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MANAGEMENT OF TYPE 2 DIABETES

Evolving Strategies for Treatment

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Diabetes encompasses a group of heterogeneous disorders characterized by a defect in insulin secretion and increased cellular resistance to the action of insulin, resulting in hyperglycemia and other metabolic disturbances. Worldwide prevalence data compiled by the World Health Organization (WHO) indicate that the prevalence of diabetes has reached epidemic proportions,[23] and that its prevalence will continue to increase at a rapid rate.[24] In 1995, an estimated 135 million people had diabetes. By 2025, the number of people with diabetes is expected to rise to about 300 million. In the United States, approximately 16 million persons have diabetes,[18] and about 20 million Americans have impaired glucose tolerance, a group that has a high risk for type 2 diabetes.[3] The prevalence of type 2 diabetes is higher in virtually every ethnic minority group when compared with the white population.[37] The incidence of type 2 diabetes in Caucasians is approximately 2.5%, in African Americans 5%, in Hispanics 12%, in American Indians 17%, and in Pima Indians 35%. Decreased physical activity, increasing obesity, and changes in food consumption have been implicated in the epidemic of diabetes.[47]

Diabetes is the leading cause of kidney failure, adult blindness, and nontraumatic lower-limb amputations in the United States.[8] [29] It is also a significant cause of cardiovascular morbidity and mortality.[8] [22] In patients with type 2 diabetes, the prevalence of heart attacks and strokes is two to four times more frequent than in persons without diabetes.[22] Many prospective randomized controlled trials consistently indicate that intensive treatment regimens in patients with type 1 and type 2 diabetes significantly reduce the risk of the development and progression of microvascular complications by 25% to 75% when compared when conventional treatment regimens.[11] [38] [40] [51] The relation of hyperglycemia to macrovascular complications in subjects with diabetes is controversial.[51] [53] Although some epidemiologic studies have suggested a significant relation of glycemia to cardiovascular disease,[15] [16] recent clinical evidence suggests that the risk of macrovascular disease is not as closely related to the

duration and severity of hyperglycemia as are microvascular complications.[51] [53]

This article examines the current classification, diagnostic criteria for diabetes, and screening recommendations and provides a therapeutic strategy for improving glycemic control in patients with type 2 diabetes.

CLASSIFICATION OF DIABETES

The new classification system recommended by the American **Diabetes** Association[41] (ADA) recognizes that **diabetes** can result from different combinations of insulin deficiency and insulin resistance, with the common endpoint hyperglycemia. The system (shown below identifies four types of **diabetes mellitus**: type 1 and type 2 **diabetes**, other specific types, and gestational **diabetes**.

Etiologic Classification of Diabetes Mellitus *

1. (Not Available)

DIAGNOSTIC CRITERIA

Based on the latest consensus report,[41] [43] there are three accepted ways to diagnose **diabetes** in nonpregnant adults. The first two methods consist of having a fasting plasma glucose level equal to or greater than 126 mg/dL (7 mmol/L) on two separate occasions or a random casual plasma glucose level greater than 200 mg/dL (11.1 mmol/L) in a subject who has symptoms of hyperglycemia (polyuria, polydipsia, or unexplained weight loss). The other option for diagnosis includes a 2-hour postprandial plasma glucose level of 2000 mg/dL (11.1 mmol/L) or higher after a glucose load of 75 g (oral glucose tolerance test or OGTT). Measurement of the fasting plasma glucose level is the preferred diagnostic test, but any combination of two abnormal test results can be used.

Although glycohemoglobin or HbA_{lc} is widely accepted as a useful index of glycemic control in the treatment of patients with **diabetes**, its use as a screening test is controversial and is not recommended for the initial diagnosis of **diabetes**.[41] [43] Recent data from the Third National Health and Nutrition Examination Survey (NHANES III) reported a specificity of 97.4% and 99.9% for an HbA_{lc} value of 6.1% and 7% (one and two standard deviations above the normal mean, respectively).[43] Because HbA_{1c} testing can be performed at any time of the day and without special patient preparation, it is a highly specific and convenient alternative method for screening for undiagnosed **diabetes**.

