Diabetes Mellitus and Metabolic Syndrome

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■ OVERVIEW OF DIABETES

The global epidemic of diabetes will challenge our generation to develop novel strategies to prevent and treat this life long condition. Every 10 seconds, two people develop diabetes and one person dies from diabetes-related causes. In 2007, 246 million people worldwide had diabetes. That number is expected to climb to 380 million by 2030.[1] In most developed countries, diabetes is the fourth or fifth leading cause of death and there is concern that it will become an epidemic in many developing and newly industrialized nations. City dwellers are at especially high risk since they tend to be less physically active and are more likely to be obese as compared to their rural counterparts.[2] Heart disease is the leading cause of death for all people with diabetes.[1] Heart disease, coupled with the other long-term complications including kidney, eye, and nerve disease, results in disability, reduced life expectancy, and enormous hearth burdens for virtually every society.[2] In 2007, the United Nations General Assembly recognized that diabetes "poses a severe risk for the families, Member States and the entire world" and passed a resolution declaring November 14 World Diabetes Day.[3]

In spite of this emerging epidemic, there is abundant evidence that diabetes can be prevented and its complications avoided. The challenge faced by health care providers is to increase awareness regarding diabetes risk factors, promote early identification, and provide treatment aimed at preventing complications and improving quality of life. The purpose of this chapter is to discuss (1) the natural history and pathophysiology of types 1 and 2 diabetes, (2) the relationship between insulin resistance and cardiovascular disease (CVD), (3) prevention of type 2 diabetes, (4) metabolic syndrome and cardiovascular complications, and (5) the goals of care and interventions aimed at complication prevention and mitigation.

Definition and Diagnosis

Diabetes can be caused by a variety of hormonal and cellular defects, which result in elevated blood glucose levels. A normal fasting glucose level is less than 110 mg/dL (6.1 mmol) according to the World Health Organization (WHO)[4] and the European Association for the Study of Diabetes (EASD).[5] According to the American Diabetes Association (ADA), normal fasting blood glucose is less than 100 mg/dL (5.7 mmol).[6] This level of fasting glucose is maintained in the body by an intricate balance of hormones, which work to maintain glucose levels at a steady state. Normally, insulin and other hormones are released in response to rising blood glucose levels. These powerful hormones activate cellular storage of glucose, amino acids, and triglycerides in target cells, including the liver, muscle, and fat, with the end result of normoglycemia. To keep glucose levels from falling too low, other hormones, such as glucagon, corticosteroids, growth hormone,

and epinephrine, increase insulin resistance to maintain adequate circulating glucose. In the presence of diabetes, there is a diminished or absent insulin response and cellular resistance to insulin. These defects, coupled with a deficiency of other glucose lowering hormones, result in higher fasting and postmeal glucose levels.

To diagnose diabetes, either fasting plasma glucose, random glucose, or a post 75 g glucose challenge glucose level can be used. Currently, there is international consensus that a fasting blood glucose level of ≥126 mg/dL (7 mmol), or a random or post meal glucose tolerance level of ≥200 mg/dL (11.1 mmol) in the presence of symptoms of hyperglycemia confers a diagnosis of diabetes (Table 39-1).[5] Blood glucose levels that are higher than normal but do not reach the criteria for diabetes indicate future risk of diabetes and heart disease. This category of blood glucose is referred to as prediabetes and includes impaired fasting glucose and impaired glucose tolerance. Impaired fasting glucose is defined as fasting blood glucose of 100 to 125 mg/dL (5.6 to 6.9 mmol/L) by the ADA[6] and 110 to 125 mg/dL (6.0 to 6.9 mmol/L) by the EASD.[5] There is international consensus that impaired glucose tolerance is defined as blood glucose of 140 to 199 mg/dL (7.8 to 11.1 mmol/L) 2 hours after a 75 g glucose challenge. Uncontrolled, chronically elevated glucose, often termed "glucose toxicity," can lead to a multiplicity of vascular complications that start long before the diagnosis of diabetes is made. Identifying and treating hyperglycemia in its earliest stages is critical to prevent complications. Unfortunately, as many as 50% of people with diabetes worldwide remain undiagnosed and untreated.[1]

Prevalence and Consequence of Diabetes

The global prevalence of diabetes will double in the next 30 years due to population growth, urbanization, increasing prevalence of obesity, aging, and physical inactivity.[7] Table 39-2 illustrates the 10 countries with the highest prevalence estimates for diabetes in 2000 and 2030. The countries with the highest rates of diabetes include India, China, and the United States. In India, the crude prevalence rate is 9% in urban areas[8] and in the United States, 7% of the population is affected by diabetes.[9] In developing countries, the highest prevalence of diabetes is the middle productive years of 45 to 64 years of age range. In contrast, the majority of people with diabetes in developed countries are greater than 64 years of age.[7]

In the United States and globally, 90% to 95% of people with diabetes have type 2 and the majority of those are overweight.[9] Over 50% of the U.S. population is overweight and more than one billion people in the world are overweight, of which at least 300 million are obese.[2] The United States and other developing countries are experiencing an epidemic of type 2 diabetes in youth. This increase in type 2 diabetes in youth strongly correlates with increasing prevalence of childhood obesity.[10]

Table 39-1 ■ DIAGNOSTIC CRITERIA FOR DIABETES

1. FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
   or
2. Symptoms of hyperglycemia and casual plasma glucose ≥200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.
   or
3. 2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. 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.*

*In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day (5).
OGTT, oral glucose tolerance test.
From American Diabetes Association. (2008). Clinical practice recommendations: Diagnosis and classification of diabetes mellitus. *Diabetes Care, 31*(Suppl. 1), S12–S54.

From an ethnic perspective, type 2 diabetes is more common in the United States among Native American, Hispanic/Latino, non-Hispanic Black, African-American, and Pacific Islander populations.[11] Internationally, however, diabetes affects many diverse ethnic groups.[7] From a global and a local perspective, the human and economic costs of this epidemic are enormous. In the United States, one out of every 10 health care dollars is spent on treating diabetes and its complications. The total annual economic cost of diabetes in 2007 was estimated to be $174 billion. This includes direct costs of treating diabetes-related complications and indirect costs of lost workdays and disability.[12] The global burgeoning increase of diabetes will inevitably increase the rate of premature deaths from CVD as well as increase the prevalence of other diabetes complications.[7] Worldwide, one in 20 deaths is due to diabetes, which equals 3.2 million deaths annually. Globally, heart disease and stroke account for about 50%

Table 39-2 ■ LIST OF COUNTRIES WITH THE HIGHEST NUMBERS OF ESTIMATED CASES OF DIABETES FOR 2000 AND 2030

	2000		**2030**	
Ranking	Country	People with Diabetes (millions)	Country	People with Diabetes (millions)
1	India	31.7	India	79.4
2	China	20.8	China	42.3
3	United States	17.7	United States	30.3
4	Indonesia	8.4	Indonesia	21.3
5	Japan	6.8	Pakistan	13.9
6	Pakistan	5.2	Brazil	11.3
7	Russian Federation	4.6	Bangladesh	11.1
			Japan	8.9
8	Brazil	4.6	Philippines	7.8
9	Italy	4.3	Egypt	6.7
10	Bangladesh	3.2		

From Wild, S., Roglic, G., Green, A., et al. (2004). Global prevalence of diabetes estimates for the year 2000 and projections for 2030. *Diabetes Care, 27*, 1047–1053.

to 80% percent of deaths in people with diabetes and this chronic condition is the leading cause of blindness, amputation, and kidney failure.[2] The pace of growth and the complications of diabetes demand a concerted, global effort to focus on prevention and appropriate treatment of this epidemic. Multiple large-scale trials have proven that changes in diet, physical activity, or pharmacologic treatment can reduce the incidence of diabetes. Other trials document that complications of diabetes can be delayed or prevented through glucose control and risk factor management. The impressive results of these trials (which will be discussed later in this chapter) provide the impetus to focus on global prevention and aggressive treatment of this serious condition.

