 1988,[55] the number of associated factors has continued to grow.

The most recent definition of the metabolic syndrome was adopted by the International Diabetes Federation (IDF) in 2005 (Table 77–5).[56]

In the IDF definition of the metabolic syndrome, central obesity is recognized as an important causative factor and is a prerequisite component for the diagnosis. Central obesity can be easily assessed

TABLE 77-5 NCEP ATP III: Five Components of the Metabolic Syndrome (Individuals Having at Least Three Components Meet the Criteria for Diagnosis)

Risk Factor	Defining Level
Abdominal obesity	Waist circumference
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
High-density–lipoprotein C	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL
The 2005 IDF definition of metabolic syndrome	
For a person to be defined as having the metabolic syndrome they must have:	
Central obesity (defined as waist circumference >94 cm for Europid men and >80 cm for Europid women, with *ethnicity specific values for other groups*)	
Plus any two of the following four factors:	
1. Raised TG level: >150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality	
2. Reduced HDL cholesterol: <40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality	
3. Raised blood pressure: systolic BP >130 or diastolic BP >85 mm Hg, or treatment of previously diagnosed hypertension	
4. Raised FPG >100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes	
If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define the presence of the syndrome.	
Ethnic specific values for waist circumference	
Country/Ethnic Group	Waist Circumference
Europids	
Men	>94 cm
Women	>80 cm
South Asians, Chinese	
Men	>90 cm
Women	>80 cm
Japanese	
Men	>85 cm
Women	>90 cm

ASP III, Adult Treatment Panel III; BP, blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test; TG, triglyceride.

In the United States, the ATP III values (102 cm male, 88 cm female) are still being used. European cut points are recommended for sub-Saharan Africans and Eastern Mediterranean and Middle East (Arab) populations. South Asian values are recommended for South and Central Americans.

Reproduced from Expert Panel on Detection.[159]

using waist circumference. The IDF has made a "first attempt" to provide ethnic group specific cut points for waist circumference. At the present time these are pragmatic estimates taken from various data sources. As more complete data becomes available these values can be modified. Table 77–5 lists the ethnic specific values for waist circumference.

The evolution of definitions of the metabolic syndrome is a result of accumulating data correlating degree of risk and specific metabolic abnormalities in various populations. As more robust data sets become available, future changes in the component cut points will be warranted.

Prevalence. Regardless of the definition used, large numbers of U.S. adults have the metabolic syndrome. The National Health and Nutrition Examination Survey (NHANES) 1999 to 2002 is the most scientifically rigorous sample of the U.S. population.[57] A total of 3,601 men and women aged >20 years were included in the survey. Using the National Cholesterol Education Program (NCEP) definition, the prevalence of metabolic syndrome was 33.7% of men and 35.4% of women. In comparison the prevalence using the IDF definition was 39.9% of men and 38.1% of women. The largest difference in prevalence was found in Mexican American men among whom the age-adjusted prevalence was 40.3% using the NCEP definition and 50.6% using the IDF definition. The percent agreement between the two definitions was 89.8% among men and 96% among women.

In a sample of 4,060 predominantly European adults from South Australia, the metabolic syndrome was present in 19.4% of men and 14.4% of women using the Adult Treatment Panel III (ATP III) definition.[58] Using the IDF definition, the metabolic syndrome was identified in 26.4% of men and 15.7% of women. In this population the IDF, using a smaller waist circumference, categorized 15 to 20% more individuals as having the metabolic syndrome. Although the prevalence of the metabolic syndrome in these surveys is staggering, these data are now more than 8 years old, and the prevalence has almost certainly increased as these populations age and become more obese.

The impact of treating the clinical components of the metabolic syndrome was demonstrated in the Steno-2 Study.[59] In this prospective study, 63 patients with diabetes and microalbuminuria were randomized to the usual therapy group, and 67 patients were treated intensively. Intensive therapy consisted of diet and exercise and pharmacologic intervention aimed at hyperglycemia, hypertension, dyslipidemia, microalbuminuria, and increased coagulopathy (aspirin therapy). Treatment goals for intensive therapy included a blood pressure <130/80 mm Hg, HbA_{1c} <6.5%, total cholesterol <175 mg/dL, and triglycerides <150 mg/dL. All patients in the intensive treatment group were given an aspirin and treated with an angiotensin-converting enzyme (ACE) inhibitor. Patients in the intensively treated group showed a 53% relative risk reduction in cardiovascular disease and a 61% relative risk reduction in nephropathy. In this small study, the magnitude of this reduction is greater than has been demonstrated with individual interventions, stressing the importance of targeting all the components of the metabolic syndrome. The study design did not allow conclusions regarding which interventions had the most impact.

CLINICAL PRESENTATION

The clinical presentations of type 1 DM and type 2 DM are very different (Table 77–6). Autoimmune type 1 DM can occur at any age. Approximately 75% will develop the disorder before age 20 years, but the remaining 25%, including relatives of index patients, develop the disease as adults. Individuals with type 1 DM are often thin and are prone to develop diabetic ketoacidosis if insulin is withheld, or under conditions of severe stress with an excess of counterregulatory hormones.[2] Twenty to forty percent of patients with type 1 DM present with diabetic ketoacidosis after several days of polyuria, polydipsia, polyphagia, and weight loss. Occasionally, patients are diagnosed as short of "metabolic bankruptcy" when they have blood tests drawn for other reasons or for early symptoms. Because newly diagnosed patients with type 1 DM often have a small amount of residual pancreatic β-cell function, they can enter a "honeymoon" phase, when their blood glucose concentrations are relatively easy to control and small amounts of insulin are needed. Once this residual insulin secretion wanes, the patients are completely insulin deficient and tend to have more labile glycemia.

TABLE 77-6 Clinical Presentation of Diabetes Mellitus[a]

Characteristic	Type 1 DM	Type 2 DM
Age	<30 years[b]	>30 years[b]
Onset	Abrupt	Gradual
Body habitus	Lean	Obese or history of obesity
Insulin resistance	Absent	Present
Autoantibodies	Often present	Rarely present
Symptoms	Symptomatic[c]	Often asymptomatic
Ketones at diagnosis	Present	Absent[d]
Need for insulin therapy	Immediate	Years after diagnosis
Acute complications	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state
Microvascular complications at diagnosis	No	Common
Macrovascular complications at or before diagnosis	Rare	Common

DM, diabetes mellitus.
[a]Clinical presentation can vary widely.
[b]Age of onset for type 1 DM is generally < 20 years of age but can present at any age. The prevalence of type 2 DM in children, adolescents, and young adults is increasing. This is especially true in ethnic and minority children.
[c]Type 1 can present acutely with symptoms of polyuria, nocturia, polydipsia, polyphagia, and weight loss.
[d]Type 2 children and adolescents are more likely to present with ketones but after the acute phase can be treated with oral agents. Prolonged fasting can also produce ketones in individuals.

Patients with type 2 DM often present without symptoms, even though complications tell us that they may have had type 2 DM for several years.[10] Often these patients are diagnosed secondary to unrelated blood testing. Lethargy, polyuria, nocturia, and polydipsia can be seen at diagnosis in type 2 diabetes, but significant weight loss at diagnosis is less common.

TREATMENT

DM

■ DESIRED OUTCOME

5 The primary goals of DM management are to reduce the risk for microvascular and macrovascular disease complications, to ameliorate symptoms, to reduce mortality, and to improve quality of life.[8] Near-normal glycemia will reduce the risk for development of microvascular disease complications, but aggressive management of traditional cardiovascular risk factors (i.e., smoking cessation, treatment of dyslipidemia, intensive blood pressure control, and antiplatelet therapy) are needed to reduce the likelihood of development of macrovascular disease. Evidence-based guidelines, as published by the ADA, can help in the attainment of these goals (Table 77–7).

Hyperglycemia not only increases the risk for microvascular disease, but contributes to poor wound healing, compromises white blood cell function, and leads to classic symptoms of DM. Diabetic ketoacidosis and hyperosmolar hyperglycemic state are severe manifestations of poor diabetes control, invariably requiring hospitaliza-

TABLE 77-7 Selected American Diabetes Association Evidence-Based Recommendations[a]

Recommendation Area	Specific Recommendation	Evidence Level[a]
Screening for diabetes	Screen overweight at 45 years old, repeat at 3-year intervals	E
	Screen with fasting plasma glucose or 2-hour 75-g OGTT	B
Monitoring	Home blood-glucose monitoring is needed if on insulin	A
	Subjects on other therapeutic interventions, including oral agents may need home blood glucose monitoring	E
	Quarterly HbA1c in individuals not meeting glycemic goals, twice yearly in individuals meeting glycemic goals should be performed	E
Glycemic goals	HbA1c goal for patients in general is <7%	B
	HbA1c goal for individuals is as close to normal (<6%) as possible without significant hypoglycemia	E
Treatment		
Medical nutrition therapy	Weight loss is recommended for all insulin-resistant/overweight or obese individuals	A
	Saturated fat should be <7% of total calories	A
	Monitoring carbohydrate intake by carbohydrate counting or exchanges is recommended.	A
	Glycemic index can give modest benefits over total carbohydrate intake.	B
	Low-carbohydrate diets (<130 g of carbohydrate) are not currently recommended as long-term effects are unknown	B
Physical activity	150 min/wk of moderate intensity exercise is recommended or 90 minutes of vigorous exercise per week	A
	Resistance-train large muscle groups 3 times per week	A
Blood pressure	Systolic blood pressure should be treated to <130 mm Hg	C
	Diastolic blood pressure should be treated to <80 mm Hg	B
	Initial drug therapy should be with an ACE inhibitor, angiotensin receptor blocker, diuretic, β-blocker, or calcium channel blocker	A
Nephropathy	Type 1 DM with any degree of albuminuria–ACE inhibitor	A
	Type 2 DM with microalbuminuria–ACE inhibitor or angiotensin receptor blocker	A
	Type 2 DM with macroalbuminuria–angiotensin receptor blocker	A
Dyslipidemia	The primary goal is an LDL<100 mg/dL	A
	If 40 years of age or older, statin therapy to reduce LDL 30–40%, regardless of baseline LDL, is recommended	A
	LDL<70 mg/dL is an optional goal in individuals with overt cardiovascular (CV) disease	C
	Triglycerides should be lowered to <150 mg/dL	C
	Increase HDL to >40 mg/dL in men and >50 mg/dL in women	C
Antiplatelet	Use aspirin (75–162 mg daily) for secondary cardioprotection	A
	Use aspirin (75–162 mg) for primary prevention in *type 2 DM* if the subject is >40 years old or has additional CV risks	A
	Use aspirin (75–162 mg) for primary prevention in *type 1 DM* if the subject is >40 years old or has additional CV risks	C

ACE, angiotensin-converting enzyme; DM, diabetes mellitus; HbA_{1c}, glycosylated hemoglobin; HDL, hight-density lipoprotein; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test.
[a]Evidence levels: A, Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered; B, supportive evidence from well-conducted cohort studies or well-conducted case-control study; C, supportive evidence from poorly controlled or uncontrolled studies or conflicting evidence with weight of evidence supporting intervention; and E, expert consensus or clinical experience.
Based on American Diabetes Association Practice Recommendations.[8]

tion. Reducing the potential for microvascular complications is targeted at adherence to therapeutic lifestyle intervention (i.e., diet and exercise programs) and drug-therapy regimens, as well as at maintaining blood pressure as near normal as possible.

GENERAL APPROACH TO TREATMENT

Appropriate care requires goal setting for glycemia, blood pressure, and lipid levels, regular monitoring for complications, dietary and exercise modifications, medications, appropriate self-monitored blood glucose (SMBG), and laboratory assessment of the aforementioned parameters.[8] Glucose control alone does not sufficiently reduce the risk of macrovascular complications in persons with DM.

GLYCEMIC GOAL SETTING AND THE HEMOGLOBIN A_{1C}

Controlled clinical trials provide ample evidence that glycemic control is paramount in reducing microvascular complications in both type 1 DM[60] and type 2 DM.[61] HbA_{1c} measurements are the gold standard for following long-term glycemic control for the previous 2 to 3 months.[62] Hemoglobinopathies, anemia, and red cell membrane defects can affect HbA_{1c} measurements. Other strategies such as measurement of fructosamine, which measures glycated plasma proteins and correlates to glucose control over the last 2 to 3 weeks, can be necessary to assess diabetes control in these patients. Unless the risk outweighs the benefit (as in elderly patients, patients with advanced complications, and patients with other advanced disease), a HbA_{1c} target of <7% is appropriate (Table 77–8), and lower values should be targeted if significant hypoglycemia and/or weight gain can be avoided.[8]

MONITORING COMPLICATIONS

The ADA recommends initiation of complications monitoring at the time of diagnosis of DM.[8] Current recommendations continue to advocate yearly dilated eye examinations in type 2 DM, and an initial eye examination in the first 3 to 5 years in type 1 DM, then yearly thereafter. Less frequent testing (every 2 to 3 years) can be implemented on the advice of an eye care specialist. The feet should be examined and the blood pressure assessed at each visit. A urine test for microalbumin once yearly is appropriate. Yearly testing for lipid abnormalities, and more frequently if needed to achieve lipid goals, is recommended.

TABLE 77-8 Glycemic Goals of Therapy

Biochemical Index	ADA	ACE and AACE
Hemoglobin A_{1c}	<7%[a]	≤6.5%
Preprandial plasma glucose	90–130 mg/dL (5.0–7.2 mmol/L)	<110 mg/dL
Postprandial plasma glucose	<180 mg/dL[b] (<10 mmol/L)	<140 mg/dL

ADA, American Diabetes Association; ACE, American College of Endocrinology; AACE, American Association of Clinical Endocrinologists; DCCT, Diabetes Control and Complications Trial.
[a]Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay. More stringent glycemic goals (i.e., a normal HbA1c, <6%) can further reduce complications at the cost of increased risk of hypoglycemia (particularly in those with type 1 diabetes).
[b]Postprandial glucose measurements should be made 1–2 hours after the beginning of the meal, generally the time of peak levels in patients with diabetes.

SELF-MONITORING OF BLOOD GLUCOSE

The advent of SMBG in the early 1980s revolutionized the treatment of DM, enabling patients to know their blood glucose concentration at any moment easily and relatively inexpensively. Frequent SMBG is necessary to achieve near-normal blood glucose concentrations and to assess for hypoglycemia, particularly in patients with type 1 DM.[62] The more intense the pharmacologic regimen is, the more intense the SMBG needs to be (four or more times daily in patients on multiple insulin injections or pump therapy). The optimal frequency of SMBG for patients with type 2 DM is unresolved. Frequency of monitoring in type 2 DM should be sufficient to facilitate reaching glucose goals. The role of SMBG in improving glycemic control in type 2 DM patients is controversial but has shown to reduce the HbA_{1c} ~0.4%.[63] What is clear is that patients must be empowered to change their therapeutic regimen (lifestyle and medications) in response to test results, or no meaningful glycemic improvement is likely to be effected.

CLINICAL CONTROVERSY

SMBG improves glycemic control when insulin is used, but few well-conducted studies have shown significant glycemic reductions with increasing use of home blood-glucose testing for type 2 DM patients not on insulin. In a recent review, the average HbA_{1c} reduction with use of SMBG in type 2 DM patients not on insulin was 0.4%, although others have reported no glycemic improvement.[63] Patients must be empowered to change their therapeutic regimen (lifestyle and medications) in response to test results, or no meaningful glycemic improvement is likely to be effected, and thus the money spent on the strip is wasted.

NONPHARMACOLOGIC THERAPY

Diet

Medical nutrition therapy is recommended for all persons with DM.[64] Paramount for all medical nutrition therapy is the attainment of optimal metabolic outcomes and the prevention and treatment of complications. For individuals with type 1 DM, the focus is on regulating insulin administration with a balanced diet to achieve and maintain a healthy body weight. A meal plan that is moderate in carbohydrates and low in saturated fat (<7% of total calories), with a focus on balanced meals is recommended. The amount (grams) and type (via the glycemic index, although controversial) of carbohydrates, whether accounted for by exchanges or carbohydrate counting, should be considered.[64] It is imperative that patients understand the connection between carbohydrate intake and glucose control. In addition, patients with type 2 DM often require caloric restriction to promote weight loss. Rather than a set diabetic diet, advocate a diet using foods that are within the financial reach and cultural milieu of the patient. As most patients with type 2 DM are overweight or obese, bedtime and between-meal snacks are not needed if pharmacologic management is appropriate.

CLINICAL CONTROVERSY

The recommended daily carbohydrate intake for type 2 DM, and even type 1 DM, has become controversial since low-carbohydrate diets such as the Atkins, South Beach, and Carbohydrate Addict's Diets have become exceptionally popular. Currently, the ADA recommends that approximately 45% to 65% of daily caloric intake should come from carbohydrates and does not recommend restricting diets to <130 grams of carbohydrate a day. Many clinicians are trying to increase the monounsaturated fat percentage and decrease the carbohydrate percentage in a patient's diet to accomplish improved glycemic control. Recent studies have documented short-term success for weight loss on low-carbohydrate diets (~6 months), without deleterious effects on the lipid panel. Weight loss can reduce cardiovascular risk factors in type 2 DM.

Activity

In general, most patients with DM can benefit from increased activity.[65] Aerobic exercise improves insulin resistance and glycemic control in the majority of individuals, and reduces cardiovascular risk factors, contributes to weight loss or maintenance, and improves well-being. The patient should choose an activity that she or he is likely to continue. Start exercise slowly in previously sedentary patients. Older patients, patients with long-standing disease (age >35 years, or >25 years with DM ≥10 years), patients with multiple cardiovascular risk factors, presence of microvascular disease, and patients with previous evidence of atherosclerotic disease should have a cardiovascular evaluation, probably including an electrocardiogram and graded exercise test with imaging, prior to beginning a moderate to intense exercise regimen. In addition, several complications (autonomic neuropathy, insensate feet, and retinopathy) can require restrictions on the activities recommended. Physical activity goals include at least 150 minutes/week of moderate (50%–70% maximal hear rate) intensity exercise. In addition, resistance training, in patients without retinal contraindications, is recommended for 30 minutes three times per week.

PHARMACOLOGIC THERAPY

Until 1995, only two options for pharmacologic treatment were available for patients with diabetes; sulfonylureas (for type 2 DM only) and insulin (for type 1 or 2). Since 1995, a number of new oral agents, injectables, and insulins have been introduced in the United States.

Currently, six classes of oral agents are approved for the treatment of type 2 diabetes: α-glucosidase inhibitors, biguanides, meglitinides, peroxisome proliferator-activated receptor γ-agonists (which are also commonly identified as thiazolidinediones [TZDs] or glitazones), DPP-IV inhibitors, and sulfonylureas. Oral antidiabetic agents are often grouped according to their glucose-lowering mechanism of action. Biguanides and TZDs are often categorized as insulin sensitizers because of their ability to reduce insulin resistance. Sulfonylureas and meglitinides are often categorized as insulin secretagogues because they enhance endogenous insulin release.

New options for implementation of insulin therapy are now available. Detemir has given an additional option for choice of basal insulin for type 1 and 2 DM patients. Exubera, the first inhaled prandial insulin, was FDA approved, but has been withdrawn from the market due to poor sales. The subsequent sections describe the current antidiabetic medications that are available to treat type 1 and type 2 DM.

Drug Class Information

Insulin ***Pharmacology.*** Insulin is an anabolic and anticatabolic hormone. It plays major roles in protein, carbohydrate, and fat metabolism. For a complete review of insulin action, the reader is referred to a diabetes physiology text.[66] Endogenously produced insulin is cleaved from the larger proinsulin peptide in the β cell to the active peptide of insulin and C-peptide, which can be used as a marker for endogenous insulin production. All commercially available insulin preparations contain only the active insulin peptide.

