

Diabetes - Type 2

Highlights

Type 2 Diabetes

Type 2 diabetes is the most common form of diabetes, accounting for 90 - 95% of cases. In type 2 diabetes, the body does not respond properly to insulin, a condition known as insulin resistance. Insulin is a hormone produced by the pancreas that regulates how the body converts sugar (glucose) into energy.

New Recommendations for Blood Sugar (Glucose) Control and Heart Disease Prevention

In December 2008, the American College of Cardiology (ACC), the American Diabetes Association (ADA), and the American Heart Association (AHA) issued revised recommendations for target goals for blood glucose control. Major recent studies of people with longstanding type 2 diabetes and high risk for heart disease have indicated that intensive blood glucose control may not have much benefit and may carry some increased risks. (However, one study did find that intensive glucose control can help prevent heart disease in people who have had diabetes for a short period of time.)

Based on the results of these trials, the ACC, ADA, and AHA recommend:

- Most people with type 2 diabetes should continue to aim for HbA1c levels at or below 7%. (HbA1c is a test that is performed at regular intervals to evaluate a patient's average blood glucose level.) There is strong evidence that achieving this goal can help prevent many diabetes complications, including eye, kidney, and nerve disease.
- Patients with certain factors may need less stringent HbA1c goals. These factors include longstanding diabetes, a history of severe low blood sugar (hypoglycemia), limited life expectancy, advanced vascular complications, and the presence of other diseases.
- All patients with type 2 diabetes should continue to follow proven measures for heart disease prevention. These include blood pressure control, lipid-lowering statin drug therapy, and lifestyle changes such as weight loss, proper nutrition, and increased physical activity.

Introduction

The two major forms of diabetes are type 1 (previously called insulin-dependent diabetes mellitus, IDDM, or juvenile-onset diabetes) and type 2 (previously called noninsulin-dependent diabetes mellitus, NIDDM, or maturity-onset diabetes).

Insulin

Both type 1 and type 2 diabetes share one central feature: elevated blood sugar (*glucose*) levels due to insufficiencies of *insulin*, a hormone produced by the pancreas. Insulin is a key regulator of the body's metabolism. It works in the following way:

- During and immediately after a meal the process of digestion breaks down carbohydrates into sugar molecules (including *glucose*) and proteins into *amino acids*.
- Right after the meal, glucose and amino acids are absorbed directly into the bloodstream, and blood glucose levels rise sharply.
- The rise in blood glucose levels signals important cells in the pancreas, called *beta cells*, to secrete insulin, which pours into the bloodstream. Within 10 minutes after a meal, insulin rises to its peak level.
- Insulin enables glucose to enter cells in the body, particularly muscle and liver cells. Here, insulin and other hormones direct whether glucose will be burned for energy or stored for future use.
- When insulin levels are high, the liver stops producing glucose and stores it in other forms until the body needs it again.
- As blood glucose levels reach their peak, the pancreas reduces the production of insulin.
- About 2 - 4 hours after a meal, both blood glucose and insulin are at low levels, with insulin being slightly higher. The blood glucose levels are then referred to as *fasting blood glucose concentrations*.

The pancreas is located behind the liver and is where the hormone insulin is produced. Insulin is used by the body to store and utilize glucose.

Type 2 Diabetes

Type 2 diabetes is the most common form of diabetes, accounting for 90 - 95% of cases. In type 2 diabetes, the body does not respond properly to insulin, a condition known as insulin resistance. The disease process of type 2 diabetes involves:

- The first stage in type 2 diabetes is *insulin resistance*. Although insulin can attach normally to receptors on liver and muscle cells, certain mechanisms prevent insulin from moving glucose (blood sugar) into these cells where it can be used. Most patients with type 2 diabetes produce variable, even normal or high, amounts of insulin. In the beginning, this amount is usually sufficient to overcome such resistance.
- Over time, the pancreas becomes unable to produce enough insulin to overcome resistance. In type 2 diabetes, the initial effect of this stage is usually an abnormal rise in blood sugar after a meal (called *postprandial hyperglycemia*).
- Eventually, the cycle of elevated glucose further damages beta cells, thereby drastically reducing insulin production and causing full-blown diabetes. This is made evident by *fasting hyperglycemia*, in which elevated glucose levels are present most of the time.

Type 1 Diabetes

In type 1 diabetes, the body does not produce insulin. Onset is usually in childhood or adolescence. Type 1 diabetes is considered an autoimmune disorder that involves:

- Beta cells in the pancreas that produce insulin are gradually destroyed. Eventually insulin deficiency is absolute.
- Without insulin to move glucose into cells, blood glucose levels become excessively high, a condition known as hyperglycemia.

- Because the body cannot utilize the sugar, it spills over into the urine and is lost.
- Weakness, weight loss, frequent urination, and excessive hunger and thirst are among the initial symptoms.
- Patients with type 1 diabetes need to take daily insulin for survival. [For more information, see *In-Depth Report #9: Diabetes - type 1.*]

Gestational Diabetes

About 5% of pregnant women develop a form of type 2 diabetes, usually temporary, in their third trimester called gestational diabetes.

Gestational diabetes is diabetes that first appears during pregnancy. It usually develops during the third trimester of pregnancy. After delivery, blood sugar (glucose) levels generally return to normal, although up to 25% of these women develop type 2 diabetes within 15 years.

Because glucose crosses the placenta, a pregnant women with diabetes can pass high levels of blood glucose to the fetus. This can cause excessive fetal weight gain, which can cause delivery complications as well as increased risk of breathing problems and higher future risk for the child to develop obesity and type 2 diabetes. In addition to endangering the fetus, gestational diabetes can also cause serious health risks for the mother, such as preeclampsia, a condition that involves high blood pressure during pregnancy.

Causes

Type 2 diabetes is caused by insulin resistance, in which the body does not properly use insulin. Generally, diabetes type 2 is thought to result from a combination of genetic factors along with lifestyle factors such as obesity, high alcohol intake, and being sedentary.

Genetic mutations likely affect parts of the insulin gene and various other physiologic components involved in the regulation of blood sugar. Some rare types of diabetes are directly linked to genes.

Diabetes Secondary to Other Conditions. Conditions that damage or destroy the pancreas, such as pancreatitis (inflammation), pancreatic surgery, or certain industrial chemicals can cause diabetes. Polycystic ovaries are highly associated with diabetes. Certain drugs can also cause temporary diabetes, including corticosteroids, beta blockers, and phenytoin. Certain genetic and hormonal disorders are associated with or increase the risk of diabetes.

Risk Factors

More than 23 million American children and adults have diabetes. Up to 95% of these cases are type 2. In addition, 57 million Americans have pre-diabetes, a condition that increases the risk for developing diabetes. Type 2 diabetes used to mainly develop after the age of 40, but it is now increasing in younger people and children. Obesity is likely the major factor behind this dramatic growth rate.

According to the National Institutes of Health, the following are major risk factors for diabetes and pre-diabetes:

- Age 45 or older
- Family history of diabetes
- Overweight
- Inactive lifestyle (exercise less than 3 times a week)
- African-American, Hispanic/Latin American, American Indian and Alaska Native, Asian-American, or Pacific Islander ethnicity
- High blood pressure (140/90 mm Hg or higher)
- HDL (“good”) cholesterol less than 35 mg/dL or triglyceride level 250 mg/dL or higher
- Have had diabetes during pregnancy (gestational diabetes) or have given birth to a baby that weighed more than 9 pounds
- Polycystic ovary syndrome (metabolic disorder that affects female reproductive system)
- Acanthosis nigricans (dark, thickened skin around neck or armpits)
- History of disease of blood vessels to the heart, brain, or legs
- Diabetes test history of impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)

Medical Conditions Associated with Increased Risk of Diabetes

Obesity and Metabolic Syndrome. Obesity is the number one risk factor for type 2 diabetes. Excess body fat appears to play a strong role in insulin resistance, but the way the fat is distributed is also significant. Weight concentrated around the abdomen and in the upper part of the body (apple-shaped) is associated with insulin resistance and diabetes, heart disease, high blood pressure, stroke, and unhealthy cholesterol levels. Waist circumferences greater than 35 inches in women and 40 inches in men have been specifically associated with a greater risk for heart disease and diabetes. (People with a "pear-shape" -- fat that settles around the hips and flank -- appear to have a lower risk for these conditions.) However, obesity does not explain all cases of type 2 diabetes. It is also common among people in countries where weights tend to be low, such as Asia or India.

