Abstract

Type 2 diabetes (T2D) is the most common form of diabetes, a metabolic disorder characterized by hyperglycemia resulting from defects in insulin action, insulin secretion, or both. Early diagnosis of T2D and the high-risk category of pre-diabetes may help reduce the associated public health and clinical burden. Available diagnostic strategies include fasting plasma glucose, oral glucose tolerance test, and casual plasma glucose in the presence of symptoms of hyperglycemia. Potential use of hemoglobin A1c as part of the strategy for screening and diagnosis has been recently proposed. Those with risk factors for T2D should be targeted including patients with overweight/obesity, those with family history of T2D, those aged 45 years and older, race/ethnic minorities (such as Native Americans, African Americans, Latinos, and Asian Americans), women with history of gestational diabetes, and those with metabolic syndrome abnormalities (high blood pressure, low HDL cholesterol, and high triglycerides). Lifestyle modification (i.e., weight loss through diet and increased physical activity) has proven effective in reducing incident T2D in high-risk groups. Prevention trials using pharmacological therapy (metformin, α-glucosidase
inhibitors, or thiazolidinediones) have also reported a significant lowering of the incidence of T2D. As a chronic condition, T2D requires continuous care to prevent damage to various organs, including the eyes, kidney, nervous system, and cardiovascular system. Appropriate glycemic control, blood pressure and lipid management, nutrition and physical activity, taking into account functional status and comorbidities, are needed to prevent microvascular and macrovascular complications. A variety of oral antihyperglycemic agents, which target different mechanisms in the pathogenesis of T2D, are as follows: insulin sensitizers, insulin secretagogues, α-glucosidase inhibitors, and the new dipeptidyl peptidase (DPP)-IV inhibitors. Injectable agents for the treatment of insulin-deficient T2D include traditional insulin preparations, newer insulin analogs, amylin, and incretin mimetics. Additional aspects of T2D management in the older adult include the assessment of geriatric syndromes and psychosocial screening. Efforts to improve T2D care following recommended guidelines are still very much needed.

**Key words:** Type 2 Diabetes; Diagnosis; Epidemiology; Prevention; Management; Insulin resistance; Insulin secretion.

**INTRODUCTION**

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia, which can result from defects in insulin secretion, insulin action, or both. Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce long-term complications.

**DIAGNOSIS**

The American Diabetes Association (ADA) diagnostic criteria for diabetes and the two high-risk categories of pre-diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), updated in 2003 are defined in Table 1. There are three ways to diagnose diabetes. Because of simplicity of use, acceptability to patients, and low cost, the fasting plasma glucose (PG) is the preferred diagnostic test. In the presence of symptoms of diabetes (polyuria, polydipsia, weight loss, etc.), a casual plasma glucose of greater or equal than 200 mg/dl is diagnostic. The 75-g oral glucose tolerance test (OGTT) is more sensitive and modestly more specific than fasting PG, but it is less reproducible and less frequently performed in clinical settings. In the absence of unequivocal hyperglycemia, any test used to diagnose diabetes must be confirmed on a subsequent day by a PG measured either in the fasting state or 2 h after an oral glucose load.
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Table 1

The diagnostic criteria for diabetes and the classification of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)

<table>
<thead>
<tr>
<th>FPG (mg/dl)</th>
<th>2-HPG (mg/dl)</th>
<th>Sx of diabetes + CPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;100</td>
<td>&lt;140</td>
</tr>
<tr>
<td>IFG</td>
<td>≥100 and &lt;126</td>
<td>–</td>
</tr>
<tr>
<td>IGT</td>
<td>–</td>
<td>≥140 and &lt;200</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥126</td>
<td>≥200</td>
</tr>
</tbody>
</table>

FPG, fasting plasma glucose (FPG); 2-HPG, plasma glucose 2 h after a challenge with 75 g glucose; CPG, casual plasma glucose; Sx (symptoms) of diabetes: polydipsia, polyuria, and unexplained weight loss.

Adapted from American Diabetes Association (1).

The 2006 joint report from the World Health Organization (WHO) and International Diabetes Federation (IDF) also provides an update on guidelines for diagnosis of diabetes (2). Their diagnostic criteria (i.e., fasting PG ≥ 7.0 mmol/l [126 mg/dl] or 2-h PG ≥ 11.1 mmol/l [200 mg/dl]) remained unchanged since these criteria distinguish a group with significantly increased premature mortality and higher risk of microvascular and cardiovascular complications.