■ PATHOPHYSIOLOGY OF DIABETES MELLITUS

Hormonal Regulation of Glucose Levels

The hallmark of diabetes is elevated blood glucose levels. This abnormal elevation is due to the decrease or absence of hormones that lower blood glucose and a cellular resistance to insulin. A review of normal fuel metabolism and the hormones responsible for glucose regulation follows.

Plasma glucose levels reflect the rate at which glucose is absorbed from the intestines and then removed from circulation to be stored as fuel. The first phase of fuel metabolism is called the fed state and encompasses the first 4 hours after ingestion of food. During this phase, the pancreas responds to increasing levels of circulating glucose by activating stored insulin called "proinsulin." Proinsulin is a protein composed of two chains "A" and "B" of amino acids, which are held together by a bridge called a connecting peptide (c-peptide). On pancreatic detection of elevating glucose, the connecting peptide of proinsulin cleaves off. The resulting activated insulin and c-peptide enter the bloodstream. This initial burst of insulin is referred to as first phase insulin response. First phase insulin is responsible for maintaining postmeal glucose within normal limits. Insulin then passes through the portal vein into the bloodstream. Once insulin enters the bloodstream, it has a half-life of a few minutes. However, since c-peptide has a longer half-life, it is can be measured by a blood test to determine how much endogenous insulin a person releases.

During these first 4 hours of the fed state, insulin promotes the storage of glucose as glycogen in the insulin-sensitive peripheral tissues, including hepatic and muscle cells. Insulin also promotes storage of amino acids as protein and excess glucose is stored as fat. The end result is a lowering of circulating blood glucose, lipids, and other energy substrates. Besides promoting the disposal of nutrients into cells, insulin has the critical role of suppressing glucagon. Glucagon, a hormone released by the α-cells of the pancreas, stimulates the release of stored glucose (glycogen) from the liver.

During this fed state, the β-cells of the pancreas also release the recently discovered hormone amylin, a 37-amino acid polypeptide.[13] Amylin compliments the action of insulin by preventing postmeal blood glucose excursions in several ways. Unlike insulin, it slows down gastric emptying, promotes a sense of satiety, and decreases the release of glucagon. People with type 1 diabetes make no amylin and those with type 2 make less than normal amounts.

Another group of newly discovered intestinal hormones, the incretins, are also released in response to nutrient ingestion. The incretins include glucose-dependent insulin-releasing peptide (GIP) and glucagon-like peptide-1 (GLP-1). GIP is secreted by the K cells of the upper intestine and GLP-1 is released from the L cells of the intestine.[13] Both are secreted in response to postmeal glucose elevations and stimulate β-cell insulin secretion. In addition to increasing glucose-dependent insulin secretion, incretin hormones inhibit glucagon secretion, slow gastric emptying, and increase feelings of satiety. Incretins help to keep postmeal blood glucose levels within normal ranges. Both GIP and GLP-1 are rapidly degraded by the enzyme dipeptidyl-peptidase-inhibitor-IV. (New therapies that imitate the incretins and inhibit their breakdown will be discussed in the section "Medication for Type 2 Diabetes.") People with type 1 diabetes make normal amounts of the incretins, while those with type 2 secrete less of this powerful glucose-lowering hormone.[13]

Four to 16 hours after eating, the body enters the phase II or the postabsorptive state. This phase most often occurs during sleep and marks the end of anabolism or energy storage and begins the phase of catabolism or energy production. During this phase, since the body is not exposed to food, it must revert to stored energy for fuel. Glucagon levels rise and insulin levels decrease to a steady state, often termed basal insulin release. The main function of insulin during this phase is not to promote energy storage, but to prevent hyperglycemia. The high levels of circulating glucagon increase the breakdown of glycogen stores in the liver (glycogenolysis) to ensure an adequate supply of glucose to the brain and other glucose-dependent tissues. In addition, fat cells (adipocytes) break down triglycerides and release free fatty acids (FFAs) to be used as energy by the liver and skeletal muscles. The brain will only use glucose for fuel due to its inability to use FFAs as fuel. Many individuals with type 2 diabetes experience morning fasting hyperglycemia due to the dominance of glycogen and the relative lack of insulin during this phase.[13]

In addition to glucagon, there are other catabolic hormones that increase the breakdown of stored fuel supplies and increase circulating glucose. They increase insulin resistance and glycogen breakdown, causing a net increase in blood glucose levels. The hormones released from the kidney, corticosteroids and epinephrine, are activated during flight-or-fight response or hypoglycemia. Other hormones including growth hormone and cortisol increase insulin resistance in early morning, causing many people with type 1 diabetes to experience the "dawn" phenomena, or an elevation in morning glucose.[14]

Glucose homeostasis is reliant on a complex interrelationship of hormones that activate anabolic and catabolic processes. When this precise balance is disrupted through the loss or dysfunction of insulin and other hormones, the end result is hyperglycemia.

Type 1 Diabetes Mellitus

Previously labeled "juvenile diabetes" or "insulin-dependent diabetes," type 1 diabetes affects approximately 10% of all people with diabetes.[6] The unique feature of type 1 is its' progressive autoimmunity resulting in complete destruction of the pancreatic β-cells. Although it can occur at any age, most new cases are expressed during childhood and puberty, when insulin-resistant pubertal hormones are at their peak. To express type 1 diabetes, a genetic propensity and an environmental trigger are necessary.[13] Research has not identified any one causative agent that triggers the autoimmune attack against the pancreas, but several agents are suspected.[15] Viral triggers such as enteroviruses, coxsackie virus B, congenital rubella, cytomegalovirus, and mumps are suspected culprits. However, these agents are only theorized to initiate the autoimmunity of type 1 diabetes, and research on causation is ongoing. From a prevention perspective, it appears that children who are breastfed are less likely to develop type 1 diabetes.[13]

When 90% of the pancreas is destroyed, there is no longer enough insulin available to maintain euglycemia and the symptoms of hyperglycemia are expressed. The rate of destruction of the β-cell mass with type 1 diabetes is rapid in youth and more gradual in the older age group.[13] Although the destruction of the β-cells is progressive, the onset of type 1 diabetes is usually abrupt. With only 10% of the pancreas working, there is no longer adequate insulin to maintain euglycemia. Without sufficient insulin to utilize glucose for energy, the body starts breaking down fat stores for fuel. The pace of this fat breakdown and resulting ketone bodies overwhelms the liver and, in a short time, it can no longer clear ketones at a fast enough pace. High levels of circulating ketones result in ketosis and acidosis—also called diabetes ketoacidosis. At this point, the body cells are starved for glucose and the person usually feels ill enough to seek medical help. Depending on the duration and severity of ketosis, the person with a new case of type 1 diabetes appears malnourished due to inability to store fuel, dehydrated due to osmotic diuresis, and may have abdominal pain and nausea from the ketone bodies. In an effort to blow off excess acids, the person may have rapid respirations and a their breath may smell fruity. Treatment includes fluids, insulin, electrolyte replacement, and patient and family education. Clinical presentation is usually enough to make a diagnosis of type 1 diabetes. If unsure, a diagnosis can be confirmed by antibody blood tests. Some tests used to confirm autoimmune β-cell destruction include antibodies to glutamic acid decarboxylase, islet cell autoantibodies, and insulin autoantibodies.[15] Patients with type 1 diabetes will require insulin replacement for the rest of their lives. There is ongoing investigation to evaluate if type 1 diabetes can be prevented or delayed in individuals at high risk of developing type 1 diabetes. To date however, large, randomized clinical trials have failed to demonstrate treatment effect.[16,17] These studies have improved the understanding of the immunopathogenesis and will hopefully lead to future strategies and treatments to prevent type 1 diabetes.

