

Diabetes: Type 2

What Is Type 2 Diabetes?

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). They share a central feature: elevated blood sugar levels due to absolute or relative insufficiencies of insulin, a hormone produced by the pancreas. Insulin is a key regulator of the body's metabolism. After meals, food is digested in the stomach and intestines; carbohydrates are broken down into sugar molecules, of which glucose is one, and proteins are broken down into amino acids. Glucose and amino acids are absorbed directly into the bloodstream, and blood glucose levels rise. Normally, the rise in blood glucose levels signals important cells in the pancreas, called beta-cells, to secrete insulin, which pours into the bloodstream. Insulin, in turn, enables glucose and amino acids to enter cells in the body, importantly, those in the muscles, where, along with other hormones, it directs whether these nutrients will be burned for energy or stored for future use. As blood sugar falls to pre-meal levels, the pancreas reduces the production of insulin, and the body uses its stored energy until the next meal provides additional nutrients.

Type 2 Diabetes

Type 2 diabetes is by far the more common form of diabetes, accounting for 90% of cases. About 16 million Americans have type 2 diabetes and half are unaware they have it. Most type 2 diabetics produce variable, even normal, amounts of insulin, but they have abnormalities in liver and muscle cells that resist its actions. Insulin attaches to the receptors of cells, but glucose does not get inside, a condition known as insulin resistance. Because many type 2 diabetics seem to be incapable of secreting enough insulin to overcome insulin resistance, it is likely that in such cases an additional defect exists in the beta-cells that impairs insulin secretion. Other factors may also play a role in type 2 diabetes.

Maturity-Onset Diabetes in Youth. Maturity-onset diabetes in youth (MODY) is a rare genetic form of type 2 diabetes that usually develops in thin teenagers; it accounts for 2% to 5% of type 2 cases. A variant has also been reported in Florida among African Americans. In about half of these families an abnormality in a liver enzyme is most likely responsible for this condition.

Gestational Diabetes. About 0.5% of pregnant women develop a form of type 2 diabetes in their third trimester called gestational diabetes. After delivery, blood glucose levels generally return to normal, although one-third to one-half of these women develop type 2 diabetes within 10 years.

Type 1 Diabetes

In type 1 diabetes, the 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, and excessive hunger and thirst are among the consequences of this "starvation in the midst of plenty." Patients become dependent on administered insulin for survival. [see, *Diabetes: Type 1, Comprehensive Version.*]

Diabetes Secondary to Other Conditions

Conditions that damage or destroy the pancreas, such as pancreatitis, pancreatic surgery, or certain industrial chemicals can cause diabetes. Certain drugs can also cause temporary diabetes, including corticosteroids, beta-blockers, and phenytoin. Rare genetic disorders (Klinefelter's syndrome, Huntington's chorea, Wolfram's syndrome, leprechaunism, Rabson-Mendenhall syndrome, lipoatrophic diabetes, and others) and hormonal disorders (Acromegaly, Cushing's syndrome, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma) also increase the risk for diabetes.

What Causes Type 2 Diabetes?

Type 2 diabetes is caused by a complicated interplay of genes, environment, insulin abnormalities (reduced insulin secretion in the beta-cells and insulin resistance in muscle cells), increased glucose production in the liver, increased fat breakdown, and possibly defective hormonal secretions in the intestine.

Causes of Insulin Resistance

Elevated levels of three factors are believed to be involved in development of obesity and insulin resistance leading to type 2 diabetes. They are: free fatty acids (acids in the blood produced by breakdown of fat), leptin (a protein produced by fat cells), and tumor-necrosis factor, or TNF (a component of the immune system). How each of these factors contributes to type 2 diabetes is under investigation.

Genetic Factors

Genetic factors play an important role in type 2 diabetes, but the pattern is complicated, since both impairment of beta-cell functions and an abnormal response to insulin are involved. Researchers have identified a number of genetic suspects. In certain Caucasian populations, a single gene may alter the metabolism of fatty acids that leads to insulin resistance. Researchers have also identified the P2 gene, which appears to be critical for the link between obesity and insulin resistance. Australian researchers have identified a defective lipoprotein lipase (LpL) gene, which poses a risk for coronary artery disease and type 2 diabetes in people who have it. Researchers also have identified a defective gene that regulates glucose metabolism, which may provide the link between low birth weight and a later risk for type 2 diabetes and insulin resistance. A defective gene has been detected that reduces activity of a protective substance called B₃-adrenergic receptor, which is found in *visceral* fat cells (those occurring around the abdominal region). The result is a slow-down in metabolism and an increase in obesity. The defective gene has been found in Pima Indians and other populations with a very high incidence of type 2 diabetes and obesity.

One theory suggests that some cases of type 2 diabetes and obesity are derived from normal genetic actions that were once important for survival. Some experts postulate the existence of a so-called "thrifty" gene, which regulates hormonal fluctuations to accommodate seasonal changes. In certain nomadic populations, hormones are released during seasons when food supplies have traditionally been low, which results in resistance to insulin and efficient fat storage. The process is reversed in seasons when food is readily available. Because modern industrialization has made high-carbohydrate and fatty foods available all year long, the gene no longer serves a useful function and is now harmful because fat, originally stored for famine situations, is not used up. Such a theory could help explain the high incidence of type 2 diabetes and obesity found in Pima tribes and other Native American tribes with nomadic histories and Western dietary habits.