A set of conditions referred to as metabolic syndrome (also called Syndrome X) is a pre-diabetic condition that is significantly associated with heart disease and higher mortality rates from all causes. The syndrome consists of obesity marked by abdominal fat, unhealthy cholesterol and triglyceride levels, high blood pressure, and insulin resistance.

Polycystic Ovary Syndrome. Polycystic ovary syndrome (PCOS) is a condition that affects about 6% of women and results in the ovarian production of high amounts of androgens (male hormones), particularly testosterone. Women with PCOS are at higher risk for insulin resistance, and about half of PCOS patients also have diabetes.

Depression. Severe clinical depression may modestly increase the risk for type 2 diabetes.

Schizophrenia. While no definitive association has been established, research has suggested an increased background risk of diabetes among people with schizophrenia. In addition, many of the new generation of antipsychotic medications may elevate blood glucose levels. Patients taking

antipsychotic medications (such as clozapine, olanzapine, risperidone, aripiprazole, quetiapine fumarate, ziprasidone) should receive a baseline blood glucose level test and be monitored for any increases during therapy.

Gestational Diabetes Risk Factors

Gestational diabetes is a type of diabetes that develops during the last trimester of pregnancy. A pregnant woman's risk factors include:

- Family history of diabetes
- African-American, Hispanic, Asian, or Pacific Islander ethnicity
- Overweight
- Older than 25 years
- Gestational diabetes with past pregnancy
- Having given birth to a child weighing over 9 pounds
- Diagnosis of pre-diabetes

Symptoms

Type 2 diabetes usually begins gradually and progresses slowly. Symptoms in adults include:

- Excessive thirst
- Increased urination
- Fatigue
- Blurred vision
- Weight loss
- In women, vaginal yeast infections or fungal infections under the breasts or in the groin
- Severe gum problems
- Itching
- Erectile dysfunction in men
- Unusual sensations, such as tingling or burning, in the extremities

Symptoms in children are often different:

- Most children are obese or overweight
- Increased urination is mild or even absent
- Many children develop a skin problem called acanthosis, characterized by velvety, dark colored patches of skin

Complications

Patients with diabetes have higher death rates than people who do not have diabetes regardless of sex, age, or other factors. Heart disease and stroke are the leading causes of death in these patients. All lifestyle and medical efforts should be made to reduce the risk for these conditions.

People with type 2 diabetes are also at risk for nerve damage (neuropathy) and abnormalities in both small and large blood vessels (vascular injuries) that occur as part of the diabetic disease

process. Such abnormalities produce complications over time in many organs and structures in the body. Although these complications tend to be more serious in type 1 diabetes, they still are of concern in type 2 diabetes. Most people with diabetes should aim for fasting blood glucose levels of less than 110 mg/dL and hemoglobin HbA1C of less than 7%.

There are two important approaches to preventing complications from diabetes:

- Intensive control of blood glucose and keeping glycosylated hemoglobin (HbA1c) levels below 7%. Tight blood glucose and HbA1c control can help prevent complications due to vascular (blood vessel) abnormalities and nerve damage (neuropathy) that can cause major damage to organs, including the eyes, kidneys, and possibly the heart.
- Managing risk factors for heart disease. Control of blood glucose also helps the heart, but its benefits occur over time. It is very important that people with diabetes control blood pressure, cholesterol levels, and other factors associated with heart disease.

Heart Disease

There is an association between high blood pressure (hypertension), unhealthy cholesterol levels, and diabetes. Some research suggests that high LDL (“bad” cholesterol) levels, low HDL (“good” cholesterol) levels, and high triglyceride levels may interfere with insulin regulation. Hypertension is more common in patients with diabetes than those without the condition.

People with diabetes are more likely than non-diabetics to have heart problems, and to die from heart complications. Heart attacks account for 60% and strokes for 25% of deaths in patients with diabetes. Diabetes affects the heart in many ways:

- Both type 1 and 2 diabetes speed the progression of atherosclerosis (hardening of the arteries). Diabetes is often associated with low HDL (“good” cholesterol) and high triglycerides. This can lead to coronary artery disease, heart attack, or stroke.
- Impaired nerve function (neuropathy) associated with diabetes also causes heart abnormalities.
- Women with diabetes are at particularly high risk for heart problems and death from heart disease and overall causes.

Kidney Damage (Nephropathy)

Kidney disease (nephropathy) is a very serious complication of diabetes. With this condition, the tiny filters in the kidney (called glomeruli) become damaged and leak protein into the urine. Over time, this can lead to kidney failure. Urine tests showing microalbuminuria (small amounts of protein in the urine) are important markers for kidney damage.

Diabetic nephropathy, the leading cause of end-stage renal disease (ESRD), occurs in about 20 - 40% of patients with diabetes. If the kidneys fail, dialysis is required. Symptoms of kidney failure may include swelling in the feet and ankles, itching, fatigue, and pale skin color.

Nerve Disorders (Neuropathy)

Diabetes reduces or distorts nerve function, causing a condition called neuropathy. Neuropathy refers to a group of disorders that affect nerves. The two main types of neuropathy are:

- *Peripheral* (affects nerves in the toes, feet, legs, hand, and arms)
- *Autonomic* (affects nerves that help regulate digestive, bowel, bladder, heart, and sexual function)

Peripheral neuropathy particularly affects sensation. It is a common complication that affects nearly half of people with type 1 or type 2 diabetes after 25 years. The most serious consequences of neuropathy occur in the legs and feet and pose a risk for ulcers and, in unusually severe cases, amputation. Peripheral neuropathy usually starts in the fingers and toes and moves up to the arms and legs (called a stocking-glove distribution). Symptoms include:

- Tingling
- Weakness
- Burning sensations
- Loss of the sense of warm or cold
- Numbness (if the nerves are severely damaged, the patient may be unaware that a blister or minor wound has become infected)
- Deep pain

Autonomic neuropathy can cause:

- Digestive problems (constipation, diarrhea, nausea, vomiting)
- Bladder infections and incontinence
- Erectile dysfunction
- Heart problems. Neuropathy may mask angina, the warning chest pain for heart disease and heart attack. Patients with diabetes should be aware of other warning signs of a heart attack, including sudden fatigue, sweating, shortness of breath, nausea, and vomiting.
- Rapid heart rates
- Lightheadedness when standing up (orthostatic hypotension)

Blood sugar control is an essential component in the treatment of neuropathy. Studies show that tight control of blood glucose levels delays the onset and slows progression of neuropathy. Heart disease risk factors may increase the likelihood of developing neuropathy. Lowering triglycerides, losing weight, reducing blood pressure, and quitting smoking may help prevent the onset of neuropathy.

Foot Ulcers and Amputations

About 15% of patients with diabetes have serious foot problems. They are the leading cause of hospitalizations for these patients.

Diabetes is responsible for more than half of all lower limb amputations performed in the U.S. Each year there are about 88,000 non-injury amputations, 50 - 75% of them due to diabetes.

About 85% of amputations start with foot ulcers, which develop in about 12% of people with diabetes.

Those most at risk are people with a long history of diabetes, and people with diabetes who are overweight or who smoke. People who have the disease for more than 20 years and are insulin-dependent are at the highest risk. Related conditions that put people at risk include peripheral neuropathy, peripheral artery disease, foot deformities, and a history of ulcers. [For more information, see *In-Depth Report #102: Peripheral artery disease and intermittent claudication.*]

In general, foot ulcers develop from infections, such as those resulting from blood vessel injury. Foot infections often develop from injuries, which can dramatically increase the risk for amputation. Even minor infections can develop into severe complications. Numbness from nerve damage, which is common in diabetes, compounds the danger since the patient may not be aware of injuries. About one-third of foot ulcers occur on the big toe.