Type 2 Diabetes Mellitus

Unlike type 1 diabetes, type 2 diabetes (formerly referred to as adult onset or non-insulin-dependent diabetes) is not an autoimmune condition. Of all people with diabetes, 90% to 95% have type 2. Most people with type 2 diabetes are overweight and develop hyperglycemia as a result of insulin resistance and insulin deficiency. Besides being overweight, some of the risk factors for developing type 2 diabetes include physical inactivity, first-degree relative with diabetes, women who delivered a baby bigger than 9 lb (4.2 kg), or who had gestational diabetes. Other risk factors include hypertension, impaired glucose tolerance, elevated triglycerides, and other conditions associated with insulin resistance.[11] In addition to these risk factors, the social milieu into which a person is born can also increase or decrease the likelihood of the expression of type 2 diabetes. Social research reveals that people of

lower socioeconomic status are more likely to express diabetes.[18] This may be due to a variety of factors including lack of access to safe places to exercise, limited knowledge of healthy eating, and increased prevalence of obesity. Being overweight and obese, especially central abdominal obesity, across all populations increases in the risk of diabetes. New research has discovered that abdominal adipose tissue acts as an endocrine organ, secreting chemical mediators that increase insulin resistance and inflammation.[19]

β-Cell Defects Associated With Type 2 Diabetes

Type 2 diabetes is a heterogeneous group of disorders that in combination result in hyperglycemia. These disorders include β-cell death, insulin resistance, excessive hepatic glucose release, and other hormonal deficiencies.[15]

The cause of β-cell mass death is not known. Studies suggest that about 40% of β-cell mass is lost in individuals with impaired glucose tolerance and 60% on clinical diagnosis of diabetes.[20] β-Cell loss starts 9 to 12 years before the diabetes is diagnosed.[15] The rate of β-cell death is much higher in people with diabetes, although the rate of new islet cell formation is unaffected.[13] Because of large clinical trials, such as the United Kingdom Prospective Diabetes Study, the natural history of type 2 diabetes is better understood. This study demonstrated that β-cell death in type 2 diabetes is progressive and continues over time.[21] Upon diagnosis of type 2 diabetes, regardless if the patient is lean or overweight, beta cell mass is decreased by half. This in part explains why 30% of people with type 2 diabetes eventually require insulin therapy.[22] In addition to β-cell death, there is diminished pancreatic sensitivity and insulin secretory response. This reduced response is caused by pancreatic overexposure to chronically abnormal high levels of blood glucose (sometimes termed glucose toxicity).[13] As insulin secretion decreases, blood glucose levels rise above normal and thus marks the beginnings of type 2 diabetes. However, more than β-cell death and insulin deficiency is to blame.

Insulin Resistance and Cardiometabolic Syndrome

Insulin Resistance. Insulin resistance refers to the inadequate response of the muscle, liver, and fat cells to insulin. As a result, glucose stays in circulation instead of being converted into energy through cellular metabolism.[5] People who are overweight and obese are more likely to be insulin resistant. Contrary to popular belief, insulin resistance is not due to deficient or malfunctioning insulin cell receptors. Studies show that people with diabetes have normal amount and function of insulin receptors.[13] The exact mechanism of insulin resistance is not understood but may be due to defective postinsulin receptor signal transduction mechanisms.[19]

Early in the process of diabetes, the pancreas oversecretes insulin in an effort to overcome insulin resistance and maintain euglycemia. Many people with insulin resistance have high levels of blood glucose and high levels of insulin circulating in their blood at the same time. As insulin resistance continues and β-cell loss worsens, blood glucose levels exceed normal levels. Morning glucose levels are elevated since there is not enough insulin to prevent nocturnal overproduction of glucose by the liver. Postmeal blood glucose levels are elevated due to several mechanisms. First, due to the defects of diabetes, the uptake of glucose by the muscle after meals is decreased by over 50%. Second, unchecked glucagon stimulates the liver to release glucose, even in a fed state. Finally,

muscle and adipocytes (fat cells) are resistant to insulin, which results in high levels of FFAs. Elevated FFA worsens insulin resistance in the liver and muscle cells, increases the formation of glucose and impairs β-cell secretion. Dysfunctional adipocytes also produce chemical mediators that contribute to atherosclerosis and insulin resistance.[13] This unrestrained hyperglycemia further reduces insulin sensitivity and pancreatic insulin secretion.[15]

In addition to decreasing β-cell function and insulin resistance, other hormone dysfunction contributes to hyperglycemia. With type 2 diabetes, the β-cells are also under producing the glucose-lowering hormone, amylin. This hormone discovered in the 1980s is secreted in a 1:1 ratio with insulin and increases satiety and lowers postmeal glucagon release. People with type 2 diabetes make less than half the normal amount of amylin. The gut hormones GLP-1 and GIP that promote satiety and decrease postmeal glucagon release are also under produced. The enzyme that breaks down these hormones called dipeptidyl-peptidase-inhibitor-IV is overactive and decreases the bioavailability of these critical hormones adding to postmeal hyperglycemia.[23]

Metabolic Syndrome Overview. The term metabolic syndrome (sometimes termed insulin-resistant syndrome or cardiometabolic syndrome) refers to a clustering of risk factors that include abdominal obesity, dyslipidemia, hyperglycemia, and hypertension.[24] This syndrome is a major public health challenge worldwide since it is associated with a five-fold elevated risk of type 2 diabetes and a two- to three-fold risk of CVD.[25]

In 1998, Reaven described a syndrome based on insulin resistance, high circulating insulin levels, hyperglycemia, elevated very-low-density lipoprotein (VLDL), decreased high-density lipoprotein (HDL) cholesterol and high blood pressure.[26] Since then, there has been ongoing interest, research, and debate on definition and utility of the metabolic syndrome. The ADA and EASD have called into question the imprecision of the definition, the lack of certainty of the pathogenesis and its value in predicting CVD. These diabetes organizations stress the importance of evaluating and treating each cardiovascular risk factor; whether the person meets the diagnostic criteria for the metabolic syndrome or not.[27] Ongoing research is needed to determine the predictive benefit of diagnosing someone with metabolic syndrome. In addition, there is no one universal definition for the metabolic syndrome. The most commonly referred to definitions are the World Health Organization (WHO) definition developed in 1999,[28] the National Cholesterol Education Program Adult Treatment Expert Panel III (NCEP III) in 2001[29] and most recently the International Diabetes Federation (IDF)[30] consensus panel in 2005 which has developed a worldwide consensus of the definition of the metabolic syndrome. In 2003, the American College of Endocrinology (ACE) published a position statement in collaboration with American Association of Clinical Endocrinologists (AACE) on "insulin resistance syndrome"[31] (their preferred term) which avoids using a set of criteria to define metabolic syndrome, but instead focuses on the cluster of abnormalities that are more likely to occur in individuals who are insulin resistant/hyperinsulinemic and stress that diagnosis should be based on clinical judgment informed by the evaluation of risk factors. In their position paper, they specifically strive to distinguish insulin-resistant syndrome from type 2 diabetes and CVD, since their stated clinical focus is to identify individuals at risk BEFORE such consequences occurred. In addition to these philosophical differences, they also use body mass index (BMI) rather than waist

circumference to measure central obesity and introduce ethnicity as a risk factor.

Metabolic Syndrome Definitions. The WHO definition of metabolic syndrome requires the presence of insulin resistance as identified by either type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance plus at least two of the following:

- BMI >30 kg/m^2 and/or waist to hip ratio >0.90 in men or >0.85 in women.
- Serum triglycerides ≥50 mg/dL (1.7 mmol/L) or HDL cholesterol <35 mg/dL (0.9 mmol/L) in men and <39 mg/dL (1.0 mmol/L) in women.
- Raised arterial blood pressure ≥140/90 mm Hg.
- Urinary albumin excretion rate >20 μg/min or albumin to creatine ratio ≥30 mg/g.