Who Gets Type 2 Diabetes?

Diabetes, particularly type 2, is reaching epidemic proportions throughout the world as more and more cultures adopt Western dietary habits. The increased incidence in obesity appears to be the primary reason for this increase. In the US alone, it is estimated that 16 million people have diabetes and that about half are unaware they have it.

Age

The onset of type 2 diabetes typically occurs after the age of 40. Aging itself may increase the risk for glucose intolerance and diabetes. In one study, diabetes occurred in only 5.9% of men and 3.8% of women younger than 60 years but in nearly 20% of men and women older than 85 years. Although still uncommon, of major concern is a significant increase in type 2 diabetes in children and adolescents, most likely due to rising rates of childhood obesity.

Low Birth Weight

Research now indicates that low birth weight is a risk factor for type 2 diabetes. Some research indicates that malnutrition in the pregnant woman may be responsible for causing metabolic abnormalities in the developing fetus that eventually lead to diabetes.

Obesity

The rate of obesity is very high in type 2 diabetics, and some studies have found that, regardless of family history, even modest weight gain is associated with an increased risk for diabetes. Excess body fat appears to play a strong role in insulin resistance, but the way it's distributed is also important. 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. Fat that settles in a "pear-shape" around the hips and flank appears to have a lower association with these conditions. One study suggested that waist circumferences greater than 35 inches in women and 40 inches in men signify increased risk for heart disease and diabetes.

Family History

Between 25% to 33% of all patients have a family history of the disease, and people with first degree relatives have a 40% lifetime risk for diabetes.

Ethnicity

The risk for diabetes type 2 is higher in African and Hispanic Americans than in non-Hispanic Caucasian-Americans. One study found that African-American women in general have a higher rate of insulin resistance from high-fat diets than do non-African-Americans, suggesting the presence of a genetic factor. One 1999 study also found that African Americans with diabetes are also at higher risk for amputations than diabetic Caucasians, which is most likely due to a higher incidence of high blood pressure and smoking as well as poorer health care. The Pima tribe in Arizona has an incidence of type 2 diabetes that is 19 times higher than that of the white population. The association between diet and diabetes remains critical, however in assessing these ethnic differences. In one study, Mexican Pimas had lower fat (but higher overall calorie) intake and more intense physical activity than Arizona Pimas. They also had only a 6% incidence of obesity and diabetes, which was equivalent to their non-Pima neighbors. The incidence of

diabetes in their Arizona Pima relatives, however, was 40%. Other Native American tribes in North America are also at high risk for type 2 diabetes.

Risk Factors for Gestational Diabetes

Even modest weight gain (11 to 22 pounds) during early adulthood increases the risk for gestational diabetes (temporary diabetes during pregnancy). Other risk factors include a family history of diabetes, smoking, belonging to African American, Hispanic, or Asian ethnic groups, gaining weight before getting pregnant, and being an older mother. In women who develop gestational diabetes during pregnancy, taking contraceptives that only have progestins while breast feeding puts them at high risk for developing type 2 diabetes.

What Are The Symptoms Of Type 2 Diabetes?

Type 2 diabetes usually begins gradually and progresses slowly. Symptoms may not appear for years, even decades. They include excessive thirst, increased urination, fatigue, blurred vision, and weight loss. In women with diabetes, vaginal yeast infections are common. Fungal infections may occur under the breasts or in the groin. Severe gum problems, worsening vision, itching, impotence, and unusual sensations, such as tingling or burning, in the extremities may also be signs of type 2 diabetes.

How Serious Is Type 2 Diabetes?

Emergency Conditions

Hypoglycemia. Intensive insulin control increases the risk of hypoglycemia (also called insulin shock), which occurs if blood glucose levels fall below normal. Hypoglycemia may also be caused by insufficient intake of food, 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. Mild symptoms usually occur at moderately low and easily correctable levels of blood glucose; they include sweating, trembling, hunger, and rapid heartbeat. Severely low blood glucose levels can precipitate neurologic symptoms: confusion, weakness, disorientation, combativeness, and in rare and worst cases, coma, seizure, and death. Patients who experience repeated episodes of hypoglycemia may become insensitive to symptoms; even a single recent episode of hypoglycemia may make it more difficult to detect the next episode. By rigorously avoiding low blood glucose, such patients can regain the ability to sense the symptoms. Patients are at highest risk for hypoglycemia at night. Bedtime snacks may be helpful. Most experts recommend that patients monitor blood levels as often as possible, four times or more per day. This is particularly important for patients who have a history of experiencing no symptoms of hypoglycemia before mental changes occur. Diabetic patients on therapies that put them at risk for hypoglycemia should always carry hard candy, juice, or sugar packets. Family and friends should be aware of the symptoms. If the patient is helpless, they should administer three to five pieces of hard candy, two to three packets of sugar, or half a cup (four ounces) of fruit juice. If there is inadequate response within 15 minutes, additional oral sugar should be provided or the patient should receive emergency medical treatment including the intravenous administration of glucose. Family members and friends can learn to inject glucagon, a hormone, which, unlike insulin, raises blood glucose.