TABLE 77-9 Available Injectable and Insulin Preparations

Trade/Generic Name	Manufacturer	Analog[a]	Administration Options	Room Temperature[b] Expiration
Rapid-acting insulins				
Humalog (insulin lispro)	Lilly	Yes	Insulin pen 3-mL, vial, and 3-mL pen cartridge	28 days
NovoLog (insulin aspart)	Novo-Nordisk	Yes	Insulin pen 3-mL, vial, or 3-mL pen cartridge	28 days
Apidra (insulin glulisine)	Sanofi-Aventis	Yes	3-mL, pen cartridge or Opticlick pen system	28 days
Exubera (inhaled human insulin)	Pfizer	No	1 and 3-mg blister packs	3 months once foil overwrap opened
Short-acting insulins				
Humulin R (regular; human insulin rDNA)	Lilly	No	100 units, 10-mL vial 500 units, 20-mL vial	28 days
Novolin R (regular; human insulin rDNA)	Novo-Nordisk	No	Insulin pen, vial, or 3-mL pen cartridge, and InnoLet[d]	Vial: 30 days; others: 28 days
Intermediate-acting insulins				
NPH				
Humulin N	Lilly	No	Vial, prefilled pen	Vial: 28 days; pen: 14 days
Novolin N	Novo-Nordisk	No	Vial, prefilled pen, and InnoLet[d]	Vial: 30 days; others: 14 days
Long-acting insulins				
Lantus (insulin glargine)	Sanofi-Aventis	Yes	Vial, 3-mL Opticlick pen cartridge	28 days
Levemir (insulin detemir)	Novo-Nordisk	Yes	Vial, 3-mL pen cartridge and pen, InnoLet[d]	42 days
Pre-mixed insulins				
Premixed insulin analogs				
Humalog Mix 75/25 (75% neutral protamine lispro, 25% lispro)	Lilly	Yes	Vial, prefilled pen	Vial: 28 days; pen: 10 days
NovoLog Mix 70/30 (70% aspart protamine suspension, 30% aspart)	Novo-Nordisk	Yes	Vial, prefilled pen, 3-mL pen cartridge	Vial: 28 days; others: 14 days
Humalog Mix 50/50 (50% neutral protamine lispro/ 50% lispro)	Lilly	Yes	3-mL pen	10 days
NPH-regular combinations				
Humulin 70/30	Lilly	No	Vial, prefilled pen	Vial: 28 days; pen: 10 days
Novolin 70/30	Novo-Nordisk	No	Vial, pen cartridge, InnoLet[c]	Vial: 30 days; others: 10 days
Humulin 50/50	Lilly	No	Vial	28 days
Other injectables				
Byetta (exenatide)	Amylin/Lilly	No	5 mcg and 10 mcg pen, ~60 injections (doses)/ pen	Pen in use can be used at room temperature (< 25°C [< 77° F])
Symlin (pramlintide)	Amylin	Yes	5-mL vial	28 days

NPH, neutral protamine Hagedern.

[a]All insulins available in the United States are now made by human recombinant DNA technology. An insulin analog is a modified human insulin molecule that imparts particular pharmacokinetic advantages.

[b]Room temperature defined as 15–30°C (59–86°F).

[c]InnoLet: A prefilled insulin pen with a "kitchen timer" type of dial for determining the number of insulin units. Can be useful in patients with impaired eyesight or dexterity.

Adapted from the Texas Diabetes Council.

Characteristics. Characteristics that are commonly used to categorize insulins include source, strength, onset, and duration of action. Additionally, insulins can be characterized as analogs, defined as insulins that have had amino acids within the insulin molecule modified to impart particular physiochemical and pharmacokinetic advantages. Table 77–9 summarizes available insulin preparations.

The strengths of injectable insulin currently available in the United States are 100 units/mL (U-100) and 500 units/mL (U-500). For individuals who require large doses of insulin to control their diabetes, 500 units/mL regular insulin is available. In the United States, all other insulins are available only in 100 units/mL strength. For some type 1 diabetes patients who require extremely low doses of insulin, dilution of 100 units/mL insulin to obtain accurate insulin doses can be necessary. Diluents and empty bottles can be obtained from the manufacturers for dilution.

Historically, insulin came from either beef or pork sources. Beef insulin differs by three amino acids and pork by one amino acid when compared to human insulin. Manufacturers in the United States have discontinued production of beef and pork source insulins as of December 2003, and now exclusively use recombinant DNA (rDNA) technology to manufacture insulin. Eli Lilly, Pfizer, and Sanofi-Aventis currently use a non–disease-producing strain of *Escherichia coli* for synthesis of insulin, whereas Novo Nordisk uses *Saccharomyces cerevisiae*, or bakers' yeast, for synthesis.

Purity of insulin refers to the amount of proinsulin and other impurities present in a given insulin product. Prior to 1980, most insulin contained enough impurities (300 to 10,000 ppm) to cause local reactions on injection, as well as systemic adverse effects from antibody production. Modern technology has provided less expensive techniques to purify insulin. As a result, all insulin products contain ≤10 ppm of proinsulin, with purified preparations (all rDNA human insulin and insulin analogs) containing <1 ppm of proinsulin.

Regular crystalline insulin naturally self-associates into a hexameric (six insulin molecules) structure when injected subcutaneously. Before absorption through a blood capillary can occur, the hexamer must dissociate first to dimers, and then to monomers. This principle is the premise for additives such as protamine and zinc described below, and modification of amino acids for insulin analogs. Lispro, aspart, and glulisine insulins dissociate rapidly to monomers, thus absorption is rapid. Lispro (B-28 lysine and B-29 proline human insulin; monomeric) insulin with two amino acids transposed, aspart (B-28 aspartic acid human insulin; mono- and dimeric) insulin with replacement of one amino acid, and glulisine (B-3 lysine and B-29 glutamic acid) are rapidly absorbed, peak faster, and have shorter durations of action when compared to regular insulin. In comparison to human insulin, with an isoelectric point of 5.4, the analog glargine insulin (A-21 glycine, B-30a-arginine, B-30a L-arginine, and B-30b L-arginine human insulin) has an isoelectric point of 6.8. In the bottle,

glargine is buffered to a pH of 4, a level at which it is completely soluble, resulting in a clear colorless solution. When injected into the neutral pH of the body, it rapidly forms microprecipitates that slowly dissolve into monomers and dimers which are then subsequently absorbed. The result is a long-acting, peakless, 24-hour duration insulin analog. Detemir, in contrast, attaches a C14 fatty acid (a 14 carbon fatty acid) at the B-29 position and removes the B-30 amino acid. This allows the fatty acid side chain to bind to interstitial albumin at the subcutaneous injection site. Also, the formulation allows stronger hexamer (six molecules of insulin associated together) associations, which prolong absorption. Once detemir dissociates from the interstitial albumin, it is free to enter a capillary, where it is again bound to albumin. It then travels to a site of action and interacts, after dissociation from albumin, with insulin receptors.

Insulin analogs are modified human insulin molecules, and safety is paramount for FDA approval. Key factors that should be considered in the approval process include local injection reactions, antigenicity, efficacy compared to human insulin, insulin receptor binding affinity, and insulin-like growth factor 1–receptor affinity (which is compared to that of human insulin to determine mitogenic potential).

Pharmacokinetics. Subcutaneous injection kinetics are dependent on onset, peak, and duration of action, and are summarized in Table 77–10. The pharmacokinetic considerations for Exubera will be discussed later in the section. Absorption of insulin from a subcutaneous depot is dependent on several factors, including: source of insulin, concentration of insulin, additives to the insulin preparations (e.g., zinc, protamine, etc.), blood flow to the area (rubbing of injection area, increased skin temperature, and exercise in muscles near the injection site can enhance absorption), and injection site. Regular or neutral protamine Hagedorn (NPH) insulin is commonly injected in (from most rapid to slowest absorption): abdominal fat, posterior upper arms, lateral thigh area, and superior buttocks area. Insulin analogs, unlike regular or NPH insulin, appear to retain their kinetic profile at all sites of injection. When compared to 100 units/mL insulin, 500 units/mL regular insulin has a delayed onset, peak, and a longer duration of action. Addition of protamine (NPH, insulin lispro protamine [NPL], and aspart protamine suspension) or excess zinc (historically lente or ultralente insulin) will delay onset, peak, and duration of the insulin's effect. Variability in absorption, inconsistent suspension of the insulin by the patient or healthcare provider when drawing up a dose, and inherent insulin action based on the pharmacokinetics of the products can all contribute to a labile glucose response. NPH should be inverted or rolled gently at least 10 times to fully resuspend the insulin prior to each use.

As detemir has a unique mechanism to prolong absorption, it should not be surprising that its pharmacokinetics are unique. The onset of detemir is consistent across doses, but the peak is delayed slightly with higher dosing. Also, at low dose (0.2 units/kg) the duration of action is approximately 14 hours, whereas at higher doses it is close to 24 hours.

The half-life of an intravenous (IV) injection of regular insulin is approximately 9 minutes. Thus the effective duration of action of a single IV injection is short, and changes in IV insulin rates will reach steady state in approximately 45 minutes. Intravenous pharmacokinetics of other soluble insulins (lispro, aspart, glulisine, and even glargine) appear similar to IV regular insulin, but they have no advantages over IV regular insulin and are more expensive.

Insulin is degraded in the liver, muscle, and kidney. Liver deactivation is 20% to 50% in a single passage. Approximately 15% to 20% of insulin metabolism occurs in the kidney. This can partially explain the lower insulin dosage requirements in patients with end-stage renal disease.

Human Insulin (rDNA Origin) Inhalation Powder (Exubera)

Due to poor sales, Exubera was recently discontinued, and subjects were asked to be switched to alternative treatments. Exubera was the first inhaled insulin, and was formulated to easily reach the alveolar space. Bronchial tubes are impermeable to insulin, but it is easily absorbed across the alveoli. The onset and peak of Exubera insulin after inhalation is similar to rapid-acting insulin analogs, but the duration of action is similar to regular insulin (see Table 77–10). Exubera consists of blister packets labeled as 1 mg or 3 mg of human insulin inhalation powder, which are administered using the Exubera inhaler. After an Exubera blister is inserted into the inhaler, the patient pumps the handle of the inhaler. When the patient presses a "fire" button, the insulin blister is pierced and the insulin inhalation powder is dispersed into the chamber, allowing inhalation. Normally, up to 45% of the 1 mg blister contents and up to 25% of the 3 mg blister contents can be retained in the blister. The 1 mg blister packet is equal to ~3 units of subcutaneously injected insulin and the 3 mg blister packet is equal to ~8 units. One puff of a 3 mg blister is not equivalent to three 1 mg blisters, which will deliver a higher dose of insulin than the one 3 mg blister. Human insulin inhalation powder should be given as prandial insulin, and the efficacy is equivalent to rapid-acting injected insulin analogs. Human insulin inhalation powder can be used in type 1 or type 2 DM, though the smallest increment between inhaled doses is equivalent to 2 to 3 units injected subcutaneously. This can restrict the usefulness in many patients with type 1 DM, who may have large reductions in glucose with a single unit of insulin. The following patient populations have relative contraindications to Exubera: chronic smoking in last 6 months, which increases

TABLE 77-10 Pharmacokinetics of Various Insulins Administered Subcutaneously or Inhaled

Type of Insulin	Onset (Hours)	Peak (Hours)	Duration (Hours)	Maximum Duration (Hours)	Appearance
Rapid-acting					
Aspart	15–30 min	1–2	3–5	5–6	Clear
Lispro	15–30 min	1–2	3–4	4–6	Clear
Glulisine	15–30 min	1–2	3–4	5–6	Clear
Inhaled human insulin	15–30 min	1–2	6	8	Powder
Short-acting					
Regular	0.5–1.0	2–3	3–6	6–8	Clear
Intermediate-acting[a]					
NPH	2–4	4–6	8–12	14–18	Cloudy
Long-acting					
Detemir	2 hours	6–9	14–24[b]	24	Clear
Glargine	4–5	–	22–24	24	Clear

NPH, neutral protamine Hagedorn.

[a]Lente and ultralente insulin has been discontinued.

[b]See text for further discussion.

Adapted from the Texas Diabetes Council.

absorption two- to fivefold when compared to nonsmokers; chronic passive smoke, which reduces absorption of insulin inhalation; asthma, which decreases Exubera absorption, but bronchodilator use prior to insulin inhalation can increase absorption; chronic obstructive pulmonary disease (COPD), which increases the absorption of insulin inhalation; and other chronic lung diseases. A dry cough near inhalation, increased sputum, and dyspnea are the three most common drug-related side effects. Hypoglycemia rates are similar to regular insulin. There was a small, but statistically significant decrease in forced expiratory volume in the first second of expiration (FEV_1) and diffusing capacity of the lung for carbon monoxide (DLCO) in type 1 DM (T1DM) patients treated with Exubera. Two-year safety data indicate that in both T1DM and type 2 DM (T2DM) changes in FEV_1 and DLCO are small (<1%–2% from baseline), occur within the first 3 months of initiation, and the defect is reversible with discontinuation of therapy. A decline in FEV_1 or DLCO of ≥20% occurred in 1.5% versus 1.3%, and 5.1% versus 3.6% for Exubera and the comparator group, respectively. Pulmonary function testing is recommended at baseline, after 6 months of therapy, and annually thereafter, even if no symptoms are present. If the FEV1 or DLCO declines by ≥20% on followup testing, the test should be repeated, and if confirmed, Exubera should be discontinued other inhaled insulin systems are in development.[67] Other inhaled insulin systems are in development.

Efficacy. The efficacy of traditional insulins (e.g., regular and NPH insulins) is unequivocal. Insulin analog efficacy is measured via the same ways as traditional insulins. Insulin analogs in most studies have not shown superior HbA_{1c} levels when compared to traditional insulins but are often preferred by patients and practitioners because of their ability to more closely mimic normal insulin secretion profiles. Lispro, aspart, glulisine, and Exubera are advantageous because of the ability to administer within 10 minutes of a meal, as compared to the recommendation to inject regular insulin approximately 30 minutes prior. Rapid-acting analogs have shown superior postprandial lowering of glucose when compared to regular insulin. Both detemir and glargine insulin injected at bedtime have shown significantly less nocturnal hypoglycemia when compared to NPH injected at bedtime.

An educated patient in conjunction with a skilled practitioner can achieve excellent glycemic control with insulin therapy. Efficacy with insulin therapy is related to achieving glycemic control while minimizing the risk of potential side effects, specifically hypoglycemia and weight gain. Insulin is recommended in patients with: extremely high FPG levels (>280 to 300 mg/dL) or HbA1c, patients with ketonuria or ketonemia, symptomatic patients (weight loss with polyuria, polydipsia, and/or nocturia), GDM, and if deemed appropriate by the clinician and patient.[68–71]

Microvascular Complications. Insulin has been shown to be as efficacious as any oral agent for treating DM. The UKPDS, which used sulfonylureas or insulin, showed equal efficacy in lowering the risk of microvascular events in newly diagnosed type 2 DM.[61] Similarly, in type 1 DM the DCCT showed efficacy in reducing microvascular complications.[60]

Macrovascular Complications. The connection between high insulin levels (hyperinsulinemia), insulin resistance, and cardiovascular events incorrectly leads some clinicians to believe that insulin therapy can cause macrovascular complications. The UKPDS and DCCT found no differences in macrovascular outcomes with intensive insulin therapy. One study, the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction study,[72] reported reductions in mortality with insulin therapy. This group assessed the effect of an insulin-glucose infusion in type 2 DM patients who had experienced an acute myocardial infarction. Those randomized to insulin infusion followed by intensive insulin therapy lowered their absolute mortality risk by 11% over a mean followup period of approximately 3 years. This was most evident in subjects who were insulin-naïve or had a low cardiovascular risk prior to the acute myocardial infarction.[72] The importance of glycemic control in hospitalized patients is covered later in the chapter.

Adverse Effects. The most common adverse effects reported with insulin are hypoglycemia and weight gain. Hypoglycemia is more common in patients on intensive insulin therapy regimens versus those on less-intensive regimens. Also, patients with type 1 DM tend to have more hypoglycemic events compared to type 2 DM patients. In the UKPDS, performed over 10 years, the percentage of diabetic patients who needed assistance (third-party or hospitalization) because of a hypoglycemic reaction was 2.3%. The UKPDS reported a rate of 36.5% for risk of any hypoglycemic event, including mild, self-treated events. In the DCCT, tighter control produced a risk three times higher for severe hypoglycemia compared to conventional therapy. Glycemic goals should incorporate hypoglycemic risk versus the benefit of lowering the glucose when HbA_{1c} levels are near normal, especially in type 1 DM.

Minimization of risk for patients on insulin should include education about the signs and symptoms of hypoglycemia, proper treatment of hypoglycemia, and blood glucose monitoring. Blood glucose monitoring is essential for those on insulin, and is particularly of value in patients with hypoglycemia unawareness. Patients with hypoglycemia unawareness do not experience the normal sympathetic symptoms of hypoglycemia (tachycardia, tremulousness, and often, sweating). Initial hypoglycemia symptoms are neuroglycopenic in nature (confusion, agitation, loss of consciousness, and/or progression to coma). Patients with hypoglycemia unawareness often should at least temporarily raise their glycemic goals (requiring a reduction in insulin dose) and check their blood glucose level prior to any activities that can be dangerous with a low blood sugar (e.g., driving and certain sports, among others). Proper treatment of hypoglycemia dictates ingestion of carbohydrates, with glucose being preferred. Unconsciousness is an indication for either IV glucose, or glucagon injection, which increases glycogenolysis in the liver. Glucagon use would be appropriate in any situation in which the patient does not have or cannot have ready IV access for glucose administration. Education for reconstitution and injection of glucagon is recommended for close friends and family of a patient who has recurrent neuroglycopenic events. The patient and close contacts should be informed that it can take 10 to 15 minutes for the injection to start increasing glucose levels, and patients often vomit during this time. Proper positioning to avoid aspiration should be emphasized.

Weight gain is predominantly from increased truncal fat, and tends to be related to daily dose and plasma insulin levels present. Weight gain is undesirable in most type 2 DM patients, but can be seen as beneficial in underweight patients with type 1 DM. Weight gain appears to be related to intensive insulin therapy, and can be somewhat minimized by physiologic replacement of insulin.

Two forms of lipodystrophy, although much less common today in people with diabetes, still occur. Lipohypertrophy is caused by many injections into the same injection site. Because of insulin's anabolic actions, a raised fat mass is present at the injection site with resultant variable insulin absorption. Lipoatrophy, in contrast, is thought to be caused by insulin antibodies, with destruction of fat at the site of injection. Injection away from the site with more purified insulin is recommended, although several reports of lipoatrophy with lispro have been reported.

Drug-Drug Interactions. There are no significant drug-drug interactions with injected insulin, although other medications that can affect glucose control can be considered. Detemir does not appear to have albumin binding interactions, as it occupies only a small percent of albumin binding sites. Table 77–11 lists common medications known to affect blood glucose levels.

TABLE 77-11 Medications That Can Affect Glycemic Control[a]

Drug	Effect on Glucose	Mechanism/Comment
Angiotensin-converting enzyme inhibitors	Slight reduction	Improves insulin sensitivity
Alcohol	Reduction	Reduces hepatic glucose production
Interferon alfa	Increase	Unclear
Diazoxide	Increase	Decreases insulin secretion, decreases peripheral glucose use
Diuretics	Increase	Can increase insulin resistance
Glucocorticoids	Increase	Impairs insulin action
Nicotinic acid	Increase	Impairs insulin action, increases insulin resistance
Oral contraceptives	Increase	Unclear
Pentamidine	Decrease, then increase	Toxic to β cells; initial release of stored insulin, then depletion
Phenytoin	Increase	Decreases insulin secretion
β-Blockers	Can increase	Decreases insulin secretion
Salicylates	Decrease	Inhibition of I-kappa-B kinase-beta (IKK-beta) (only high doses, e.g., 4–6 g/day)
Sympathomimetics	Slight increase	Increased glycogenolysis and gluconeogenesis
Clozapine and olanzapine	Increase	Decrease insulin sensitivity; weight gain

[a]This list is not inclusive of all medications reported to cause glucose changes.