According to the NCEP III, hyperglycemia is not the critical factor to enter the risk stratification for metabolic syndrome; instead, adults who are diagnosed with metabolic syndrome must have *three* or more of the following:

- Waist circumference >40 in (102 cm) in men and >35 in (88 cm) in women.
- Serum triglycerides ≥150 mg/dL (1.7 mmol/L).
- Blood pressure ≥130/≥85 mm Hg.
- HDL cholesterol <40 mg/dL (103 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women.
- Fasting glucose ≥110 mg/dL (6.1 mmol/L).

Here, there is a shift from waist to hip ratio to waist circumference and elevated glucose levels may be included but are not critical for diagnosis of diabetes. In this stratification, the risk factors carry a similar weight.

The IDF organized a consensus panel to create a worldwide definition of metabolic syndrome. The results of the consensus group were presented in 2005 in Berlin at the First International Conference on prediabetes and the metabolic syndrome. This new definition of metabolic syndrome is more user friendly for those in clinical practice. While the underlying cause of the metabolic syndrome is still the subject of intense debate, the IDF consensus statement identifies both abnormal abdominal fat distribution and insulin resistance as critical, interrelated causes. To be defined as having metabolic syndrome, the IDF definition requires the following: central obesity (defined as waist circumference >37 in (94 cm) in European men and >31.5 in (88 cm) for European women with ethnicity specific values for other groups, *plus two of the following four additional factors*:

- Raised triglycerides: >150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality.
- Reduced HDL cholesterol: <40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women or specific treatment for this lipid abnormality.
- Raised blood pressure: systolic BP ≥130 mm Hg or diastolic BP ≥85 or treatment of previously diagnosed hypertension.
- Raised fasting plasma glucose level FPG ≥100 mg/dL (5.6 mmol/L) or previously diagnosed diabetes. If above 100 mg/dL or 5.6 mmol/L, oral glucose tolerance test is strongly recommended but not necessary to define the presence of the syndrome.

With the creation of an international definition, it is now possible to estimate the prevalence of metabolic syndrome and make comparisons between nations. According to the IDF, up to 25% of the world's adults have metabolic syndrome.[1]

Although debate exists about which definition of the metabolic syndrome is the best, in clinical practice it is important to assess for insulin resistance, risk factors for heart disease, and diabetes in all patients. The position of ACE highlights a main feature of insulin resistance; it is not only associated with heart disease and diabetes, but with a multitude of other conditions that interlink with increased risk of hyperglycemia and vascular disease. According to ACE, risk factors that increase the likelihood of the insulin resistance syndrome include the following:

- Diagnosis of CVD, hypertension, polycystic ovary syndrome, nonalcoholic fatty liver disease, or acanthosis nigricans
- Family history of type 2 diabetes or glucose intolerance
- Non-Caucasian ethnicity
- Sedentary lifestyle
- BMI >25.0 kg/m^2 (or waist circumference >40 in (102 cm) in men and >35 in (88 cm) in women)

Some authors have argued that since there is no unifying cause of the syndrome and that the CVD or diabetes risk prediction is no greater than the sum of its parts and treatment of the syndrome is no different from treatment of its components, that we put aside the metabolic syndrome as a unique disease. Instead, until the relationship and etiology of the clustering of these risk factors is better understood, the focus should be on assessing for the well-known diabetes and heart disease risk factors and treating according to guidelines with a special emphasis on regular exercise and weight management.[27] This alternative perspective being promoted by the ADA is called the cardiometabolic risk initiative. The risk factor map (Fig. 39-1) describes a pathway from obesity to insulin resistance to type 2 diabetes and/or CVD. It is designed to highlight the individual risk factors and their interrelationships. The ADA is also promoting the use of a well-validated global risk assessment tool called Diabetes Personal Health Decisions (Diabetes PHD)[32] that is a user friendly online algorithm that can provide a personalized risk assessment based on user health data (including height, weight, lipid level, family history, blood pressure, etc.). In addition to providing a risk assessment, it also provides strategies to decrease risk through lifestyle and pharmacologic interventions. Improvements and patient outcomes should certainly improve as the understanding of the complex interrelationships between insulin resistance, obesity, heart disease, and hyperglycemia expand.

Prevention of Type 2 Diabetes

Since even mildly elevated blood glucose levels indicate greater risk for heart disease and the development of diabetes, it is critical to identify people at risk for developing type 2 diabetes and provide risk reduction interventions. People at risk for type 2 diabetes are easily identified through standardized risk assessments, blood glucose measurements, or by ascertainment of family history, lifestyle, and BMI or waistline measurements.[5] The risk of developing diabetes is a complex interaction of genetics and lifestyle. A person at risk of diabetes who is not overweight and exercises regularly has less chance of developing diabetes during their lifetime than their counterpart who leads a sedentary lifestyle and is overweight. Certainly, if a particular family has several members with type 2 diabetes, this may be due to not only genetic susceptibility but also shared environment and similar lifestyles, demonstrating that a combination of genetics and behavioral influences work to increase or decrease risk of disease expression.[13]
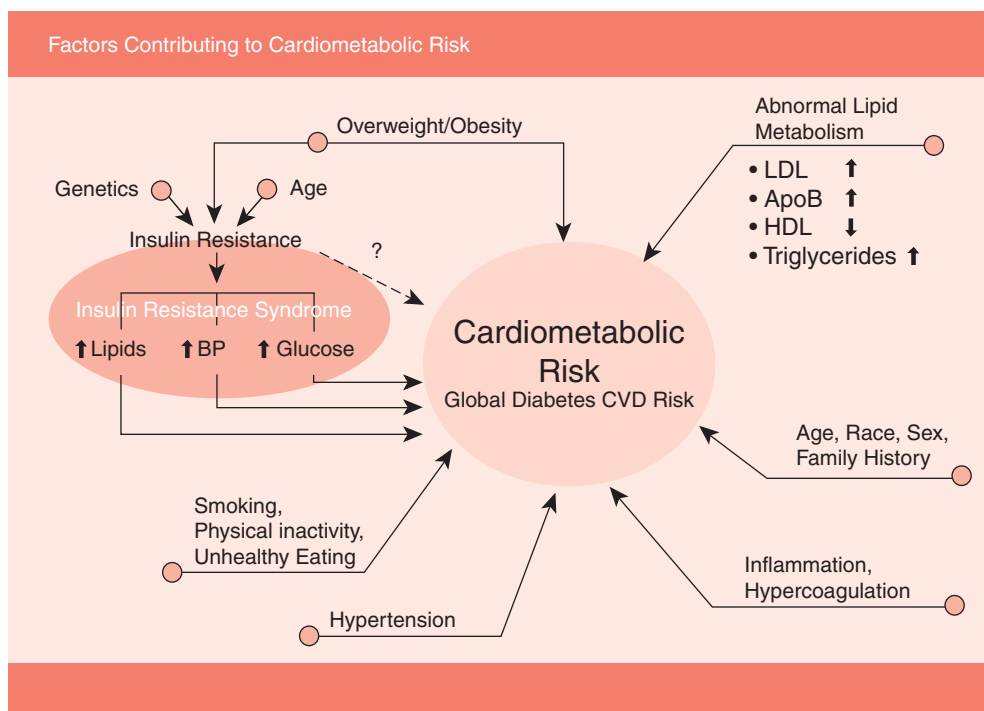
■ **Figure 39-1** The cardiometabolic risk initiative.

The expression of type 2 diabetes is a reflection of many years of metabolic dysregulation, including impaired glucose tolerance, lipid abnormalities, and insulin resistance. For people with impaired glucose tolerance on the metabolic pathway to diabetes, carefully conducted clinical studies have demonstrated that these individuals can prevent the expression of type 2 diabetes by more than 50% through lifestyle changes alone. Other studies have demonstrated risk reduction through pharmacologic interventions. An understanding of the interventions and outcomes of these trials can provide health care professionals with strategies and tools to help instruct and motivate their clients with impaired glucose tolerance to take action to prevent the onset of diabetes.