Recently, a committee of experts in the area of diagnosis, monitoring, and management of diabetes provided a review of the available evidence and made recommendations regarding the screening and diagnosis of diabetes using hemoglobin A1c (HbA1c) (3). The main factors in support of using HbA1c as a screening and diagnostic test included (a) HbA1c does not require patients to be fasting; (b) HbA1c reflects longer-term glycemia than does PG; (c) HbA1c laboratory methods are now well standardized and reliable (more information in the National Glycohemoglobin Standardization Program web site at www.ngsp.org); (d) errors caused by non-glycemic factors affecting HbA1c, such as hemoglobinopathies, are infrequent and can be minimized by confirming the diagnosis of diabetes with a PG-specific test. Several recommendations were made: (1) screening standards should be established that prompt further testing and closer follow-up, including fasting PG ≥100 mg/dl, random PG ≥130 mg/dl, or HbA1c > 6.0% (2) HbA1c ≥ 6.5–6.9%, confirmed by a PG-specific test (fasting PG or OGTT), should establish the diagnosis of diabetes; (3) HbA1c ≥ 7%, confirmed by another HbA1c or a PG-specific test (FPG or OGTT) should establish the diagnosis of diabetes.

Hyperglycemia insufficient to meet the diagnostic criteria for diabetes is categorized as either IFG or IGT, depending on whether it is identified by a fasting PG or by an OGTT. According to the ADA, IFG is diagnosed when
the fasting PG level is $\geq 100$ mg/dl ($\geq 110$ mg/dl based on WHO/IDF criteria) but $< 126$ mg/dl. IGT exists when the PG level 2 h after a 75-g oral glucose load is $\geq 140$ mg/dl but $< 200$ mg/dl. These are considered to be pre-diabetic states. Furthermore, an international committee (IDF/ADA/EASD) reported that a HbA1c $\geq 6\%$ but $< 6.5\%$ helps identifying people at very high-risk of developing diabetes (http://care.diabetesjournals.org/content/32/7/1327).

**EPIDEMIOLOGY**

Diabetes and its complications constitute a significant public health problem worldwide and are an important cause of morbidity and mortality. In fact, diabetes has reached epidemic proportions throughout the world, and the prevalence is expected to continue to rise. The International Diabetes Federation estimates that more than 245 million people around the world have diabetes (4). This total is expected to rise to 380 million within 20 years. Each year a further 7 million people develop diabetes. Diabetes, mostly type 2 diabetes (T2D), now affects 5.9% of the world’s adult population with almost 80% of the total in developing countries. The regions with the highest rates are the Eastern Mediterranean and Middle East, where 9.2% of the adult population is affected, and North America (8.4%). The highest numbers, however, are found in the Western Pacific, where some 67 million people have diabetes, followed by Europe with 53 million.

According to new 2007 prevalence data estimates recently released by the Centers for Disease Control and Prevention (CDC), diabetes now affects nearly 24 million people in the United States (USA), an increase of more than 3 million in approximately 2 years (5). Among adults, diabetes increased in both men and women and in all age groups, but still disproportionately affects the elderly. Almost 25% of the population aged 60 years and older had diabetes in 2007. Another 57 million people are estimated to have pre-diabetes. It has been projected that one in three Americans born in 2000 will develop diabetes, with the highest estimated lifetime risk among Latinos (males, 45.4% and females, 52.5%) (6).

A rise in obesity rates is to blame for much of the increase in T2D (7). Nearly two-thirds of American adults are overweight or obese (8). The prevalence of abdominal obesity (i.e., large waist circumference) among US adults has increased continuously during the past 15 years. Over one-half of US adults have abdominal obesity (9). This is a major concern given the strong association between measures reflecting abdominal obesity and the development of T2D (10).

The risk of developing diabetes rises not only with overweight/obesity (body mass index, $\text{BMI} \geq 25 \text{kg/m}^2$) and lack of physical activity, but with
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increasing age (≥45 years) and family history (1). Specific population subgroups have a higher prevalence of diabetes than the population as a whole. Recent data showed that compared to white non-Hispanics (6.6%) diabetes remains higher in race/ethnic minority groups: Native Americans and Alaska Natives (16.5%), African Americans (11.8%), Latinos (10.4%), which includes rates for Puerto Ricans (12.6%), Mexican Americans (11.9%), and Cubans (8.2%), and Asian Americans (7.5%) (11). Women with a history of prior gestational diabetes or polycystic ovarian syndrome are at increased risk. Also, the predictive value of traditional and non-traditional risk factors has been evaluated in cohort studies (12, 13). In addition to age, family history of diabetes, obesity and pre-diabetes, and those with other metabolic syndrome components (high blood pressure, low HDL cholesterol, and high triglycerides) are at higher risk. The greater the number of these metabolic risk factors in a given person, the higher the chance of that individual developing diabetes.