Dosing and Administration. The dose of insulin for any person with altered glucose metabolism must be individualized. In type 1 DM, the average daily requirement for insulin is 0.5 to 0.6 units/kg, with approximately 50% being delivered as basal insulin, and the remaining 50% dedicated to meal coverage. During the honeymoon phase it can fall to 0.1 to 0.4 units/kg. During acute illness or with ketosis or states of relative insulin resistance, higher dosages are warranted. In type 2 DM a higher dosage is required for those patients with significant insulin resistance. Dosages vary widely depending on underlying insulin resistance and concomitant oral insulin sensitizer use. Strategies on how to initiate and monitor insulin therapy will be described later in the therapeutics section.

Storage. It is recommended that unopened injectable insulin be refrigerated (2.2° to 7.7°C [36° to 46°F]) prior to use. The manufacturer's expiration date printed on the insulin is used for unopened, refrigerated insulin. Once the insulin is in use, the manufacturer-recommended expiration dates will vary based on the insulin and delivery device. Table 77–9 outlines manufacturer-recommended expiration dates for room temperature (15° to 30°C [59° to 86°F]) insulin, including Exubera. For financial reasons, patients can attempt to use insulins longer than their expiration dates, but careful attention must be paid to monitoring for glycemic control deterioration and signs of insulin decay (clumping, precipitates, discoloration, etc.) if this is attempted.

Exenatide ***Pharmacology.*** Exendin-4 is a 39-amino acid peptide isolated from the saliva of the Gila monster (*heloderma suspectum*) and shares approximately 50% amino acid sequence with human GLP-1. Exenatide is the synthetic analog to exendin-4. Exenatide (Byetta) has been shown to bind to GLP-1 receptors in many parts of the body including the brain and pancreas. Exenatide and GLP-1 have common glucoregulatory actions. Exenatide enhances glucose dependent insulin secretion while suppressing inappropriately high postprandial glucagon secretion in the presence of elevated glucose concentrations, resulting in a reduction in hepatic glucose production. Exenatide reduces food intake, which can result in weight loss, and slows gastric emptying so that the rate of glucose appearance into the plasma better matches the glucose disposition. Unlike GLP-1, exenatide does not increase gastric secretions.

Pharmacokinetics. Exenatide concentrations are detectable in plasma within 10 to 15 minutes after subcutaneous injection, and the drug has a time of maximal concentration (t_{max}) of ~2 hours and a plasma half life of ~3.3 to 4.0 hours. Exenatide plasma concentrations increase in a dose-dependent manner and plasma exenatide concentrations are detectable for up to 10 hours postinjection, although pharmacodynamically, effects last for approximately 6 hours. Bioavailability of exenatide after injection in the abdomen, upper arm, or the thigh is similar. Elimination of exenatide is primarily by glomerular filtration with subsequent proteolytic degradation. When exenatide is administered to subjects with worsening degrees of renal insufficiency, there is a progressive prolongation of the half-life, and in dialysis patients, plasma clearance of exenatide is markedly reduced. The incidence of GI side effects appears to be increased in individuals with impaired renal function, possibly because of higher plasma levels, thus caution is advised.

No significant differences in exenatide pharmacokinetics have been observed with obesity, race, gender, or advancing age (up to 73 years old).

Efficacy. The average HbA_{1c} reduction is approximately 0.9% with exenatide, although, similar to oral agents, it is dependent on the baseline HbA_{1c} values. Three phase III trials reported similar HbA_{1c} reduction in patients on metformin, sulfonylureas, or both. Exenatide significantly decreases postprandial glucose excursions but has only a modest effect on FPG values. If a patient has significant elevations in FPG levels, these should be corrected with other agents, and the exenatide added on. Exenatide can allow some patients to lose weight. The average weight loss in controlled trials was 1 to 2 kg over 30 weeks, without dietary advice being given to the patients, although long-term, open-label followup on 10 mcg twice daily shows continued weight loss for at least 2.5 years. Exenatide, through decreasing appetite and slowing gastric emptying, can reduce the number of calories a patient eats at a meal.

Microvascular Complications. Exenatide reduces the HbA_{1c} level, which have been shown to be related to the risk of microvascular complications.

Macrovascular Complications. No published clinical trials have examined the effect of exenatide on cardiovascular outcomes. However, improvements in several cardiovascular risk factors have been reported. Plasma triglycerides (–37 ± 10 mg/dL) decreased and, plasma HDL cholesterol (+4.5 ± 0.4 mg/dL) increased on exenatide 10 mcg twice daily. Nonsignificant reductions in systolic and diastolic blood pressure were observed. The greatest improvement in cardiovascular risk factors was seen in subjects who had the greatest weight loss.[73]

Adverse Effects. The most common adverse effects associated with exenatide are GI in nature. Nausea occurs in ~40% of subjects on 5 mcg, and ~45% to 50% of subjects on 10 mcg twice daily. Vomiting or diarrhea occurs in approximately 10% of patients placed on exenatide. GI adverse effects appear to decrease over time, but approximately 1 in 20 patients can have prolonged problems with one of the above side effects, possibly requiring discontinuation. As these adverse effects appear to be dose-related, the patient should be started on 5 mcg twice daily and titrated to 10 mcg twice daily only if the adverse effects are mostly gone. Also, when the patient is increased to the 10 mcg twice daily dose, these adverse effects can recur for a short period of time. Many episodes of nausea would be better characterized as stomach fullness, and patients should be instructed to eat slow and stop eating when full, or risk nausea and vomiting. Also, weight loss appears not to be related to adverse effects but rather to a reduction in calories consumed. Exenatide

provides glucose-dependent insulin secretion, thus hypoglycemic rates when combined with metformin or a TZD are not increased, but when combined with a sulfonylurea or insulin, significant hypoglycemia can occur. Although exenatide reduces glucagon when the glucose is high, no suppression of counter-regulatory hormones has been noted during hypoglycemia. Exenatide antibodies can occur, but generally decrease over time and do not affect glycemic control. In approximately 5% of patients, titers can increase over time, resulting in a blunting of glycemic control in approximately one-half of these patients.

Drug Interactions. Exenatide delays gastric emptying, thus it can delay the absorption of other medications. Examples of medications that can be affected include oral pain medications and antibiotics dependent on threshold levels for efficacy. If rapid absorption of the medication is necessary, it is best to take the medication 1 hour before, or at least 3 hours after the injection of exenatide. In addition, if the patient has gastroparesis, exenatide is not recommended.

Dosing and Administration. Exenatide dosing should be started with 5 mcg twice daily, and titrated to 10 mcg twice daily in 1 month or when tolerability allows and if warranted. Exenatide should be injected 0 to 60 minutes before the morning and evening meals. If the patient does not eat breakfast, they can take the first injection of the day at lunch. The peak effect of exenatide is at approximately 2 hours, so anecdotally the patient can get better appetite suppression if injected 30 minutes to 1 hour prior to the meal. Storage and dosage availability information can be found in Table 77–9.

Pramlintide ***Pharmacology.*** Pramlintide (Symlin) is an antihyperglycemic agent used in patients currently treated with insulin. Pramlintide is a synthetic analog of amylin (amylinomimetic), a neurohormone co-secreted from the β cells with insulin. Pramlintide suppresses inappropriately high postprandial glucagon secretion, reduces food intake, which can result in weight loss, and slows gastric emptying so that the rate of glucose appearance into the plasma better matches the glucose disposition.

Pharmacokinetics. The absolute bioavailability of pramlintide after subcutaneous injection is 30% to 40%. The t_{max} is approximately 20 minutes, but the maximal drug concentration (C_{max}) is dose dependent and appears to be linear. The half-life ($t_{1/2}$) is approximately 45 minutes, thus the pharmacodynamic duration of action is approximately 3 to 4 hours. Pramlintide does not extensively bind to albumin, and should not have significant binding interactions. Metabolism is primarily by the kidneys, and one active metabolite (2–37 pramlintide) has a similar half-life as the parent compound. No accumulation has been seen in renal insufficiency, but caution is advised. Injection into the arm can increase exposure and variability of absorption, so injection into the abdomen or thigh is recommended.

Efficacy. The average HbA_{1c} reduction is approximately 0.6% with pramlintide, although optimization of the insulin and pramlintide doses can result in further drops in HbA_{1c}. If the 120 mcg dose is used in type 2 DM patients on insulin, it can also result in 1.5 kg weight loss. In type 1 DM patients, the average reduction in HbA_{1c} was 0.4% to 0.5%. Pramlintide decreases prandial glucose excursions but has little effect on the FPG concentration. The main advantage of pramlintide is in type 1 DM, where it helps to stabilize wide postprandial glycemic swings. The average weight loss in controlled trials was 1 to 2 kg, without dietary advice being given to the patients. Pramlintide, through decreasing appetite and slowing gastric emptying, can reduce the number of calories a patient eats at a meal.

Microvascular Complications. Pramlintide reduces the HbA_{1c} level, which has been shown to be related to the risk of microvascular complications.

Macrovascular Complications. No published clinical trials have examined the effect of pramlintide on cardiovascular outcomes.

Adverse Effects. The most common adverse effects associated with pramlintide are GI in nature. Nausea occurs in ~20% of type 2 DM patients, and vomiting or anorexia occurs in approximately 10% of type 1 or type 2 DM patients. Nausea is more common in type 1 DM, occurring in ~40% to 50% of patients. GI adverse effects appear to decrease over time and are dose related, thus starting at a low dose and slowly titrating as tolerated is recommended. Pramlintide alone does not cause hypoglycemia, but it is indicated for use in patients on insulin, thus hypoglycemia can occur. The risk of severe hypoglycemia early in therapy is higher in type 1 DM than in type 2 DM patients. A twofold increase in severe hypoglycemic reactions in type 1 DM patients has been reported.

Drug Interactions. Pramlintide delays gastric emptying, thus it can delay the absorption of other medications. Examples of medications that can be affected include oral pain medications and antibiotics dependent on threshold levels for efficacy. If rapid absorption of the medication is necessary, it is best to take the mediation 1 hour before, or at least 3 hours after the injection of pramlintide.

Dosing and Administration. Pramlintide dosing varies in type 1 and type 2 DM. It is imperative that the prandial insulin dose, if used, be reduced 30% to 50% when pramlintide is started to minimize severe hypoglycemic reactions. Basal insulin may need to be adjusted only if the FPG is close to normal. In type 2 DM, the starting dose is 60 mcg prior to major meals, and can be titrated to the maximally recommended 120 mcg dose as tolerated and warranted based on postprandial plasma glucose concentrations. In type 1 DM dosing starts at 15 mcg prior to each meal and can be titrated up to a maximum of 60 mcg prior to each meal if tolerated and warranted. Pramlintide comes in a vial, allowing individualization of titration at even smaller increments (by units) than the package insert recommends. Each 2.5 units on a 100 units/mL insulin syringe equals 15 mcg of pramlintide. In addition, pramlintide has a pH of 4, and it is not recommended that pramlintide be mixed with any other insulin, thus this potentially adds two to four additional injections a day. Storage information can be found in Table 77–9.

Sulfonylureas ***Pharmacology.*** The primary mechanism of action of sulfonylureas is enhancement of insulin secretion. Sulfonylureas bind to a specific sulfonylurea receptor (SUR) on pancreatic β cells. Binding closes an adenosine triphosphate–dependent potassium ion (K^+) channel, leading to decreased potassium efflux and subsequent depolarization of the membrane. Voltage-dependent calcium ion (Ca^{+2}) channels open and allow an inward flux of Ca^{+2}. Increases in intracellular Ca^{+2} cause translocation of secretory granules of insulin to the cell surface and resultant exocytosis of the granule of insulin. Elevated secretion of insulin from the pancreas travels via the portal vein and subsequently suppresses hepatic glucose production.

Classification. Sulfonylureas are classified as first-generation and second-generation agents. The classification scheme is largely derived from differences in relative potency, relative potential for selective side effects, and differences in binding to serum proteins (i.e., risk for protein-binding displacement drug interactions). First-generation agents consist of acetohexamide, chlorpropamide, tolazamide, and tolbutamide. Each of these agents is lower in potency relative to the second-generation drugs: glimepiride, glipizide, and glyburide (Table 77–12). It is important to recognize that all sulfonylureas are equally effective at lowering blood glucose when administered in equipotent doses.

Pharmacokinetics. All sulfonylureas are metabolized in the liver; some to active, others to inactive metabolites (see Table 77–12).

TABLE 77-12 Oral Agents for the Treatment of Type 2 Diabetes Mellitus

Generic Name (generic version available? Y = yes, N = no)	Brand	Dose (mg)	Recommended Starting Dosage (mg/day)		Equivalent Therapeutic Dose (mg)	Maximum Dose (mg/day)	Duration of Action	Metabolism or Therapeutic Notes
			Nonelderly	*Elderly*				
Sulfonylureas								
Acetohexamide (Y)	Dymelor	250, 500	250	125–250	500	1,500	Up to 16 hours	Metabolized in liver; metabolite potency equal to parent compound; renally eliminated
Chlorpropamide (Y)	Diabinese	100, 250	250	100	250	500	Up to 72 hours	Metabolized in liver; also excreted unchanged renally
Tolazamide (Y)	Tolinase	100, 250, 500	100–250	100	250	1,000	Up to 24 hours	Metabolized in liver; metabolite less active than parent compound; renally eliminated
Tolbutamide (Y)	Orinase	250, 500	1,000–2,000	500–1,000	1,000	3,000	Up to 12 hours	Metabolized in liver to inactive metabolites that are renally excreted
Glipizide (Y)	Glucotrol	5, 10	5	2.5–5	5	40	Up to 20 hours	Metabolized in liver to inactive metabolites
Glipizide (Y)	Glucotrol XL	2.5, 5, 10, 20	5	2.5–5	5	20	24 hours	Slow-release form; do not cut tablet
Glyburide (Y)	DiaBeta Micronase	1.25, 2.5, 5	5	1.25–2.5	5	20	Up to 24 hours	Metabolized in liver; elimination $^1/_2$ renal, $^1/_2$ feces
Glyburide, micronized (Y)	Glynase	1.5, 3, 6	3	1.5–3	3	12	Up to 24 hours	Equal control, but better absorption from micronized preparation
Glimepiride (Y)	Amaryl	1, 2, 4	1–2	0.5–1	2	8	24 hours	Metabolized in liver to inactive metabolites
Short-acting insulin secretagogues								
Nateglinide (N)	Starlix	60, 120	120 with meals	120 with meals	NA	120 mg three times a day	Up to 4 hours	Metabolized by cytochrome P450 (CYP450), CYP2C9, and CYP3A4 to weakly active metabolites; renally eliminated
Repaglinide (N)	Prandin	0.5, 1, 2	0.5–1 with meals	0.5–1 with meals	NA	16	Up to 4 hours	Metabolized by CYP3A4 to inactive metabolites; excreted in bile
Biguanides								
Metformin (Y)	Glucophage	500, 850, 1,000	500 mg twice a day	Assess renal function	NA	2,550	Up to 24 hours	No metabolism; renally secreted and excreted
Metformin extended-release (Y)	Glucophage XR	500, 750, 1,000 mg	500–1,000 mg with evening meal	Assess renal function	NA	2,550	Up to 24 hours	Take with evening meal or may split dose; can consider trial if intolerant to immediate-release
Thiazolidinediones								
Pioglitazone (N)	Actos	15, 30, 45	15	15	NA	45	24 hours	Metabolized by CYP2C8 and CYP3A4; two metabolites have longer half-lives than parent compound
Rosiglitazone (N)	Avandia	2, 4, 8	2–4	2	NA	8 mg/day or 4 mg twice a day	24 hours	Metabolized by CYP2C8 and CYP2C9 to inactive metabolites that are renally excreted
α-Glucosidase inhibitors								
Acarbose (N)	Precose	25, 50, 100	25 mg one to three times a day	25 mg one to three times a day	NA	25–100 mg three times a day	1–3 hours	Eliminated in bile
Miglitol (N)	Glyset	25, 50, 100	25 mg one to three times a day	25 mg one to three times a day	NA	25–100 mg three times a day	1–3 hours	Eliminated renally
Dipeptidyl peptidase-IV inhibitors (DPP-IV inhibitors)								
Sitagliptin (N)	Januvia	25, 50, 100	100 mg daily	25 to 100 mg daily based on renal function	NA	100 mg daily	24 hours	50 mg daily if: creatinine clearance >30 to <50 mL/minute 25 mg if: creatinine clearance < 30 mL/min

(continued)

TABLE 77-12 Oral Agents for the Treatment of Type 2 Diabetes Mellitus (continued)

Generic Name (generic version available? Y = yes, N = no)	Brand	Dose (mg)	Recommended Starting Dosage (mg/day)		Equivalent Therapeutic Dose (mg)	Maximum Dose (mg/day)	Duration of Action	Metabolism or Therapeutic Notes
			Nonelderly	*Elderly*				
Combination products								
Glyburide/metformin (Y)	Glucovance	1.25/250 2.5/500 5/500	2.5–5/500 twice a day	1.25/250 twice a day; assess renal function	NA	20 of glyburide, 2,000 of metformin	Combination medication	Use as initial therapy: 1.25/250 mg twice a day
Glipizide/metformin (N)	Metaglip	2.5/250 2.5/500 5/500	2.5–5/500 twice a day	2.5/250; assess renal function	NA	20 of glipizide, 2,000 of metformin	Combination medication	Use as initial therapy: 2.5/250 mg twice a day
Rosiglitazone/metformin (N)	Avandamet	1/500 2/500 4/500 2/1,000 4/1,000	1–2/500 twice a day	1/500 twice a day; assess renal function	NA	8 of rosiglitazone; 2,000 of metformin	Combination medication	Past manufacturing problems but recently reintroduced to market. Can use as initial therapy
Rosiglitazone/glimepiride (N)	Avandaryl	4/1 4/2 4/4	4/1 or 4/2 once a day	4/1 daily	NA	8 mg of rosiglitazone, 8 mg of glimepiride	Combination medication	Recent labeling that it can increase cardiovascular events in patients with concomitant heart failure—caution
Pioglitazone/metformin (N)	ACTOplus Met	15/500 15/850	15/500 to 15/850 once or twice daily	15/500 daily to twice daily; assess renal function	NA	45 mg of pioglitazone, 2,550 mg of metformin	Combination medication	
Pioglitazone/glimepiride (N)	Duetact	30/2 30/4	30/2 or 30/4 daily	30/2 daily to avoid hypoglycemia	NA	45 mg pioglitazone, 8 mg glimepiride	Combination medication	Maximum dose cannot be given of either medication because of formulations available
Sitagliptin/metformin (N)	Janumet	50/500 50/1,000	50/500 twice daily with meals up to 50/1,000 twice daily with meals	Either given twice daily; assess renal function prior to use	NA	100 mg sitagliptin daily	Combination medication	Follow renal precautions for metformin.

Data from Gerich JE. Oral hypoglycemic agents. N Engl J Med 1989;321:1231–1245.

Cytochrome P450 (CYP) 2C9 is involved with the hepatic metabolism of the majority of sulfonylureas. Agents with active metabolites or parent drug that are renally excreted require dosage adjustment or use with caution in patients with compromised renal function. The half-life of the sulfonylurea also relates directly to the risk for hypoglycemia. The hypoglycemic potential is therefore higher with chlorpropamide and glyburide. The long duration of effect of chlorpropamide can be particularly problematic in elderly individuals, whose renal function declines with age, and therefore it has great potential for accumulation, resulting in severe and protracted hypoglycemia. Individuals at high risk for hypoglycemia (e.g., elderly individuals and those with renal insufficiency or advanced liver disease) should be started at a very low dose of a sulfonylurea with a short half-life. Hypoglycemia on low-dose sulfonylureas can dictate a short-acting insulin secretagogue (nateglinide or repaglinide) in lieu of a sulfonylurea.