Charcot Foot. Charcot foot or Charcot joint (medically referred to as neuropathic arthropathy) occurs in up to 2.5% of people with diabetes. Early changes appear similar to an infection, with the foot becoming swollen, red, and warm. Gradually, the affected foot can become deformed. The bones may crack, splinter, and erode, and the joints may shift, change shape, and become unstable. It typically develops in people who have neuropathy to the extent that they cannot feel sensation in the foot and are not aware of an existing injury. Instead of resting an injured foot or seeking medical help, the patient often continues normal activity, causing further damage.

Charcot foot is initially treated with strict immobilization of the foot and ankle; some centers use a cast that allows the patient to move and still protects the foot. When the acute phase has passed, patients usually need lifelong protection of the foot using a brace initially and custom footwear.

People with diabetes are prone to foot problems because the disease can cause damage to the blood vessels and nerves, which may result in decreased ability to sense trauma to the foot. The immune system is also altered, so that the patient cannot efficiently fight infection.

Retinopathy and Eye Complications

Diabetes accounts for thousands of new cases of blindness annually and is the leading cause of new cases of blindness in adults age 20 - 74. The most common eye disorder in diabetes is retinopathy. People with diabetes are also at higher risk for developing cataracts and certain types of glaucoma, such as primary-open angle glaucoma (POAG). The risk for POAG is especially high for women with type 2 diabetes. [For more information, see *In-Depth Report #26: Cataracts* and *In-Depth Report #25: Glaucoma.*]

Retinopathy. Retinopathy is a condition in which the retina in the eye becomes damaged. The two primary abnormalities that occur are a weakening of the blood vessels in the retina and the obstruction in the capillaries -- probably from very tiny blood clots. Retinopathy generally occurs in one or two phases:

- The early and more common type of this disorder is called *nonproliferative or background retinopathy*. The blood vessels in the retina are abnormally weakened. They

rupture and leak, and waxy areas may form. If these processes affect the central portion of the retina, swelling may occur, causing reduced or blurred vision.

- If the capillaries become blocked and blood flow is cut off, soft, "woolly" areas may develop in the retina's nerve layer. These woolly areas may signal the development of *proliferative retinopathy*. Often there are no symptoms of progressing retinopathy. In this more severe condition, new abnormal blood vessels form and grow on the surface of the retina. They may spread into the cavity of the eye or bleed into the back of the eye. Major hemorrhage or retinal detachment can result, causing severe visual loss or blindness. The sensation of seeing flashing lights may indicate retinal detachment.

Mental Function and Dementia

Some studies indicate that patients with type 2 diabetes face a higher than average risk of developing dementia caused either by Alzheimer's disease or problems in blood vessels in the brain. Problems in attention and memory can occur even in people under age 55 who have had diabetes for a number of years.

Infections

Respiratory Infections. People with diabetes face a higher risk for influenza and its complications, including pneumonia, possibly because the disorder neutralizes the effects of protective proteins on the surface of the lungs. Everyone with diabetes should have annual influenza vaccinations and a vaccination against pneumococcal pneumonia.

Urinary Tract Infections. Women with diabetes face a significantly higher risk for urinary tract infections, which are likely to be more complicated and difficult to treat than in the general population.

Depression

Diabetes doubles the risk for depression. Depression, in turn, may increase the risk for hyperglycemia and complications of diabetes.

Hypoglycemia

Tight blood sugar (glucose) control increases the risk of low blood sugar (hypoglycemia). Hypoglycemia, also called insulin shock, occurs if blood glucose levels fall below normal. It is generally defined as blood sugar level below 70 mg/dL, although this level may not necessarily cause symptoms in all patients. Hypoglycemia may also be caused by insufficient intake of food, or excess exercise or alcohol. Usually the condition is manageable, but occasionally, it can be severe or even life threatening, particularly if the patient fails to recognize the symptoms, especially while continuing to take insulin or other hypoglycemic drugs.

Mild hypoglycemia is common among people with type 2 diabetes, but severe episodes are rare, even among those taking insulin. Still, all patients who intensively control blood sugar (glucose) levels should be aware of warning symptoms.

Risk Factors for Severe Hypoglycemia. Specific risk factors for severe hypoglycemia include:

- Patients attempting tight control of blood glucose and HbA1c levels
- Long-term diabetes
- Patients who do not comply with treatment (including those who are underinsured, have psychiatric disorders, or who are poorly educated about diabetes)
- Infections such as gastroenteritis or respiratory illnesses

Hypoglycemia unawareness. Hypoglycemia unawareness is a condition in which people become insensitive to hypoglycemic symptoms. It affects about 25% of patients who use insulin, nearly always people with type 1 diabetes. In such cases, hypoglycemia appears suddenly, without warning, and can escalate to a severe level. Even a single recent episode of hypoglycemia may make it more difficult to detect the next episode. With vigilant monitoring and by rigorously avoiding low blood glucose levels, patients can often regain the ability to sense the symptoms. However, even very careful testing may fail to detect a problem, particularly one that occurs during sleep.

Hypoglycemia Symptoms. Mild symptoms usually occur at moderately low and easily correctable levels of blood glucose. They include:

- Sweating
- Trembling
- Hunger
- Rapid heartbeat

Severely low blood glucose levels can cause neurologic symptoms such as:

- Confusion
- Weakness
- Disorientation
- Combativeness
- In rare and worst cases, coma, seizure, and death

Diabetic Ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) is a life-threatening complication caused by insulin deficiency. Until recently, it was a complication almost exclusively of type 1 diabetes. In such cases, it is nearly always due to noncompliance with insulin treatments. However, DKA is being reported increasingly in patients with type 2 diabetes. It is not clear what causes total insulin depletion in these patients.

Other Complications

Diabetes increases the risk for other conditions, including:

- Hearing loss
- Periodontal disease

- Carpal tunnel syndrome
- Nonalcoholic fatty liver disease, also called nonalcoholic steatohepatitis (NASH), a particular danger for people who are obese
- Colorectal cancer
- Uterine cancer

Specific Complications in Women

Diabetes can cause specific complications in women. Women with diabetes have an increased risk of recurrent yeast infections. In terms of sexual health, diabetes may cause decreased vaginal lubrication, which can lead to pain or discomfort during intercourse.

Women with diabetes should also be aware that certain types of medication can affect their blood glucose levels. For example, birth control pills can raise blood glucose levels. Long-term use (more than 2 years) of birth control pills may increase the risk of health complications. Thiazolidinediones can prompt renewed ovulation in premenstrual women who are not ovulating, and can weaken the effect of birth control pills.

Diabetes and Pregnancy. Both temporary diabetes that occurs during pregnancy (gestational diabetes) and pregnancy in a patient with existing diabetes can increase the risk for birth defects. Studies indicate that high blood sugar levels (hyperglycemia) can affect the developing fetus during the critical first 6 weeks of organ development. Therefore, it is important that women with pre-existing diabetes (both type 1 and type 2) who are planning on becoming pregnant strive to maintain good glucose control for 3 - 6 months before pregnancy. It is also important for women to closely monitor their blood sugar levels during pregnancy. For women with type 2 diabetes who take insulin, pregnancy can affect their insulin dosing needs. Insulin dosing may also need to be adjusted during and following delivery.

Diabetes and Menopause. The changes in estrogen and other hormonal levels that occur during perimenopause can cause major fluctuations in blood glucose levels. Women with diabetes also face an increased risk of premature menopause, which can lead to higher risk of heart disease.

Diagnosis

Healthy adults age 45 and older should get tested for diabetes every 3 years. Patients who are younger than age 45 and who have certain risk factors should ask their doctors about testing. These risk factors include:

- A weight that is 20% more than ideal body weight
- Sedentary lifestyle
- High blood pressure (greater than 140/90) or unhealthy cholesterol levels -- especially for patients with low HDL ("good") cholesterol and high triglyceride levels
- History of heart disease, stroke, or peripheral artery disease
- A close relative (parent, sibling) with diabetes
- A high-risk ethnic group background (African-American, Latino, Native American, Asian American, Pacific Islander)

- Having delivered a baby weighing over 9 pounds or having a history of gestational diabetes (in women)
- Polycystic ovary disease (in women)

Children age 10 and older should be tested for type 2 diabetes (even if they have no symptoms) every 3 years if they are overweight and have at least two risk factors.