Ketoacidosis. Diabetic ketoacidosis is a life-threatening complication caused by insulin depletion that results in an excessive amount of glucose present in the bloodstream. Fat breakdown accelerates and increases the production of fatty acids; these are converted into chemicals called ketone bodies, which are toxic at high levels. Ketoacidosis is almost always associated with type

1 diabetes and has been thought to be rare in type 2 because some insulin exists in these patients. A 1999 study reported, however, that ketoacidosis may occur with some frequency in type 2 diabetes, especially among Hispanic and African Americans. Research is needed to find which patients are at particular risk. In type 1, ketoacidosis is almost always caused by noncompliance with insulin treatments and is usually preceded by a stressful event such as an illness. It is not clear, however, what causes total insulin depletion in some type 2 diabetics or what triggers the event. Symptoms of ketoacidosis include nausea and vomiting. Breathing may be abnormally deep and rapid with frequent sighing. The heartbeat may be rapid. If the condition persists, coma and, eventually death, may occur, although over the past 20 years, death from ketoacidosis has decreased to about 2% of all cases. Other serious complications from ketoacidosis include aspiration pneumonia and adult respiratory distress syndrome. Life-saving treatment employs rapid rehydration using a saline solution followed by low-dose insulin and potassium replacement.

Long-Term Complications of Diabetes

The major complications in diabetes are due to vascular (blood vessel) abnormalities and nerve damage (neuropathy). Injuries in large blood vessels endanger the heart, particularly in people with existing heart disease or high blood pressure and can cause leg problems. Small blood vessel (microvascular) changes can harm the eyes and kidneys.

Cardiovascular Complications. Heart attacks account for 60% and strokes for 25% of deaths in all diabetics. A 1998 study reported that people with type 2 diabetes and no history of heart disease have the same seven-year risk for a heart attack as nondiabetics with heart disease. Long-term insulin resistance, even without type 2 diabetes, appears to have significant damaging effects on the heart, including contributing to very unhealthy cholesterol and lipid balances (high triglyceride levels and lower high density lipoprotein), blood clotting problems, and high blood pressure. Insulin resistance injures the heart whether or not the patient is obese or has unhealthy fat distribution. Hypertension is a major factor in the higher risk for stroke in people with diabetes but insulin resistance strokes also play a strong role. Research is indicating that abnormalities in secretion of stress hormones (particularly cortisol) may be the link between insulin resistance and hypertension.

Neuropathy, Vascular Injury, and Amputations. Neuropathy is a common complication that affects about 45% of both type 1 and type 2 diabetics after 25 years. Neuropathy is decreased or distorted nerve function; it particularly affects sensation. Symptoms include numbness, tingling, weakness, and burning sensations, usually starting in the fingers and toes and moving up to the arms and legs (called a glove and stocking distribution). If the nerves are damaged as well, the person may be unaware that even a blister or minor wound has become infected. The problem is compounded in diabetes because of circulatory problems resulting from blood vessel injury, which may be severe enough to cause tissue damage in the legs and feet. Even minor infections can develop into deep tissue injury. Extensive surgery may be required, and, in extreme cases, amputation of the foot or leg may be necessary. Charcot foot is a condition associated with neuropathy that causes bone deformity. It can occur as an isolated complication or after foot or ankle surgery. Charcot foot may cause little pain, but should be suspected in cases of swelling and redness in a single leg or foot. It results in abnormal pressure on the foot and increases the risk for foot ulcers and amputation. Diabetes is responsible for more than half of all the lower limb amputations performed in the US each year, many of which can be prevented by early and aggressive treatment of feet and ankle problems.

If diabetes affects the nerves in the autonomic nervous system, then abnormalities of blood pressure control, bowel and bladder function, and male sexual function can also occur. In some cases, neuropathy may block angina, the warning chest pain for heart disease and heart attack.

Diabetic patients should be aware of other warning signs of a heart attack, including sudden fatigue, sweating, shortness of breath, nausea, and vomiting.

Eye Complications. Diabetes accounts for 12,000 to 24,000 of new cases of blindness annually and is the leading cause of new cases of blindness in adults ages 20 to 74. Given long duration of the disease, most type 2 patients will develop retinopathy, abnormalities of the blood vessels in the retina, at some point in their lives. However only a minority will develop retinopathy so severely that partial or total blindness results. About 20% of type 2 patients have some eye damage when diagnosed, and blurred vision is common. In nonproliferative or background retinopathy, the early and more common type of this disorder, abnormally weakened blood vessels in the retina 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 weak blood vessels become blocked and blood flow is cut off, soft, "woolly" areas may develop in the retina's nerve layer. These areas may signal the development of proliferative 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, possibly causing severe visual loss or blindness. Although the sensation of seeing flashing lights may indicate retinal detachment, often there are no symptoms of progressing retinopathy. People with diabetes are also at higher risk for developing cataracts and certain types of glaucoma.

Kidney Damage (Nephropathy). Kidney disease is a very serious complication of diabetes. The risk for this complication is compounded by the presence of hypertension, coronary artery disease, and problems in the urinary tract. Symptoms include swelling in the feet and ankles, fatigue, and pale skin color.

Mental Function and Dementia. 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 55 who have had diabetes for a number of years.