The Expert Committee recognized an intermediate group of subjects with impaired glucose homeostasis in whom glucose concentration was above normal levels but below the criteria for **diabetes**. A normal fasting plasma glucose level is 110 mg/dL (6.1 mmol/L), and a normal 2-hour postprandial glucose is less than 140 mg/dL (7.75 mmol/L). Persons with a fasting plasma glucose between 110 and 126 mg/dL are considered to have impaired fasting glucose. Persons with 2-hour values in the OGTT of 140 mg/dL or greater but less than or equal to 200 mg/dL are consider to have impaired glucose tolerance. Criteria for the diagnosis of **diabetes** and impaired glucose tolerance are summarized in the following list[41] :

- **Diabetes mellitus**
  1. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) on two separate occasions. Fasting is defined as no caloric intake for at least 8 hours.
  2. Casual blood glucose ≥200 mg/dL (11.1 mmol/L) with symptoms of **diabetes** (polyuria, polydipsia, and unexplained weight loss). Casual is defined as any time of day without regard to time since last meal.
  3. 2-Hour postprandial plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO using a glucose sample containing the equivalent of 75 g anhydrous glucose in water.
- Impaired glucose tolerance

  2-Hour postprandial glucose ≥140 mg/dL (7.8 mmol/L) but <200 mg/dL (11.1 mmol/L) on OGTT

- Impaired fasting glucose

  Fasting plasma glucose ≥110 mg/dL but <126 mg/dL (6.1 to 7.0 mmol/L)

- Normal

  Fasting plasma glucose 110 mg/dL (6.1 mmol/L)

  2-Hour postprandial plasma glucose <140 mg/dL (7.8 mmol/L)

SCREENING

Because most patients with type 1 **diabetes** present with an acute decompensated metabolic state, most cases are diagnosed after symptoms develop. Widespread clinical testing of asymptomatic individuals for the presence of autoantibodies related to type 1 **diabetes** cannot be recommended as the means to identify persons at risk.[2] Because early detection and prompt treatment of disease may reduce the burden of type 2 **diabetes** and its complications, screening for **diabetes** is recommended for individuals 45 years or older and should be performed every 3 years if normal. Based on expert opinion, screening of high-risk subjects should be started before the age of 45 years (*see* previous list).[2] The fasting plasma glucose and the OGTT are suitable tools for **diabetes** screening; however, fasting plasma glucose is strongly preferred.[1] [2] [41]

ASSESSMENT OF GLYCEMIC CONTROL

Targets for metabolic control in persons who have **diabetes** are shown in Table 1 (Table Not Available) .[26] The rationale for glucose control is supported by prospective and randomized studies of type 1 and type 2 **diabetes** that correlate the onset and progression of microvascular complications with the severity of hyperglycemia and HbA_{1c} levels.[11] [40] [51] [53] Self-monitoring of blood glucose and measurements of $HgbA_{1c}$ have commonly been used to monitor glycemic status in persons with **diabetes mellitus**. Self-monitoring of blood glucose is especially important for patients treated with insulin or sulfonylureas to monitor for and prevent asymptomatic hypoglycemia and extreme hyperglycemia.[1] [2] [3] Although urine glucose testing was previously used to assess glycemic control in patients with **diabetes**, self-monitoring of blood glucose has replaced urine testing because studies

have shown a poor relationship between blood glucose and urine glucose.[36] For patients who cannot or will not perform self-monitoring of blood glucose, urine glucose testing could be considered an alternative that can provide useful, albeit limited, information.

TABLE 1 -- TARGET FOR GLYCEMIC CONTROL IN PERSONS WITH **DIABETES**

(Not Available)

Adapted from Kitabchi AE, Bryer-Ash M: NIDDM: New aspects of management. Hosp Pract 32:135-164, 1997; with permission.