Testing for Diabetes and Pre-Diabetes

Pre-diabetes precedes the onset of type 2 diabetes. People who have pre-diabetes have fasting blood glucose levels that are higher than normal, but not yet high enough to be classified as diabetes. (Pre-diabetes used to be referred to as “impaired glucose tolerance.”) Pre-diabetes greatly increases the risk for diabetes.

The fasting plasma glucose (FPG) test, alone or in combination with the oral glucose tolerance test (OGTT) can help diagnose pre-diabetes and diabetes.

Fasting Plasma Glucose. The fasting plasma glucose (FPG) test is the standard test for diabetes. It is a simple blood test taken after 8 hours of fasting. FPG levels indicate:

- Normal. 100 mg/dL (or 5.5 mmol/L) or below.
- Pre-Diabetes. Between 100 - 125 mg/dL (5.5 - 7.0 mmol/L).
- Diabetes. 126 mg/dL (7.0 mmol/L) or higher.

The FPG test is not always reliable, so a repeat test is recommended if the initial test suggests the presence of diabetes, or if the test is normal in people who have symptoms or risk factors for diabetes.

Glucose Tolerance Test. The oral glucose tolerance test (OGTT) is more complex than the FPG and may over-diagnose diabetes in people who do not have it. Some doctors recommend it as a follow-up after FPG, if the latter test results are normal but the patient has symptoms or risk factors of diabetes. The test uses the following procedures:

- The patient first has an FPG test.
- The patient has a blood test 2 hours later, after drinking a special glucose solution.

OGTT levels indicate:

- Normal. 140 mg/dL or below.
- Pre-Diabetes. Between 140 - 199 mg/dL
- Diabetes. 200 mg/dL or higher.

The patient cannot eat for at least 8 hours prior to the FPG and OGTT tests.

Glycosylated Hemoglobin Test. This test examines blood levels of glycosylated hemoglobin, also known as hemoglobin A1c (HbA1c). The test is not affected by recent food intake so it can be taken at any time.

The results of a blood glucose test tell the patient and doctor how well the diabetes is controlled for only the day of the test. An elevated hemoglobin A1c level tells the doctor and the patient how well controlled the patient's diabetes has been over the last 3 months or so.

Measuring glycosylated hemoglobin is generally not used for making an initial diagnosis of diabetes, since a normal level does not rule out diabetes. In people without diabetes, a normal HbA1c range is between 4 - 6%. Elevated levels of glycosylated hemoglobin are strongly associated with most if not all of the complications of diabetes.

In general, most patients with diabetes should aim for HbA1c levels below 7%. Your doctor may adjust this goal depending on your individual health profile.

Screening Tests for Complications

Screening for Heart Disease. All patients with diabetes should be tested for hypertension and unhealthy cholesterol and lipid levels and given an electrocardiogram. Other tests may be needed in patients with signs of heart disease.

The electrocardiogram (ECG or EKG) is used extensively in the diagnosis of heart disease, from congenital heart disease in infants to myocardial infarction and myocarditis in adults. Several different types of electrocardiogram exist.

Screening for Kidney Damage. The earliest manifestation of kidney damage is microalbuminuria, in which tiny amounts (30 - 300 mg per day) of protein called albumin are found in the urine. Microalbuminuria typically shows up in patients with type 2 diabetes who have high blood pressure.

The American Diabetes Association recommends that people with diabetes receive an annual microalbuminuria urine test. Patients should also have their blood creatinine tested at least once a year. Creatinine is a waste product that is removed from the blood by the kidneys. High levels of creatinine may indicate kidney damage. A doctor uses the results from a creatinine blood test to calculate the glomerular filtration rate (GFR). The GFR is an indicator of kidney function; it estimates how well the kidneys are cleansing the blood.

Screening for Retinopathy. The American Diabetes Association recommends that patients with type 2 diabetes get an initial comprehensive eye exam by an ophthalmologist or optometrist shortly after they are diagnosed with diabetes, and once a year thereafter. (People at low risk may need follow-up exams only every 2 - 3 years.) The eye exam should include dilation to check for signs of retinal disease (retinopathy).

Screening for Neuropathy. All patients should be screened for nerve damage (neuropathy), including a comprehensive foot exam. Patients who lose sensation in their feet should have a foot exam every 3 - 6 months to check for ulcers or infections.

Screening for Thyroid Abnormalities. Thyroid function tests should be performed.

Lifestyle Changes

Diet

The treatment goals for a diabetes diet are:

- Achieve near-normal blood glucose levels. People with type 1 diabetes must coordinate calorie intake with medication or insulin administration, exercise, and other variables to control blood glucose levels. New forms of insulin now allow more flexibility in timing meals.
- Protect the heart and aim for healthy lipid (cholesterol and triglyceride) levels and control of blood pressure.
- Achieve healthy weight. (A reasonable weight is usually defined as a weight that is achievable and sustainable, rather than one that is culturally defined as desirable or ideal.) Children, pregnant women, and people recovering from illness should be sure to maintain adequate calories for health.
- Manage or prevent complications of diabetes. People with diabetes, whether type 1 or 2, are at risk for a number of medical complications, including heart and kidney disease. Dietary requirements for diabetes must take these disorders into consideration.
- Promote overall health.

Overall Guidelines. There is no such thing as a single diabetes diet. Patients should meet with a professional dietitian to plan an individualized diet within the general guidelines that takes into consideration their own health needs.

Healthy eating habits along with good control of blood glucose are the basic goals, and several good dietary methods are available to meet them. General dietary guidelines for diabetes recommend:

- Carbohydrates should provide 45 - 65% of total daily calories. The type and amount of carbohydrate are both important. Best choices are vegetables, fruits, beans, and whole grains. These foods are also high in fiber. Patients with diabetes should monitor their carbohydrate intake either through carbohydrate counting or meal planning exchange lists.
- Fats should provide 25 - 35% of daily calories. Monounsaturated (olive, peanut, and canola oils; avocados; nuts) and omega-3 polyunsaturated (fish, flaxseed oil, and walnuts) fats are the best types. Limit saturated fat (red meat, butter) to less than 7% of daily calories. Choose nonfat or low-fat dairy instead of whole milk products. Limit trans-fats (hydrogenated fat found in snack foods, fried foods, commercially baked goods) to less than 1% of total calories.
- Protein should provide 12 - 20% of daily calories, although this may vary depending on a patient's individual health requirements. Patients with kidney disease should limit protein intake to less than 10% of calories. Fish, soy, and poultry are better protein choices than red meat.

[For more information, see *In-Depth Report #42: Diabetes diet.*]

Weight Management

Being overweight is the number one risk factor for type 2 diabetes. Even modest weight loss can help prevent type 2 diabetes from developing. It can also help control or even stop progression of type 2 diabetes in people with the condition and reduce risk factors for heart disease. Patients should lose weight if their body mass index (BMI) is 25 - 29 (overweight) or higher (obese).

The American Diabetes Association recommends that patients aim for a small but consistent weight loss of ½ - 1 pound per week. Most patients should follow a diet that supplies at least 1,000 - 1,200 kcal/day for women and 1,200 - 1,600 kcal/day for men.

Unfortunately, not only is weight loss difficult to sustain, but many of the oral medications used in type 2 diabetes cause weight gain as a side effect. For obese patients who cannot control weight using dietary measures alone, weight-loss drugs, such as orlistat (alli, Xenical) or sibutramine (Meridia), may be helpful. [For more information, see *In-Depth Report #53: Obesity*.]

Exercise

Sedentary habits, especially watching TV, are associated with significantly higher risks for obesity and type 2 diabetes. Regular exercise, even of moderate intensity (such as brisk walking), improves insulin sensitivity and may play a significant role in preventing type 2 diabetes -- regardless of weight loss.

Aerobic Exercise. Aerobic exercise has significant and particular benefits for people with diabetes. Regular aerobic exercise, even of moderate intensity, improves insulin sensitivity. The heart-protective effects of aerobic exercise are also important, even if patients have no risk factors for heart disease other than diabetes itself.

For improving blood sugar control, the American Diabetes Association recommends at least 150 minutes per week of moderate-intensity physical activity (50 - 70% of maximum heart rate) or at least 90 minutes per week of vigorous aerobic exercise (more than 70% of maximum heart rate). Exercise at least 3 days a week, and do not go more than 2 consecutive days without physical activity.