Other Complications. People with diabetes are at 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. Women with type 2 diabetes face a higher risk for uterine cancer, although only if they are obese. Both women and men with diabetes appear to have a higher risk for colon and rectal cancers.

Complications in Pregnancy. Both preexisting diabetes in pregnant women and temporary diabetes that occur during pregnancy (gestational diabetes) can increase the risk for birth defects. Because glucose crosses the placenta, a woman with diabetes can pass high levels of blood glucose to the fetus. In response, the fetus secretes large amounts of insulin. This combination of high fetal blood levels of insulin and glucose leads to excessive fetal growth. It may also contribute to delayed maturation of the lungs or to the death of the fetus. In addition to endangering the fetus, diabetes also presents risks to the pregnant woman, particularly preeclampsia, a potentially dangerous condition involving very high blood pressure. Studies indicate that hyperglycemia may effect the developing fetus as soon as it is conceived. Diabetic women who want to become pregnant should be diligent about controlling blood glucose levels before and during pregnancy. It is not clear whether women with mild gestational diabetes should control blood glucose levels as intensely since some studies have indicated that lower birth weights may result.

What Are The Diagnostic Tests For Type 2 Diabetes?

Diagnosing Diabetes

Experts now recommend that everyone over age 45 be tested regularly for diabetes. Younger adults should be tested under the following conditions: if they weigh 20% more than ideal body weight, have high blood pressure, low HDL cholesterol levels (under 35 mg/dl), high triglyceride levels (over 250 mg/dl), have a close relative with diabetes, are from a high-risk ethnic group, have delivered a baby weighing over nine pounds, or have a history of gestational diabetes. All pregnant women should be tested for gestational diabetes between their 24th and 28th week. Pregnant women at high risk for diabetes should be tested earlier.

Testing for Diabetes

Fasting Plasma Glucose. In order to simplify the diagnosis of diabetes, the American Diabetes Association has recommended the sole use of the fasting plasma glucose (FPG) test. It is a simple blood test taken after eight hours of fasting. FPG levels are considered normal up to 110 mg/dl (or 6.1 mmol/L). Levels between 110 and 125 (6.1 to 6.9 mmol/L) are referred to as impaired fasting glucose, which is considered to be a risk factor for developing diabetes type 2 and its complications and is treated with diet and exercise. Diabetes is diagnosed when FPG levels are 126 mg/dl (7.0 mmol/L) or higher on two different days. The FPG test is not always reliable and there is considerable controversy about using it as the sole basis for diagnosing diabetes. Some experts argue that the 126 mg/dl cut-off causes many people to be diagnosed with diabetes type 2 who are only at very small risk for complications. Others argue that, on the other hand, it misses many people with normal FPG levels who are at risk for complications. Some research indicates that the FPG is not as accurate as the glucose tolerance test for detecting diabetes in certain people, such as women with a history of gestational diabetes or certain Asian populations. It is also not as useful as the glucose tolerance test in identifying people who have an increased risk for heart disease or death. At this time, even if a person has normal FPG levels but still has symptoms of diabetes and a family history or other risk factors, then diabetes should not be ruled out and a glucose tolerance test should also be performed.

Glucose Tolerance Test. A glucose tolerance test first employs an FPG test; a blood test is then taken two hours later after drinking a special glucose solution. Normally, blood sugar increases modestly after drinking the glucose beverage and decreases after two hours; in the diabetic, the initial increase is excessive and the level remains high, 200 mg/dL (11.1 mmol/L) or more. Many experts believe this test is still important as an initial diagnostic tool for identifying people whose FPG tests are normal but who still may have impaired glucose tolerance, putting them at higher risk for heart disease and death.

Test for Glycosylated Hemoglobin. Another test examines blood levels of hemoglobin A_{1c} (HbA_{1c}) also called glycosylated hemoglobin. Hemoglobin, a protein molecule found in red blood cells, becomes modified by having glucose bound to it. Much evidence exists that this process, called glycosylation, affects a number of proteins and is strongly associated with complications of diabetes. Measuring glycosylated hemoglobin is useful for predicting complications in patients with existing diabetes. The test is not affected by food intake so it can be taken at any time. A glycosylated hemoglobin level of 1% above normal range identifies diabetes in 98% of patients. Normal HbA_{1c} levels do not necessarily rule out diabetes, but if diabetes is present and levels are normal, the risk for complications is low. The test is not currently used for an initial diagnosis, but some experts think it should be used to help predict complications in people who have FPG levels that are above normal but do not indicate full-blown diabetes (110-139 mg/dL).

Screening Tests for Complications

The earliest manifestation of kidney damage is microalbuminuria, in which tiny amounts (30 to 300 mg per day) of protein called albumin are found in the urine. About 20% of type 2 patients show evidence of microalbuminuria upon diagnosis of diabetes. It should be noted, however, that only a small percentage of type 2 diabetics eventually develop kidney disease. Microalbuminuria is also a marker for other complications involving blood vessel abnormalities. (Contrary to previous reports, microalbuminuria does not appear to be an indicator of heart disease.) A blood test that indicates elevated levels of a substance called metalloproteinase-9 may be an even earlier predictor for kidney damage, allowing early intervention to prevent complications. All patients should be tested for hypertension. Tests for cholesterol and lipid levels, an electrocardiogram, and possibly thyroid function tests should be performed.