Efficacy. As mentioned earlier, when given in equipotent doses, all sulfonylureas are equally effective at lowering blood glucose. On average, HbA_{1c} will decrease 1.5% to 2%, with FPG reductions of 60 to 70 mg/dL. A majority of patients will not reach glycemic goals with sulfonylurea monotherapy. Patients who fail sulfonylurea usually fall into two groups: Those with low C-peptide levels and high (>250 mg/dL) FPG levels. These patients are often primary failures on sulfonylureas (<30 mg/dL drop of FPG) and have significant glucose toxicity or slow-developing type 1 DM. The other group is those with a good initial response (>30 mg/dL drop of FPG), but which is insufficient to reach their glycemic goals. More than 75% of patients fall into the second group. Factors that portend a positive response include newly diagnosed patients with no indicators of type 1 DM, high fasting C-peptide levels, and moderate fasting hyperglycemia (<250 mg/dL). If glycemic goals are met, a secondary failure rate of approximately 5% to 7% per year can be expected.

Microvascular Complications. Sulfonylureas showed a reduction of microvascular complications in type 2 DM patients in the UKPDS.[61] A more in-depth discussion follows later in the chapter.

Macrovascular Complications. In the largest study to date, the UKPDS, no significant benefit or harm was seen in newly diagnosed type 2 DM patients given sulfonylureas over 10 years. The University Group Diabetes Program study documented higher rates of coronary artery disease in type 2 patients given tolbutamide, when compared to patients given insulin or placebo, although this study has been widely criticized.[74,75] Some sulfonylureas bind to the SUR-2A receptor that is found in cardiac tissue. Binding to the SUR-2A receptor has been implicated in blocking ischemic preconditioning via K^+ channel closure in the heart. Ischemic preconditioning is the premise that prior ischemia in cardiac tissue can provide greater tolerance of subsequent ischemia. Thus patients with heart disease potentially have one compensatory mechanism to protect the heart from ischemia blocked. Conclusions are controversial, and readers are referred to the pertinent articles for further discussion.[76–78]

Adverse Effects. The most common side effect of sulfonylureas is hypoglycemia. The pretreatment FPG is a strong predictor of hypoglycemic potential. The lower the FPG is on initiation, the higher the potential for hypoglycemia. Also, in addition to the high-risk individuals outlined in the pharmacokinetics section, those who skip meals, exercise vigorously, or lose substantial amounts of weight are also more likely to experience hypoglycemia.

Hyponatremia (serum sodium <129 mEq/L) is reportedly associated with tolbutamide, but it is most common with chlorpropamide and occurs in as many as 5% of individuals treated. An increase in antidiuretic hormone secretion is the mechanism for hyponatremia. Risk factors include age >60 years, female gender, and concomitant use of thiazide diuretics.

Weight gain is common with sulfonylureas. In essence, patients who are no longer glycosuric and who do not reduce caloric intake with improvement of blood glucose will store excess calories. Other notable, although much less common, adverse effects of sulfonylureas are skin rash, hemolytic anemia, GI upset, and cholestasis. Disulfiram-type reactions and flushing have been reported with tolbutamide and chlorpropamide when alcohol is consumed.

Drug Interactions. Several drugs are thought to interact with sulfonylureas, and Table 77–13 summarizes them by proposed mechanisms of action.[79] Drug interactions from protein-binding changes should occur shortly after the interacting medication is given, as the concentration of free (thus active) sulfonylurea will acutely increase. First-generation sulfonylureas, which bind to proteins ionically, are more likely to cause drug-drug interactions than second-generation sulfonylureas, which bind nonionically.[80] The clinical importance of protein-binding interactions has been questioned, as the majority of these drug interactions have been found to truly be caused by hepatic metabolism. Drugs that are inducers or inhibitors of CYP2C9 should be monitored carefully when used with a sulfonylurea. Additionally, other drugs known to alter blood glucose should be considered (see Table 77–11).

Dosing and Administration. The usual starting dose and maximum dose of sulfonylureas are summarized in Table 77–12. Lower dosages are recommended for most agents in elderly patients and those with compromised renal or hepatic function. The dosage should be titrated every 1 to 2 weeks (use a longer interval with chlorpropamide) to achieve glycemic goals. This is possible because of the rapid increase of insulin secretion in response to the sulfonylurea. Of note, immediate-release glipizide's maximal dose is 40 mg/day, but its maximal effective dose is about 10 to 15 mg/day. The maximal effective dose of sulfonylureas tends to be approximately 60% to 75% of their stated maximum dose.

Short-Acting Insulin Secretagogues ***Pharmacology.*** Although the binding site is adjacent to the binding site of sulfonylureas, nateglinide and repaglinide stimulate insulin secretion from the β cells of the pancreas, similarly to sulfonylureas. Repaglinide, a benzoic acid derivative, and nateglinide, a phenylalanine amino acid derivative, both require the presence of glucose to stimulate insulin secretion. As glucose levels diminish to normal, stimulated insulin secretion diminishes.

TABLE 77-13 Drug Interactions with Sulfonylureas

Interaction	Drugs
Displacement from protein binding sites[a]	Warfarin, salicylates, phenylbutazone, sulfonamides
Alters hepatic metabolism (cytochrome P450)	Chloramphenicol, monoamine oxidase inhibitors, cimetidine, rifampin[b]
Altered renal excretion	Allopurinol, probenecid

[a]Many of these drug interactions may be metabolism-based.
[b]Inducer.
Reproduced from Gerich.[79]

Pharmacokinetics. Both nateglinide and repaglinide are rapid-acting insulin secretagogues that are rapidly absorbed (~0.5 to 1 hour) and have a short half-life (1 to 1.5 hours). Nateglinide is highly protein-bound, primarily to albumin, but also to α_1-acid glycoprotein. Nateglinide is predominantly metabolized by CYP2C9 (70%) and CYP3A4 (30%) to less active metabolites. Glucuronide conjugation then allows rapid renal elimination. Repaglinide is mainly metabolized by the CYP3A4 system to inactive metabolites that are excreted in the bile.

Efficacy. In monotherapy, both significantly reduce postprandial glucose excursions and reduce HbA_{1c} levels. Repaglinide, dosed 4 mg three times a day, when compared to glyburide in diet-treated drug-naïve patients reduced HbA_{1c} levels less (1% vs. 2.4%, from baseline, respectively).[81] Nateglinide, dosed 120 mg three times a day in a similar population reduced HbA_{1c} values by 0.8%.[82] The lower efficacy of these agents versus sulfonylureas should be considered when patients are >1% above their HbA_{1c} goal. These agents can be used to provide increased insulin secretion during meals, when it is needed, in patients close to glycemic goals. Also, it should be noted that addition of either agent to a sulfonylurea will not result in any improvement in glycemic parameters.

Adverse Effects. Hypoglycemia is the main side effect noted with both agents. Hypoglycemic risk appears to be less than with sulfonylureas. In part, this is because of the glucose-sensitive release of insulin. If the glucose concentration is normal, less glucose-stimulated release of insulin will occur. In two separate studies, nateglinide rates of hypoglycemia were 3% and repaglinide 15% versus glyburide and glipizide rates of 15% and 19%, respectively. Weight gain of 2 to 3 kg has been noted with repaglinide, whereas weight gain with nateglinide appears to be <1 kg.

Drug Interactions. Glycemic control and hypoglycemia should be closely monitored when inducers or inhibitors of CYP3A4 are given with repaglinide. Gemfibrozil, a common medication used to treat hypertriglyceridemia in DM, more than doubles the half-life of repaglinide and has resulted in prolonged hypoglycemic reactions. Nateglinide appears to be a weak inhibitor of CYP2C9 based on tolbutamide metabolism, although no significant drug-drug interactions have been reported.

Dosing and Administration. Nateglinide and repaglinide should be dosed prior to each meal (up to 30 minutes prior). The recommended starting dose for repaglinide is 0.5 mg in subjects with HbA_{1c} <8% or treatment-naïve patients, increased weekly to a total maximum daily dose of 16 mg (see Table 77–12). The maximal effective dose of repaglinide is likely 2 mg with each meal, as a dose of 1 mg prior to each meal provides approximately 90% of the maximal glucose-lowering effect. Nateglinide should be dosed at 120 mg prior to meals, and does not require titration. A 60-mg dose is available, but the HbA_{1c} decrement is small (0.3% to 0.5%). If a meal is skipped, the medication can be skipped, and meals extremely low in carbohydrate content may not need a dose. Both agents can be used in patients with renal insufficiency and offer an excellent alternative in patients experiencing hypoglycemia with low-dose sulfonylurea. Caution is advised for patients with moderate to severe hepatic impairment, as nateglinide has not been studied and the half-life is prolonged with use of repaglinide.

Biguanides ***Pharmacology.*** Metformin is the only biguanide available in the United States. Metformin has been used clinically for 45 years and has been approved in the United States since 1995. Metformin enhances insulin sensitivity of both hepatic and peripheral (muscle) tissues. This allows for an increased uptake of glucose

into these insulin-sensitive tissues. The exact mechanisms of how metformin accomplishes insulin sensitization are still being investigated, although adenosine 5-monophosphate–activated protein kinase activity, tyrosine kinase activity enhancement, and glucose transporter-4 all play a part. Metformin has no direct effect on the β cells, although insulin levels are reduced, reflecting increases in insulin sensitivity.

Pharmacokinetics. Metformin has approximately 50% to 60% oral bioavailability, low lipid solubility, and a volume of distribution that approximates body water. Metformin is not metabolized and does not bind to plasma proteins. Metformin is eliminated by renal tubular secretion and glomerular filtration. The average half-life of metformin is 6 hours, although pharmacodynamically, metformin's antihyperglycemic effects last >24 hours.

Efficacy. Metformin consistently reduces HbA_{1c} levels by 1.5% to 2.0%, FPG levels by 60 to 80 mg/dL, and retains the ability to reduce FPG levels when they are extremely high (>300 mg/dL). The sulfonylureas' ability to stimulate insulin release from β cells at extremely high glucose levels is often impaired, a concept commonly referred to as *glucose toxicity*. Metformin also has positive effects on several components of the insulin resistance syndrome. Metformin decreases plasma triglycerides and LDL-C by approximately 8% to 15%, as well increasing HDL-C very modestly (2%). Metformin reduces levels of plasminogen activator inhibitor-1 and causes a modest reduction in weight (2 to 3 kg).

Microvascular Complications. Metformin ($n = 342$) was compared to intensive glucose control with insulin or sulfonylureas in the UKPDS. No significant differences were seen between therapies with regard to reducing microvascular complications.

6 ***Macrovascular Complications.*** Although normal weight type 2 DM subjects may not receive benefit, metformin reduced macrovascular complications in obese subjects in the UKPDS.[83] Metformin significantly reduced all-cause mortality and risk of stroke versus intensive treatment with sulfonylureas or insulin. Metformin also reduced diabetes-related death and myocardial infarctions as opposed to the conventional treatment arm of the UKPDS. Metformin should be included in the therapy for all type 2 DM patients, if tolerated and not contraindicated, as it is the only oral antihyperglycemic medication proven to reduce the risk of total mortality and is generic.

Adverse Effects. Metformin causes GI side effects, including abdominal discomfort, stomach upset, and/or diarrhea in approximately 30% of patients. Anorexia and stomach fullness is likely part of the reason loss of weight is noted with metformin. These side effects are usually mild and can be minimized by slow titration. GI side effects also tend to be transient, lessening in severity over several weeks. If encountered, make sure patients are taking metformin with or right after meals and reduce the dose to a point at which no GI side effects are encountered. Increases in the dose can be tried again in several weeks. Anecdotally, extended-release metformin (Glucophage-XR) can lessen some of the GI side effects. Metallic taste, interference with vitamin B_{12} absorption, and hypoglycemia during intense exercise have been documented but are clinically uncommon.

Metformin therapy rarely (3 cases per 100,000 patient-years) causes lactic acidosis. Any disease state that can increase lactic acid production or decrease lactic acid removal can predispose to lactic acidosis. Tissue hypoperfusion, such as that caused by congestive heart failure, hypoxic states, shock, or septicemia, via increased production of lactic acid; and severe liver disease or alcohol, through reduced removal of lactic acid in the liver, all increase the risk of lactic acidosis. The clinical presentation of lactic acidosis is often nonspecific flu-like symptoms, thus the diagnosis is usually made by laboratory confirmation. Metformin use in renal insufficiency, defined as a serum creatinine of 1.4 mg/dL in women and 1.5 mg/dL in men or greater, is contraindicated, as it is renally eliminated. Elderly patients, who often have reduced muscle mass, should have their glomerular filtration rate estimated by a 24-hour urine creatinine collection. If the estimated glomerular filtration rate is less than 70 mL/min, metformin should not be given. Because of the risk of acute renal failure during intravenous dye procedures, metformin therapy should be withheld starting the day of the procedure and resumed in 2 to 3 days, after normal renal function has been documented.

Drug Interactions. Cimetidine competes for renal tubular secretion of metformin and concomitant administration leads to higher metformin serum concentrations. At least one case report of lactic acidosis with metformin therapy implicates cimetidine. Other cationic drugs may interact similarly such as procainamide, digoxin, quinidine, trimethoprim, and vancomycin.[84]

Dosing and Administration. Metformin immediate-release is usually dosed 500 mg twice a day with the largest meals to minimize GI side effects. Metformin can be increased by 500 mg weekly until glycemic goals or 2,000 mg/day is achieved (see Table 77–12). Metformin 850 mg can be dosed daily and then increased every 1 to 2 weeks to the maximum dose of 850 mg three times a day (2,550 mg/day). Approximately 80% of the glycemic-lowering effect can be seen at 1,500 mg, and 2,000 mg/day is the maximal effective dose.

Extended-release metformin can be initiated at 500 mg a day with the evening meal and titrated weekly by 500 mg as tolerated to a single evening dose of 2,000 mg/day. Twice daily to three times a day dosing of extended-release metformin can help minimize GI side effects and improve glycemic control. Metformin extended-release 750 mg tablets can be titrated weekly to the maximum dose of 2,250 mg/day, although as stated above, 1,500 mg/day provides the majority of the glycemic-lowering effect.

Thiazolidinediones *Pharmacology.* Thiazolidinediones are also referred to as TZDs or glitazones. Pioglitazone and rosiglitazone are the two currently approved TZDs for the treatment of type 2 DM (see Table 77–12). TZDs work by binding to the peroxisome proliferator-activated receptor-γ (PPAR-γ), which are primarily located on fat cells and vascular cells. The concentration of these receptors in the muscle is very low; thus this is unlikely to be the main site of action. TZDs enhance insulin sensitivity at muscle, liver, and fat tissues indirectly. TZDs cause preadipocytes to differentiate into mature fat cells in subcutaneous fat stores. Small fat cells are more sensitive to insulin and more able to store FFAs. The result is a flux of FFAs out of the plasma, visceral fat, and liver into subcutaneous fat, a less insulin-resistant storage tissue. Muscle intracellular fat products, which contribute to insulin resistance, also decline. TZDs also affect adipokines, (e.g., angiotensinogen, tissue necrosis factor-α, interleukin-6, plasminogen activator inhibitor-1), which can positively affect insulin sensitivity, endothelial function, and inflammation. Of particular note, adiponectin is reduced with obesity and/or diabetes but is increased with TZD therapy, which improves endothelial function, insulin sensitivity, and has a potent antiinflammatory effect.

Pharmacokinetics. Pioglitazone and rosiglitazone are well absorbed with or without food. Both are highly (>99%) protein bound to albumin. Pioglitazone is primarily metabolized by CYP2C8, and to a lesser extent by CYP3A4 (17%), with the majority being eliminated in the feces. Rosiglitazone is metabolized by CYP2C8, and to a lesser extent by CYP2C9, then conjugated with two-thirds found in urine and one-third in feces. The half-life of pioglitazone and rosiglitazone is 3 to 7 hours and 3 to 4 hours, respectively. Two active metabolites of pioglitazone with longer half-lives deliver the majority of activity at steady state. Both medications have a duration of antihyperglycemic action of more than 24 hours.

Efficacy. Pioglitazone and rosiglitazone, given for approximately 6 months, reduce HbA_{1c} values ~1.5% and reduce FPG levels by approximately 60 to 70 mg/dL at maximal doses. Glycemic-lowering onset is slow, and maximal glycemic-lowering effects may not be seen until 3 to 4 months of therapy. It is important to inform patients of this fact and that they should not stop therapy even if minimal glucose lowering is initially encountered. The efficacy of both drugs is dependent on sufficient insulinemia. If there is insufficient endogenous insulin production (β-cell function) or exogenous insulin delivery via injections, neither will lower glucose concentrations efficiently. Interestingly, patients who are more obese, or who gain weight on either medication tend to have a larger reduction in HbA_{1c} values. Pioglitazone consistently decreases plasma triglyceride levels by 10% to 20%, whereas rosiglitazone tends to have a neutral effect. LDL-C concentrations tend to increase with rosiglitazone 5% to 15% but do not significantly increase with pioglitazone. Both appear to convert small, dense low-density lipoprotein (LDL) particles, which have been shown to be highly atherogenic, to large, fluffy LDL particles that are less dense. Large, fluffy LDL particles may be less atherogenic, but any increase in LDL must be of concern. Both drugs increase HDL similarly, up to 3 to 9 mg/dL. TZDs also affect several components of the insulin resistance syndrome. PAI-1 levels are decreased, and many other adipocytokines are affected, endothelial function improves, and blood pressure can decrease slightly.

Microvascular Complications. TZDs reduce HbA_{1c} levels, which have been shown to be related to the risk of microvascular complications.

Macrovascular Complications. Macrovascular complications with TZDs are controversial. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, pioglitazone 45 mg was added to standard therapy in patients who had experienced a macrovascular event or had peripheral vascular disease.[85] The two groups were well matched at baseline, and the reported average observation time period was approximately 3 years. The primary end point (reduction in death, myocardial infarction, stroke, acute coronary syndrome, coronary revascularization, leg amputation, and leg revascularization) was reduced 10% ($P = 0.095$). The main secondary end point (all-cause mortality, nonfatal myocardial infarction, or stroke) was reduced 16% ($P = 0.027$). The seemingly dichotomous results relate to the inclusion of leg revascularization, which were increased in the pioglitazone group. Reasons for the increase are speculative, but can relate to more testing and inspection because of peripheral edema. Also of note, the pioglitazone group had 209 nonadjudicated admissions for heart failure occur versus 153 in the placebo group ($P = 0.007$), although fatal heart failure was not increased. Several nonpublished meta-analyses of rosiglitazone reported higher myocardial infarction rates with rosiglitazone. Recently, a hazard ratio of 1.43 (95% confidence intervals 1.03–1.98; $P = 0.03$) for the risk of a myocardial infarction with rosiglitazone versus other oral agents was reported, but has been widely criticized.[86] A prospective cardiovascular outcome trial with rosiglitazone is underway, but the FDA will likely require a black box warning about cardiovascular events with rosiglitazone.

Adverse Effects. Troglitazone, the first TZD approved, caused idiosyncratic hepatotoxicity and had 28 deaths from liver failure, which prompted removal from the U.S. market in March, 2000. Approximately 1.9% of patients placed on troglitazone had alanine aminotransferase (ALT) levels more than three times the upper limit of normal. The incidence, using these criteria for elevated liver enzymes, with pioglitazone (0.25%) and rosiglitazone (0.2%) has been low. No evidence of hepatotoxicity was reported in an analysis of more than 5,000 patients given rosiglitazone or pioglitazone.[87] Several case reports of hepatotoxicity with rosiglitazone or pioglitazone have been reported, but improvement in ALT was consistently noted when the drug was discontinued. Prior to therapy, it is recommended that an ALT be checked. ALT monitoring vigilance has been lowered, and it is now recommended that the ALT be checked periodically at the practitioner's discretion. Patients with ALT levels >2.5 times the upper limit of normal should not start either medication, and if the ALT is >3 times the upper limit of normal the medication should be discontinued.