Glycated hemoglobin testing is recommended at least twice a year in patients who are meeting treatment goals and who have stable glycemic control. Such testing should be performed more frequently (quarterly) in patients who are not meeting glycemic goals or in whom therapy has changed.[1]

TREATMENT REGIMEN

Education

Health care workers who treat patients with **diabetes** must provide appropriate education. This instruction should be carried out in the physician's office, or the patient can be referred to a facility or organization certified by the ADA and American Association of **Diabetes** Educators. A well-informed patient (regardless of the level of education) is the key to good **diabetes** care. A quality **diabetes** education program should provide comprehensive instruction relevant to the target population and to the participants served. A quality **diabetes** self-management education program should offer a **diabetes** overview; nutrition, exercise, and activity recommendations; indications on the use of glucose-monitoring devices; prevention, detection, and treatment of acute and chronic diabetic complications; foot, skin, and dental care, and a smoking cessation program (if medicated); a discussion of benefits, risks, and management options for improving **diabetes** control; and, if indicated, a review of preconception care, pregnancy, and gestational **diabetes**.

Diet Therapy

Medical nutrition therapy is an essential component of successful **diabetes** management. An effective dietary program requires an individualized approach, with consideration given to personal lifestyle, eating habits, and management goals in the individual patient. The overall goal of nutrition therapy is to assist persons with **diabetes** in making changes in nutrition and exercise to improve metabolic control. A meal plan should be determined and used as a basis for integrating insulin or oral glucose-lowering medications and activity level. Because of the complexity of nutrition issues, a registered dietitian should provide nutritional education or be available for consultation.

Table 2 outlines the steps in calculating ideal body weight and BMI, caloric needs, and dietary composition of a healthy diet. The BMI should be used to assess overweight and obesity and to monitor changes in body weight. Current clinical guidelines defines a normal body weight as a BMI between 18.5 and 24.9 kg/m^2, overweight between 25 and 29.9 kg/m^2, and obesity as a BMI of 30 kg/m^2 or greater.[14] [33] The BMI is calculated as weight in kilograms divided by height in meters squared. The following formulas can be used to estimate BMI: [weight (kg)/height (m^2)] or [weight (pounds)/height (inches)^2] $\times$ 703.

TABLE 2 -- CALCULATION FOR IDEAL BODY WEIGHT AND BODY MASS INDEX AND RECOMMENDATIONS OR PROPER DIETARY COMPOSITION

Parameter	Calculation or Recommendation
Ideal body weight	
Women	100 pounds for first 5 feet + 5 pounds for each additional inch
Men	106 pounds for first 5 feet + 6 pounds for each additional inch
Body mass index	[weight (kg)/height (m^2]) or [weight (pounds)/height (inches)^2] × 703
Calorie requirements	
Basal requirement	Ideal body weight (pounds) × 10
Average activity	Add 30% to basal requirement
Strenuous activity	Add 100% to 200% to basal requirement
Weight loss	Subtract 500 calories/day to lose 1 pound/week
Pregnancy	Add 300 calories/day
Lactation	Add 500 calories/day
Dietary composition	
Carbohydrate	50%-55% of total calories
Protein	15%-20% of total calories
Fat	30% of total calories (<10% saturated fat)
Fiber	20-35 g/day

The percent of calories from carbohydrate, protein, and fat on a dietary plan should be individualized based on the patient's eating habits and glucose and lipid goals. For most patients, the authors recommend a healthy diet consisting of 50% to 55% carbohydrate, 10% to 20% protein, no more than 30% fat (of which no more than 10% should be saturated), and about 30 g of soluble fiber a day. To preserve renal function, total protein should not exceed 60 g/day and should be derived primarily from vegetable sources (e.g., lentils, kidney beans). The percentage of calories from fat is dependent on the presence of lipid disorder and body weight. If low-density lipoprotein (LDL) cholesterol is elevated, further reduction of saturated fat to 7% of total calories and dietary cholesterol to less than 200 mg/day is recommended.