PATHOGENESIS

There are two underlying mechanism that lead to the onset of clinical T2D: inadequate insulin action in target tissues (insulin resistance) and inadequate secretion from pancreatic β-cells (Fig. 1) (14). Insulin resistance arises prior to the onset of clinical disease, but predicts the development of diabetes (15–17). Environmental factors, particularly obesity and a sedentary lifestyle, are important contributors to the development of diabetes, largely because of their effects on insulin sensitivity (18–20). When target tissues become insulin resistant, glucose uptake is decreased, hepatic glucose production increases, and lipolysis is enhanced. In muscle, the increased free fatty acid (FFA) availability accelerates fat oxidation, resulting in decreased insulin-mediated glucose uptake and disposal. In the liver, elevated FFAs promote gluconeogenesis and increase hepatic glucose output.

When inadequate insulin secretion from pancreatic β-cell dysfunction is also present, hyperglycemia develops, heralding the onset of T2D (14–17). In the natural history of progression to diabetes, β-cells initially increase insulin secretion in response to insulin resistance and, for a period of time, are able to effectively maintain glucose levels below the diabetic range. However, when β-cell function begins to decline, insulin production is inadequate to overcome the insulin resistance, and blood glucose levels rise. Insulin resistance, once established, remains relatively stable over time. Therefore, progression of T2D is a result of worsening β-cell function with pre-existing insulin resistance.
Fig. 1. Defects in the pancreas and in target tissues for insulin action in type 2 diabetes. In the non-diabetic individual, insulin suppresses hepatic glucose output, stimulates glucose uptake and utilization in muscle and adipose tissue, and suppresses lipolysis in adipose tissue. When these tissues become resistant to the actions of insulin, hepatic glucose production increases, glucose uptake is decreased, and lipolysis is enhanced. Increased free fatty acids (FFAs) from lipolysis stimulate cellular uptake of FFAs and lipid oxidation. In muscle, the increased FFA availability accelerates fat oxidation, resulting in decreased insulin-mediated glucose uptake and utilization. In the liver, elevated FFAs stimulate gluconeogenesis and increase hepatic glucose output. When β-cell dysfunction is present, insulin resistance in the target tissues leads to hyperglycemia and to the development of type 2 diabetes. (From DeFronzo, R. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Copyright © 2009 American Diabetes Association from Diabetes, 2009; 58:773–795. Reprinted with permission from the American Diabetes Association.)

Despite major advances in understanding the pathophysiology of T2D, unraveling the complex link between genetic risk and environmental factors in this burgeoning epidemic has proven difficult (21). Linkage approaches have clarified the etiology of monogenic diabetic syndromes and congenital lipodystrophies, and candidate gene association studies have identified a number of common variants implicated in T2D. Several genetic loci have now been reproducibly associated with T2D in genome-wide scans. For example, common variants in the gene that encodes the transcription factor 7-like 2 (TCF7L2), involved in the control of insulin secretion, have been strongly associated with T2D (22). At the individual level,
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carrying the TCF7L2-risk allele increases T2D risk 50%. However, at the population level, the attributable risk is lower than 25% and varies with the allele frequency. The presence of the TCF7L2 rs7903146-risk allele increases TCF7L2 gene expression in β-cells, possibly impairing glucagon-like peptide-1-induced insulin secretion and/or the production of new mature β-cells. It is expected that the detection of other such genes in genome-wide association scans will help elucidate the genetic architecture and pathophysiology of T2D.

PREVENTION OR DELAY OF TYPE 2 DIABETES

Prevention efforts may start with promotion of healthy lifestyle and appropriate screening in those at higher risk: individuals ≥ 45 years of age and those with a BMI ≥ 25 kg/m² (22). Screening should also be considered for people who are <45 years of age and are overweight if they have another risk factor for diabetes: physical inactivity, first-degree relative with diabetes, members of high-risk ethnic populations (e.g., African American, Latino, Native American, Asian American, Asian American, and Pacific Islander), women who delivered a baby weighing > 9 lb or were diagnosed with gestational diabetes, hypertension, low HDL cholesterol, high triglycerides, women with polycystic ovarian syndrome, IGT, or IFG on previous testing, other clinical conditions associated with insulin resistance (e.g., severe obesity and acanthosis nigricans), and history of cardiovascular disease (CVD). Repeat testing may be carried out at 3-year intervals.