Retention of fluid leads to many different possible side effects with rosiglitazone and pioglitazone. The etiology of the fluid retention has not been fully elucidated but appears to include peripheral vasodilation and/or improved insulin sensitization with a resultant increase in renal sodium and water retention. A reduction in plasma hemoglobin (2% to 4%), attributed to a 10% increase in plasma volume, can result in a dilutional anemia, which does not require treatment. Edema is also commonly (4% to 5% in mono- or combination therapy) reported. When a TZD is used in combination with insulin, the incidence of edema (~15%) is increased. TZDs are contraindicated in patients with New York Heart Association class III and IV heart failure, and great caution should be exercised when given to patients with class I and II heart failure or other underlying cardiac disease, as pulmonary edema and heart failure have been reported. Edema tends to be dose related and if not severe, a reduction in the dose as well as use of diuretics (anecdotally spironolactone appears to help selected patients) will allow the continuation of therapy in the majority of patients.[88] In addition, rarely, TZDs have been reported to worsen macular edema in the eye.

Weight gain, which is also dose related, can be seen with both rosiglitazone and pioglitazone. Mechanistically, both fluid retention and fat accumulation play a part in explaining the weight gain. TZDs, besides stimulating fat cell differentiation, also reduce leptin levels, which stimulate appetite and food intake. Average weight gain varies, but a 1.5- to 4-kg weight gain is not uncommon. Rarely, a patient will gain large amounts of weight in a short period of time, and this may necessitate discontinuation of therapy. Weight gain positively predicts a larger HbA_{1c} reduction but must be balanced with the well documented effects of long-term weight gain.

TZDs have also been associated with an increased fracture rate in the upper and lower limbs in postmenopausal women, but not men. As opposed to comparative diabetes therapy, TZDs can double the risk of fracture in this population. The underlying pathophysiology is speculative but can relate to the effect of TZD in bone marrow, with a reduction in osteoblast activity and an increase in bone marrow fat. It would be prudent to consider a patient's risk factors for fractures if prescribed a TZD and possibly have a lower threshold for additional assessment in postmenopausal women.

As a caution, anovulatory patients can resume ovulation on TZDs. Adequate pregnancy and contraception precautions should be explained to all women capable of becoming pregnant, as both agents are pregnancy category C.

Drug Interactions. No significant drug interactions have been noted with either medication. Neither pioglitazone nor rosiglitazone appear to be inhibitors or inducers of CYP3A4 and CYP2C8 or CYP2C8 and CYP2C9, respectively, although drugs that are strong inhibitors or inducers of these pathways (e.g., gemfibrozil or rifampin) necessitate close monitoring.

Dosing and Administration. The recommended starting dosages of pioglitazone and of rosiglitazone are 15 to 30 mg once daily and 2 to 4 mg once daily, respectively. Dosages can be increased slowly based on therapeutic goals and side effects. The maximum dose and maximum effective dose of pioglitazone is 45 mg, and rosiglitazone is 8 mg once daily, although 4 mg twice a day can reduce HbA_{1c} by 0.2% to 0.3% more as opposed to 8 mg once daily.

α-Glucosidase Inhibitors

Pharmacology. Currently, there are two α-glucosidase inhibitors available in the United States (acarbose and miglitol). α-Glucosidase inhibitors competitively inhibit

enzymes (maltase, isomaltase, sucrase, and glucoamylase) in the small intestine, delaying the breakdown of sucrose and complex carbohydrates.[89,90] They do not cause any malabsorption of these nutrients. The net effect from this action is to reduce the postprandial blood glucose rise.

Pharmacokinetics. The mechanism of action of α-glucosidase inhibitors is limited to the luminal side of the intestine. Some metabolites of acarbose are systemically absorbed and renally excreted, whereas the majority of miglitol is absorbed and renally excreted unchanged.

Efficacy. Postprandial glucose concentrations are reduced (40 to 50 mg/dL), whereas fasting glucose levels are relatively unchanged (~10% reduction). Efficacy on glycemic control is modest (average reductions in HbA_{1c} of 0.3% to 1%), affecting primarily postprandial glycemic excursions. Thus patients near target HbA_{1c} levels with near-normal FPG levels, but high postprandial levels, might be candidates for therapy.

Microvascular Complications. α-Glucosidase inhibitors modestly reduce HbA_{1c} levels, which have been shown to be related to the risk of microvascular complications.

Macrovascular Complications. The Study to Prevent Non–Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), in subjects with impaired glucose tolerance, reported a significant reduction in the risk of cardiovascular events, although the total number of events were small.[91,92] No large cardiovascular study confirming these preliminary results has been done in prediabetes or diabetes patients.

Adverse Effects. The GI side effects, such as flatulence, bloating, abdominal discomfort, and diarrhea, are very common and greatly limit the use of α-glucosidase inhibitors. Mechanistically, these side effects are caused by distal intestinal degradation of undigested carbohydrate by the microflora, which results in gas (carbon dioxide [CO_2] and methane) production. α-Glucosidase inhibitors should be initiated at a low dose and titrated slowly to reduce GI intolerance. Beano, an α-glucosidase enzyme, can help to decrease GI side effects but can decrease efficacy slightly.[93]

If a patient develops hypoglycemia within several hours of ingesting an α-glucosidase inhibitor, oral glucose is advised because the drug will inhibit the breakdown of more complex sugar molecules. Milk, with lactose sugar, can be used as an alternative when no glucose is available, as acarbose only slightly (10%) inhibits lactase.

Rarely, elevated serum aminotransferase levels have been reported with the highest doses of acarbose. It appeared to be dose and weight related and is the premise for the weight-based maximum doses.

Dosing and Administration. Dosing for both miglitol and acarbose are similar. Initiate with a very low dose (25 mg with one meal a day); increase very gradually (over several months) to a maximum of 50 mg three times a day for patients ≤60 kg or 100 mg three times a day for patients >60 kg (see Table 77–12). Both α-glucosidase inhibitors should be taken with the first bite of the meal so that drug may be present to inhibit enzyme activity. Only patients consuming a diet high in complex carbohydrates will have significant reductions in glucose levels. α-Glucosidase inhibitors are contraindicated in patients with short-bowel syndrome or inflammatory bowel disease, and neither should be administered in patients with serum creatinine >2 mg/dL, as this population has not been studied.

DPP-IV inhibitors Sitagliptin is currently approved for use in the United States, whereas vildagliptin has received an approvable letter from the FDA.

Pharmacology. DPP-IV inhibitors prolong the half-life of an endogenously produced glucagon-like peptide-1 (GLP-1). It has clearly been shown that in type 2 DM, GLP-1 levels are deficient. DPP-IV inhibitors partially reduce the inappropriately elevated glucagon postprandially and stimulate glucose-dependent insulin secretion. As these agents block nearly 100% of the DPP-IV enzyme activity for at least 12 hours, near normal, nondiabetic GLP-1 levels are achieved. These drugs do not alter gastric emptying.

Pharmacokinetics. Sitagliptin appears to have rapid absorption, with t_{max} and C_{max} of approximately 1.5 hours. Absolute bioavailability after oral intake is approximately 87%. The $t_{1/2}$ of sitagliptin is approximately 12 hours, and 79% of the dose of sitagliptin is excreted unchanged in the urine by active tubular secretion. Sitagliptin exposure is increased by approximately 2.3-, 3.8-, and 4.5-fold relative to healthy subjects for patients with moderate renal insufficiency (creatinine clearance 30 to <50 mL/min), severe renal insufficiency (creatinine clearance <30 mL/min), and end-stage renal disease (on dialysis), respectively. Pharmacodynamically, DPP-IV inhibition appeared to mirror directly the plasma concentration of sitagliptin. Doses of 50 mg produced at least 80% inhibition of DPP-IV enzyme activity at 12 hours, and 100 mg produced 80% inhibition of DPP-IV enzyme activity at 24 hours. Food had no effect on absorption kinetics of sitagliptin or vildagliptin.

Vildagliptin is rapidly and almost completely (85%) absorbed after oral intake. Within 1 to 2 hours, t_{max} is achieved. The plasma $t_{1/2}$ varies with dose and is approximately 1.5 to 4.5 hours over a range or 25 mg to 200 mg. Approximately 55% of the drug is metabolized by hydrolysis, with the majority of the remaining drug eliminated unchanged by the kidneys. Vildagliptin dose-dependently inhibits the DPP-IV enzyme activity, approximately a 70% inhibition at 50 mg and 90% inhibition at 100 mg at 12 hours, with a continued 40% inhibition at 24 hours.

Efficacy. The average reduction in HbA_{1c} with vildagliptin or sitagliptin is approximately 0.7% to 1% at a dose of 100 mg a day. The HbA_{1c} decrement is dependent on the baseline value, with a larger reduction being seen with a higher baseline HbA_{1c}. As they are well tolerated, adjustment in the dose for adverse effects is unlikely.

Microvascular and Macrovascular Complications. HbA_{1c} levels are reduced, which have been related to a reduction in microvascular complications, but no outcome data are available to date.

Drug-Drug Interactions. Both are unlikely to have significant drug-drug interactions. Sitagliptin is metabolized approximately 20% by CYP3A4 with some CYP2C8 involvement but is neither an inhibitor nor inducer of any CYP450 enzyme system. Sitagliptin is a p-glycoprotein substrate, but had negligible effects on digoxin kinetics, and cyclosporine A increased the area under the curve (AUC) by only 30%. Neither drug is extensively plasma protein bound. Vildagliptin is neither an inhibitor nor inducer of CYP450 enzymes.

Adverse Effects. Both drugs are very well tolerated, weight neutral, and do not cause GI side effects. Mild hypoglycemia appears to be the only significant adverse effect, and the rate is similar to metformin. No significant increases in peripheral edema, hypertension, or cardiac outcomes have been noted to date. In regards to long-term safety, DPP-IV enzymes metabolize a wide variety of peptides (peptide YY [PYY], neuropeptide Y, growth hormone releasing hormone, and vasoactive intestinal polypeptide, and others) potentially affecting other regulatory systems. DPP-IV (also known as CD26) plays an important role for T-cell activation and theoretically the inhibition of DPP-IV could be associated with adverse immunologic reactions. Additionally DPP-8/9 inhibition in animals produced multiple toxicities. Both compounds have explored their binding to DPP-8/9, and have found minimal binding to these subtypes. Long-term safety data is still limited, but to date no adverse effects have been clearly linked to this issue.

Dosing and Administration. Vildagliptin will be dosed orally, likely at 50 mg to 100 mg daily. Sitagliptin is dosed orally at 100 mg daily unless renal insufficiency is present. The 50 mg dose is recommended if the creatinine clearance is 30 to less than 50 mL/min, or 25 mg if less than 30 mL/min. Equivalent serum creatinine levels are: sitagliptin 50 mg daily in men, greater than 1.7 to 3.0 mg/dL, women, greater than 1.5 to 2.5 mg/dL; 25 mg daily in men, greater than 3.0 mg/dL, women, greater than 2.5 mg/dL. No short-term adverse effects have been noted with increased exposure. Because of their excellent tolerability profile and a fairly flat dose-response curve, it seems logical that these drugs should be maximally dosed, unless cautions exist.

■ PIVOTAL TRIALS

Diabetes Control and Complications Trial

7 Much of the last century in diabetes care was dominated by the debate over whether glycemic control actually was causative in complications of DM. Animal studies and some human studies suggested that the worse the glycemia the greater the risk of complications. But "the glucose hypothesis" was not ultimately accepted as proven until the publication of the DCCT in 1993.[60] One thousand four hundred forty-one patients with type 1 DM were divided into two groups: those without complications (726 subjects, primary prevention), and those with early microvascular complications (715 subjects, secondary prevention). These two groups were then again divided into two groups, one randomized to receive conventional therapy (one or two shots of insulin daily and infrequent SMBG with no attempt to change therapy based on home blood glucose readings), and the other to receive intensive therapy (three or more injections of insulin daily or insulin pump, with frequent SMBG and alteration of insulin therapy based on SMBG results, plus frequent contact with a health professional). After 6.5 years mean followup with a difference in HbA_{1c} between the two groups being ~2% (~9% vs. ~7%), retinopathy was decreased by 76% in the primary prevention cohort, with retinopathy progression reduced 54% in the secondary prevention group. Neuropathy was decreased by 60% in both groups combined. Microalbuminuria was decreased 39%, whereas macroproteinuria was reduced 54% with intensive therapy. Hypoglycemia was more common and weight gain greater with intensive therapy. A nonstatistically significant reduction in coronary events was seen in the intensively treated group as compared to the conventional group. Followup studies 8 years after the DCCT ended continued to show an advantage of good glycemic control over what was previously considered conventional therapy.[94] The DCCT revolutionized therapy of DM, demanding that stricter glycemic control be the goal. Long-term followup of former DCCT subjects in the Epidemiology of Diabetes Interventions and Complications (EDIC) trial reported that, despite similar HbA_{1c} values 11 years later, renal and cardiovascular outcomes continued to be lower in intensively treated subjects from the DCCT as opposed to those who received conventional treatment.[95]

Implications of the United Kingdom Prospective Diabetes Study

The UKPDS was a landmark study for the care of patients with type 2 DM, confirming the importance of glycemic control for reducing the risk of microvascular complications.[61] More than 5,000 patients with newly diagnosed type 2 DM were entered into the study. Patients were followed for an average of 10 years. The major portion of the study assessed "conventional therapy" (no drug therapy unless the patient was symptomatic or had FPG >270 mg/dL), versus intensive therapy starting with either sulfonylureas or insulin, aimed at keeping the FPG <108 mg/dL. A subset of obese patients was studied using metformin as the primary therapeutic agent.

CLINICAL CONTROVERSY

Preservation of β-cell function, and thus arresting the progression of type 2 diabetes, appears to be the future goal of treatment. The UKPDS clearly showed that sulfonylureas, metformin, and insulin are ineffective in stopping the progressive β-cell failure. In animal models TZDs, exenatide, and DPP-IV inhibitors have been able to arrest β-cell failure, and in humans, short-term indirect β-cell function measures have improved. Confirmatory human data showing arrest or delay of the progressive β-cell decline in type 2 DM is needed. Rosiglitazone data in prediabetes and newly diagnosed diabetes, although measured by the homeostatic model assessment (HOMA)-β, has not shown significant preservation of β-cell function. Long-term data is underway with incretin based therapies.

Significant findings from the study include:

- Microvascular complications (predominantly the need for laser photocoagulation on retinal lesions) are reduced by 25% when median HbA_{1c} is 7% as compared to 7.9%.[53]
- A continuous relationship exists between glycemia and microvascular complications, with a 35% reduction in risk for each 1% decrement in HbA_{1c}. No glycemic threshold for microvascular disease exists.[96]
- Glycemic control has minimal effect on macrovascular disease risk.[61] Excess macrovascular risk appears to be related to conventional risk factors such as dyslipidemia and hypertension.[97]
- Sulfonylureas and insulin therapy do not increase macrovascular disease risk.[61]
- Metformin reduces macrovascular risk in obese patients.[84]
- Vigorous blood pressure control reduces microvascular and macrovascular events.[97] There was no evidence for a threshold systolic blood pressure above 130 mm Hg for protection against complications. β-Blockers and ACE inhibitors appear to be equally efficacious.[98]

■ THERAPEUTICS

8 Knowledge of the patient's quantitative and qualitative meal patterns, activity levels, pharmacokinetics of insulin preparations and other injectables, and pharmacology of oral and antidiabetic agents for type 2 DM are essential to individualize the treatment plan and optimize blood glucose control while minimizing risks for hypoglycemia and other adverse effects of pharmacologic therapies.

Type 1 DM

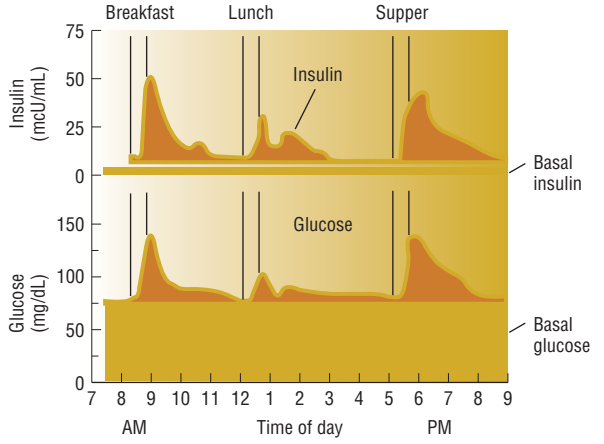
The choice of therapy for type 1 DM is simple: All patients need insulin. However, how that insulin is delivered to the patient is a matter of considerable practice difference among patients and clinicians. Historically, after the discovery of insulin by Banting and Best in 1921, frequent injections of regular insulin (initially the only insulin available) were given. Modifications of insulin led to longer-acting insulin suspensions and the use by many patients of one or two shots of longer-acting insulin each day. Because SMBG and HbA_{1c} testing were not available at that time, patients and practitioners had no idea how well their patients' blood glucose concentrations were controlled, other than a vague sense from an indirect method, measurement of glucose in the urine. Although the renal threshold for glucose is relatively predictable in young healthy subjects, it is highly variable in older patients and patients with renal disease. The advent of SMBG and HbA_{1c} testing in the 1980s revolutionized the care of diabetes, enabling patients and practitioners to directly access blood glucose for assessment, and enabling

the patient to make instantaneous changes in the insulin regimen if need be. Modern diabetes management would be impossible without these two tools.

Contemporary management of type 1 DM attempts to match carbohydrate intake with glucose-lowering processes, most commonly insulin, as well as with exercise. Diet is still the cornerstone of diabetes therapy, but unlike in previous years, attempts are made to allow the patient to live as normal a life as possible. Understanding the principles of glucose input and glucose egress from the blood will allow the practitioner and the patient great latitude in the management of patients with type 1 DM.

Simplistically speaking, one can break down normal insulin secretion into a relatively constant background level of insulin (*basal*) for the fasting and postabsorptive period, and prandial spikes of insulin after eating (*bolus*) (Fig. 77–8).[99] Insulin sensitivity and insulin secretion are not constant throughout the day, rendering the basal concept inaccurate. However, in most clinical situations, this approach provides a useful paradigm for understanding and applying insulin treatment for type 1 DM. The other basic principle to consider is that the timing of insulin onset, peak, and duration of effect must match meal patterns and exercise schedules to achieve near-normal blood glucose values throughout the day.

Historically, complexity of insulin regimens has usually been related to the number of injections of insulin administered per day.



Intensive insulin therapy regimens

	7AM	11AM	5PM	Bedtime
1. 2 doses,[a] R or rapid acting + N	R, L, A, E, GLU + N		R, L, A, E, GLU + N	
2. 3 doses, R or rapid acting + N	R, L, A, E, GLU + N	R, L, A, E, GLU	R, L, A, E, GLU + N	
3. 4 doses, R or rapid acting + N	R, L, A, E, GLU	R, L, A, E, GLU	R, L, A, E, GLU	N
4. 4 doses R or rapid acting + N	R, L, A, E, GLU + N	R, L, A, E, GLU	R, L, A, E, GLU	N
5. 4 doses,[b] R or rapid acting + long acting	R, L, A, E, GLU	R, L, A, E, GLU	R, L, A, E, GLU	G or D[b] (G may be given anytime every 24 hours)
	← Adjusted Basal →			
6. CS-II pump	Bolus	Bolus	Bolus	

[a] Many clinicians may not consider this intensive insulin therapy

[b] May be given BID in type 1 DM= 5 doses

FIGURE 77-8. Relationship between insulin and glucose over the course of a day and how various insulin regimens could be given. (A, aspart; CS-II, continuous subcutaneous insulin infusion; D, detemir; E, Exubera; G, glargine; GLU, glulisine; L, lispro; N, NPH; R, regular.)

This is a reasonable classification. Clearly one injection of any insulin preparation daily will in no way mimic normal physiology, and therefore is unacceptable. Similarly, two injections of any insulin daily will fail to replicate normal insulin release patterns. Injection regimens that begin to approximate physiologic insulin release start with "split-mixed" injections of a morning dose of NPH and regular insulin before breakfast, and again before the evening meal. The presumption is made that the morning NPH insulin gives basal insulin for the day and covers the midday meal, the morning regular insulin covers breakfast, the evening NPH insulin gives basal insulin for the rest of the day, and the evening regular covers the evening meal. If patients are very compulsive about consistency of timing of their injections and meals and intake of carbohydrate, such a strategy can be successful. However, most patients are not sufficiently predictable in their schedule and food intake to allow "tight" glucose control with such an approach.