Exercise

Physical activity has important physiologic and psychologic benefits for all people, and an exercise program has a key role in the management of **diabetes**.[4] Clinical studies have demonstrated a consistent beneficial effect of exercise on carbohydrate metabolism by enhancing insulin sensitivity, decreasing cardiovascular risk factors, and increasing muscular strength and the sense of well-being.[45]

For young diabetic individuals in good metabolic control, the emphasis must be on adjusting the therapeutic regimen to allow safe participation in all forms of physical activity. Middle-age and older

individuals with **diabetes** should also be encouraged to be physically active. All patients should be made aware that physical exercise may be associated with some risk, including the development of hypoglycemia, cardiovascular ischemia, and lower-extremity injuries. Before beginning an exercise program, the diabetic patient should undergo a detailed medical evaluation to uncover previously undiagnosed microvascular and macrovascular complications.[1] [26] To improve metabolic control and diminish cardiovascular risk factors, the ADA has recommended that an exercise program for patients with type 2 **diabetes** include aerobic exercise for 20 to 45 minutes at least 3 days per week appropriate to the individual's lifestyle and general physical condition.[5] The authors recommend that all patients carry a carbohydrate-containing supplement during the exercise period and that they wear a MediAlert badge.

PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES

Current therapeutic agents available for type 2 **diabetes** include sulfonylureas, meglitinides, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, and insulin. All of these agents have tissue-specific actions that improve glycemia. They can be used as monotherapy or in combination to take advantage of the different mechanisms of action to reverse the multifactorial pathophysiology of beta-cell dysfunction, insulin resistance, increased hepatic glucose production, and decreased peripheral glucose use. The choice of a particular agent may be suggested by specific conditions, such as obesity, or dictated by problems, such as renal insufficiency. The characteristics of each therapeutic class must be weighed carefully before initiating therapy. Table 3 lists available oral antidiabetic agents. The following sections provide a brief description of each classification of oral agents.

TABLE 3 -- AVAILABLE ORAL ANTIDIABETIC AGENTS

Generic Name	Brand Name	Daily Dose (mg)	Duration of Actior (hours)
First-generation sulfonylureas			
Tolbutamide	Orinase	500-3000	6-12
Chlorpropamide	Diabinese	100-500	60
Tolazamide	Tolinase	100-1000	12-24
Second-generation sulfonylureas			
Glipizide	Glucotrol	2.5-20.0	12-24

	Glucotrol XL	5-20	24
Glyburide	Diabeta	1.25-20.0	16-24
	Micronase Glynase Pres Tab	0.75-12.0	12-24
Glimepiride	Amaryl	1-4	24
Meglitinides			
Repaglinide	Prandin	1-16	~1
Biguanides			
Metformin	Glucophage	1500-2550	~5.5*
alpha-**Glucosidase inhibitors**			
Acarbose	Precose	25-150	8*
Miglitol	Glyset	25-300	8*
Thiazolidinediones			
Rosiglitazone	Avandia	4-8	12
Pioglitazone	Actos	15-45	24

*Plasma half-life.

Sulfonylureas

The sulfonylureas have been the mainstay of diabetic therapy since 1942.[31] All of the currently available sulfonylureas bind to specific receptors on pancreatic beta-cells, resulting in closure of potassium-dependent ATP channels leading to depolarization of the beta-cell membrane and increased calcium flux that stimulates insulin release. The increase in insulin secretion decreases hepatic glucose production and enhances glucose uptake in peripheral tissues, primarily muscle, leading to a reduction in plasma glucose.[31] In addition, glimepiride has been reported to induce GLUT 4 mRNA in in vitro studies.[13] Approximately 25% of patients who begin therapy on sulfonylureas achieve a fasting plasma glucose less than 7.8 mmol/L (140 mg/dL) and are considered complete responders. Approximately 20% have little or no reduction in plasma glucose values (<1.1 mmol/L or <20 mg/dL) and are considered primary failures. The rest, 60% to 70% of patients, have a partial response but do not reach glycemic targets. Secondary failure of effectiveness is common, occurring in 5% to 10% of patients per year.[31] After 10 years of **diabetes**, most patients require combination therapy with a second oral agent or insulin to achieve metabolic control.[51] [53]