Strength Training. Strength training, which increases muscle and reduces fat, is also helpful for people with diabetes who are able to do this type of exercise. The American Diabetes Association recommends performing resistance exercise three times a week. Build up to three sets of 8 - 10 repetitions using weight that you cannot lift more than 8 - 10 times without developing fatigue. Be sure that your strength training targets all of the major muscle groups.

Exercise Precautions. The following are precautions for all people with diabetes, both type 1 and type 2:

- Because people with diabetes are at higher than average risk for heart disease, they should always check with their doctors before undertaking vigorous exercise. For fastest results, frequent high-intensity (not high-impact) exercises are best for people who are

cleared by their doctors. For people who have been sedentary or have other medical problems, lower-intensity exercises are recommended.

- Strenuous strength training or high-impact exercise is not recommended for people with uncontrolled diabetes. Such exercises can strain weakened blood vessels in the eyes of patients with retinopathy. High-impact exercise may also injure blood vessels in the feet.

Patients who are taking medications that lower blood glucose, particularly insulin, should take special precautions before starting a workout program:

- Monitor glucose levels before, during, and after workouts (glucose levels swing dramatically during exercise).
- Avoid exercise if glucose levels are above 300 mg/dL or under 100 mg/dL.
- Drink plenty of fluids before and during exercise; avoid alcohol, which increases the risk of hypoglycemia.
- Before exercising, avoid alcohol and if possible certain drugs, including beta-blockers, which make it difficult to recognize symptoms of hypoglycemia.
- Insulin-dependent athletes may need to decrease insulin doses or take in more carbohydrates prior to exercise, but may need to take an extra dose of insulin after exercise (stress hormones released during exercise may increase blood glucose levels). Inject insulin in sites away from the muscles used during exercise; this can help avoid hypoglycemia.
- Wear good, protective footwear to help avoid injuries and wounds to the feet.
- Some blood pressure drugs can interfere with exercise capacity. Patients who use blood pressure medication should talk to their doctors about how to balance medications and exercise. Patients with high blood pressure should also aim to breathe as normally as possible during exercise. Holding the breath can increase blood pressure, especially during strength training.

[For more information, see *In-Depth Report #29: Exercise*.]

Improving Sleep

Some research suggests that not getting enough sleep may impair insulin use and increase the risk for obesity. More research is needed, but it is always wise to improve sleep habits.

Treatment

Management of Pre-Diabetes

Treatment of pre-diabetes is very important. Research shows that lifestyle and medical interventions can help prevent, or at least delay, the progression to diabetes, as well as lower their risk for heart disease.

- The most important lifestyle treatment for people with pre-diabetes is to lose weight through diet and regular exercise. Even a modest weight loss of 10 - 15 pounds can significantly reduce the risk of progressing to diabetes.

- Patients should have an exercise goal of 30 - 60 minutes, at least 5 days a week, and follow a low-fat, high-fiber diet. Quitting smoking is also essential.
- It is also important to have your doctor check your cholesterol and blood pressure levels on a regular basis. Your doctor should also check your fasting blood glucose and microalbuminuria levels every year, and your hemoglobin A1c and lipids every 6 months.
- While doctors sometimes prescribe insulin-regulating drugs such as metformin (Glucophage) and acarbose (Precose), evidence indicates that lifestyle changes can be at least as effective as drug therapy.

Management of Type 2 Diabetes

The major treatment goals for people with type 2 diabetes are to control blood glucose levels and to treat all conditions that place patients at risk for heart disease, stroke, kidney disease, and other major complications.

Approach to controlling blood glucose levels includes:

- Achieving fasting blood glucose levels of less than 110 mg/dL and glycosylated hemoglobin (HbA1c) levels of less than 7%. (However, patients who have a history of severe hypoglycemia, vascular complications or other diseases, or longstanding diabetes may benefit from looser control of blood sugar. Patients should discuss individualized treatment goals with their doctors.)
- Close monitoring of blood sugar and hemoglobin HbA1c levels.
- Use of oral anti-hyperglycemic drugs such as metformin are first-line drug treatments, and insulin if needed.

Approach for reducing complications includes:

- Healthy lifestyle changes, such as regular exercise, heart-healthy diet, quitting smoking.
- Use of various drugs provided by your doctor to control high blood pressure (such as ACE inhibitors and diuretics), lower cholesterol (statins and fibrates), and to prevent clots, such as aspirin or clopidogrel (Plavix).
- Close follow-up with your doctor.

Glucose Goals for Patients with Diabetes		
	Normal	Goal
Blood glucose levels before meals	Less than 110 mg/dL	90 - 130 mg/dL for adults 100 - 180 mg/dL for children under age 6 90 - 180 mg/dL for children 6 - 12 years old 90 - 130 mg/dL for children 13 - 19 years old
Bedtime blood glucose levels	Less than 120 mg/dL	110 - 150 mg/dL for adults 110 - 200 mg/dL for children under age 6 100 - 186 mg/dL for children 6 - 12 years old 90 - 150 mg/dL for children 13 - 19 years old

Glycosylated hemoglobin (HbA1c) levels	4 - 6%	Less than 7%
Source: <i>Standards of Medical Care In Diabetes -- 2008</i> , American Diabetes Association.		

Treating Special Populations

Different goals may be necessary for specific individuals, including pregnant women, very old and very young people, and those with accompanying serious medical conditions. Treating children with type 2 diabetes depends on the severity of the condition at diagnosis. Metformin is approved for children. Formerly, only insulin was approved for treating children with diabetes.

Treatment of Complications

High Blood Pressure and Heart Disease

All patients with diabetes and high blood pressure should make lifestyle changes. These include losing weight (when needed), following the Dietary Approaches to Stop Hypertension (DASH) diet, quitting smoking, limiting alcohol intake, and limiting salt intake to no more than 1,500 mg of sodium per day.

Reducing Blood Pressure. Strict control of blood pressure is critical for preventing complications of diabetes and has proven to improve survival rates. Patients should strive for blood pressure levels of less than 130/80 mm Hg (systolic/diastolic).

Patients with diabetes and high blood pressure need an individualized approach to drug treatment, based on their particular health profile. Dozens of anti-hypertensive drugs are available. The most beneficial fall into the following categories:

- Diuretics rid the body of extra sodium (salt) and water. There are three main types of diuretics: Potassium-sparing, thiazide, and loop.
- Angiotensin-converting enzyme (ACE) inhibitors reduce the production of angiotensin, a chemical that causes arteries to narrow.
- Angiotensin-receptor blockers (ARBs) block angiotensin's action on arteries.
- Beta blockers block the effects of adrenaline and ease the heart's pumping action.
- Calcium-channel blockers (CCBs) decrease the contractions of the heart and widen blood vessels.

Nearly all patients who have diabetes and high blood pressure should take an ACE inhibitor (or ARB) as part of their regimen for treating hypertension. These drugs help prevent kidney damage. [For more information, see *In-Depth Report #14: High blood pressure.*]

Improving Cholesterol and Lipid Levels. Abnormal cholesterol and lipid levels are common in diabetes. High LDL ("bad") cholesterol should always be lowered, but people with diabetes also often have additional harmful imbalances, including low HDL ("good") cholesterol and high triglycerides.

Adult patients should aim for LDL levels below 100 mg/dL, HDL levels over 50 mg/dL, and triglyceride levels below 150 mg/dL. Patients with diabetes and heart disease should strive for even lower LDL levels; the American Diabetes Association recommends LDL levels below 70 mg/dL for these patients.

Pediatric patients should be treated for LDL cholesterol above 160 mg/dL, or above 130 mg/dL if other cardiovascular risk factors are present.

For medications, statins are the best cholesterol-lowering drugs. They include atorvastatin (Lipitor), lovastatin (Mevacor and generics), pravastatin (Pravachol), simvastatin (Zocor and generics), fluvastatin (Lescol), and rosuvastatin (Crestor). These drugs are very effective for lowering LDL cholesterol levels.