The first modification that is frequently made to such a regimen is the movement of the evening NPH to bedtime (now three total injections per day) because the fasting glucose in the morning is too high. This approach improves glycemic control and reduces hypoglycemia, sufficiently intensifying the insulin therapy for some patients.[100] However, many patients need a more intense approach that also allows greater flexibility in their lifestyle.

9 The basal-bolus concept is an attempt to replicate normal insulin physiology with a combination of intermediate- or long-acting insulin to give the basal component, and short-acting insulin to give the bolus component. Various strategies have been used for the former, including once- or twice-daily NPH or detemir, or once-daily insulin glargine. Most type 1 DM patients require two shots of all of the above insulins except insulin glargine. Also, all of the above insulins, with the exception of insulin glargine, have some degree of peak effect that must be considered in planning meals and activity. Insulin glargine or insulin detemir is a feasible basal insulin supplement for most patients with type 1 DM. The bolus insulin component is given before meals with regular insulin, insulin lispro, insulin aspart, or insulin glulisine. The rapid onset of action and short time course of rapid-acting insulin analogs more closely replicate normal physiology. This approach allows the patient to vary the amount of insulin injected, depending on the preprandial SMBG level, the anticipated activity (upcoming exercise can reduce insulin requirement), and anticipated carbohydrate intake. Most patients will have a prescribed dose of insulin preprandially that they vary by use of a *sliding scale*. This type of adjusted scale insulin is intended to optimize the insulin regimen. In light of the negative connotation of the term *sliding scale* (usually referring to giving insulin only after the blood glucose increases, rather than treating the underlying disorder), a better descriptor for the adjusted-dose insulin is *variable-dose prandial insulin, correction factor*, or *insulin algorithm*. A rough correction factor can be calculated by taking 1,500 divided by the total daily dose of insulin. This gives the approximate glucose lowering (mg/dL) effect of one unit of insulin. Carbohydrate counting is a very effective tool for determining the amount of insulin to be injected preprandially. Although general algorithms give rough guidelines, each patient will have to adjust the prescribed preprandial insulin dosage to achieve optimal glucose control. A rough estimate of how much carbohydrate (grams) one unit of rapid-acting insulin will cover is to divide 500 by the total daily dose of insulin.

Empirically, patients can begin on ~0.6 unit/kg per day with basal insulin 50% of total dose and prandial insulin 20% of total dose prebreakfast, 15% prelunch, and 15% presupper. Type 1 DM patients generally require between 0.5 and 1 unit/kg per day. The need for significantly higher amounts of insulin suggests the presence of insulin antibodies or insulin resistance (coexistent endocrinopathy or type 2 DM).

Obviously, insulin pump therapy (continuous subcutaneous insulin infusion [CSII], generally using lispro or aspart insulin to diminish aggregation) is the most sophisticated form of basal bolus insulin delivery system. CSII can be slightly more efficacious in achieving good glycemic control than multiple-dose insulin injections.[101,102] Extensive discussion of this mode of therapy is beyond the scope of this text.[103] Nevertheless, the basic principles for implementation are the same. The one advantage of pump therapy is that the basal insulin dose can be varied, consistent with changes in insulin requirements throughout the day. In selected patients, this feature will allow greater glycemic control with CSII. However, insulin pumps require even greater attention to detail and frequency of SMBG than four injections daily.[104] In appropriately selected patients willing to pay sufficient attention to detail of SMBG and insulin administration, CSII can be a very useful form of therapy.

Intensive therapy (basal-bolus) to all adult patients with type 1 DM at the time of diagnosis is recommended to reinforce the importance of glycemic control from the outset rather than change strategies over time after lack of control. Occasional patients with an extended honeymoon period may need less intense therapy initially but should be converted to basal-bolus therapy at the onset of glycemic lability. For patients insisting on two injections daily, NPH and regular insulin (starting at 0.6 units/kg with two-thirds in the morning, two-thirds of morning dose as NPH, and one-half of evening dose as NPH) may be sufficient. Regardless of the regimen chosen, gross adjustments in the total insulin dose can be made based on HbA_{1c} measurements and symptoms such as polyuria, polydipsia, and weight gain or loss. Finer insulin adjustments can be determined on the basis of the results of frequent SMBG.

All patients receiving insulin should have extensive education in the recognition and treatment of hypoglycemia. Yearly (or more often) questioning about the recognition of hypoglycemia is warranted. Documentation of frequency of hypoglycemia, particularly that requiring assistance of another person, visit to an emergent or urgent care facility, or hospitalization, should be recorded. In type 1 DM, the development of hypoglycemia unawareness is common. It can result from progression of disease with autonomic neuropathy. Loss of adrenergic warning signs in such a situation is a relative contraindication to intensive insulin therapy. More commonly, type 1 DM patients have loss of warning signs because of a presumed lower set point for release of counterregulatory hormones as a result of frequent episodes of hypoglycemia ("hypoglycemia begets hypoglycemia").[105] In such situations, more normal hypoglycemia awareness can be restored by reduction or redistribution of the insulin dose to eliminate significant hypoglycemic episodes. A recent publication has found that short-term treatment with theophylline will improve hypoglycemia awareness.[106] This therapy should not routinely be employed but can be considered in refractory cases.

Children and pubescent adolescents are relatively protected from microvascular complications and must be managed with consideration of what is practical. Therefore it is not unreasonable to use less intense management (two shots per day, premixed insulins) until the patient is postpubertal.[107]

Occasional patients have antibodies to injected insulin, but the significance of the antibodies is usually minimal.[108] Human insulin therapy has not totally eliminated insulin allergies, although most patients have a local reaction that will dissipate over time. If the allergic reaction does not improve or is systemic, insulin desensitization can be carried out.[109] Protocols for desensitization are available from major insulin manufacturers. Although more common in the animal insulin era, lipohypertrophy is still seen in some patients with long-standing type 1 DM. Such patients give their insulin injections in the same site to minimize discomfort. Because insulin absorption from an area of lipohypertrophy is unpredictable, avoidance of injections into these areas is mandatory.

Several common errors can occur in the therapy of patients with type 1 DM, causing erratic glucose fluctuations:

- Failure to take into account peaks of insulin action when using a peaking insulin and planning meals and/or activity. Eating should be planned around the peaks of the insulin.
- Random rotation of insulin injection sites. There is sufficient variability of insulin absorption from site to site that this practice alone can cause wide glucose swings. The most consistent absorption of insulin is from the abdominal wall. We try to get our patients to take all their injections in the abdomen. If the patient is unable or unwilling to follow this advice, then systematic site rotation is the next preferable option. The patient always gives the insulin injection in the same region of the body the same time of the day each day. For instance, the arms are always used every morning. Needless to say, the patient would not inject in a limb and then go out and exercise that limb, increasing blood flow and insulin absorption.
- Overinsulinization is a very common problem. The answer to all high blood glucose is not necessarily more insulin, as the patient may be insulinopenic, or may be "rebounding" from a previous low glucose and treating it with excessive amounts of carbohydrate. Fastidious SMBG, particularly during the night (or selected use of continuous glucose monitoring) will help sort this out. Also, practitioners sometimes do not adequately differentiate type 1 DM from type 2 DM when using insulin. Patients with type 1 DM are insulinopenic but have normal insulin sensitivity. Patients with type 2 DM have varying degrees of insulin resistance. Therefore one unit change in the dose of insulin for a patient with type 1 DM can have a dramatic effect on glucose concentrations, whereas in some patients with type 2 DM 10 to 20 times that amount of insulin can have little effect on glucose. Large changes in insulin dose in patients with type 1 DM are not usually indicated unless the patient's blood glucose control is very poor. Widely erratic SMBG results and/or weight gain often suggest overinsulinization.
- When in doubt, always double check the patient's technique for insulin dosing, insulin injection, and SMBG. Sometimes the simplest of errors results in miserable glycemic control.

Pramlintide in type 1 DM patients who continue to have erratic postprandial control despite consideration or implementation of the above strategies can be appropriate. It is imperative at initiation of therapy with pramlintide that each dose of prandial insulin (rapid acting analog or regular insulin) be reduced by 30% to 50%, or severe hypoglycemic reactions have occurred. Pramlintide should be judiciously titrated based on GI adverse effects and postprandial glycemic goals. As pramlintide is not recommended for mixing, you are adding an additional prandial injection at each meal. A patient who is cognizant of the hypoglycemic risk, GI side effects, and effective strategies to reduce both is needed.

Islet cell and whole pancreas transplantation are occasionally used in patients, usually renal transplants, who require immunosuppressive therapy for other reasons.[110] There has been considerable interest in islet cell transplantation since investigators in Edmonton reported success without using glucocorticoids as immunosuppressive agents.[111] Some of these patients are able to come off insulin altogether.

Type 2 DM

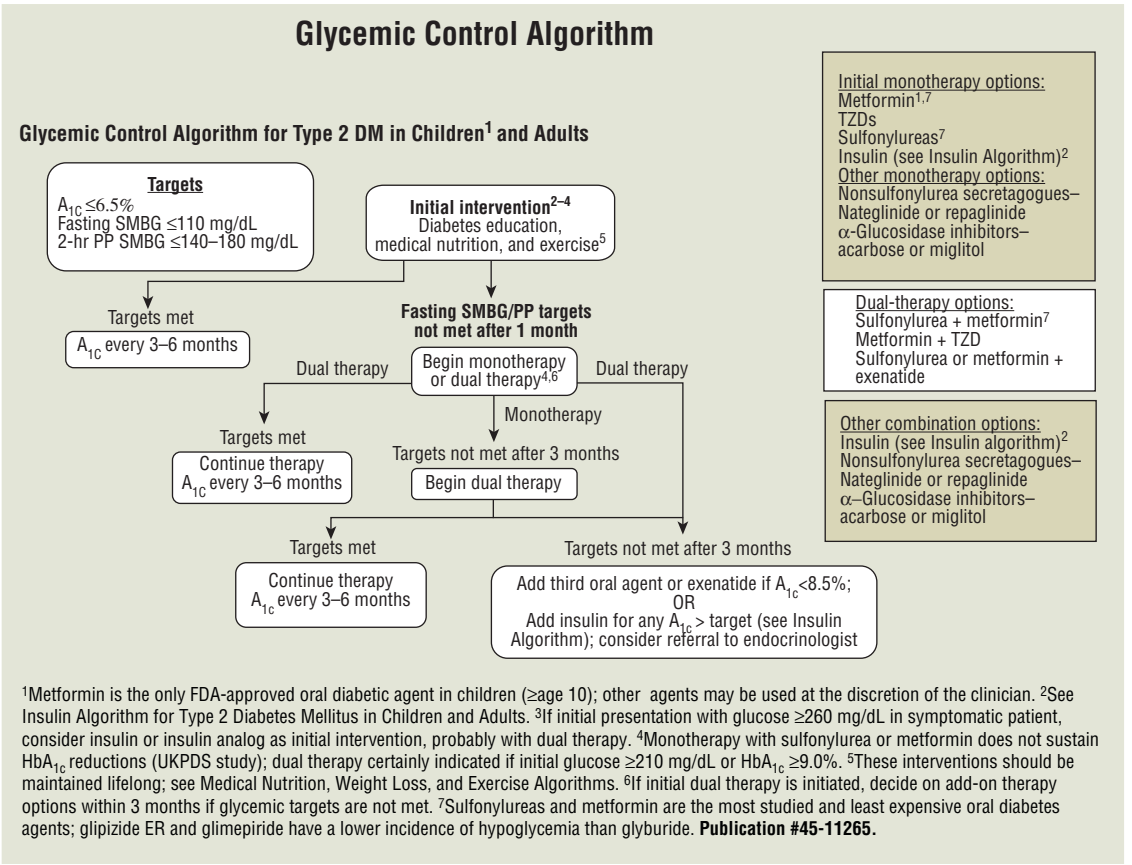
Pharmacotherapy for type 2 DM has changed dramatically in the last few years with the addition of several new drug classes and recommendations to achieve more stringent glycemic control. Symptomatic patients may initially require treatment with insulin or combination oral therapy to reduce glucose toxicity (which can reduce β-cell

insulin secretion and worsen insulin resistance). Patients with HbA_{1c} ~7% or less are usually treated with therapeutic lifestyle measures and an agent that will not cause hypoglycemia. Those with HbA_{1c} >7% but <8% could be initially treated with single oral agents, or low dose combinations. Patients with higher initial HbA_{1c} can benefit from initial therapy with two oral agents, or even insulin.

10 Depending on patient motivation and adherence to therapeutic lifestyle changes, most patients with HbA_{1c} greater than 9% to 10% will likely require therapy with two or more agents to reach glycemic goals. Treatment of type 2 DM often necessitates use of multiple therapeutic agents (combination therapy), to obtain glycemic goals.

The best initial oral therapy for patients with type 2 DM is widely debated. Based on the results of the UKPDS and safety record, obese patients (>120% ideal body weight) without contraindications should be started on metformin titrated to ~2,000 mg/day.[112] Near-normal weight patients can be treated with insulin secretagogues. Failure of initial therapy should result in addition rather than substitution (reserve substitution for intolerance to a drug because of side effects) of another class of drug. For cost and glycemic efficacy reasons, metformin and an insulin secretagogue are often first- and second-line therapy, although combination with other agents for potential cardioprotection or potential β-cell preservation may be preferred. Initial oral combination therapy for patients with HbA_{1c} >9% to 10% should be considered, and several oral combination products are available. Oral combination agents that have metformin in combination with a sulfonylurea are often very effective in lowering initially high HbA_{1c} levels. Figure 77–9 is an algorithm developed by the Texas Diabetes Council for glycemic control. TZDs can be substituted in situations in which a patient is intolerant of, or has a contraindication to, metformin as an insulin sensitizer, understanding that TZDs should be used with caution in heart failure.

The paradigm of treatment is slowly changing, as potentially preserving β-cell function, thus arresting the progressive nature of type 2 DM, is becoming a priority. In the UKPDS, insulin, metformin, or sulfonylureas did not halt β-cell failure. TZDs, exenatide, vildagliptin, and sitagliptin can potentially preserve β-cell function.[113,114] Despite long-term success at preventing diabetes or treating newly diagnosed diabetes, HOMA-β measures have not shown β-cell benefit with rosiglitazone. Long-term β-cell studies with pioglitazone are underway. If positive human results are found long-term, any of these medications could become potential first-line therapy. For dual therapy, HbA_{1c} reductions vary according to the medication added to the current therapy (Table 77–14). After a patient has inadequate control on two drugs, adding a third drug can be considered. Triple therapy with a TZD is often instituted, but a significant number of patients either have inadequate glycemic improvement or significant side effects. An alternative is to add exenatide, DPP-IV inhibitor, basal insulin, or even the prandial inhaled insulin, Exubera. Therapy should be guided by the HbA_{1c}, FPG, cost, additional benefits (such as weight loss), and avoidance of contraindications and side effects. If the HbA_{1c} is >8.5% to 9% on multiple therapies, insulin therapy should be considered first. If the patient is obese and the HbA_{1c} is ≤8.5%, addition of exenatide or potentially a DPP-IV inhibitor can be considered. Sulfonylureas are often stopped when insulin is added, but continuing the sulfonylurea is permissible until multiple daily injections are started, at which time it should definitely be discontinued.



[1]Metformin is the only FDA-approved oral diabetic agent in children (≥age 10); other agents may be used at the discretion of the clinician. [2]See Insulin Algorithm for Type 2 Diabetes Mellitus in Children and Adults. [3]If initial presentation with glucose ≥260 mg/dL in symptomatic patient, consider insulin or insulin analog as initial intervention, probably with dual therapy. [4]Monotherapy with sulfonylurea or metformin does not sustain HbA_{1c} reductions (UKPDS study); dual therapy certainly indicated if initial glucose ≥210 mg/dL or HbA_{1c} ≥9.0%. [5]These interventions should be maintained lifelong; see Medical Nutrition, Weight Loss, and Exercise Algorithms. [6]If initial dual therapy is initiated, decide on add-on therapy options within 3 months if glycemic targets are not met. [7]Sulfonylureas and metformin are the most studied and least expensive oral diabetes agents; glipizide ER and glimepiride have a lower incidence of hypoglycemia than glyburide. **Publication #45-11265.**

FIGURE 77-9. Glycemic control algorithm for type 2 diabetes mellitus (DM) in children and adults. See *www.texasdiabetescouncil.org* for current algorithms. (A_{1c}, glycosylated hemoglobin; ER, extended release; PP, postprandial; SMBG, self-monitoring of blood glucose; TZD, thiazolidinedione; UKPDS, United Kingdom Prospective Diabetes Study.) *(Reprinted with permission from the Texas Diabetes Council.)*

TABLE 77-14 Add-On Dual Therapy: Average HbA_{1c} Reductions[a]

Drug Combination	Change in HbA_{1c} (%)	Number of Studies	Number of Subjects
Sulfonylurea + metformin	−2.2	8	458
Sulfonylurea + insulin	−1.9	17	88
Meglitinide + thiazolidinedione	−1.7	1	434
Metformin + insulin	−1.7	8	138
Sulfonylurea + α-glucosidase inhibitor	−1.6	3	177
Metformin + meglitinide	−1.4	3	226
Insulin + α-glucosidase inhibitor	−1.2	1	20
Insulin + thiazolidinedione	−1.2	7	850
Sulfonylurea + thiazolidinedione	−1.1	12	1,315
Metformin + exenatide	−0.8	2	1,070
Metformin + vildagliptin	−0.7	1	416
Metformin + thiazolidinedione	−0.9	3	284
Metformin + α-glucosidase inhibitor	−0.4	3	173

HbA_{1c}, glycosolated hemoglobin.
[a]Reductions are averages and do not imply superiority or inferiority of a combination.
Adapted from American Diabetes Association. Dyslipidemia management in adults with diabetes. Diabetes Care 2004;27:568-571.

Exenatide and DPP-IV inhibitors add a new mechanistic way to lower blood glucose. Exenatide is advantageous because it can allow weight loss in type 2 DM patients, but is a twice-a-day injection and has some GI adverse effects. DPP-IV inhibitors are advantageous because they are orally active, weight neutral, and are very well tolerated but lack long-term safety data. It should be remembered that both classes work mainly to lower postprandial glucose excursions and have only a modest effect on the FPG. Thus, if the patient's fasting glucose is significantly elevated, additional therapy to lower the FPG will often be needed. Metformin, sulfonylureas, repaglinide, TZDs, and basal insulin all effectively lower the FPG.

Virtually all patients with type 2 DM ultimately become relatively insulinopenic and will require insulin therapy. Insulin therapy for type 2 DM has changed dramatically in the last few years. Specifically, patients are often "transitioned" to insulin by using a bedtime injection of an intermediate- or long-acting insulin, and using oral agents primarily for control during the day.[115,116] This strategy leads to less hyperinsulinemia during the day and is associated with less weight gain than the more traditional insulin strategies. Because most patients are insulin resistant, insulin sensitizers are commonly used with insulin therapy. Patients with type 2 DM are usually well buffered against hypoglycemia. Patients should be monitored for hypoglycemia by asking about nocturnal sweating, nightmares (both indicative of nocturnal hypoglycemia), palpitations, tremulousness, and neuroglycopenic symptoms, as well as SMBG. When bedtime insulin plus daytime oral medications fail to achieve glycemic goals, a conventional multiple daily dose insulin regimen while continuing the insulin sensitizers is often tried. Alternatively, off-label use of exenatide for prandial control can be considered, if covered by insurance. Concerns and problems with insulin administration as addressed in the section on type 1 DM generally relate to the therapy of type 2 DM. However, patients with type 2 DM rarely have hypoglycemia unawareness. Also, the variability of insulin resistance means that insulin doses can range from 0.7 to 2.5 units/kg or more. Figure 77–10 is an algorithm for insulin therapy options in type 2 diabetes developed by the Texas Diabetes Council.

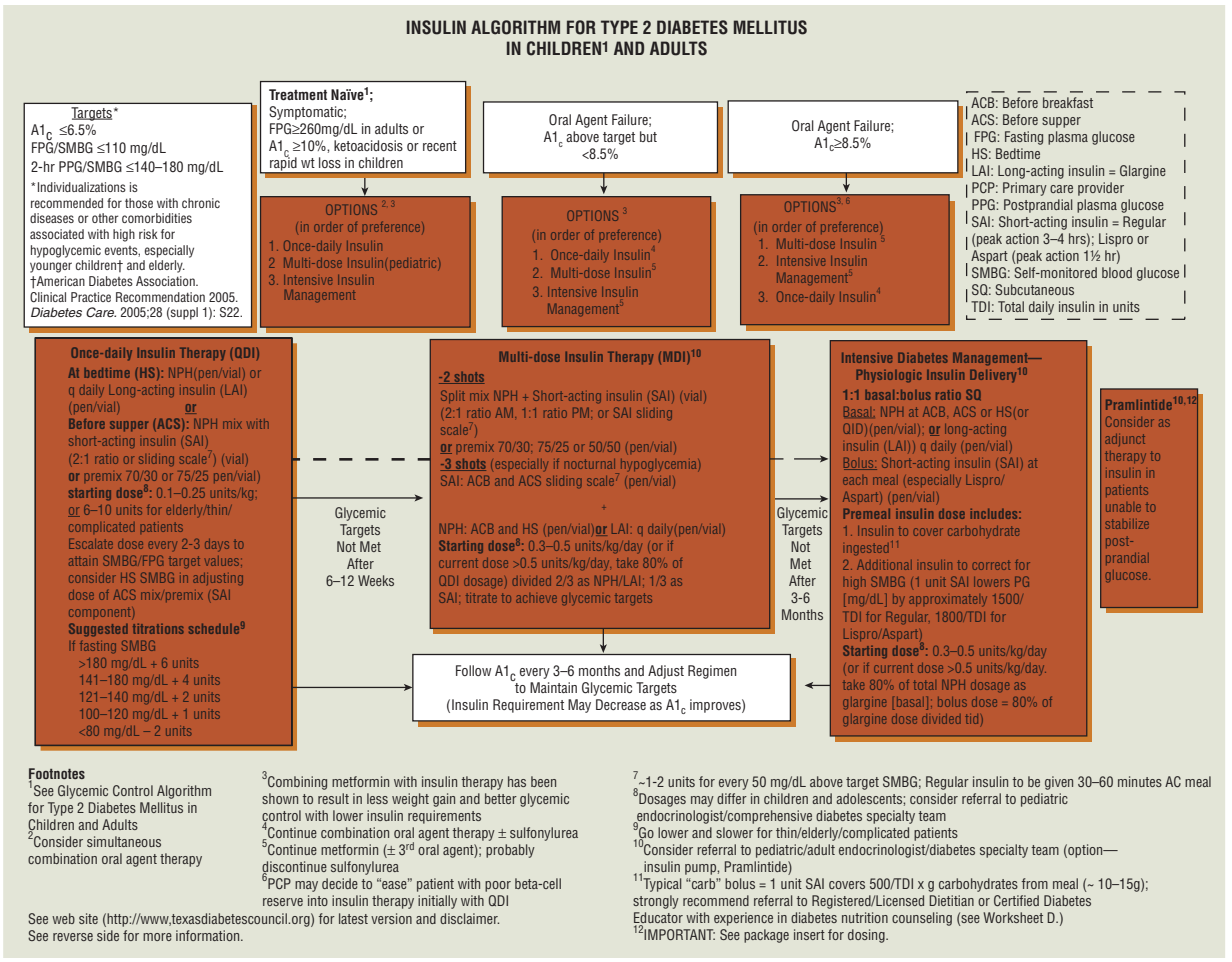


FIGURE 77-10. Insulin algorithm for type 2 diabetes mellitus (DM) in children and adults. See *www.texasdiabetescouncil.org* for current algorithms. *(Reprinted with permission from the Texas Diabetes Council.)*

The availability of short-acting insulin secretagogues, rapid-acting insulin analogs, human insulin inhalation powder, exenatide, DPP-IV inhibitors, and α-glucosidase inhibitors, all of which target postprandial glycemia, has reminded practitioners that glycemic control is a function of fasting and preprandial glycemia and postprandial glycemic excursions.[117] Therefore postprandial glucose measurements may need more emphasis if the HbA_{1c} is near the glycemic goal. Currently, it remains controversial whether targeting after-meal glucose excursions will have more of an effect on complications risk than more conventional strategies. Importantly, postprandial excursions proportionally contribute more than the FPG to the HbA_{1c} percentage when the HbA_{1c} nears goals, and thus will need to be targeted for optimal glycemic control in many patients. Also controversial are the American College of Endocrinology/American Association of Clinical Endocrinologists postprandial glycemic goals (see Table 77–8). These guidelines use epidemiologic studies with post–glucose challenge glucose measurements in diabetic and nondiabetic subjects to state that postprandial glycemia is a better predictor of macrovascular disease risk in DM.[118] In contrast, the ADA continues to recommend peak postprandial blood glucose levels less than 180 mg/dL.

■ SPECIAL POPULATIONS

Children and Adolescents with Type 2 DM

Type 2 DM is increasing in adolescence.[10] Obesity and physical inactivity seem to be particular culprits in the pathogenesis of this disease. Given the many years that the patient will have to live with diabetes, and recent evidence that the timeline for complications may mimic that of older adults, extraordinary efforts should be expended on lifestyle modification measures in an attempt to normalize glucose levels. Failing that strategy, the only labeled oral agent for use in children (10 to 16 years of age) is metformin, although sulfonylureas are also commonly used in therapy. TZDs have not been studied in children, but studies to ascertain safety and efficacy are currently underway. Off-label use of exenatide, as it potentially helps the child to lose weight, is also increasing, but the long-term effects of this therapeutic modality are unknown. In adolescent females, the possibility of future pregnancy should be considered in the prescription of any drug regimen.

Elderly Patients with DM

Elderly patients with newly diagnosed DM (almost always type 2 DM) present a different therapeutic challenge. Consideration of the risks of hypoglycemia in this population and the probable life span should help determine if less-stringent glycemic goals should be set. Thinner, older patients can primarily be treated with shorter-acting insulin secretagogues, low-dose sulfonylureas (preferably not long-acting ones), DPP-IV inhibitors, or α-glucosidase inhibitors. The risk for lactic acidosis, which increases with older age and the age-related decline in renal function, makes metformin therapy more problematic. In a patient whom weight gain or loss may not be unwelcome, TZDs or exenatide, respectively, can be considered. DPP-IV inhibitors or α-glucosidase inhibitors can be advantageous because of low risk of hypoglycemia. Simple insulin regimens such as an injection of basal insulin daily can be appropriate for glycemic control in elderly patients with newly diagnosed DM.

Gestational DM

GDM is diagnosed as previously described. Dietary therapy to minimize wide fluctuations in blood glucose is of paramount importance.[5] Intensive educational efforts are usually necessary. Pregnant women without DM maintain plasma glucose concentrations between 50 and 130 mg/dL. Frequent SMBG is needed to tell whether dietary interventions are successful. If FPG is >105 mg/dL, or 1-hour postprandial plasma glucose levels are >155 mg/dL, or if 2-hour postprandial plasma glucose levels are >130 mg/dL, insulin therapy is usually begun. One shot of NPH or a mixture of NPH and regular insulin in a 2:1 ratio given before breakfast may be adequate to reach glucose targets. Titration of insulin and switching to more complicated regimens is guided by SMBG results. Use of basal insulins other than NPH is still debated, but with the ease of use of detemir or glargine insulin, their use in GDM will likely increase. In addition, pump therapy for the duration of the pregnancy is often instituted, as it can obtain excellent glycemic control and is quickly adjustable. In spite of the long-standing labeling of sulfonylureas as contraindicated in pregnancy, one randomized, open-label, controlled trial evaluated the efficacy of glyburide as compared to insulin initiated after 11 weeks' gestation.[119] Adequate control of blood glucose was achieved as compared to traditional insulin therapy, with less hypoglycemia in the glyburide group. No evidence of any difference in complications, specifically cord-serum insulin concentrations, incidence of macrosomia (birth weight of 4 kg or more), cesarean delivery, or neonatal hypoglycemia between regimens were noted. Glyburide was not detected in the cord serum of any infant. As the study limited enrollment beyond 11 weeks' gestation, no conclusions regarding teratogenicity can be made from this study. The ADA cites this study in a position paper and mentions its usefulness, but also warns that it is not a labeled use of the drug and suggests further studies are needed to establish its safety.[12] Patients with GDM should be evaluated 6 weeks after delivery to ensure that normal glucose tolerance has returned. Because these patients' long-term risk for the development of type 2 DM is considerable, periodic assessment after that is warranted.

■ SPECIAL SITUATIONS

Sick Days

Acute self-limited illness rarely presents a major problem for patients with type 2 DM but can be a significant challenge for insulinopenic type 1 DM patients.[120] Although caloric intake generally declines, insulin sensitivity also decreases, meaning that it can take greater amounts of insulin to control blood glucose concentrations. Patients need to be adept at frequent SMBG, checking urine ketones, use of short-acting insulin, and understanding that sugar intake in this situation is not "bad" but can be necessary to "cover" the insulin therapy given to keep the patient out of diabetic ketoacidosis. We encourage patients to continue their usual insulin regimen and to use supplemental rapid-acting insulin based on SMBG results, with further additional insulin given if ketonuria develops. Sugar and electrolyte solutions, such as sports drinks, can be used to maintain hydration, to provide needed electrolytes if there are significant GI or urinary losses, and to provide sugar to keep the patient from developing hypoglycemia because of the extra insulin that is usually needed. In contrast, type 2 patients may need to switch to sugar-free drinks if blood glucose levels are continually elevated. Most patients can be taught how to sufficiently manage sick days and avoid hospitalization.

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

Diabetic ketoacidosis and hyperosmolar hyperglycemic state are true diabetic emergencies.[121,122] A comprehensive discussion of their treatment is beyond the scope of this chapter. In patients with known diabetes, diabetic ketoacidosis is usually precipitated by insulin omission in type 1 DM, and intercurrent illness, particularly infection, in both type 1 and type 2 DM. However, patients with type 1 or type 2 DM (the latter being usually nonwhites or Hispan-

ics) can present at initial presentation.[123] It is possible that some of the patients deemed to have type 2 DM actually have type 1 idiopathic DM. Patients with diabetic ketoacidosis can be alert, stuporous, or comatose at presentation. The hallmark diagnostic laboratory values include hyperglycemia, anion gap acidosis, and large ketonemia or ketonuria. Afflicted patients have fluid deficits of several liters and sodium and potassium deficits of several hundred milliequivalents. Restoration of intravascular volume acutely with normal saline, followed by hypotonic saline to replace free water, potassium supplements, and constant infusion insulin restore the patient's metabolic status relatively quickly. A flow sheet is often helpful in tracking the fluid and insulin therapies and laboratory parameters in these patients. Bicarbonate administration is generally not needed and may be harmful, especially in children.[124] Treatment of the inciting medical condition is also vital. Hourly bedside monitoring of glucose and frequent monitoring (every 2 to 4 hours) of potassium is essential. Metabolic improvement is manifested by an increase in the serum bicarbonate or pH. Serum phosphorus usually starts high and plummets to lower-than-normal levels, although replacing phosphorus, although not unreasonable, is of questionable benefit in most patients. Fluid administration alone will reduce the glucose concentration, so a decrement in glucose values does not necessarily mean that the patient's metabolic status is improving. Rare patients will require larger amounts of insulin than those usually given (5 to 10 units/h). We double the patient's insulin dose if the serum bicarbonate has not improved after the first 4 hours of insulin therapy. Constant infusion of a fixed dose of insulin and the administration of intravenous glucose when the blood glucose level decreases to <250 mg/dL is preferable to titration of the insulin infusion based on the glucose level. The latter strategy may delay clearance of the ketosis and prolong treatment. The insulin infusion should be continued until the urine ketones clear and the anion gap closes. Long-acting insulin should be given 1 to 3 hours prior to discontinuing the insulin infusion. Intramuscular regular insulin or subcutaneous insulin lispro or aspart given every 1 to 2 hours can be used rather than an insulin infusion in patients without hypoperfusion. Patients can develop hyperchloremic metabolic acidosis with treatment if they have been given large volumes of normal saline in the course of their treatment. Such a situation does not require any specific treatment.

Hyperosmolar hyperglycemic state usually occurs in older patients with type 2 DM, at times undiagnosed, or in younger patients with prolonged hyperglycemia and dehydration or significant renal insufficiency. Large ketonemia is usually not seen, as residual insulin secretion suppresses the production of ketones. Infection or another medical illness is the usual precipitant. Fluid deficits are usually greater and blood glucose concentrations higher (at times >1,000 mg/dL) in these patients than in patients with diabetic ketoacidosis. Blood glucose levels should be lowered very gradually with hypotonic fluids and low-dose insulin infusions (1 to 2 units/h). Rapid correction of the glucose levels, a drop greater than 75 to 100 mg/dL per hour, is not recommended, as it can result in cerebral edema. This is especially true for children with diabetic ketoacidosis. Mortality is high with the hyperosmolar hyperglycemic state.

Hospitalization for Intercurrent Medical Illness

Patients on oral agents can need transient therapy with insulin to achieve adequate glycemic control. In patients requiring insulin, patients should receive scheduled doses of insulin with additional short-acting insulin. "Sliding-scale" insulin is to be discouraged, as it is notorious for not controlling glucose and for sometimes resulting in therapeutic misadventures, with wide swings in the blood glucose as the patient "bounces" from hypoglycemia to hyperglycemia.[125] In-hospital mortality is increased in many hyperglycemic conditions. At least one study documented a reduction in mortality in type 2 diabetes patients with acute myocardial infarctions[126] who receive constant intravenous insulin during the acute phase of the event to maintain near-normal glucose concentrations. Similar mortality results have been documented in some intensive care unit settings using intravenous insulin and tight glucose control.[127,128] Currently the American College of Endocrinology recommends preprandial levels <110 mg/dL, and postprandial level <180 mg/dL, but the ADA lists these data as evidence based level B.[129] Many protocols for IV insulin infusion are currently available, and implementation for an inpatient setting should use a well established protocol. It is prudent to stop metformin in all patients who arrive in acute care settings until full elucidation of the reason for presentation can be ascertained, as contraindications to metformin are prevalent in hospitalized patients.[130]

Perioperative Management

Surgical patients can experience worsening of glycemia for reasons similar to those listed above for intercurrent medical illness.[131] Patients on oral agents can need transient therapy with insulin to control blood glucose. In patients requiring insulin, scheduled doses of insulin or continuous insulin infusions are preferred. For patients who can eat soon after surgery, the time-honored approach of giving one-half of the usual morning NPH insulin dose with dextrose 5% in water intravenously is acceptable, with resumption of scheduled insulin, perhaps at reduced doses, within the first day. For patients requiring more prolonged periods without oral nutrition and for major surgery, such as coronary artery bypass grafting and major abdominal surgery, constant infusion intravenous insulin is preferred. Use of intravenous insulin infusion has been shown to reduce deep sternal wound infections in patients undergoing coronary artery bypass grafting. Metformin should be discontinued temporarily after any major surgery until it is clear that the patient is hemodynamically stable and normal renal function is documented.

Reproductive-Age Women and Preconception Care for Women

An increasing prevalence of DM has been noted in reproductive-age women.[132,133] Prepregnancy planning is absolutely mandatory, as organogenesis is largely completed within 8 weeks, so good glycemic control should be obtained prior to conception. Unfortunately, major congenital malformations because of poor glucose control remain the leading cause of mortality and serious morbidity in infants of mothers with type 1 or type 2 diabetes. For women with DM controlled by lifestyle measures alone, conversion to insulin as soon as the pregnancy is confirmed is appropriate. For women with polycystic ovary disease who ovulate and become pregnant with insulin sensitizer therapy, conversion to insulin is mandatory as soon as pregnancy is confirmed. Insulin is the only acceptable pharmacologic therapy during pregnancy for women with DM in the United States. In Europe, metformin and glyburide are sometimes used in pregnancy for type 2 DM, but their use is controversial in the United States. Patients previously treated with insulin can need intensification of their regimen to achieve therapeutic goals. Normal pregnancy is associated with a decrease in the blood glucose concentration as fuel is diverted to the fetus. Pregnant patients will be ingesting both meals and snacks daily. SMBG is generally intensified to try to reach glycemic targets and reduce fetal and maternal morbidity. Whether preprandial or postprandial glucose concentrations should be the target of therapy is hotly debated. Ketosis should be avoided, requiring urine monitoring for ketones in the morning and if the blood sugar is >200 mg/dL.

There has been some concern about the safety of insulin analogs in pregnancy, both for fetal development and advancement of microvascular complications. One study has shown no increase in

retinopathy or progression of same with the use of insulin lispro in pregnancy.[134]

SPECIAL TOPICS

Prevention of DM

⑫ Efforts to prevent type 1 DM with immunosuppressives[135] or injected[136] or oral insulin therapy[137] have been unsuccessful. The Diabetes Prevention Program[138] confirmed that modest weight loss in association with exercise can have a dramatic impact on insulin sensitivity and the conversion from impaired glucose tolerance to type 2 diabetes. In this study approximately 2,000 individuals with impaired glucose tolerance were randomized to lifestyle changes (diet, exercise, and weight loss) as opposed to usual care. The study, which was originally planned to be ongoing for 5 years, was stopped after 2.8 years because the results were so conclusive. The usual care group developed diabetes at the rate of 11% each year. The lifestyle arm developed diabetes at a rate of 5% per year, a 58% reduction in the risk of developing diabetes.[138] Surprisingly, a modest amount of diet and exercise yielded impressive results. The exercise program in the lifestyle group was walking 30 minutes, 5 days each week. The mean weight loss over the 2.8 year study period was only 3.6 kg (8 lb). Similar results were seen in the Finnish Diabetes Study.[139] In the Diabetes Prevention Program[138] discussed above, approximately 1,000 of the study patients were randomized to metformin therapy. The metformin-treated patients showed a 1.8-kg (4-lb) weight loss [138] Interestingly, young and overweight individuals on metformin had a greater reduction in the risk of developing diabetes than normal weight and older study patients.[138]

Metformin and acarbose[92] appear to mostly be treating early diabetes, because when the drugs were stopped, diabetes rates were close to the conversion rates for placebo. In contrast, the Troglitazone in the Prevention of Diabetes (TRIPOD) study[140] evaluated the ability of troglitazone to prevent the development of diabetes in women with a history of gestational diabetes. The rate of development of diabetes in the placebo arm of the study was approximately 12% per year, compared to about 5% in the treatment group. Total preservation of β-cell function was demonstrated over a 5-year period in women who had near normal β-cell function at baseline and who initially responded to the drug.[140] The preservation of β-cell function was observed for at least 8 months after the drug had been discontinued. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial evaluating rosiglitazone and/or ramipril treatment for the delay or prevention of type 2 DM in impaired glucose tolerant subjects was recently published.[141,142] Rosiglitazone 8 mg daily, over approximately 3 years, reduced the incidence of type 2 diabetes by 60%. In addition, a 37% nonsignificant increase in cardiovascular events was reported. Ramipril 15 mg daily did not significantly prevent the conversion to diabetes. It is possible that longer exposure could have made a difference, but the study was stopped prematurely. It should be noted that no pharmacologic agents are currently FDA approved or recommended for prevention of type 2 diabetes, though the ADA recommends metformin in conjunction with lifestyle changes if the patient is younger, obese, has a family history of diabetes, dyslipidemia, hypertension, or a HbA_{1c} above 6%.[143] Prevention studies are still underway using pioglitazone, nateglinide, and valsartan.