Four major studies have examined the effects of lifestyle changes for people at risk with diabetes. These studies demonstrated a 31% to 63% risk reduction and include the Malmo Study in Finland,[33] the Da Qing Study from China,[34] the Finnish Diabetes Prevention Study,[35] and the U.S. based Diabetes Prevention Program.[16] Although the design for each study is slightly different, each program identified people with impaired glucose tolerance and assigned participants to either a control or a intervention group. In the Finnish study which included 522 participants, the intervention groups received detailed counseling by a nutritionist with the goal of reducing weight by at least 5%. This was achieved by reducing total fat intake to <30% of calories and saturated fat to <10% of calories, increasing fiber intake to at least 15 g per 1000 calories and participating in at least 30 minutes a day of physical activity. Participants received seven individual sessions with the nutritionist during the first year and one session every 3 months thereafter. They also received individually tailored guidance on increasing physical activity. In this 3-year study, the incidence of progressing to diabetes was 11% in the lifestyle intervention group and 23% in the control group. This equaled a 58% reduction in risk of developing diabetes

in the intervention group. The reduction in the incidence of diabetes was directly associated with the degree of change in lifestyle.

The goal of the U.S. Diabetes Prevention Program was to determine the safest and most effective approach to preventing progression to type 2 diabetes among an ethnically diverse group of individuals with impaired glucose tolerance. In addition to lifestyle intervention, this 3-year trial with over 3,000 participants also included a pharmacologic intervention (metformin) compared to placebo. The lifestyle goals were similar to the Finnish study, to lose at least 7% of body weight by decreasing daily caloric intake by 500 to 1000 calories with less than 25% of calories from fat and participating in 150 minutes of physical activity a week. Participants met with a lifestyle coach 16 times in the first 24 weeks to review a 16-lesson curriculum which included detailed instruction on diet, physical activity, and behavioral modification strategies. Every month participants also met in person or by phone with the lifestyle coach to address specific barriers to adherence and if desired they could attend group classes. The results confirmed the Finnish findings. Among the lifestyle intervention group, there was a 58% reduction in developing diabetes over a 3-year period.

The metformin arm of the Diabetes Prevention Program compared the results of 850 mg of metformin twice daily versus a placebo. Metformin was nearly ineffective in individuals over 60 years old or those with BMI less than 30. However, a 31% overall risk reductions in developing diabetes was observed in the Metformin group.

In addition to decreasing the risk of developing diabetes, most of the studies also documented improvements in other clinical outcomes such as blood pressure, lipids, and participants required dose reductions in blood pressure and lipid medications.

For overweight patients with a family history of type 2 diabetes or CVD, assessment of risk and measurement of fasting glucose

levels, lipids, and blood pressure can be helpful in guiding treatment. Lifestyle interventions, including at least a 5% weight loss and engaging in 150 minutes of physical activity a week, can stop the progression to diabetes.

Pharmacologic interventions to prevent diabetes have also had some success as evidenced by the Metformin arm of the Diabetes Prevention Program. In addition to the DPP, in the double-blind Study to Prevent Non-Insulin Dependent Diabetes Mellitus[36] trial, participants with impaired glucose tolerance were randomized to receive either acarbose (a medication that decreases postmeal glucose by delaying the absorption of carbohydrates) or placebo. Over a 3.3-year period, there was a 36% relative risk reduction in progression to diabetes. In addition, treatment participants experienced a 53% relative risk reduction in cardiovascular events. The results from this trial highlight the importance of managing postprandial glucose levels. Other trials demonstrated a decrease in the progression to diabetes with the use of thiazolidinediones (TZDs). These studies include the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medications[37] and the Troglitazone in Prevention of Diabetes Study.[38]

Given the predicted global epidemic of diabetes, health care professionals are encouraged to identify high-risk patients and promote lifestyle changes to improve health outcomes.

■ MACROVASCULAR COMPLICATIONS OF DIABETES

The NCEP III has termed diabetes a coronary heart disease risk equivalent.[40] CVD is the major cause of mortality and morbidity for individuals with diabetes and is the largest contributor to the direct and indirect costs of diabetes.[11] Given the prevalence and severity, an understanding of the pathophysiology and manifestations of CVD will be presented. Risk reduction and treatment will be addressed in "Goals of the Diabetes Care" section.

Pathophysiology of Macrovascular Disease in Diabetes

Hyperglycemia is associated with defects in the vascular endothelium, the lining of the blood vessels, and chemical mediators that increase vascular dysfunction. Current research has shown that the vascular endothelium is an active endocrine organ that secretes a number of factors, which provide an environment that inhibits the adhesion of leukocytes, platelets, prevents clot formation, and inhibits vasopasm.[13] A bioactive substance of particular importance is nitric oxide (NO). NO causes vasodilatation and platelet inhibition, reduces vascular wall inflammation, prevents vasoconstriction and thrombus formation.[5] However, in the presence of cardiovascular risk factors and hyperglycemia, levels of NO are diminished and there is decreased vasodilatation in response to NO. This defect contributes to the high prevalence of hypertension associated with hyperglycemia.

Diabetes also increases the inflammatory response often seen in damaged vessels due to oxidative stress, diminished NO production, and high postmeal circulating levels of FFAs. Inflammatory mediators enhance the creation of foam cells, decrease plaque stability, and increase risk of plaque rupture triggering acute thrombotic events. Cardiovascular risk is closely linked to the platelet dysfunction and coagulation disorders commonly seen in people with diabetes. In diabetes, plaque formation is amplified due to the propensity for platelet activation, aggregation, and hypercoagulation. Arterial stiffness and decreased compliance of the arterial wall increases systolic blood pressure and pulse pressure. These elevated pressures increase shear stress on the endothelium. In type 2 diabetes, elevated systolic pressure is associated with vascular events and left ventricular hypertrophy. In summary, hypertension, endothelial dysfunction, inflammation, increased thrombosis production, and arterial stiffness are all contributors to the high risk of cardiovascular complications associated with diabetes.[13]

Manifestations of Macrovascular Disease in Diabetes

Coronary artery disease occurs in 9.1% of people with diabetes versus 2.1% in the general population[40] and accounts for 56% to 60% of all deaths.[13] There is still debate whether coronary artery bypass grafting, aggressive risk factor management or percutaneous transluminal coronary angioplasty is the superior treatment for patients with diabetes. When completed, the Bypass Angioplasty Revascularization Study[41] should provide some answers and help direct care for post-MI patients with diabetes.

Cerebrovascular accidents are more likely to occur in people with diabetes at a younger age and when there is a history of myocardial infarction. Stroke occurs in 6.6% of the diabetes population and 1.8% in persons without diabetes.[40] Management includes vascular surgery or management of risk factors, with a special focus on managing hypertension, smoking cessation, and initiation of antiplatelet therapy.[13]

Diabetes increases the risk of the development of congestive heart failure (CHF), especially in women;[13] 7.9% of people with diabetes have CHF, versus 1.1% in the general population. [40] Possible mechanisms for this increased risk include decreased ventricular elasticity due to cross-linking of collagen, inflammatory cytokines, and oxidative stress. Other risk factors include hypertension, hyperglycemia, and endothelial inflammation. The end result is diminished relaxation of the ventricle and impaired diastolic filling, both of which increase the risk of developing CHF.[13]

Peripheral arterial disease (PAD) affects approximately 20% to 30% of people with diabetes and is frequently under diagnosed and under treated.[42] Assessment of PAD includes determining if the patient suffers from intermittent claudication and measuring ankle brachial index. Main risk factors for development of PAD include tobacco use and diabetes. Since people with diabetes and PAD are at increased risk for lower extremity complications including amputations and cardiovascular events, it is important to help patients identify and reduce vascular risk factors.