The primary safety concern with statins has involved myopathy, an uncommon condition that can cause muscle damage and, in some cases, muscle and joint pain. A specific myopathy called rhabdomyolysis can lead to kidney failure. People with diabetes and risk factors for myopathy should be monitored for muscle symptoms.

Although lowering LDL cholesterol is beneficial, statins are not as effective as other medications -- such as niacin and fibrates -- in addressing HDL and triglyceride imbalances. This is a common problem in type 2 diabetes. Combining a statin with one of these drugs may be helpful for people with diabetes who have heart disease, low HDL levels, and near-normal LDL levels. Although combinations of statins and fibrates or niacin increase the risk of myopathy, both combinations are considered safe if used with extra care.

Fibrates, such as gemfibrozil (Lopid) and fenofibrate (Tricor), are usually the second choice after statins. Niacin has the most favorable effect on raising HDL and lowering triglycerides of all the cholesterol drugs. However, some patients who take high-dose niacin experience increased blood glucose levels. Moderate doses of niacin can achieve lipid control without causing serious blood glucose problems. [For more information, see *In-Depth Report #23: Cholesterol.*]

Aspirin for Reducing the Risk for Blood Clots. Taking a daily aspirin reduces the risk for blood clotting and may help protect against heart attacks. The recommended dose is 75 - 162 mg/day. Patients with diabetes for whom aspirin is recommended include those who have:

- Age over 40 years old
- History of heart problems
- Family history of heart disease
- High blood pressure or elevated cholesterol and
- Smokers

Prevention and Treatment of Retinopathy

Prevention of Retinopathy. Fortunately, severe and even moderate vision loss is largely preventable with tight control of blood glucose levels. (Intense glucose control can cause early worsening of retinopathy, although this is nearly always counterbalanced by long-term benefits.)

Tight control of blood pressure can also help protect against retinopathy. Aspirin therapy does not help prevent retinopathy.

Treatment of Retinopathy. Patients with severe diabetic retinopathy or macular edema (swelling of the retina) should be sure to see an eye specialist who is experienced in the management and treatment of diabetic retinopathy. Once damage to the eye develops, laser or photocoagulation eye surgery may be needed. Laser surgery can help reduce vision loss in high-risk patients.

Treatment of Foot Ulcers

About a third of foot ulcers will heal within 20 weeks with good wound care treatments. Some treatments are as follows:

- Antibiotics are generally given. In some cases, hospitalization and intravenous antibiotics for up to 28 days may be needed for severe foot ulcers.
- In virtually all cases, wound care requires debridement, the removal of injured tissue until only healthy tissue remains. Debridement may be accomplished using chemical (enzymes), surgical, or mechanical (irrigation) means.
- Hydrogels (such as Nu-Gel), may help to soothe and heal ulcers.
- Felted foam may help heal ulcers on the sole of the foot. Felted foam uses a multi-layered foam pad over the bottom of the foot with an opening over the ulcer.

Other Treatments for Foot Ulcers. Doctors are also using or investigating other treatments to heal ulcers. These include:

- Administering hyperbaric oxygen (oxygen given at high pressure) is showing promise in promoting healing. It is generally reserved for patients with severe, full thickness diabetic foot ulcers that have not responded to other treatments, particularly when gangrene, or an abscess, is present.
- Total-contact casting (TCC) uses a cast that is designed to match the exact contour of the foot and to distribute weight along the entire length of the foot. It is usually changed weekly. It may be helpful for ulcer healing and for Charcot foot. Although it is very effective in healing ulcers, recurrence is common.

Treatment of Neuropathy

A number of different drugs are used for peripheral neuropathy pain relief: They include:

- Nonprescription analgesics, such as aspirin, acetaminophen, and non-steroidal anti-inflammatory drugs (NSAIDs). (Patients with stomach or kidney problems should check with their doctors before using these drugs.)
- Prescription painkillers, such as tramadol (Ultram). Tramadol is a drug that is similar to opioids. It can help relieve pain but has significant side effects, including nausea, constipation, and headache.
- Topical medications, particularly capsaicin (the active ingredient in hot peppers), are applied to the skin to relieve minor local pain. A 5% lidocaine patch has also shown good results in clinical trials.

- Tricyclic antidepressants, such as amitriptyline (Elavil) or doxepin (Sinequan), are effective in reducing pain from neuropathy for many patients. A combination of doxepin and capsaicin (applied to the skin) may also be helpful. Unfortunately, tricyclics may cause heart rhythm problems, so patients at risk need to be monitored carefully.
- Duloxetine (Cymbalta), a serotonin and norepinephrine reuptake inhibitor, is approved for treatment of pain associated with diabetic peripheral neuropathy.
- Anti-seizure drugs used for peripheral neuropathy pain relief include gabapentin (Neurontin), pregabalin (Lyrica), carbamazepine (Tegretol), and valproate (Depakote).

Although not proven to be beneficial, patients may also try transcutaneous electrostimulation (TENS), a treatment that involves administering mild electrical pulses to painful areas. Alternative treatments, such as hypnosis, biofeedback, relaxation techniques, and acupuncture, have also been reported to help some patients manage pain. Doctors also recommend lifestyle measures, such as walking and wearing elastic stockings.

Treatments for Other Complications of Neuropathy. Neuropathy also impacts other functions, and treatments are needed to reduce their effects. If diabetes affects the nerves in the autonomic nervous system, then abnormalities of blood pressure control and bowel and bladder function may occur. Erythromycin, domperidone (Motilium), or metoclopramide (Reglan) may be used to relieve delayed stomach emptying caused by neuropathy. Patients need to watch their nutrition if the problem is severe.

Erectile dysfunction is also associated with neuropathy. Studies indicate that phosphodiesterase type 5 (PDE-5) drugs, such as sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis), are safe and effective, at least in the short term, for many patients with diabetes. Typical side effects are minimal but may include headache, flushing, and upper respiratory tract and flu-like symptoms. Patients who take nitrate medications for heart disease cannot use PDE-5 drugs.

Treatment of Kidney Problems

Tight control of blood sugar and blood pressure is essential for preventing the onset of kidney disease. Strict control of these two conditions produces a reduction in new cases of nephropathy and a delay in progression of the disease.

ACE inhibitors are the best class of blood pressure medications for delaying kidney disease and slowing disease progression in patients with diabetes. Angiotensin-receptor blockers (ARBs) are also very helpful.

- For patients with diabetes who have microalbuminuria, the American Diabetes Association strongly recommends ACE inhibitors or ARBs. Microalbuminuria is an accumulation of protein in the blood, which can signal the onset of kidney disease (nephropathy).
- Nearly all patients who have diabetes and high blood pressure should take an ACE inhibitor (or ARB) as part of their regimen for treating their hypertension.

A doctor may recommend a low-protein diet for patients whose kidney disease is progressing despite tight blood sugar and blood pressure control. Protein-restricted diets can help slow

disease progression and delay the onset of end-stage renal disease (kidney failure). However, patients with end-stage renal disease who are on dialysis generally need higher amounts of protein. [For more information, see *In-Depth Report #42: Diabetes diet.*]

Anemia. Anemia is a common complication of end-stage kidney disease. Patients on dialysis usually need injections of erythropoiesis-stimulating drugs to increase red blood cell counts and control anemia. However, these drugs -- darbepoetin alfa (Aranesp) and epoetin alfa (Epogen and Procrit) -- can increase the risk of blood clots, stroke, heart attack, and heart failure in patients with end-stage kidney disease when they are given at higher than recommended doses.

The FDA recommends that patients with end-stage kidney disease who receive erythropoiesis-stimulating drugs should:

- Maintain hemoglobin levels between 10 - 12 g/dL.
- Receive frequent blood tests to monitor hemoglobin levels.
- Contact their doctors if they experience such symptoms as shortness of breath, pain, swelling in the legs, or increases in blood pressure.

[For more information, see *In-Depth Report #57: Anemia.*]

Medications

Many anti-hyperglycemic drugs are available to help patients with type 2 diabetes control their blood sugar levels. Most of these drugs are aimed at using or increasing sensitivity to the patient's own natural stores of insulin.

For the most part older oral hypoglycemic drugs -- particularly metformin -- are less expensive than, and work as well as, newer diabetes drugs. They are generally recommended as first-line drugs to use. Metformin is a safe and effective drug because it does not cause weight gain or too-low blood sugar. Metformin can also help lower LDL (“bad”) cholesterol.