Hypoglycemia and weight gain are the most common side effects. Severe hypoglycemia occurs in less than 0.4 cases per 1000 patient-treatment years.[31] Contraindications to sulfonylureas include known hypersensitivity to the drug, type 1 **diabetes**, and pregnancy.

Meglitinides

Repaglinide (Prandin) is the most recent insulin secretagogue approved by the US Food and Drug Administration (FDA) for the treatment of type 2 **diabetes**. It works by binding to and closing ATP-dependent potassium channels on pancreatic beta-cells. It is structurally different from sulfonylureas and binds to a nonsulfonylurea receptor site. Repaglinide is rapidly absorbed (0.5 to 1 hour) and has a limited duration of action (half-life <1 hour). The drug is taken before meals to increase insulin release and prevent excessive postprandial hyperglycemia. It can be use as monotherapy, with a similar reduction of HbA_{1c} of 1.0 to 1.5 percentage points seen with other oral agents, or in combination with insulin sensitizers. The recommended dose is 0.5 to 4 mg three times daily given 15 minutes before each meal. Weekly dosage adjustment is recommended to a maximum dose of 16 mg/day. To minimize the risk for hypoglycemia, patients should not take repaglinide if they are not going to eat within 30 minutes. Metabolism is by the liver, and 90% of repaglinide is recovered in the feces; therefore, it is not contraindicated in renal insufficiency.

Biguanides

Metformin (Glucophage), the only drug in this class currently available in the United States, received FDA approval in 1995, although it has been in clinical use for more than 40 years in other parts of the world. Metformin has no direct effect on beta-cell function. Its glucose-lowering effect results primarily from reducing hepatic glucose production and to a lesser extent from increasing muscle glucose use.[12] [19] The drug acts by causing the translocation of glucose transporters from the microsomal fraction to the plasma membrane of hepatic and muscle cells and by increasing insulin receptor tyrosine kinase activity and glycogen synthesis in muscles.[48] Metformin has been shown to reduce fasting plasma glucose by 50 to 70 mg/dL and the HbA_{1c} by 1.4% to 2.0%. Hypoglycemia is not a danger with metformin monotherapy, and, unlike the sulfonylureas, it is not associated with weight gain. Metformin monotherapy is associated with an increase in HDL cholesterol and a reduction in triglyceride, LDL cholesterol, and total cholesterol levels.

Metformin has been shown to be effective in combination with other agents, such as insulin secretagogues, other insulin-sensitizing drugs,[12] [31] [34] inhibitors of glucose absorption, and insulin therapy. The combination of a sulfonylurea with metformin has been most widely used. In sulfonylurea-treated patients with persistently elevated fasting plasma glucose (>140 mg/dL), metformin can be added in a gradually titrated dose. One should not discontinue sulfonylurea therapy in these patients because a discontinuation of sulfonylurea and substitution to metformin will not decrease the plasma glucose level below that observed with sulfonylurea alone.

Metformin has a benign side-effect profile characterized by transient gastrointestinal discomfort and nausea. Because of the risk of lactic acidosis, which has been reported in 3 cases per 100,000 patient-years, metformin should be avoided in patients with metabolic acidosis or hypoxic states, including renal failure, renal dysfunction with serum creatinine greater than 1.5 mg/dL, liver failure, and in patients with congestive heart failure requiring pharmacologic intervention. Additionally, metformin should be withheld from patients undergoing major surgical interventions or contrast studies from the time of the procedure until 48 hours after the procedure; it may be started again when renal function is determined to be normal by serum creatinine.[39]

alpha-Glucosidase Inhibitors

Acarbose (Precose) and miglitol (Glyset) are alpha-glucosidase inhibitors currently available for clinical use in the US. The drugs work by inhibiting the absorption of carbohydrate from the gut after a meal, thereby directly affecting postprandial hyperglycemia. As monotherapy, these agents decrease fasting blood glucose by 1.4 to 1.7 mmol/L (25 to 30 mg/dL), postprandial plasma glucose by 2.2 to 2.8 mmol/L (40 to 50 mg/dL), and the HbA_{1c} value by 0.7% to 1%.[9] The drugs are indicated in patients with newly diagnosed **diabetes** with fasting glucose less than 140 mg/dL and an HbA_{1c} value above 7.5% to 8% (suggesting marked postprandial hyperglycemia), and in patients with inadequate glucose control despite therapy with insulin or oral agents. alpha-Glucosidase inhibitors can be used in combination with other oral agents, in which case the glucose-lowering effect is enhanced.[10] Hypoglycemia and weight gain do not occur when these drugs are used as monotherapy; however, gastrointestinal side effects, including bloating, flatulence, and diarrhea reported in as many as 30% of patients, limit their use. The frequency of side effects may be reduced by incremental changes in the drug by 25 mg/week to the maximal dose of 50 mg three times a day with meals.[10] These compounds are contraindicated in patients with major gastrointestinal disorders, including inflammatory bowel disease, malabsorption, partial intestinal obstruction, and severe hepatic or renal disease.

Thiazolidinediones

Rosiglitazone (Avandia) and Pioglitazone (Actos) are members of a new class of insulin sensitizers available for patient care. Troglitazone (Rezulin), the first member of this class, is no longer available owing to reported cases of hepatocellular toxicity. The thiazolidinediones bind to peroxisome proliferator-activated receptor-gamma in muscle and fat.[44] Their major metabolic effect is to enhance the sensitivity to insulin in peripheral tissues, primarily muscle, although, at higher doses, they may also reduce hepatic glucose production. Rosiglitazone and pioglitazone have been shown to be effective as monotherapy in drug-naive patients or in patients who do not respond to sulfonylureas, as well as in combination therapy with sulfonylureas, metformin, or insulin. Clinical trials have shown equipotent glucose-lowering effects of approximately 1.6 to 2.5 mmol/L (23 to 45 mg/dL) and reduction of HbA_{1c} of 1.2 to 1.5 percentage points. Overall, 20% to 30% of patients fail to respond when thiazolidinediones are used in monotherapy or added to the treatment of patients failing therapy with sulfonylureas. Weight gain, possibly related to the improvement in glycemic control, fluid retention, and expansion of plasma volume, has been reported with the thiazolidinediones. The incidence of elevated liver enzyme levels in diabetic patients treated with rosiglitazone and pioglitazone is 0.2% and 0.25%, respectively.[31] [44] Although no cases of acute liver failure or severe liver dysfunction have been reported with the use of rosiglitazone or pioglitazone,

the FDA has recommended monitoring liver function every 2 months for the first 12 months and then periodically thereafter. These agents should not be started or should be discontinued in patients with alanine transferase greater than 2.5 times the upper limit of normal.

Insulin

Insulin administration is the cornerstone of therapy in type 1 **diabetes** because the insulinopenia caused by beta-cell destruction requires insulin therapy for survival. Table 4 (Table Not Available) summarizes the time of, and duration of action of, different insulin preparations, including the new long-acting insulin (Glargine) available in the United States.[20] [27] In patients with type 1 **diabetes**, the type of insulin, the route of administration, and the appropriate insulin dosage are dependent on the glycemic response of the individual to diet and exercise programs, lifestyle, and glycemic control goals. During the past decade, it has become clear that conventional insulin therapy using one or two injections of primarily intermediate-acting insulin or a combination of intermediate- and short-acting insulin (e.g., NPH and Regular) almost never achieves desired glycemic goals in patients with type 1 **diabetes**.[11] Physicians should clarify to the type 1 diabetic patient that intensive insulin therapy using multiple injections (more than three) per day might be necessary for optimal **diabetes** control.

TABLE 4 -- CHARACTERISTICS OF AVAILABLE HUMAN INSULINS IN THE UNITED STATES

(Not Available)

*Adapted from Kitabchi AE, Bryer-Ash M: NIDDM: New aspects of management. Hosp Pract 32:135-164, 1997; and Heinemann L, Linkeschova R, Rave K, et al: Time-action profile of the long-acting insulin analog insulin Glargine (HOEGOI) in comparison with those of NPH insulin and placebo. **Diabetes** Care 23:644-649, 2000.*

The dosage regimen for patients with type 1 **diabetes** is consistent with the average dose in recent clinical trials[11] and ranges from 0.6 to 0.9 U/kg body weight. Continuous subcutaneous insulin infusion with an infusion pump is a valid alternative to conventional injection therapy for achieving glycemic control. An insulin pump may provide greater lifestyle flexibility, particularly with regard to meal schedules and travel. In addition, it may decrease the risk of hypoglycemia in patients with brittle **diabetes** and has been shown to improve **diabetes** control during pregnancy. The use of an infusion pump may be demanding for the nontechnical individual. Infections or inflammation at the needle site may also complicate insulin pump therapy but can be minimized by careful hygiene and frequent site changes. Appropriate use of an insulin pump requires careful selection of patients who will be willing to measure blood glucose several times per day and have access to continuing available care by skilled professionals.

In patients with type 2 **diabetes**, insulin therapy is indicated during severe hyperglycemia despite maximal doses of oral agents or during intercurrent illness (e.g., infection, acute medical illness), a perioperative period, pregnancy, and severe liver or renal disease. In patients with newly diagnosed **diabetes** or with a short duration of **diabetes** who present with symptoms of hyperglycemia or weight loss, short-term insulin therapy guided to control blood glucose aggressively for several weeks may induce long-lasting metabolic improvement. The most common indication for long-term insulin therapy in type 2 **diabetes** is the patient who has experienced primary or secondary failure to oral diabetic therapy. Although a substitution to insulin alone may improve glycemic control, combining oral agents (sulfonylurea, metformin, or other insulin sensitizers) with intermediate-acting insulin (NPH) has been shown to decrease insulin dosage[28] and improve glycemic control.[42] [46] Availability of different preparations of insulin and different forms of delivery, such as insulin pens, might increase the use of insulin in clinical practice.

TREATMENT OF COMORBID CONDITIONS

Diabetes is a strong risk factor for all manifestations of atherosclerotic vascular disease, including coronary heart disease, cerebrovascular disease, and peripheral vascular disease. Of adult diabetic patients, approximately 60% to 75% die of cardiovascular complications. Patients with **diabetes** have a two to four time higher risk for coronary mortality and morbidity than the general population.[29] Substantial evidence indicates that the treatment of comorbid conditions, including dyslipidemia, hypertension, and obesity, is critically important for achieving optimal outcomes in patients with **diabetes**.

Dyslipidemia

Diabetic dyslipidemia is characterized by multiple lipoprotein defects, including moderately high serum levels of cholesterol and triglycerides, small dense LDL particles, and low levels of HDL cholesterol. Long-term epidemiologic studies have indicated that patients with **diabetes** have a threefold higher mortality rate for cardiovascular events at each level of serum cholesterol when compared with the nondiabetic population.[17]

Several clinical trials have indicated that the benefit of cholesterol lowering in terms of the reduction in the risk of cardiovascular events is at least as marked in diabetic patients as in nondiabetic patients. Aggressive treatment in accordance with National Cholesterol Education Program guidelines is advised.[1] For most patients with **diabetes**, the primary target is an LDL cholesterol less than 100 mg/dL. A somewhat higher target may be appropriate in patients with **diabetes** who are not at high, short-term risk for coronary heart disease. For patients with LDL cholesterol levels in the range of 100 to 129 mg/dL, hygienic measures should be used. If the target of therapy is not achieved with these measures, consideration should be given to lipid-lowering drugs. For patients with LDL cholesterol levels greater than 130 mg/dL, lipid-lowering therapy may have to be initiated simultaneously with hygienic measures and hypoglycemic drugs. Statins are the drug of choice for diabetic patients with elevated total cholesterol or LDL cholesterol who are not controlled with a diet and exercise program. In such patients, clinical studies have shown a relative risk reduction in cardiovascular events of 19% to 55% when a statin drug is compared with placebo.[17]

The most common dyslipidemia in **diabetes** is hypertriglyceridemia.[17] This effect results from an increased production of triglyceride-rich lipoproteins and impaired clearance of very low-density lipoproteins (VLDL) owing to decreased lipoprotein lipase activity. When compared with patients with primary increases in LDL cholesterol levels, patients with hypertriglyceridemia and increased VLDL cholesterol levels may be more responsive to improvement of glycemic control with hygienic measures and hypoglycemic drugs and may achieve desirable levels of non-HDL cholesterol even without lipid-lowering drugs. Maximal application of hygienic measures and hypoglycemic therapy may allow the use of a small dose of lipid-lowering drugs to achieve target LDL or non-HDL cholesterol levels. If these measures are not sufficient to achieve desired goals, fibric acid derivatives are the drug of choice for diabetic patients with hypertriglyceridemia.[17]

Hypertension

Hypertension is common among patients with type 2 **diabetes**. Prevalence rates range from 40% to 75%. The Hypertensive Optimal Treatment study[19] reported a 51% reduction in major cardiovascular events in diabetic patients who were randomly assigned to a diastolic blood pressure goal at or below 80 mm Hg. The United Kingdom Prospective **Diabetes** Study (UKPDS) [52] demonstrated that intensive control of blood pressure in patients with hypertension reduced all **diabetes** complications by 24%, diabetes-related deaths by 32%, strokes by 44%, heart failure by 56%, and microvascular complications by 37%. A recent study of elderly patients with type 2 **diabetes** and isolated systolic hypertension showed that reduction of systolic blood pressure reduced

relative and absolute risks of fatal and nonfatal cardiovascular events (coronary and cerebral).[50] Based on these data, the ADA and the joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[49] recommend a blood pressure of less than 130/85 mm Hg as a goal in diabetic patients.

There is no clear consensus regarding the best antihypertensive drug to use in diabetic patients. For achieving control of hypertension, the authors prefer the initial use of angiotensin-converting enzyme (ACE) inhibitors, along with a thiazide diuretic, beta-adrenergic-blocking agent, or a calcium channel blocker. ACE inhibitors may confer an additional benefit by slowing the progression of diabetic nephropathy in patients with type 1 and type 2 **diabetes**.[32] Recently, ACE inhibitors have been shown to improve endothelial function in type 2 **diabetes**[49] [50] and to reduce the conversion of patients with impaired glucose tolerance to **diabetes**.[58] Although some clinical trials in hypertensive diabetic subjects treated with ACE inhibitors have reported significantly fewer major cardiovascular events when compared with other agents, the UKPDS study found no difference in cardiovascular and microvascular outcomes when captopril was compared with atenolol.[52] It is possible that the maximum reduction of cardiovascular risk is more dependent on reaching target blood pressure levels than on the choice of antihypertensive drug. Clinicians should be aware that the treatment of hyperglycemia and hypertension in patients with type 2 **diabetes** frequently requires combination therapy with two or more agents to reach acceptable levels of glycemic and blood pressure control.[51] [52] [53]

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