■ NURSING MANAGEMENT OF DIABETES

Nurses are positioned to play a pivotal role in curbing the diabetes epidemic. Nurses can initiate diabetes detection initiatives, such as evaluation of all glucose levels in the hospital or outpatient settings to find those who are undiagnosed. In the clinical setting, they can review patient's history, symptoms, and lab values to determine if they are at risk for prediabetes, undiagnosed diabetes, or heart disease. Important nursing roles include explaining the

importance of treating hyperglycemia and encouraging at risk patients to seek follow-up care from their provider. Providing patients with a written record of abnormal glucose levels and encouraging follow-up testing is critical.

Since diabetes occurs throughout the lifespan, it is important to tailor education to meet the needs of patients and families. Nursing care includes providing the patient and family with skills to cope with both the medical and psychosocial issues that often coexist with a new diagnosis of diabetes. Younger clients with newly diagnosed type 1 diabetes benefit from management by a diabetes specialist or endocrinologist.[15] The patient and family members also benefit from the expertise of a mental health professional to deal with the emotional impact of a new diagnosis of diabetes.[43]

Since the majority of people with diabetes are over 65 years of age, age is an important factor in patient assessment.[42] Given the high rate of comorbidities for older people with diabetes, they often require a long list of medications to manage not only diabetes, but hypertension, hyperlipidemia, and other conditions. Many older clients on fixed incomes cannot afford all of their prescribed medications. Nurses can encourage patients to collaborate with their pharmacist and provider to determine the safest and most economical strategy to manage their medications. Older clients are also at risk for depression, feelings of isolation, physical limitations, and lack of transportation and other barriers to self care.[13] Identification of these barriers and provision of resources and support can improve adherence and quality of life for these patients.

For patients with new or longstanding diabetes, nurses play an important role in informing the patient of the goals of care for diabetes specifically focusing on A_{1c}, blood pressure and cholesterol, the "ABCs of diabetes care."[44] (This will be discussed in the next section.) Nurses can reinforce with patients that meeting these goals of care will improve every day quality of life and reduce the risk of long-term complications, especially heart disease. Focusing on the positive outcomes helps motivate patients to action. In addition, nurses can assist patients to identify one or two achievable and measurable goals. This helps patients focus on concrete activities that will directly improve their health and ultimately increase their feelings of self-efficacy and independence. Diabetes is largely a self-managed condition that requires an informed and motivated patient supported by the expertise and encouragement of nurses and an interdisciplinary team.

Goals of Diabetes Care

Glycemic Control

Getting glucose levels as close to normal as possible reduces the risk of diabetes complications. In diabetes, two measurements reflect glucose control, the A_{1c} and daily blood glucose testing. A landmark study in 1993, the Diabetes Control and Complications Trial demonstrated that intensive insulin management and maintaining an A_{1c} of less than 7% reduced the development of microvascular (retinopathy, nephropathy, and neuropathy) complications in people with type 1 diabetes by up to 75%.[45] The A_{1c} test provides a 3-month overview of overall glucose control and is a reliable predictor of diabetes-related complications (Table 39-3). In type 2 diabetes, the Kumamoto study[46] and the United Kingdom Prospective Diabetes Study[47] also demonstrated significant reductions in complications with intensive diabetes management. Each of these large clinical trials demonstrated that treatment reg-

Table 39-3 ■ ESTIMATED AVERAGE GLUCOSE

A1c(%)	mg/dl*	mmol/l†
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% Cls.
*Linear regression eAG (mg/dl) = 28.7 × A1C–46.7.
†Linear regression eAG (mmol/l) = 1.59 × A1c − 2.59.
From D.M. Nathan, J Kuenen, R Borg, H Zheng, D Schoenfeld, R J. Heine for the A1c-Derived Average Glucose (ADAG) Study Group (2008). Translating the A1C Assay Into Estimated Average Glucose Values. *Diabetes Care August 2008 vol. 31 no. 8 1473–1478.*

imens that lower A_{1c} to 7% (about 1% above the upper limits of normal) reduce microvascular complications. Further analysis suggests that lowering the A_{1c} from 7% to 6% is associated with further risk reduction.[11] Since intense glucose control also increases the risk of hypoglycemia, the benefit of a lower A_{1c} level must be weighed against the risk. As such, glucose and A_{1c} goals are individualized based on the patient's self-care ability and risk profile. To evaluate achievement of glucose levels, A_{1c} is measured every 3 to 6 months (more often if above goal and less often if within goal range).[11] The ADA A_{1c} goal is less than 7% for everyone, but a more stringent glycemic goal (normal A_{1c}) may be appropriate for certain individuals.[11] The IDF and the AACE set the A_{1c} goal at 6.5%.[15,48] As with the ADA, the A_{1c} goal is individualized based on hypoglycemic risk and the patient's self-care ability.

In addition to this long-range view of glycemia, people with diabetes are also encouraged to check blood glucose levels in the home setting. Home testing provides a snapshot of glucose level at any given moment. This information provides immediate feedback on the effectiveness of the treatment plan, including the interaction of medications, food choices and quantity, and exercise. The frequency of checking is based on the type of diabetes, individual ability, and the negotiated goals. For patients with type 1 diabetes, ADA and AACE recommend testing at least three times a day. For patients with type 2 diabetes, the frequency of testing is based on the stability of glucose levels, patient ability and willingness, and therapeutic goals. To get a complete picture, it is important to evaluate premeal blood glucose levels and 1 to 2 hour postmeal levels. The goals for premeal blood glucose levels are 70 to 130 mg/dL (ADA) and less than 110 mg/dL (AACE and IDF). One to 2 hours after a meal, blood glucose goals are less than 180 mg/dL (ADA), less than 145 mg/dL (IDF), and less than 140 mg/dL (AACE). Patients and providers work together to determine safe and realistic targets and then negotiate strategies to achieve goals.

Blood Pressure Goals and Treatment

People with type 2 diabetes are up to three times as likely to have hypertension and hypertension is often found in those with type 1.[5] Hypertension amplifies the effects of hyperglycemia and increases the risk of diabetes complications. Many randomized trials[49,50] have demonstrated that blood pressure control reduces morbidity

and mortality and is cost-effective. The internationally agreed upon goals are systolic blood pressure ≤130 mm Hg and diastolic blood pressure ≤80 mm Hg.[5,11,15,51] If tolerated, an even lower blood pressure may be attempted.[5] Blood pressure should be measured each office visit and home blood pressure monitoring devices may also be beneficial.[52] Promoting lifestyle changes including weight reduction, reducing sodium and alcohol intake, and regular exercise can help lower blood pressure. However, they are generally insufficient by themselves to achieve blood pressure goals.[51] According to the ADA, if blood pressure goals are not met within 3 months through lifestyle intervention then pharmacologic intervention is warranted. Studies have shown that the use of antihypertensives not only provide renal protection, but can help reduce endothelial inflammation and reduce the risk of CAD.[15,51] Most people with diabetes require combination therapy to lower blood pressure and improve outcomes.[15,51] Effective first line agents include angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin receptor blocker. The IDF also includes β-adrenergic blockers as a first line agent, although the AACE strongly argues against their use due to accumulating literature that questions their benefit. If one class is not tolerated, than the other should be substituted. According to ADA, if blood pressure control is not achieved with one or a combination of these, a diuretic may be added. In addition, the ADA and EASD note that for patients with a prior myocardial infarction, the addition of β-blockers reduces mortality.

Cardiovascular Risk Protection

Since CVD is the major cause of mortality and morbidity in people with diabetes, assessment and aggressive management of CVD risk factors is a core part of care.[5] Risk assessment of CVD should be performed at diagnosis and at least annually thereafter. Areas to assess include history of heart disease, BMI and abdominal adiposity, presence of hypertension, smoking, dyslipidemia, family history of premature heart disease, and presence of microalbuminuria (a marker of heart disease).[53]

People with diabetes typically present with abnormal, atherogenic lipid profiles, including small dense LDLs, elevated triglycerides, and low HDL levels. This profile increases the risk of heart disease and requires aggressive treatment. The goals for lipids are as follows: For LDL, ADA states the level should be less than 100 mg/dL. The EASD and IDF goal is slightly lower at <95 mg/dL (2.5 mmol/L). Both the ADA and EASD agree, that for those with overt CVD an LDL cholesterol goal of <70 mg/dL (1.8 mmol/L) is desirable. This more aggressive goal is in line with the National Cholesterol Education Adult Treatment Program III. The goal for HDL cholesterol is greater than 40 mg/dL (1.0 mmol/L). The ADA and EASD guidelines recommend a slightly higher target for women of 50 g/dL (1.3 mmol/L) and 46 mg/dL (1.2 mmol/L), respectively. Triglyceride targets are less than 200 mg/dL (2.3 mmol) according to the IDF. The EASD and ADA triglyceride goals are more stringent at less than 150 mg/dL (1.7 mmol/L).

Lifestyle treatment to lower the risk of heart disease includes reduction of saturated fat, trans fat, and cholesterol intake, weight loss if indicated, and increased physical activity. Patients who smoke should receive education, support, and pharmacologic intervention if appropriate to quit smoking.[54] In addition to these lipid-lowering measures, pharmacologic therapy to achieve lipid goals is a priority. In the Heart Protection Study,[55] patients over 40 years of age who were treated with a statin reduced their risk of coronary artery events by 25%, independent of baseline LDL levels. Based on the results of this study and others which had similar findings, the IDF guidelines state that statin therapy should be initiated in people over 40 years of age with diabetes or all those with diabetes and heart disease. The EASD state that statin therapy should be considered in adults with type 2 diabetes and heart disease regardless of baseline LDL cholesterol with a treatment target of <70 mg/dL (1.8 mmol). For patients with diabetes without CVD, if total cholesterol is >135 mg/dL (3.5 mmol/L) statin therapy should be considered aiming to reduce LDL by 30% to 40%. The ADA guidelines state that statin therapy should be added to lifestyle therapy regardless of baseline lipid levels for patients with diabetes if they have overt CVD or if they are over 40 years of age and have one or more CVD risk factors. For patients without CVD and under 40 years of age, statin therapy should be added to lifestyle in LDL is >100 mg/dL (2.6 mmol/L). Even though these goals to initiate treatment are slightly different, research has demonstrated that statin therapy is a powerful primary and secondary intervention that effectively lowers LDL and prevents cardiovascular events. Triglycerides and HDL usually improve in response to lower LDL and glucose levels. According to the EASD and IDF if goals are not met, a specific inhibitor of cholesterol absorption, ezetimibe, can be added in addition to lifestyle and statin therapy. All agree that if goals are still not met, a combination of fenofibrates and nicotinic acid (niacin) may be considered.

In addition to lipid lowering, there is international agreement regarding provision of aspirin therapy to as an antiplatelet agent. The EASD also recommends the use of ADP receptor-dependent platelet activation (clopidogrel) in addition to aspirin for patients with acute coronary syndrome and the ADA recommends its addition for those with severe and progressive CVD. The ADA cautions against aspirin therapy for patients under 30 years of age due to lack of evidence of benefit and for patients under 21 years of age due to associated risk of Reye's syndrome.

Aggressive management of glucose and cardiovascular risk factors can improve daily quality of life and long-term complications for people with diabetes. Informing patients of the goals and steps to achieve these goals can dramatically improve outcomes.

Strategies to Achieve Glucose Control

Lifestyle Management

Since many of the risk factors associated with diabetes can be improved by changes in lifestyle, it is important to encourage healthy eating and exercise when working with patients with diabetes. All patients with diabetes should meet with a health care professional trained in the principles of nutrition at the time of diagnosis and on an ongoing basis to assess their current nutritional status and develop an individualized meal plan that works within the context of their life and addresses their particular risk factors.[56] Some basic initial recommendations include limiting foods with high amounts of sugars and fats—especially saturated and trans fats and teaching patient to monitor intake of carbohydrate-containing foods.[57] Eating fresh fruits, vegetables, and whole grains and limiting alcohol should also be encouraged. Weight loss of 5% to 7% of current body weight reduces insulin resistance and other risk factors and can be accomplished gradually through calorie reduction and regular physical activity. In addition to healthy eating, exercise is also a cornerstone of diabetes self care. Besides helping with weight maintenance, exercise also reduces cardiac risk factors and

improves an individual's sense of well-being. Introduce physical activity gradually, based on the person's willingness, ability, and cardiac risk factors. Current recommendations include accumulation of 150 minutes of exercise a week, however goals should be individualized and structured so that they are achievable and realistic.[11,46] Particular attention should be paid to proper footwear and injury prevention for anyone with diabetes nerve disease or a history of feet problems.[58]

People with diabetes who succeed in weight loss and exercise regularly may need to decrease their dose of glucose lowering medications and insulin. Ongoing monitoring of glucose levels and symptoms will provide the feedback needed to make adjustments. While lifestyle changes can lower glucose levels, due to the progressive nature of diabetes, most people will need pharmacologic intervention to keep their diabetes and risk factors at target.[46] The next section provides a review of pharmacologic interventions to help achieve glycemic goals.

Medication for Type 2 Diabetes

Secretagogues. There are two categories of secretagogues or medications that increase insulin release. Sulfonylureas are the oldest class of oral medications used to treat type 2 diabetes. The most commonly used agents in this class include glyburide, glipizide, and glimiperide. The main action of these agents is to stimulate pancreatic insulin secretion. They effectively lower A_{1c} by approximately 1.0% to 2.0%.[15] The main concerns with this class include weight gain and hypoglycemia. In addition, since these drugs are excreted renally, the duration of action may be prolonged in those with kidney failure. All patients taking these medications are at risk for hypoglycemia, so instruction on symptoms and treatment of low blood glucose is imperative, especially for elderly patients or those with renal dysfunction.

Meglitinides. A newer addition to the secretagogue category is the meglitinides, which include repaglinide, and nateglinide. Like sulfonylureas, these agents reduce glucose by stimulating a burst of insulin from the pancreas. Unlike the sulfonylureas, the meglitinides target postmeal blood glucose since they start working in 15 to 30 minutes and last for 1 to 2 hours.[15] They lower A_{1c} by approximately 1.5%.[59] These medications are given three times a day with meals. As with the sulfonyulureas, teaching points include identification and treatment of hypoglycemia and the possibility of weight gain. Patients should also be instructed to skip a dose of their medication if they plan to skip a meal.

Incretin Mimetics. People with type 2 diabetes have lower than normal circulating amounts of the gut hormone or incretin GLP-1 that is normally released by the L cells of the intestine.[23] The medications in this class mimic the action of GLP-1 and lower glucose levels by increasing insulin release in response to food, decreasing postmeal glucagon release, slowing the rate of digestion, and promoting satiety. In addition to lowering A_{1c} by 0.8% to 9%, many patients taking this medication experience a weight loss of 2 to 3 kg over 6 months.[15] The incretin mimetic exenatide is injected twice a day before meals. There is a longer acting version of exenatide LAR in the pipeline that would require only once weekly injections.[60] Only people with type 2 diabetes can benefit from exenatide, since it promotes insulin release from the pancreas. Teaching points include giving injections about 60 minutes before meals and nausea as a potential side effect. There is no risk

of hypoglycemia with exenatide, unless it is used in combination with a secretagogue or insulin.

DPP-4 Inhibitors. These oral agents promote the effectiveness of the incretin hormone GLP-1, since it blocks the dipeptidyl peptidase-4 inhibitor (DPP-4) enzyme which deactivates GLP-1. Like the incretin mimetics, the end result is an increase in glucose-dependent insulin production, prevention of postmeal rise in glucagon, and a slowing of gastric emptying.[23] Currently sitagliptin is the only approved DPP-4 inhibitor in the United States; however, a newer DPP-4 inhibitor, vildagliptin, has been approved for use in the European Union. Although this class only lowers A_{1c} by 0.6% to 0.8%, it has the advantage of no associated weight gain or hypoglycemia.[15] The dose of these agents may need to be reduced in the presence of kidney or liver failure.

Biguanides. The biguanide metformin is recommended as a first line agent upon diagnosis of type 2 diabetes.[59] The primary action of metformin is to decrease hepatic glucose production. It is very effective and lowers A_{1c} by approximately 1.0% to 2.0%. It is usually taken twice daily, however there is a long-acting formulation which is taken once daily. In addition to lowering glucose, metformin also lowers LDL and triglycerides and increases HDL levels. Metformin will not cause weight gain and often contributes to weight loss.[15] To avoid decrease gastrointestinal upset (nausea, anorexia, and diarrhea), instruct patients to take metformin with meals. To prevent the risk of lactic acidosis, metformin should be avoided in patients who are at risk for renal impairment, those with liver failure, excessive alcohol use, and congestive heart failure requiring medication. Metformin should be held during intravenous contrast dye studies and during any acute illness that might cause renal dysfunction or tissue hypoperfusion[61] (AADE).

Thiazolidinediones. This class of agents increases insulin sensitivity in target tissues and decreases insulin resistance. The two TZDs available include rosiglitazone and pioglitazone. In addition to lowering A_{1c} up to 1.5%, (AACE) this class also modestly reduces blood pressure, enhances fibrinolysis, and improves endothelial function. These agents are usually used in combination with another class of glucose lowering medications and can take up to 8 weeks to reach their maximal effect (AADE). Teaching points include advising patients to inform their provider if they experience unusual weight gain or edema when starting these medications. TZDs should not be used in patients with congestive heart failure (New York Heart Association class III or IV cardiac disease and functional capacity). Rosiglitazone and pioglitazone both have black box warnings, highlighting the increased risk of CHF secondary to fluid retention.[62] In addition, due to the findings of a 2007 meta-analysis of rosiglitazone, the Food and Drug Administration issued a warning that rosiglitazone is associated with an increased risk of heart attack and heart failure-related deaths.[63] TZDs should be avoided in patients with hepatic failure. As such, evaluate baseline liver enzymes on initiation of therapy and if patients exhibit any signs of hepatic dysfunction. Women taking TZDs are also at greater risk of peripheral fractures.

Glucosidase Inhibitors. These medications delay carbohydrate absorption and are helpful in decreasing postprandial hyperglycemia. The glucosidase inhibitors include acarbose and miglitol. Patients take this medication with the first bite of food at each meal and experience reductions in A_{1c} levels of about 0.5% to 1.0%.[59] These medications are better tolerated when dosing is

Table 39-4 ■ PHARMACOKINETICS OF AVAILABLE INSULIN PREPARATIONS

Insulin, Generic Name (Brand Name)	Onset	Peak	Effective Duration
Rapid-acting, Bolus			
Insulin aspart injection (NovoLog)			
Insulin lispro injection (Humalog)	5 to 15 min	30 to 90 min	<5 h
Insulin glulisine injection (Apidra)			
Short-acting, Bolus			
Regular	30 to 60 min	2 to 3 h	5 to 8 h
Intermediate, basal			
NPH	2 to 4 h	4 to 10 h	10 to 16 h
Insulin detemir injection (Levemir)*,† (3)	3 to 8 h	No peak	5.7 to 23.2 h
Long-acting, basal			
Insulin glargine injection (Lantus)*,†	2 to 4 h‡	No peak	20 to 24 h

*May require two daily injections in patients with type 1 diabetes mellitus.
†Assumes 0.1 to 0.2 U/kg per injection. Onset and duration may vary significantly greatly by injection site.
‡Time to steady state.
NPH, neutral protamine Hagedorn.
Adapted from American Association of Clinical Endocrinologists. (2007). Medical guidelines for clinical practice for the management of diabetes mellitus. *Endocrine Practice, 13*.

started at a low range with gradual increase since they can cause severe flatulence and abdominal discomfort.

Given its action, people with chronic intestinal diseases, inflammatory bowel disease, or bowel obstruction should not take this class of medication. If a patient is taking a secretagogue and/or insulin and a glucosidase inhibitor, they need to treat hypoglycemia with oral glucose (dextrose) such as glucose tablets to reverse hypoglycemia. Products containing sucrose (table sugar, candy, and sodas) are not effective because this class of agents will delay absorption.

Amylin Analogs. Pramlintide is the synthetic version of the human amylin, a hormone that lowers blood glucose by suppressing glucagon production, slowing gastric emptying, and increasing satiety. It is only available in injectable form and is given before meals to lower postmeal glucose levels. Patients with type 1 or 2 on insulin therapy can utilize this therapy that lowers A_{1c} by about 0.5% to 7% and often result in weight loss.[59] Teaching points include reduction of rapid-acting insulin dose by about 50% while starting amylin therapy to reduce the potential of hypoglycemia, which is most common after 3 hours of injection. This medication frequently causes nausea and should not be used in patients with gastroparesis or hypoglycemia unawareness.[15]

Insulin Replacement Therapy

Many patients regard the need to start insulin therapy as a personal failure to successfully manage their diabetes. Avoiding the threat of insulin therapy if patients do not comply with self-care changes is critical, since this puts a negative light on a very powerful and effective hormone that will always lower blood glucose levels. Since only 50% of U.S. adults with diabetes have A_{1c} levels less than the target of 7%[41] in spite of a wealth of oral medications, there is a movement to initiate insulin therapy earlier in patients with type 2 diabetes.[59]

Understanding the normal cycle of insulin release is helpful to determine strategies to replace insulin in a therapeutic and effective manner.[64] An average person releases about 0.5 to 0.1 units of insulin per kg per day.[13] This insulin release happens in two different and overlapping phases. The first phase bolus insulin is released in response to glucose elevations associated with meals. This bolus of insulin serves to regulate the blood glucose from the ingested meals to prevent postprandial (after meal) hyperglycemia. People with type 1 secrete no insulin in response to meals and people with type 2 secrete less than normal. Replacement of this insulin is accomplished by the use of the short-acting insulin (regular) or the rapid-acting insulins including aspart, lispro, and glulisine (Table 39-4). The dose of this insulin is adjusted depending on the patient's glucose level prior to a meal and the amount of carbohydrate they plan to eat.

Small amounts of basal insulin are released throughout the day to maintain between meal and nighttime blood glucose levels at target range. People with type 1 diabetes secrete no basal insulin and those with type 2 diabetes secrete diminished amounts. In type 2 diabetes, this lack of basal insulin is most often reflected in elevated fasting glucose levels. Insulins that imitate the basal insulin release include the intermediate-acting insulins, NPH, and or long-acting insulins such as glargine or detemir.[65] The dose of insulin is based on the patient's weight, morning glucose levels, and usually compromises about half the total dose.[13]

People with diabetes who are more on insulin therapy are more likely to reach glucose goals with thoughtful insulin management strategies that include a combination of bolus and basal insulins.

■
■ SUMMARY

Diabetes is a global epidemic that will continue to affect the lives of millions of people, their families, and health care systems. The evidence is overwhelming that diabetes can be prevented through lifestyle changes and medications. In addition, aggressive risk factor management, with particular focus on blood glucose, lipid, and blood pressure control can mitigate the complications associated with diabetes. By promoting prevention, early treatment and risk reduction of diabetes, nurses and health care professionals can improve diabetes outcomes in their own backyard and globally. Educating individuals and their families, promoting changes in delivery of care, tracking outcomes and working within communities to promote access to safe places to exercise and healthy foods are all activities that health care professionals can participate in to raise awareness and motivate change. Nurses and health care

providers, through advocacy, education, and one-to-one personal care and connection to people with diabetes and their families, will help to slow the pace of this global epidemic, one person at a time.

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