In general, these drugs will reduce hemoglobin A1c levels by 1 - 2%. Adding a second oral hypoglycemic is usually recommended if inadequate control is not achieved with the first medication. For the most part, doctors should add a second drug rather than trying to push the first drug dosage to the highest levels.

Biguanides (Metformin)

Metformin (Glucophage) is a biguanide, which works by reducing glucose production in the liver and by making tissues more sensitive to insulin. Doctors recommend it as a first choice for most patients with type 2 diabetes who are insulin resistant, particularly if they are overweight. Metformin may also be used in combination with other drugs.

Metformin does not cause hypoglycemia or add weight, so it is particularly well-suited for obese patients with type 2 diabetes. Metformin also appears to have beneficial effects on cholesterol and lipid levels and may help protect the heart. Some research has suggested that it significantly reduces the risk for heart attack and death from heart disease. It is also the first choice for

children who need oral drugs and is helpful for women with polycystic ovary syndrome and insulin resistance.

Side Effects. Side effects include:

- A metallic taste
- Gastrointestinal problems, including nausea, and diarrhea
- Interference with absorption of vitamin B12 and folic acid
- Rare reports of lactic acidosis, a potentially life-threatening condition, particularly in people with risk factors for it. Major studies, however, found no greater risk with metformin than with any of the other drugs used for type 2 diabetes.

Certain people should not use this drug, including anyone with heart failure or kidney or liver disease. It is rarely suitable for adults over age 80.

Sulfonylureas

Sulfonylureas are oral drugs that stimulate the pancreas to release insulin. They are also first-line oral drugs. For adequate control of blood glucose levels, the drugs should be taken 20 - 30 minutes before a meal. A number of brands are available, including chlorpropamide (Diabinese), tolazamide (Tolinase), acetohexamide (Dymelor), glipizide (Glucotrol), tolbutamide (Orinase), glyburide (Micronase), glimepiride (Amaryl), and repaglinide (Prandin).

Most patients can take sulfonylureas for 7 - 10 years before they lose effectiveness.

Combinations with small amounts of insulin or other oral anti-hyperglycemic drugs (such as metformin or a thiazolidinedione) may extend their benefits. A combination of glyburide and metformin in one pill (Glucovance) is available. Glucovance may be particularly beneficial for patients with unhealthy cholesterol levels and poor control of their blood sugar levels. Some doctors recommend the combination as first-line treatment.

Side Effects and Complications. In general, women who are pregnant or nursing or by individuals who are allergic to sulfa drugs should not use sulfonylureas. Side effects may include:

- Weight gain (some sulfonylureas, such as glimepiride, may produce less weight gain than others)
- Water retention
- Although sulfonylureas pose a lower risk for hypoglycemia than insulin does, the hypoglycemia produced by sulfonylureas may be especially prolonged and dangerous. The newer sulfonylureas, such as glimepiride, have much less risk of hypoglycemia than older sulfonylureas.
- Some sulfonylureas may pose a slight risk for cardiac events.

Sulfonylureas interact with many other drugs, and patients must inform their doctor of any medications they are taking, including alternative or over-the-counter drugs.

Meglitinides

Meglitinides stimulate beta cells to produce insulin. They include repaglinide (Prandin), nateglinide (Starlix), and mitiglinide. These drugs are rapidly metabolized and short-acting. If taken before every meal, they actually mimic the normal effects of insulin after eating. Patients, then, can vary their meal times with this drug. These drugs may be particularly helpful in combination with metformin or other drugs. They may also be a good choice for people with potential kidney problems.

Side Effects. Side effects include diarrhea and headache. As with the sulfonylureas, repaglinide poses a slightly increased risk for cardiac events. (Newer drugs, such as nateglinide, may pose less of a risk.) People with heart failure or liver disease should use them with caution and be monitored.

Thiazolidinediones

Thiazolidinediones, also known as peroxisome proliferator-activated receptor (PPAR) agonists, include pioglitazone (Actos) and rosiglitazone (Avandia). They improve insulin sensitivity by activating certain genes involved in fat synthesis and carbohydrate metabolism. These drugs are usually taken once or twice per day; however, it may take several days before the patient notices any results from them and several weeks before they take full effect. Thiazolidinediones are usually taken in combination with other oral drugs or insulin. Thiazolidinediones available as 2-in-1 pills include rosiglitazone and metformin (Avandamet), rosiglitazone and glimepiride (Avandaryl), and pioglitazone and glimepiride (Duetact).

Side Effects. Thiazolidinediones can have serious side effects. They can increase fluid build-up, which can cause or worsen heart failure in some patients. Combinations with insulin increase the risk. Patients with heart failure should not use them. People with risk factors for heart failure should use these medications with caution. Rosiglitazone may also increase the risk for heart attack. Patients who take rosiglitazone, especially those who have heart disease or who are at high risk for heart attack, should talk to their doctor about their treatment options.

Thiazolidinediones may cause more weight gain than other diabetes medications or insulin. Any patient who has sudden weight gain, water retention, or shortness of breath should immediately call their doctor. These drugs have also been linked to increased risks for bone fracture.

There have been rare reports of rosiglitazone causing or worsening diabetic macular edema. This is an eye condition associated with diabetic retinopathy that causes swelling in the macular area of the retina. Symptoms include blurred vision and decreased color sensitivity. Most patients who had this side effect also had swelling in the feet and legs (peripheral edema). The condition resolved or improved when patients stopped taking the drug.

Thiazolidinediones can also cause liver damage. Patients who take these drugs should have their liver enzymes checked regularly.

Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors, including acarbose (Precose, Glucobay) and miglitol (Glyset), reduce glucose levels by interfering with the absorption of starch in the small intestine. Acarbose tends to lower insulin levels after meals, a particular advantage, since higher levels of insulin after meals are associated with an increased risk for heart disease. Some evidence suggests that early use of these drugs may reduce heart risk factors, including high blood pressure. Alpha-glucosidase inhibitors are not as effective alone as other single oral drugs, but combinations, such as with metformin, insulin, or a sulfonylurea, increase their effectiveness.

Side Effects. These medications need to be taken with meals. Unfortunately, about a third of patients stop taking the drug because of flatulence and diarrhea, particularly after high-carbohydrate meals. The drug may also interfere with iron absorption.

Alpha-glucosidase inhibitors do not cause hypoglycemia when used alone, but combinations with other drugs do. In such cases, it is important that the patient receive a solution that contains glucose or lactose, not table sugar. This is because acarbose inhibits the breakdown of complex sugar and starches, which includes table sugar.

GLP-1 Inhibitors (Exenatide)

Incretin mimetics belong to a new class of drugs that help improve blood sugar control. Incretins include glucagon-like peptide-1 (GLP-1) inhibitors and DDP-4 inhibitors.

In 2005, the FDA approved exenatide (Byetta), the first GLP-1 inhibitor drug. Exenatide is an injectable drug that is a synthetic version of the hormone found in the saliva of the Gila monster, a venomous desert lizard. Exenatide is injected twice a day, 1 hour before morning and evening meals. It is prescribed for patients with type 2 diabetes who have not been able to control their glucose with metformin or a sulfonylurea drug. It can be taken in combination with these drugs or alone.

Side Effects. Exenatide stimulates insulin secretion only when blood sugar levels are high and so has less risk for causing low blood sugar (hypoglycemia) when it is taken alone. However, the risk for hypoglycemia increases when exenatide is taken along with a sulfonylurea drug. There does not appear to be a risk for hypoglycemia when exenatide is used along with metformin. Other side effects may include nausea, vomiting, and diarrhea.

Exenatide has been associated with cases of acute pancreatitis, which is sudden inflammation of the pancreas. Symptoms of acute pancreatitis include severe abdominal pain that may radiate to the back. The pain may or may not be accompanied by nausea and vomiting. Patients who feel severe stomach pain that does not go away should seek prompt medical attention. In rare cases, exenatide has been associated with hemorrhagic and necrotizing pancreatitis, which can potentially be life threatening.