CLINICAL CONTROVERSY

DM is associated with a substantially higher risk of morbidity and mortality. Pharmacologic prevention or delay of type 2 DM has been widely discussed since the release of the Diabetes Prevention Program results. Although lifestyle changes were effective, with a 58% lower relative risk of progression to diabetes, metformin 850 mg twice a day reduced the risk by 31%, and was essentially as effective as diet and exercise in young/obese subjects. Rosiglitazone, acarbose, and even orlistat all have, to one extent or another, been able to delay the onset of type 2 DM. Despite these data, there are no FDA-approved drugs for the delay or prevention of diabetes. The ADA-recommended medications, in conjunction with lifestyle, for the delay or prevention of type 2 DM include metformin. It should be remembered that medications require monitoring and can have serious side effects. Many feel they are simply treating diabetes early, as β-cell dysfunction can be documented in early impaired glucose tolerant subjects. Other than troglitazone, which is not on the market, no medication has clearly shown β-cell preservation. It is logical to try to use medications if they alter the decline of β-cell function, but this is currently off-label use and any attempt to use medication in these situations should be clearly and frankly discussed with the patient.

Patient Education

⑬ It is not satisfactory to give patients with DM brief instructions with a few pamphlets and expect them to manage their disease adequately. Thinking that diabetes education is limited to one or two encounters is misguided; education is a lifetime exercise. Successful treatment of DM involves lifestyle changes for the patient (e.g., medical nutrition therapy, physical activity, self-monitoring of blood glucose and possibly of urine for ketones, and taking prescribed medications). The patient must be involved in the decision-making process and must learn as much about the disease and associated complications as possible. Emphasis should be placed on the evidence that indicates that complications can be prevented or minimized with glycemic control and management of risk factors for cardiovascular disease. Recognition of the need for proper patient education to empower them into self-care has generated programs for certification in diabetes education. Certified diabetes educators must document their patient education hours and sit for a certification examination that assesses the knowledge, tasks, and skills of an educator in order to become certified. An increasing number of nurses, pharmacists, dietitians, and physicians are becoming certified diabetes educators to document to the public that they meet a minimum standard for diabetes education and to fulfill quality initiatives in meeting guidelines for education recognition.[144]

TREATMENT OF CONCOMITANT CONDITIONS AND COMPLICATIONS

Retinopathy

Patients with established retinopathy should see an ophthalmologist or optometrist trained in diabetic eye disease.[145] A dilated eye examination is required to fully evaluate diabetic eye disease. Early background retinopathy can reverse with improved glycemic control. More advanced retinopathy will not regress with improved glycemia and can actually worsen with short-term improvements in glycemia. Studies are underway to determine whether medical therapy independent of glucose control will prevent the development of advanced retinopathy. Laser photocoagulation has markedly improved sight preservation in diabetic patients.

Neuropathy

Peripheral neuropathy is the most common complication seen in type 2 DM patients in outpatient clinics.[146] Paresthesias, numbness, or pain can be the predominant symptom. The feet are involved far more often than the hands. Improved glycemic control can alleviate some of

the symptoms. If neuropathy is painful, symptomatic therapy is empiric, including low-dose tricyclic antidepressants, anticonvulsants (gabapentin, pregabalin, carbamazepine, and maybe phenytoin), duloxetine, venlafaxine, topical capsaicin, and various pain medications, including tramadol and nonsteroidal antiinflammatory drugs. Recently, another anticonvulsant, topiramate, has shown promise in the reduction of symptoms, with the positive side effect of weight loss in type 2 diabetes patients, although tolerability is problematic. The numb variant of peripheral neuropathy is not treated with medication. Clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction (anhidrosis, heat intolerance, gustatory sweating, and/or dry skin), impaired neurovascular function, and hypoglycemic autonomic failure. Gastroparesis can be a severe and debilitating complication of DM. Improved glycemic control, discontinuation of medications that slow gastric motility, and the use of metoclopramide (preferably for only a few weeks at a time) or erythromycin can be helpful. Gastric pacemakers as therapeutic hardware are rarely used, although available. Orthostatic hypotension can require pharmacologic management with mineralocorticoids or adrenergic agonist agents. In severe cases, supine hypertension is extreme, mandating that the patient sleep in a sitting or semirecumbent position. Patients with cardiac autonomic neuropathy are at a higher risk for silent myocardial infarction and mortality. The hallmark of diabetic diarrhea is its nocturnal occurrence. Diabetic diarrhea frequently responds to a 10- to 14-day course of an antibiotic such as doxycycline or metronidazole. In more unresponsive cases, octreotide can be useful. Erectile dysfunction is common in diabetes, and initial treatment should include a trial of one of the oral medications currently available to treat erectile dysfunction. People with diabetes often require the highest doses of these medications to have an adequate response. Sudomotor dysfunction, as earlier defined, results in loss of sweating and resultant dry, cracked skin. Use of hydrating creams and ointments is needed.

Microalbuminuria and Nephropathy

DM, and particularly type 2 DM, is the biggest contributor statistically to the development of end-stage renal disease in the United States.[147] The ADA recommends a screening urinary analysis for albumin at diagnosis in persons with type 2 DM. Precise onset of type 2 DM can rarely be ascertained, and patients will often present at diagnosis with microvascular complications. In type 1 DM, microalbuminuria rarely occurs with short duration of disease or before puberty. Screening individuals with type 1 DM should begin with puberty and after 5 years' disease duration. There are three methods for assessing microalbuminuria: (1) measurement of the urine albumin-to-creatinine ratio in a random spot collection (preferably the first morning void); (2) 24-hour timed collection; and (3) timed (e.g., 4-hour or 10-hour overnight) collection. Microalbuminuria on a spot urine specimen is defined as a ratio of 30 to 300 mg/g albumin-to-creatinine. On timed collections, microalbuminuria is defined as 30 to 300 mg/24 hours or an albumin excretion rate of 20 to 200 mcg/min. Because of day-to-day variability, microalbuminuria should be confirmed on at least two of three samples over 3 to 6 months. Additionally, when assessing urine protein or albumin, conditions that can cause transient elevations in urinary albumin excretion should be excluded. These conditions include: intense exercise, recent urinary tract infections, hypertension, short-term hyperglycemia, heart failure, and acute febrile illness.[147]

In type 2 DM, the presence of microalbuminuria is a strong risk factor for macrovascular disease and is frequently present at the time of diagnosis. Microalbuminuria is a weaker predictor for future kidney disease in type 2 versus type 1 DM.

Glucose and blood pressure control are most important for the prevention of nephropathy, and blood pressure control is the most important for retarding the progression of established nephropathy. ACE inhibitors and angiotensin receptor blockers, considered first-line recommended treatment modalities, have shown efficacy in preventing the clinical progression of renal disease in patients with type 2 DM.[148–150] Diuretics frequently are necessary because of the volume-expanded state of the patient and are recommended second-line therapy. The ADA and the National Kidney Foundation blood pressure goal of <130/80 mm Hg can be difficult to achieve. Three or more antihypertensives are often needed to treat to goal blood pressures.

Peripheral Vascular Disease and Foot Ulcers

Claudication and nonhealing foot ulcers are common in type 2 DM patients.[151] Smoking cessation, correction of lipid abnormalities, and antiplatelet therapy are important strategies in treating claudicants. Pentoxifylline or cilostazol can be useful in selected patients. Revascularization is successful in selected patients. Local débridement and appropriate footwear and foot care are vitally important in the early treatment of foot lesions. In more advanced lesions, topical treatments can be of benefit. Diabetic foot care is an excellent example of the adage, "an ounce of prevention is worth a pound of cure."

Coronary Heart Disease

The risk for coronary heart disease (CHD) is two to four times greater in diabetic patients than in nondiabetic individuals. CHD is the major source of mortality in patients with DM. Recent studies suggest that multiple risk-factor intervention (lipids, hypertension, smoking cessation,[152] and antiplatelet therapy)[153] will reduce the burden of excess macrovascular events. Epidemiologic data suggest that CHD prevention guidelines for type 2 DM apply equally to patients with type 1 DM.[154] β-Blocker therapy supplies an even greater protection from recurrent CHD events in diabetic patients than in nondiabetic subjects. Masking of hypoglycemic symptoms is a greater problem in type 1 DM patients than in patients with type 2 DM.

Lipids The Collaborative Atorvastatin Diabetes Study (CARDS) randomized diabetes subjects with no documented cardiovascular disease to atorvastatin 10 mg daily ($n = 1,428$) or placebo ($n = 1,410$). The trial was stopped 2 years early (mean duration of followup was 3.9 years) after meeting the primary efficacy end point of major cardiovascular events, which were reduced by 37% ($P = 0.001$). All-cause death was reduced 27% ($P = 0.059$) and potentially could have had its significance influenced by the early stoppage of the trial.[155] The Heart Protection Study randomized 5,963 patients age >40 years with diabetes and total cholesterol >135 mg/dL. A significant 22% reduction (95% confidence interval [CI], 13–30) in the event rate for major cardiovascular events was seen with simvastatin 40 mg per day. This was evident even at lower LDL levels (<116 mg/dL), and suggests that ~30% reduction in LDL levels regardless of starting LDL levels can be appropriate.[156] The proper use of fibrates in diabetes continues to be controversial. The diabetic subgroup in the Veterans Administration HDL Intervention Trial (VA-HIT) of CHD patients with low HDL-C and low LDL-C showed approximately 22% reduction in CHD events in diabetic patients with known CHD when HDL-C was increased by approximately 6% by gemfibrozil.[157] The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) was conducted in 9,795 subjects (22% with previously documented cardiovascular disease) with type 2 DM given fenofibrate 200 mg daily or placebo. A relative reduction of 11% ($P = 0.16$) was seen in any coronary event in conjunction with a slight increase in the risk of all-cause mortality. (0.7%, $P = 0.18$). Reasons for this have been speculated on, including the increased use of statins in the placebo group, but it continues to be controversial.[158]

The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III)[159] guidelines classify the presence of DM

TABLE 77-15 Classification of Lipid and Lipoprotein Levels in Adults

Parameter	Goal		Treatment (in order of preference)
LDL cholesterol	<100 mg/dL <70 mg/dL[a]		Lifestyle; HMG-CoA reductase inhibitors; cholesterol absorption inhibitor; niacin or fenofibrate
HDL cholesterol	Men >40 mg/dL	Women >50 mg/dL	Lifestyle; nicotinic acid; fibric acid derivatives
Triglycerides	<150 mg/dL		Lifestyle; glycemic control; fibric acid derivatives; high-dose statins (in those with high LDL)

HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein.

[a]Can be optimal goal in patients with preexisting cardiovascular disease.

Data from American Diabetes Association. Dyslipidemia managment in adults with diabetes. Diabetes Care 2004;27:568–571.

as a CHD risk equivalent, and therefore recommend that LDL-C be lowered to <100 mg/dL. An optional LDL goal in high-risk DM patients, such as those who already have CHD, has been updated to be <70 mg/dL.[160] Unlike previous guidelines, more consideration is now given to HDL-C and triglycerides. The primary target is the treatment of LDL-C. After the LDL-C goal is reached (usually with a statin), triglycerides are possibly considered for pharmacologic management, assuming unresponsiveness to glycemic control efforts, weight management, and exercise. In such situations, a non-HDL-C goal is established (a surrogate for all apolipoprotein B–containing particles). The non-HDL-C goal for patients with DM is <130 mg/dL. Niacin or a fibrate can be added to reach that goal if triglycerides are 201 to 499 mg/dL. Niacin or a fibrate can also be added if the LDL-C goal is reached, but the patient has low HDL-C (<40 mg/dL). Patients with marked hypertriglyceridemia (≥500 mg/dL) are at risk for pancreatitis. Efforts to reduce triglycerides with glycemic control, elimination of other secondary causes (including medications), and drug therapy (fibrate and/or niacin) are effective treatment strategies. The ADA also recommends similar LDL goals but places raising HDL as the second priority (Table 77–15). The definitive role of pharmacologic therapy of HDL-C and/or hypertriglyceridemia in type 2 DM patients (beyond that seen with statin therapy) has yet to be proven in clinical trials.

Hypertension

The role of hypertension in increasing microvascular and macrovascular risk in patients with DM has been confirmed in the UKPDS[97] and Hypertension Optimization Treatment[161] trials. The ADA recommends aggressive goals for blood pressure (<130/80 mm Hg) in patients with DM.[8] ACE inhibitors and angiotensin receptor blockers are generally recommended for initial therapy. The National Kidney Foundation also suggests that the blood pressure goal be less than 130/80 mm Hg, as well as recommending diuretics as second-line therapy in patients with diabetic kidney disease.[162] Many patients require multiple agents, on average three agents, to obtain goals, so diuretics, calcium channel blockers, and β-blockers frequently are useful as second and third agents. Blood pressure goals are generally more difficult to achieve than glycemic goals or lipid goals in most diabetic patients.[163]

CLINICAL CONTROVERSY

Initial therapy choices for hypertension in DM usually include ACE inhibitors or an angiotensin receptor blocker because of their well documented renoprotective effects. Currently, angiotensin receptor blockers have less robust data to support cardiovascular reduction compared to other therapeutic choices, yet the data that exists appears to be positive in patients with type 2 DM. Also, in the diabetic subset of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), diuretics have shown equivalent results to an ACE inhibitor. The ADA currently recommends the use of any class (ACE inhibitors, angiotensin receptor blockers, β-blockers, diuretics, or calcium channel blockers) of antihypertensive medication that has shown benefit in prevention of poor cardiovascular outcomes. Choice of monotherapy may not be important, as an average of two to three antihypertensive medications are needed to reach blood pressure goals.

Transplantation

Whole pancreas and islet cell transplantation are still relatively experimental procedures in patients with type 1 DM; those with end-stage renal disease also receive kidney transplantation.[164]

PHARMACOECONOMIC CONSIDERATIONS

As described in the introduction, the direct and indirect costs of DM are substantial. Much of the indirect costs are related to loss of productivity because of the significant morbidity (hospitalizations, loss of vision, lower extremity amputations, kidney failure, and cardiovascular events) associated with the disease. For a disease that affects about 9% of the population, it is responsible for 11% to 12% of health expenditures. With evidence from the DCCT and UKPDS to support intensive blood glucose control to reduce the risk of complications, the question of cost effectiveness comes into play.

An economic model based on the DCCT approximates that 120,000 persons in the United States would meet criteria for intensive intervention. The cost of implementing intensive therapy over the lifetime of the population is estimated at $4 billion dollars. The benefits of this strategy are net gains of 920,000 years of sight, 691,000 years free from end-stage renal disease, and 678,000 years free from lower extremity amputations. The incremental cost per year of life gained is $28,661.[165] This is well within the limits of a cost-effective strategy and compares favorably to treatment of high blood pressure or hypercholesterolemia.

Economic analysis of intensive therapy for type 2 DM is more complex. Outcomes must also factor in the burden of cardiovascular disease as the major cause of mortality. One model analyzed the health benefits and economics of treating type 2 DM with the goal of achieving normoglycemia but using outcomes based on the DCCT trial results. Accounting for the prevalence of cardiovascular disease in type 2 DM, an estimate of $16,002 incremental cost per quality-adjusted life year gained was obtained. The limitation of this analysis is that although the UKDPS did demonstrate an improvement in diabetes-related outcomes, the overall efficacy on microvascular disease complications was not mirrored by the DCCT.

Two economic analyses were performed on data generated from the UKPDS, one assessing cost effectiveness of an intensive blood glucose control policy in type 2 DM, and the other assessing improved blood pressure control in hypertensive patients with type 2 DM. In the first analysis, outcome was measured as the incremental cost per event-free year gained within the trial. Based on trial outcomes and assumptions, the incremental cost in the intensive treatment group per event-free year gained is $1,366. Although intensive treatment costs were higher, the cost per event-free year gained appears cost-effective. The second analysis showed the incremental cost per extra year free from microvascular and macrovascu-

lar end points from intensive blood pressure control in a standard clinical practice model to be $1,498. The incremental cost per life year gained was estimated at $619, again demonstrating the cost-effectiveness of intensive intervention.[166,167]

EVALUATION OF THERAPEUTIC OUTCOMES

MONITORING OF THE PHARMACEUTICAL CARE PLAN

A comprehensive pharmaceutical care plan for the patient with DM will integrate considerations of goals to optimize blood glucose control and protocols to screen for, prevent, or manage microvascular and macrovascular complications. In terms of standards of care for persons with DM, one can review the document published by the ADA that outlines initial and ongoing assessments for patients with DM.[8] For quality-of-care measures, one can refer to the National Diabetes Quality Improvement Alliance website at *www.nationaldiabetesalliance.org*, whose members include many of the governmental and physician organizations concerned with diabetes quality-of-care measures.

The major performance measures, such as Health Plan Employer Data and Information Set (HEDIS), should assess the ability to meet current standards of care and recognize the minimal treatment goals for glycemia, lipids, and hypertension, and provide targets for monitoring and adjusting pharmacotherapy as discussed in various sections above. Publicly reported quality measures continue to move closer to current guidelines. Glycemic control (percentage of patients with HbA_{1c} <7%), lipid (percentage of patients with LDL <100 mg/dL), and hypertension (percentage of patients with blood pressure <130/80 mm Hg) are now quality measures congruent with the current goals recommended by the ADA. Glycemic control is paramount in managing type 1 or type 2 DM but as readily identified from the above discussion, it requires frequent assessment and adjustment in diet, exercise, and pharmacologic therapies. Minimally, HbA_{1c} should be measured twice a year in patients meeting treatment goals on a stable therapeutic regimen. Quarterly assessments are recommended for those whose therapy has changed or who are not meeting glycemic goals. Fasting lipid profiles should be obtained as part of an initial assessment and thereafter at each followup visit if not at goal, annually if stable and at goal, or every 2 years if the lipid profile suggests low risk. Documenting regular frequency of foot exams (each visit), urine albumin assessment (annually), dilated ophthalmologic exams (yearly or more frequently with identified abnormalities), and office visits for followup are also important. Assessment for pneumococcal vaccine administration, annual administration of influenza vaccine, and routine assessment for and management of other cardiovascular risks (i.e., smoking and antiplatelet therapy) are components of preventive medicine strategies. The multiplicity of assessments for each patient visit are likely to be better facilitated using an integrative computer program and electronic medical record, standardized progress note forms, or flow sheets, which assist the clinician in identifying whether the patient has met standards of care in the frequency of monitoring and achievement of defined targets of therapy.

ABBREVIATIONS

ACE: angiotensin-converting enzyme

ADA: American Diabetes Association

ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

ALT: alanine aminotransferase

BMI: body mass index

CHD: coronary heart disease

CSII: continuous subcutaneous insulin infusion

CYP450: cytochrome P450

DCCT: Diabetes Control and Complications Trial

DM: diabetes mellitus

DPP-IV: dipeptidyl peptidase IV

DREAM: Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (study)

FFA: free fatty acid

GDM: gestational diabetes mellitus

GIP: glucose-dependent insulin-releasing peptide

GLP-1: glucagon-like peptide-1

HbA_{lc}: hemoglobin A_{lc}

HDLC: high-density lipoprotein cholesterol

IFG: impaired fasting glucose

IGT: impaired glucose tolerance

LADA: latent autoimmune diabetes in adults

LDLC: low-density lipoprotein cholesterol

MODY: maturity onset diabetes of youth

NCEP-ATP: National Cholesterol Education Program Adult Treatment Panel

NHANES III: The Third National Health and Nutrition Evaluation Survey

NPH: neutral protamine Hagedorn

OGTT: oral glucose tolerance test

PAI-1: activator-1 plasminogen-inhibitor

PPAR-γ: peroxisome proliferator activator receptor-γ

PROactive: Prospective Pioglitazone Clinical Trial in Macrovascular Events

SMBG: self-monitored blood glucose

STOP-NIDDM: Study to Prevent Non–Insulin-Dependent Diabetes Mellitus

SUR: sulfonylurea receptor

TRIPOD: Troglitazone in the Prevention of Diabetes

TZD: thiazolidinedione

UKPDS: United Kingdom Prospective Diabetes Study

VAT: visceral adipose tissue

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