What Are Life-Style Measures For Treating And Preventing Type 2 Diabetes?

Diet and Weight Loss

For most people with diabetes, diet control is the key to managing this complicated disease. It is also extremely difficult. The current state of the diabetic diet is in flux, and at this time, there is no single diet that meets all the needs of everyone with diabetes. Patients should meet with a professional dietitian to plan an individualized diet that takes into consideration all health needs. There are some constants, however. The general rules for healthy eating apply to everyone: limit fats (particularly saturated fats and trans-fatty acids), protein, and cholesterol, and consume plenty of fiber and fresh vegetables. All people with diabetes should aim for healthy lipid (cholesterol and triglyceride) levels and control of blood pressure. For overweight type 2 diabetics, both weight loss and blood glucose control are important. Health benefits are highest with the first pounds lost, and losing only 10% of body weight can control progression of diabetes. Unfortunately, many of the oral medications used in type 2 diabetes cause weight gain. For obese patients who cannot control weight using dietary measures alone, weight-loss drugs, such as orlistat (Xenical) or sibutramine (Meridia), may be beneficial. In one study, orlistat not only helped reduce weight but also improved glucose, cholesterol, and lipid levels. Surgical procedures are proving to be extremely beneficial in selected cases. [For detailed information, see *Diabetes Diet and Obesity, Comprehensive Version.*]

Exercise

Exercise helps lower blood glucose and increases insulin sensitivity; it also helps lower blood pressure, improve cholesterol levels, decrease body fat, and reduce the risk of cardiovascular disease. Aerobic exercise is best. Regular exercise, even of moderate intensity, improves insulin sensitivity and can even prevent type 2 diabetes. In fact, studies of older people who engage in regular moderate aerobic exercise (eg, brisk walking, biking) lower their risk for diabetes even if they don't lose weight. For best and fastest results, experts advise frequent high-intensity (not high-impact) exercises for people who are cleared by their physicians. For people who have been sedentary or have other medical problems, lower-intensity exercises are recommended using regimens designed with physicians. Patients who are taking medications that lower blood glucose, particularly insulin, should take special precautions before embarking on a workout program. Because diabetics may have silent heart disease, they should always check with their physicians before undertaking vigorous exercise. Exercise, particularly resistance or high impact exercises, can strain weakened blood vessels in the eyes of patients with retinopathy. High-impact exercise may also injure blood vessels in the feet. [For more detailed information, see *Exercise, Comprehensive Version.*]

Monitoring Blood Glucose

In patients being treated with insulin or insulin-producing or sensitizing drugs, it is important to monitor blood glucose levels carefully to avoid hypoglycemia. Patients should aim for pre-meal glucose levels of between 80 and 120 and bedtime levels of between 100 and 140. Blood glucose levels are generally more stable in type 2 diabetes than in type 1, so experts usually recommend measuring blood levels only once or twice a day. Usually, a drop of blood obtained by pricking the finger is applied to a chemically treated strip. The glucose level is read on a standard meter or a small, portable digital display device.

Daily Foot Care

Preventive foot care could reduce the risk of amputation by 44% to 85%. Patients 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. Moisturizers should be applied, but not between the toes. Corns and calluses should be gently pumiced and toenails trimmed short and the edges filed to avoid cutting adjacent toes. Patient should not use medicated pads or try to shave the corns or calluses themselves. They should avoid high heels, sandals, thongs, and going barefoot. Shoes should be changed often during the day. Tight stockings or any clothing that constricts the legs and feet should be avoided. A specialist in foot care should be consulted for any problems.

What Are Drug Treatments For Type 2 Diabetes?

General Guidelines

Although many type 2 diabetics can control their condition with diet and exercise alone for years, most eventually need medications. Unlike type 1 diabetes, in type 2 diabetes some insulin is still produced, although not in the amounts necessary to overcome insulin resistance. Patients, then, who need medications usually start out with drugs that enhance residual insulin production or sensitivity rather than replacing insulin directly, the standard treatment for type 1 diabetics. Such drugs usually have a lower risk for hypoglycemia and weight gain than insulin has. The drugs currently recommended for initial treatment are the sulfonylureas, which produce insulin secretion, or metformin, which makes tissue more sensitive to residual insulin. Others are also proving to be very effective. A recent approach, for example, involves the use of new, rapid-acting insulin-secreting drugs, such as repaglinide, at meal times in order to avoid high blood glucose levels after eating (postprandial hyperglycemia). Patients may be able to control their glucose levels with single drugs, although one study reported that after three years, half of the patients needed more than one, and at nine years, only 25% could remain on a single agent. Eventually, natural insulin may completely fail and insulin replacement is needed.

Different goals may be required for specific individuals, including pregnant women, very old and very young people and those with accompanying serious medical conditions. Studies are now indicating that, as in type 1 patients, rigorous control of blood glucose levels can help reduce the risk for complications of diabetes, particularly retinopathy, but also kidney and nerve damage. People with diabetes, then, should aim for glycolated hemoglobin levels of less than 7% and fasting plasma glucose concentrations below 110 mg/dL. Taking such actions can reduce the complication rates by between 25% and 33%. Controlling risk factors for heart disease and stroke, particularly high blood pressure (which is also a risk factor for kidney disease) as well as unhealthy cholesterol levels, is also essential. Patients should aim for blood pressure below 130/80 mmHg and LDL cholesterol below 100 mg/dL. Intensive insulin-secreting drugs or insulin itself, however, put patients at increased risk for weight gain and atherosclerosis. Because of the weight gain often produced by rigorous control of blood sugar some, experts argue that it may do more harm than good in type 2 diabetics, who tend to be overweight in the first place.