DPP-4 Inhibitors (Gliptins)

Dipeptidyl peptidase-4 (DPP-4) inhibitors, also called gliptins, are the second class of incretin drugs. In October 2006, the FDA approved the first DPP-4 inhibitor, sitagliptin (Januvia). It can be used alone or in combination with metformin or a thiazolidinedione drug. It may also be used as add-on therapy to a sulfonylurea drug. In 2007, the FDA approved Janumet, which combines sitagliptin with metformin in one pill. Other DPP-4 drugs being studied include vildagliptin (Galvus) and saxagliptin.

DPP-4 inhibitors work in a similar way to GLP-1 inhibitors. However, unlike exenatide, which is given by injection, DPP-4 inhibitor drugs are taken as pills by mouth.

Like exenatide, DPP-4 inhibitors do not cause weight gain, have low risks for hypoglycemia, and have few severe side effects. The most common side effects include upper respiratory tract infection, sore throat, and diarrhea.

Pramlintide (Symlin)

Approved in 2005, pramlintide (Symlin) is a new type of injectable drug that may help patients who take insulin but still need better blood sugar control. Pramlintide is a synthetic form of amylin, a hormone that is related to insulin. Pramlintide is used in combination with insulin to lower blood sugar levels in the 3 hours after meals.

Insulin Replacement

Insulin replacement may be necessary when natural insulin reserves are depleted. It is typically started in combination with an oral drug (usually metformin).

Because type 2 diabetes is progressive, many patients eventually need insulin. However, when a single oral drug fails to control blood sugar it is not clear whether it is better to add insulin replacement or a second or third oral drug.

Some doctors advocate using insulin as early as possible for optimal control. However, in patients who still have insulin reserves, there is concern that extra natural insulin will have adverse effects. Low blood sugar (hypoglycemia) and weight gain are the main side effects of insulin therapy. It is still not clear if insulin replacement improves survival rates compared to oral drugs, notably metformin.

Fortunately, studies to date have not reported any adverse cardiac effects in patients with type 2 diabetes who take insulin. In fact, insulin has been associated, in some cases, with improvement in heart risk factors. More research is needed to clarify these important issues.

Forms of Insulin. There are two main insulin types:

- **Fast-Acting Insulins for Surges.** Insulin lispro and aspart are fast-acting insulins. They mimic insulin's response to food intake. They are taken before meals, and their short action reduces the risk for hypoglycemia afterward.
- **Slower Insulins for Base Levels.** Intermediate forms (including NPH and lente) and long-acting forms (glargine, ultralente) were developed to provide a steady level of insulin throughout the day. To date, glargine (Lantus) seems to be the most successful in achieving this goal in type 2 diabetes.

In general, there is no advantage to dosing insulin more than two times a day for patients with type 2 diabetes.

[For more information, see *In-Depth Report #9: Diabetes - type 1.*]

Warning on Dietary Supplements

Various fraudulent products are often sold on the Internet as “cures” or treatments for diabetes. These dietary supplements have not been studied or approved. The FDA warns patients with diabetes not to be duped by bogus and unproven remedies.

Home Management

Monitoring Glucose (Blood Sugar) Levels

Both low blood sugar (hypoglycemia) and high blood sugar (hyperglycemia) are of concern, especially for patients who take insulin. Blood glucose levels are generally more stable in type 2 diabetes than in type 1, so doctors usually recommend measuring blood levels only once or twice a day. For patients who have become insulin-dependent, more intensive monitoring is necessary. Patients should aim for the following measurements:

- Pre-meal glucose levels of between 90 - 130 mg/dL
- Bedtime levels of between 110 - 150 mg/dL

Different goals may be required for specific individuals, including pregnant women, very old and very young people, and those with accompanying serious medical conditions.

Finger-Prick Test. A typical blood sugar test includes the following:

- A drop of blood is obtained by pricking the finger.
- The blood is then applied to a chemically treated strip.
- Monitors read and provide results.

Home monitors are about 10 - 15% less accurate than laboratory monitors, and many do not meet the standards of the American Diabetes Association. Most doctors believe, however, that they are accurate enough to indicate when blood sugar is too low.

Some simple procedures may improve accuracy:

- Testing the meter once a month.
- Recalibrating it whenever a new packet of strips is used.
- Using fresh strips; outdated strips may not provide accurate results.
- Keeping the meter clean.
- Periodically comparing the meter results with the results from a laboratory.

For patients who have trouble controlling hypoglycemia (low blood sugar) or fluctuating blood sugar levels, continuous glucose sensor monitors are also available. Continuous glucose sensor monitors do not replace fingerstick glucose meters and test strips, but are used in combination with them. [For more information, see *In-Depth Report #9: Diabetes - type 1.*]

To monitor the amount of glucose within the blood a person with diabetes should test their blood regularly. The procedure is quite simple and can often be done at home.

Glycosylated Hemoglobin

Hemoglobin A1c (also called HbA1c , HA1c, or A1C) is measured periodically every 2 - 3 months, or at least twice a year, to determine the average blood-sugar level over the lifespan of the red blood cell. While fingerprick self-testing provides information on blood glucose for that day, the HbA1c test shows how well blood sugar has been controlled over the period of several months. For most people with well-controlled diabetes, HbA1c levels should be below 7%. Home tests are also available for measuring A1C but they tend not to be as accurate as the laboratory tests ordered by doctors.

Preventing Hypoglycemia

The following tips may help avoid hypoglycemia or prepare for attacks:

- Patients are at highest risk for hypoglycemia at night. Bedtime snacks are advisable if blood glucose levels are below 180 mg/dL (10 mmol/L). Protein snacks may be best
- Patients who intensively control their blood sugar should monitor blood levels as often as possible, four times or more per day. This is particularly important for patients with hypoglycemia unawareness.
- In adults, it is also particularly critical to monitor blood glucose levels before driving, when hypoglycemia can be very hazardous.
- Patients who use medications that put them at risk for hypoglycemia should always carry hard candy, juice, sugar packets, or commercially available glucose substitutes designed for individuals with diabetes.

Family and friends should be aware of the symptoms and be prepared:

- If the patient is helpless (but not unconscious), family or friends should administer three to five pieces of hard candy, two to three packets of sugar, half a cup (four ounces) of fruit juice, or a commercially available glucose solution.
- If there is inadequate response within 15 minutes, the patient should receive additional sugar by mouth and may need emergency medical treatment, possibly including an intravenous glucose solution.
- Family members and friends can learn to inject glucagon, a hormone, which, in contrast to insulin, raises blood glucose.

Patients are encouraged to wear at all times a medical alert ID bracelet or necklace that states they have diabetes. If patients take insulin, that information should be included as well.

Foot Care

Measures to Prevent Foot Ulcers. Preventive foot care can significantly reduce the risk of ulcers and amputation. Some tips for preventing problems include:

- Patients should inspect their feet daily and watch for changes in color or texture, odor, and firm or hardened areas, which may indicate infection and potential ulcers.
- When washing the feet, the water should be warm (not hot) and the feet and areas between the toes should be thoroughly dried afterward. Check water temperature with the hand or a thermometer before stepping in.
- Apply moisturizers, but NOT between the toes.
- Gently use pumice to remove corns and calluses (patients should not use medicated pads or try to shave the corns or calluses themselves).
- Trim toenails short and file the edges to avoid cutting adjacent toes.
- Well-fitting footwear is very important. People should be sure the shoe is wide enough. Patients should also avoid high heels, sandals, thongs, and going barefoot. Shoes with a rocker sole reduce pressure under the heel and front of the foot and may be particularly helpful. Custom-molded boots increase the surface area over which foot pressure is distributed. This reduces stress on the ulcers and allows them to heal.
- Change shoes often during the day.
- Wear socks, particularly with extra padding (which can be specially purchased).
- Patients should avoid tight stockings or any clothing that constricts the legs and feet.
- Consult a specialist in foot care for any problems.

Resources

- www.diabetes.org -- American Diabetes Association
- www.niddk.nih.gov -- National Institute of Diabetes and Digestive and Kidney Diseases
- www.americanheart.org -- American Heart Association
- www.kidney.org -- National Kidney Foundation
- www.nei.nih.gov -- National Eye Institute
- www.medicalert.org -- Medic Alert
- www.eatright.org -- American Dietetic Association