Lifestyle modification (i.e., weight loss through diet and increased physical activity) has proven effective in reducing incident T2D in high-risk groups. The Da Qing Study (China) randomly allocated 33 clinics (557 persons with IGT) to 1 of 4 study conditions: control, diet, exercise, or diet plus exercise (23). Compared with the control group, the incidence of diabetes was reduced in the three intervention groups by 31, 46, and 42%, respectively, and with a modest weight loss in study participants. The Finnish Diabetes Prevention Study evaluated 522 obese persons with IGT randomly allocated on an individual basis to a control group or a lifestyle intervention group that emphasized physical activity, weight loss, limited total dietary intake and intake of saturated fat, and increased intake of dietary fiber (24). During the trial, the incidence of diabetes was reduced by 58% in the lifestyle group compared with the control group. The US Diabetes Prevention Program is the largest trial of primary prevention of diabetes to date and was conducted at 27 clinical centers with 3,234 overweight and obese participants with IGT randomly allocated to 1 of 3 study conditions: control, use of metformin, or intensive lifestyle intervention (25). The goal of lifestyle
intervention was to achieve and maintain 7% or greater weight loss through a low-calorie, low-fat diet and 150 or more minutes of moderate physical activity weekly. Nearly half the participants were African American, Hispanic American, Asian American, or Native American. Over 3 years, the incidence of diabetes was reduced by 31% in the metformin group and by 58% in the lifestyle group; the latter value is identical to that observed in the Finnish Study. To prevent 1 case of diabetes, only 7 patients needed to be treated with lifestyle change, compared with 14 patients treated with metformin. The magnitude of risk reduction in the lifestyle intervention group was similar across all ethnic groups, and participants in all age and BMI subgroups achieved a clinically significant reduction in risk. In contrast, metformin was relatively ineffective in older and less obese participants.

Type 2 diabetes prevention trials using other forms of pharmacological therapy have also reported a significant lowering of the incidence of diabetes. The α-glucosidase inhibitor acarbose reduced the risk by 32% in the STOP-NIDDM trial (26), and the thiazolidinedione troglitazone reduced the risk by 56% in the TRIPOD Study (27).

More recently, the investigators from the DREAM trial, a study in 5,269 adults with IGT, IFG, or both and no previous CVD were recruited from 191 sites in 21 countries and randomly assigned in a 2-by-2 factorial design to receive rosiglitazone 8 mg/day and/or ramipril 15 mg/day. There was no statistical evidence of an interaction between the ramipril and the rosiglitazone arms. After a mean follow-up of 3 years, the use of ramipril did not reduce the incidence of diabetes (28), while the treatment with rosiglitazone reduced by almost 60% the incidence of T2D and increased the likelihood (+70%) of regression to normoglycemia (29).

Whether diabetes prevention strategies also ultimately prevent the development of diabetic vascular complications is unknown, but cardiovascular risk factors are favorably affected (30). Preventive strategies that can be implemented in routine clinical settings have been developed and evaluated. Widespread application has, however, been limited by local financial considerations, even though cost-effectiveness might be achieved at the population level.

MANAGEMENT

Prevention of Complications

Chronic poor glycemic control is associated with the development of diabetic vascular complications, including microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (coronary, cerebrovascular and peripheral vascular disease). CVD is the cause of 65% of deaths in patients with T2D (31). Epidemiologic studies have shown that the risk of
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a myocardial infarction (MI) or CVD death in a diabetic individual with no prior history of CVD is comparable to that of an individual who has had a previous MI (32, 33).

Microvascular complications can be delayed or prevented by maintaining excellent chronic glycemic control, as has been demonstrated in a number of interventional trials, including the Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective Diabetes Study (UKPDS), the Kumamoto Study, and the Stockholm Diabetes Intervention Study (34–39). Further, even in acute illness, several studies have shown that intensive insulin therapy and improved glycemic control are associated with better outcomes (40, 41).

Intensive glycemic control also results in reduced macrovascular complications, i.e., CVD, as demonstrated in a number of epidemiological studies (42–44). From the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study of type 1 diabetes, it is clear that intensive glycemic control prior to the onset of vascular disease has long-term beneficial effects on the risk of CVD in this population (45). Patients with newly diagnosed T2D, aged 25–65 years at baseline, whose HbA1c was reduced from 7.9 to 7% in the UKPDS, did not exhibit a reduction in cardiovascular events, although a subgroup of patients treated with metformin showed a trend to a lower incidence of events (46). However, 10-year follow-up data from this study showed persistence of microvascular benefits and long-term appearance of macrovascular benefits in the insulin and sulfonylurea groups despite the fact that the differences in HbA1c between the groups had disappeared (47).

Three recent trials in older adults with T2D have assessed the effect of lowering blood glucose to near-normal levels on cardiovascular risk. First, patients in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (n = 10,251) had a mean age of 62.2 years at entry and 10 years of diabetes duration. Sixty-two percent were men, and 30% had prior macrovascular disease and a baseline median HbA1c level of 8.1% (48). Study patients were assigned to receive intensive therapy (median HbA1c level achieved of 6.4%) or standard therapy (median HbA1c level achieved of 7.5%). After a median follow-up of 3.4 years, compared to the standard-therapy group, those in the intensive-therapy group had higher overall mortality (4% vs. 5%) and cardiovascular mortality (1.8% vs. 2.6%) and greater-number of hypoglycemic events (1% vs. 3.1%). Second, patients in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) Study (n = 11,140) had a mean age of 66 years at entry and 8 years of diabetes duration. Fifty-seven percent were men and 32% had prior macrovascular disease and a baseline median HbA1c level of 7.2% (49). Study patients were assigned to receive
intensive therapy (median HbA1c level achieved of 6.4%) or standard therapy (median HbA1c level achieved of 7%). After a median follow-up of 5 years, compared to the standard-therapy group those in the intensive-therapy group achieved a reduction in the incidence of nephropathy (5.2% vs. 4.1%), although severe hypoglycemia was more common (1.5% vs. 2.7%). There were no differences in overall mortality (9.6% vs. 8.9%), cardiovascular mortality (5.2% vs. 4.5%), or major macrovascular events (10.6% vs. 10%). Finally, patients in the Veterans Affairs Diabetes Trial (VADT) \((n = 1,792)\) had a mean age of 60.4 years at entry and 11.5 years of diabetes duration. Ninety-seven percent were men and 40% had prior macrovascular events and a baseline mean HbA1c level of 9.4% (50). They were assigned to receive intensive therapy (median HbA1c level achieved of 6.9%) or standard therapy (median HbA1c level achieved of 8.4%). After a median follow-up of 6 years, there was no significant difference in the rate of the composite primary endpoint (MI, congestive heart failure, invasive revascularization, inoperable coronary artery disease, amputation for ischemia, stroke, or cardiovascular death) between the intensive- and the standard-therapy groups (25.9% vs. 29.3%, \(p = 0.12\)). Fewer cardiovascular events than expected were observed in both groups, in part because of the aggressive management of blood pressure (reduction from 131/77 to 127/70 mmHg) and lipids (LDL-cholesterol and triglycerides fell from 106 and 157 mg/dl to 78 and 135 mg/dl, respectively, while HDL rose from 34 to 40 mg/dl) as well as lifestyle changes (40–57% exercised regularly, 60–68% adhered to diet, and cigarette smoking was reduced from 16% to 10%) and the increased use of antiplatelet/anticoagulants (from 76% at entry to 92% at the end of the study). Intensive therapy was associated with lower risk of the primary endpoint only in those with diabetes for less than 15 years and those who had low arterial calcium (AC) scores (AC < 100). Severe hypoglycemia requiring medical assistance was higher than expected and more frequent in the intensive than in the standard group (21.1% vs. 9.7%, \(p < 0.01\)). In fact, hypoglycemic events that led to impaired or loss of consciousness were independent predictors of major cardiovascular events and cardiovascular and total mortality.

**Glycemic Goals**

Based on results from clinical trials of glycemic control and the impact on diabetic microvascular complications, recommendations for targets of glycemic control have been put forth (1). Glycemic control is fundamental to the management of diabetes. The HbA1c is the most accepted indicator of chronic control, reflecting fasting and postprandial glucose concentrations. The goal of therapy is to achieve an HbA1c as close to normal
as possible in the absence of hypoglycemia. Recommended glycemic goals for non-pregnant individuals are shown in Table 2. Less stringent treatment goals may be appropriate for patients with limited life expectancies and in individuals with co-morbid conditions (51). Severe or frequent hypoglycemia is an indication for the modification of treatment regimens, including setting higher glycemic goals.

**Table 2**
**Glycemic goals**

<table>
<thead>
<tr>
<th>Goal</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c goal for patients in general</td>
<td>&lt;7%</td>
</tr>
<tr>
<td>HbA1c goal for the frail elderly patient</td>
<td>&lt;8%</td>
</tr>
<tr>
<td>Pre-prandial capillary plasma glucose*</td>
<td>90–130 mg/dl</td>
</tr>
<tr>
<td>Peak postprandial capillary plasma glucose*</td>
<td>&lt;180 mg/dl</td>
</tr>
</tbody>
</table>

*Capillary plasma glucose = fingerstick glucose.

Adapted from American Diabetes Association (1) and Brown et al. (75).

**Nutrition and Physical Activity**

Overweight and obesity are strongly linked to the development of T2D and can complicate its management. Moderate weight loss improves glycemic control and reduces CVD risk. Therefore, weight loss is an important therapeutic strategy in all overweight or obese individuals who have T2D. All patients with diabetes should be encouraged to maintain a healthy lifestyle by exercising and following an appropriate diet (52). The primary approach for achieving weight loss is therapeutic lifestyle change, which includes a reduction in energy intake and an increase in physical activity.

**Oral Antidiabetic Agents**

A variety of antidiabetic pharmaceutical agents for the treatment of T2D are available, which target different mechanisms in the underlying pathogenesis of the disease (53–56) (Fig. 2). There are five categories of oral agents on the market, which can be used initially in most cases of T2D, until insulin deficiency becomes severe and insulin replacement is required. Sulfonylureas and the glitinsides (repaglinide, nateglinide) are insulin secretagogues that stimulate release of insulin from the β-cells of the pancreas. Metformin, a biguanide, improves insulin sensitivity chiefly by reducing insulin resistance in the liver, thereby decreasing hepatic glucose production. The thiazolidinediones (rosiglitazone, pioglitazone) improve insulin sensitivity primarily in the muscle, thereby increasing peripheral uptake and utilization of glucose. The α-glucosidase inhibitors (acarbose) prevent the breakdown of carbohydrates to glucose in the gut, by
Fig. 2. Antidiabetic agents and their mechanisms of action. The variety of antidiabetic agents for the treatment of type 2 diabetes target different mechanisms in the underlying pathogenesis of the disease. Sulfonylureas and the glitinites (repaglinide, nateglinide) are insulin secretagogues that stimulate release of insulin from the pancreas. Metformin, a biguanide, improves insulin sensitivity chiefly by reducing insulin resistance in the liver, thereby decreasing hepatic glucose production. The thiazolidinediones (rosiglitazone, pioglitazone) improve insulin sensitivity primarily in the muscle, thereby increasing peripheral uptake and utilization of glucose. The \( \alpha \)-glucosidase inhibitors (acarbose, precose) prevent the breakdown of carbohydrates to glucose in the gut, by inhibiting the enzymes that catalyze this process, thereby delaying carbohydrate absorption. Insulin and insulin analogs increase insulin levels in the presence of declining \( \beta \)-cell function and diminished endogenous insulin secretion. Exenatide and the synthetic amylin, pramlintide exploit novel mechanisms related to effects on glucagon secretion, gastric emptying, and satiety. (From DeFronzo (53). Reprinted from Annals of Internal Medicine with permission from American College of Physicians.)

Inhibiting the enzymes that catalyze this process, thereby delaying carbohydrate absorption. Sitagliptin, a dipeptidyl-peptidase (DPP)-IV inhibitor, is an agent that reduces blood glucose with less risk of hypoglycemia. Metformin is recommended as first choice for pharmacologic treatment and has good efficacy to lower HbA1c by approximately 1–1.5% as monotherapy (57). However, most patients will eventually require treatment with combinations of oral medications with different mechanisms of action simultaneously in order to attain adequate glycemic control. Table 3 lists the available classes of oral antidiabetic medications, their mechanisms of action, and side effects.
### Table 3
Available oral antidiabetic agents

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Mechanism of action</th>
<th>Major side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Stimulate insulin secretion</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Suppress hepatic glucose production (major)</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Metformin</td>
<td>Improve insulin sensitivity in target tissues (minor)</td>
<td>GI side effects Lactic acidosis (rare)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Improve insulin sensitivity in target tissues (major)</td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td>Suppress hepatic glucose production (minor)</td>
<td>Edema Congestive heart failure</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Delay carbohydrate absorption from the intestine</td>
<td>Flatulence or abdominal discomfort</td>
</tr>
</tbody>
</table>

Adapted and summarized from Florez et al. (56).

### Injectable Therapy

Injectable agents for treatment of insulin-deficient T2D include traditional insulin preparations, newer insulin analogs, amylin, and incretin mimetics (see Fig. 2). Insulin and the insulin analogs increase circulating insulin levels in the presence of declining β-cell function and diminished endogenous insulin secretion. Insulin and analogs, available in both long-acting and rapid-acting formulations, can be used in combination with oral agents in T2D or as insulin replacement therapy in long-standing, insulin-deficient T2D (56). The recent additions to the market, the incretin mimetic exenatide and the synthetic amylin, pramlintide, exploit novel mechanisms related to effects on glucagon secretion, gastric emptying, and satiety to improve glycemic control (58, 59).

### Other Strategies for Reduction of Comorbidities and Complications

In addition to hyperglycemia, individuals with T2D often have a constellation of other metabolic abnormalities which increase their CVD risk (60–64). Risk determinants of CVD include the presence or absence of coronary heart disease (CHD), other clinical forms of atherosclerotic disease, and the major risk factors: high LDL cholesterol, cigarette smoking, hypertension, low HDL cholesterol, family history of premature CHD (defined as a relative with CHD younger than 65 years for women and 55
years for men), and age (men $\geq 45$ years, women $\geq 55$ years). It is important to point out that diabetes is considered to be a CHD equivalent, so the goal for LDL cholesterol is $<100$ mg/dl. Based on these risk determinants, the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) identifies three categories of risk that modify the goals and modalities of LDL-lowering therapy (65) (Tables 4 and 5). In very high-risk persons, an LDL-C goal of $<70$ mg/dl is a therapeutic option on the basis of available clinical trial evidence (66). The justification for the more aggressive LDL targets in patients with diabetes with CVD is based on three large statin-outcome trials: the Heart Protection Study (HPS), the Treating to New Targets (TNT) Study, and the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) Study, which also identified the diabetic subgroup as a cohort of patients with high residual risk even on statin therapy (67–69).

### Table 4

**ATP III classification of LDL, total, and HDL cholesterol (mg/dl).**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL cholesterol</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>Optimal</td>
</tr>
<tr>
<td>100–129</td>
<td>Near-optimal</td>
</tr>
<tr>
<td>130–159</td>
<td>Borderline high</td>
</tr>
<tr>
<td>160–189</td>
<td>High</td>
</tr>
<tr>
<td>$\geq 190$</td>
<td>Very high</td>
</tr>
<tr>
<td><strong>Total cholesterol</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>Optimal</td>
</tr>
<tr>
<td>200–239</td>
<td>Borderline high</td>
</tr>
<tr>
<td>$\geq 240$</td>
<td>High</td>
</tr>
<tr>
<td><strong>HDL cholesterol</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>Low</td>
</tr>
<tr>
<td>$&gt;60$</td>
<td>High</td>
</tr>
</tbody>
</table>

*ATP indicates Adult Treatment Panel; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

Adapted from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (65).

Risk reduction strategies have been demonstrated to be highly effective in a number of studies (70). The MICRO-HOPE Study included 3,577 individuals with diabetes, with and without hypertension, and compared the cardiovascular event rates with the angiotensin-converting enzyme (ACE) inhibitor, ramipril, vs. placebo (71). The results showed that treatment with
Table 5

<table>
<thead>
<tr>
<th>Risk category</th>
<th>LDL goal (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD risk equivalents</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Multiple (2+) risk factors</td>
<td>&lt;130</td>
</tr>
<tr>
<td>0–1 risk factor</td>
<td>&lt;160</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease. Diabetes is a CHD equivalent. Adapted from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (65).

ramipril lowered the risk of the primary outcome of combined MI, stroke, or CVD mortality by 25%, MI by 22%, stroke by 33%, and cardiovascular death by 37%. Lowering serum cholesterol has been demonstrated in many studies to be effective at reducing CVD risks, both as primary and secondary prevention. Recent studies have questioned whether even more aggressive LDL-cholesterol lowering in high-risk individuals should be the appropriate target of such treatment (67, 72).

An important study used a focused, multifactorial intervention with strict targets and individualized risk assessment in patients with T2D and microalbuminuria who were at increased risk for macrovascular and microvascular complications (73, 74). These data suggest that a long-term, targeted, intensive intervention involving multiple risk factors reduces the risk of both cardiovascular and microvascular events by about 50% among these patients. The advantages of a multifactorial approach to the reduction of cardiovascular risk are obvious. The challenge remains to ensure that this approach can be widely adopted.