Furthermore, only a relatively small number of people may actually derive additional benefits from intensive treatments, since only a small percentage of type 2 diabetics actually develop the serious kidney and eye complications that are common in type 1 diabetes. Heart disease is a far greater problem. Newer insulin-sensitizing medications may pose less of a risk for weight gain, however, and new weight loss drugs are also proving to be helpful for some patients. Patients should discuss all options with their physicians.

Sulfonylureas and Other Insulin Secreting Drugs

Sulfonylureas. Sulfonylureas are oral drugs that stimulate the pancreas to release insulin. A number of brands are available, including chlorpropamide (Diabinese), tolazamide (Tolinase), acetohexamide, glipizide (Glucotrol), tolbutamide (Orinase), glimepiride (Amaryl), glyburide (DiaBeta, Micronase), glibenclamide, and gliclazide. Gliclazide may have specific benefits for the heart. For adequate control of blood glucose levels, the drugs should only be taken 20 to 30 minutes before a meal. Sulfonylureas can cause weight gain, so leaner patients are better candidates than those who are overweight. Water retention may also occur. Although sulfonylureas pose a lower risk for hypoglycemia than insulin does, the hypoglycemia produced by sulfonylureas may be prolonged and dangerous. They may pose a slight risk for cardiac events. They also interact with many other drugs. In general, sulfonylureas should not be used by women who are pregnant or nursing or by individuals who are allergic to sulfa drugs. The drugs are effective for about seven to 10 years in most patients, although combinations with small amounts of insulin or with other newer drugs, particularly metformin or a thiazolidinedione, may extend their benefits.

Other Insulin-Secreting drugs. Repaglinide (Prandin) stimulates beta-cells to produce insulin as sulfonylureas do but are particularly effective for preventing high levels of blood glucose after eating (postprandial hyperglycemia), because they are rapidly metabolized and short acting. Repaglinide is taken before every meal and mimics the normal effects of insulin after eating. Patients can vary meal times with this drug, since it only needs to be taken before eating. It is particularly effective in combination with metformin. It also appears to be a good drug for people with potential kidney problems. Side effects include diarrhea and headache. As with the sulfonylureas, it has a slightly increased risk for cardiac events. Long-term studies are underway. Other, similar drugs are under investigation. Nateglinide, for example, also stimulates insulin secretion and is effective in controlling blood glucose, but may produce less stress on heart tissue than repaglinide or the sulfonylureas.

Metformin

Metformin (Glucophage) is a biguanide drug, which appears to work by reducing glucose production in the liver and by making tissues more sensitive to insulin. Combinations with insulin-secreting, other insulin-sensitizing drugs, or insulin itself are proving to be particularly effective. Metformin does not cause hypoglycemia or add weight, so it is particularly well suited for obese type-2 patients. (In some studies, in fact, patients lost weight.) Metformin also appears to have a beneficial effect on cholesterol and lipid levels. Side effects include a metallic taste, nausea, and diarrhea. It may also reduce absorption of vitamin B12 and folic acid, which are important for protection against heart disease. Some studies have shown a risk for lactic acidosis, a potentially life-threatening condition, but more recent ones suggest that metformin poses no additional risk for this side effect and previous results may have been due to coincidence. People with kidney or liver disease should still avoid this drug.

Thiazolidinedione

Thiazolidinediones improves insulin sensitivity by activating certain genes involved in fat synthesis and carbohydrate metabolism. They include troglitazone (Rezulin), rosiglitazone (Avandia), and pioglitazone (Actos). Thiazolidinediones do not cause hypoglycemia when used alone, although they are usually taken in combination with sulfonylureas, insulin, or metformin. Troglitazone was the first approved and most studied to date. Troglitazone has downsides, however, some considerable. Between 2% and 4% of people taking the drug experience toxic but reversible effects in the liver. There have been reports of liver failure and death. It should be noted that the risks for these very severe effects on the liver are only 1 in 57,000 and the manufacturer claims that no cases have been reported after 11 months of use. The FDA now requires that the drug be used only for patients who cannot control their diabetes with other medications. It should not be used as initial single-drug treatment and anyone taking it should have an initial liver function test before starting followed by additional tests every month during the first year and quarterly thereafter. This severe effect does not appear to apply to rosiglitazone and pioglitazone. Long-term effects are not yet known for the newer drugs, however, and at this time patients taking them must follow the same monitoring guidelines as for Rezulin. About 50 cases of heart failure have been attributed to the use of troglitazone, although some studies suggest that the drug may have some long-term benefits for the heart, including positive effects on hypertension and abnormal cholesterol and lipid levels (lower triglycerides and higher HDL cholesterol). The effects of the other thiazolidinediones on the heart are not clear. Weight gain can be a problem for any of these drugs, although one interesting study on Rezulin reported that while patients gained weight overall, they *lost* weight in the abdominal area, where it is most dangerous. Other side effects of thiazolidinediones include anemia and fluid-build up (edema). (In some cases, the fluid may contribute to weight gain.)

Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors, including acarbose (Precose, Glucobay) and glyset (Miglitol) reduce glucose levels by interfering with its absorption in the small intestine. Acarbose tends to lower insulin levels after meals, an advantage, since higher levels of insulin after meals are associated with an increased risk for heart disease. It is not as effective alone as other single oral drugs, but combinations, such as with metformin, insulin, or a sulfonylurea, increase its effectiveness. It does 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, since acarbose inhibits the breakdown of complex sugar and starches, including table sugar. The most common unpleasant side effect is flatulence, particularly after high-carbohydrate meals, which causes about a third of patients to stop taking it. The drug may also interfere with iron absorption.

Insulin

For some people who cannot control their diabetes with diet or insulin-enhancing or sensitizing drugs alone, a night time dose of insulin along with a sulfonylurea is effective. Insulin may also be a temporary option, such as during pregnancy. Eventually, however, the disease deteriorates in many people with type 2 diabetes and full insulin replacement is required. Some experts are investigating the use of starting insulin earlier in certain patients with type 2 diabetes in order to ensure strict control of blood glucose. Inhaled insulin may prove to be particularly beneficial for type 2 diabetics. Some studies to date indicate, however, that patients do just as well or even better over the long-term starting with the less intensive, standard oral medications. More research is needed. [For detailed information on insulin therapy, see *Diabetes: Type 1, Comprehensive Version*.]

Hormone Replacement Therapy

Hormone replacement therapy (HRT) may be particularly beneficial for women with diabetes and may even prevent type 2 diabetes. A number of studies are reporting better glucose control in women taking HRT and even improvement in beta-cell function.

Investigative Agents

Glucagon-like Insulinotropic Peptide (GLP-1). Glucagon-like insulinotropic peptide (GLP-1) appears to help metabolize glucose and reduce appetite. In one study, GLP-1 reduced requirements for additional insulin and appeared to inhibit the surge in blood glucose following meals. Until recently, it was administered only through injections, but it can now be taken as a transmucosal tablet (placed between the lip and gum). In one study, a single tablet reduced glucose minutes and had a 90-minute duration. Overnight and 48-hour infusions are also showing benefits.

Pramlintide. Pramlintide (Symlin), known as an amylin analog, is derived from a natural hormone that acts in concert with the body's insulin in the pancreas to control hyperglycemia. It slows stomach emptying and delays absorption of nutrients in the intestine. Some studies indicate that it helps control glucose levels without increasing the risk for hypoglycemia or increasing weight when added to insulin regimens. It is being tested for both type 1 and type 2 insulin-dependent diabetes.

Niacin Derivatives. Acipimox, a drug derived from niacin (vitamin B3), reduces free fatty acid (FFA) levels, which are involved in insulin resistance. One study reported that it improved glucose levels, although another indicated the benefits may be transient.

Benfluorex. Benfluorex lowers insulin resistance in the liver and muscle and may be more effective than a biguanide.

How Are Complications Of Type 2 Diabetes Treated?

Treating and Preventing Heart Disease

One study reported that people with type 2 diabetes and no history of heart disease had the same seven-year risk for a heart attack as patients with established heart disease. People with diabetes have still not achieved the reductions in mortality rates from heart disease as the rest of the population, although a number of advances may improve these findings. Some studies are showing that cholesterol-lowering medications, particularly those known as statins (eg, simvastatin, pravastatin), can reduce the risk for adverse heart events in people with diabetes, even if their cholesterol levels are normal or if their diabetes is mild. Taking a daily aspirin is also protective. The anti-hypertensive drugs angiotensin-converting enzyme (ACE) inhibitors are proving to have remarkable benefits for people with diabetes. They have been shown to reduce the risks of heart attack, stroke, and death in people with diabetes and to delay the onset and progression of kidney disease by 30% to 60%, even in patients without hypertension. ACE inhibitors may even help prevent or limit progression of foot ulcers and retinopathy. Some experts recommend ACE inhibitors for *all* middle-aged type 2 diabetics. [For more information, see *Cholesterol, Other Lipids, and Lipoproteins* and *Angina and Coronary Artery Disease, Comprehensive Version.*]

Treatment and Prevention of Nephropathy

Strict blood glucose control may delay progression of kidney disease and other diabetic-related complications in type 2 diabetics as well as type 1. A number of studies have shown that tight

blood glucose control using intensive insulin therapy delays progression of kidney disease. High hemoglobin A_{1c} (glycolated hemoglobin) levels may relate directly to a risk for kidney dysfunction. One study indicated, in fact, that patients could reduce the risk for kidney disease by maintaining glycolated hemoglobin levels at 8% or below rather than trying to keep strict control of glucose levels. (Such a strategy might also help prevent retinopathy.) Control of existing high blood pressure is extremely important not only for heart disease, stroke, and heart failure but also for preventing progression to kidney failure. [For more detailed information, see *High Blood Pressure*.]