Management of Diabetes in the Older Adult

The degree of benefit controlling blood glucose, lipids, and blood pressure in older adults with diabetes to reduce microvascular and macrovascular complications may depend on the patient’s life expectancy, functional status, and comorbidities (75). The heterogeneity of this population is a key consideration for clinicians developing intervention strategies and establishing clinical targets. The goals of physicians and other providers caring for the elderly diabetic patient should be to optimize glycemic control and reduce associated cardiovascular risk factors in an effort to maximize long-term quality of life. On the other hand, for frail older adults, particularly those with severe comorbidities and disabilities, aggressive management is not likely to provide benefit and may even result in harm as a consequence of frequent hypoglycemia associated with aggressive glycemic control (56).
In the management of diabetes in older adults, it is necessary to assess for the presence of geriatric syndromes, a group of conditions associated with functional decline and disability that are more prevalent in the elderly. These syndromes and the different comorbidities in the elderly make the management of diabetes in this population a challenging task. Common geriatric syndromes in older adults with diabetes include depression, cognitive impairment/dementia, urinary incontinence, falls, and polypharmacy (75). Diabetes is associated with depression in the elderly and mood disorders may lead to worsening of glycemic control and more diabetic complications. Hyperglycemia is associated with a greater risk for cognitive impairment, especially Alzheimer’s disease (AD) and vascular dementia. It is known that the longer the duration of diabetes, the higher the prevalence of dementia and also that those treated with insulin are at higher risk. Urinary incontinence can be exacerbated because of poor glycemic control and/or because of comorbidities like heart failure and prostate disease or by medication-related side effects. All elderly diabetic patients should be screened for falls, since comorbidities, diabetic neuropathy, and medications may increase the risk of falls. Many older adults with diabetes use five or more medications (a common definition of polypharmacy), which may or may not be appropriately prescribed and may interact with other medications or with a disease process.

**Psychosocial Screening**

Basic assessment of psychosocial status should be included as part of the medical management of diabetes. Psychosocial screening should include patient attitudes about illness, expectations for medical care and outcomes, affect/mood, general and diabetes-related quality of life, available resources (financial, social, and emotional), and psychiatric history. It is best to incorporate psychological assessment into routine care rather than wait for identification of a specific problem or deterioration in psychological status. Opportunities for screening of psychosocial status occur at diagnosis, during regularly scheduled management visits, during hospitalizations, at discovery of complications, or at the discretion of the clinician when problems in glucose control or adherence are suspected or identified.

**NEED FOR IMPROVING DIABETES CARE**

Standards of care for diabetes recommended by the American Diabetes Association are revised periodically and published yearly in the journal *Diabetes Care*. The implementation of the standards of care has been suboptimal in most clinical settings. A report from the National Health and Nutrition Education Survey (NHANES) 1999–2000 and NHANES III
surveys demonstrated that only 37% of US adults with diabetes achieved an HbA1c of <7%, only 36% had a blood pressure < 130/80 mmHg, and only 48% had a cholesterol < 200 mg/dl (76). Only 7.3% had overall “good control,” i.e., attained target goals for all vascular risk factors. Another study addressing quality of diabetes care in the United States showed that during 1988–1995 there was a gap between recommended diabetes care (HbA1c < 7%, annual dilated eye exam, annual foot exam, evaluation for urine albumin or protein excretion, achieving blood pressure and lipid goals), and the care that patients actually received (77). In that study, only 28.8% of diabetics even had an HbA1c measurement, 63.3% reported a dilated eye exam, and 54.8% had had a foot exam within the previous year. Eighteen percent of these diabetic individuals had an HbA1c > 9.5%.

While many interventions to improve adherence to the recommended standards have been implemented, providing uniformly effective diabetes care remains a challenge. Education of health professionals and patients alike is one key to better success. Improved access to health care and education for all is critical. Multidisciplinary teams are ideal to provide care for people with chronic conditions like diabetes and to encourage patients to be involved in appropriate disease self-management. Cooperative efforts between health care providers, health policy experts, public health officials and patients are needed to change the climate and outcomes for individuals with diabetes and at risk for diabetes in the United States (Table 6).

**Table 6**

<table>
<thead>
<tr>
<th><strong>Summary of recommendations for adults with diabetes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycemic control</strong></td>
</tr>
<tr>
<td>HbA1c</td>
</tr>
<tr>
<td>Preprandial capillary plasma glucose</td>
</tr>
<tr>
<td>Peak postprandial capillary plasma glucose†</td>
</tr>
<tr>
<td>Blood pressure</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
</tr>
<tr>
<td>LDL</td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
<tr>
<td>HDL</td>
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</tbody>
</table>

*HbA1c goal for selected individual patients (those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease) may be lower than the general goal if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Conversely, less stringent HbA1c goal may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advance microvascular or macrovascular complications, extensive comorbid conditions, or frail elderly patients.

HbA1c, hemoglobin A1c; LDL, low density lipoprotein; HDL, high density lipoprotein (Adapted from: American Diabetes Association) (1).
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