Treatment of Neuropathy

Studies show that tight control of blood glucose levels also delays the onset and slows progression of neuropathy, although there is some concern that the increased incidence of hypoglycemia with intensive insulin control may actually cause nerve damage . The tricyclic antidepressant amitriptyline (Elavil) and topical capsaicin (the active ingredient in hot peppers) are commonly used for neuropathy pain. Amitriptyline is effective in up to 75% of patients. Unfortunately tricyclics also carry some distressing side effects. Other antidepressants with fewer side effects, including sertraline (Zoloft) and nefazodone (Serzone), are showing promise. The anti-seizure drug gabapentin (Neurontin) may be an effective alternative to amitriptyline, but it is more expensive and patients report as many side effects. Tramadol (Ultram), a pain killer that is similar to opioids, achieved moderate pain reduction in one study and may have fewer side effects than anti-seizure drugs or tricyclics, although it carries a risk for addiction; nausea, headache, and constipation are common. If foot pain, numbness, or tingling is worse at night, diphenhydramine (Benadryl) may help. Vitamin E supplements may be helpful. Delayed stomach emptying caused by neuropathy may be relieved by erythromycin or metoclopramide (Reglan). Investigators are testing a number of nerve-protective substances, particularly nerve-growth and insulin-like growth factor. In recent trials, patients taking nerve-growth factor experienced both greater sensation and reduced levels of pain and discomfort with few side effects.

Treatment and Prevention of Retinopathy

Tight insulin control is also proving to help prevent retinopathy in patients with either type 1 or 2 diabetes. It should be noted that intense glucose control can cause early worsening of retinopathy, although this is nearly always counterbalanced by long-term benefits. Reducing the risks for heart disease using blood pressure lowering medications (particularly ACE inhibitor or beta-blockers) and drugs that improve cholesterol levels may also have protective benefits for the eyes. Once damage to the eye develops, eye surgery may be needed. Argon or diode laser photocoagulation is proving to be particularly effective in reducing severe visual loss from retinopathy, and is useful for patients with macular edema when fluid build-up threatens the retina. A surgical technique called vitrectomy removes scarred tissue in the eye, helps flatten areas of detached retinal material, and can improve vision in patients with severe eye hemorrhage.

Treatment of Foot Problems

Daily foot care is extremely important for people with diabetes who are at risk for nerve damage and poor blood flow to the feet. Preventive foot care could reduce the risk of amputation in people with diabetes by 44% to 85%. Patients should make a daily inspection 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. Moisturizers should be applied, but not between the toes. Corns and calluses should be gently pumiced and toenails trimmed short and the edges filed to avoid cutting adjacent toes. Patients should not use medicated pads or try to

shave the corns or calluses themselves. People with diabetes should avoid high heels, sandals, thongs, and going barefoot. Shoes should be changed often (three times a day if possible). They should not wear tight stockings or any clothing that constricts the legs and feet. A new hand-held device that uses a nylon fiber brush may enable the physician to identify nerve damage that can lead to ulcers by pressing it against several points on the foot and eliciting the patient's response to the pressure. About one-third of foot ulcers will heal within 20 weeks with good wound care treatments. A number of treatments (Dermagraft, Apligraf, Regranex) are now available that stimulate new cell growth and help heal skin ulcers or use cultures of human skin cells, although their benefits are still unproven. Hospitalization and intravenous antibiotics for up to 28 days may be needed for severe foot ulcers. Granulocyte-colony stimulating factor, or G-CSF (filgrastim, Neupogen, Amgen) is showing promise as an effective alternative to antibiotics. One study showed that G-CSF accelerated healing and significantly reduced the need for surgery. Another study indicated that administering hyperbaric oxygen (given at high pressure) promoted healing and helped prevent amputation. There was no follow-up however, and more research is needed. 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.

Prevention of Infections

Everyone with diabetes who is at risk for complications should have annual influenza vaccinations and a vaccination against pneumococcal pneumonia.

Where Else Can Information On Type 2 Diabetes Be Obtained?

American Diabetes Association, ADA National Service Center, 1660 Duke Street, Alexandria, VA 22314. Call (800-232-3472) or (call 800-DIABETES) or on the Internet (<http://www.diabetes.org/>)

This is the primary source for information on diabetes.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Building 31, Room 9A04, 9000 Rockville Pike, Bethesda, MD 20892. Call (301-654-3327) or on the Internet (<http://www.niddk.nih.gov/>)

A source of information for research advances and clinical trials currently underway. For those who have relatives with diabetes and may be at risk and are interested in participating in a trial on prevention (call 800-Halt-DM-1).

National Eye Health Education Program, National Eye Institute, Box 20/20, Bethesda MD 20892. Call (301-496-5248) or (800-869-202) or on the Internet (<http://www.nei.nih.gov/>)

Medic Alert, 2323 Colorado Ave., Turlock, CA 95380. Call (800-825-3785) or (800-ID-ALERT) or on the Internet (<http://www.medicalert.org>)

This organization provides bracelets or neck chain emblems with critical personal medical information.

American Dietetic Association, 216 West Jackson Boulevard, Suite 800, Chicago IL 60606-6995.
Call (312/899-0040) or on the Internet (<http://www.eatright.org/>)

This organization provides names of local dietitians and programs through their Dietitian Referral Hotline (call 800-366-1655) from 9AM to 4PM. For customized answers to food and nutrition questions call (900-225-5267); charge is \$1.95 for the first minute and \$.95 for each additional minute.

Special Instructions: