

## SANTA MARTHA MEDICAL CLINIC

### EDGARD ALFONSO ARCIA-BRAVO

677 Richmond St. Suite # 1  
London, Ontario N6A5M1  
519-850-3335

# Diabetes: Type 2

## 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 diabetes type 1 and type 2 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 normally 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 ten minutes after a meal, insulin rises to its peak level.
- Insulin then enables glucose and amino acids to enter cells in the body, particularly muscle and liver cells. Here, insulin and other hormones direct whether these nutrients will be burned for energy or stored for future use. (Note that the brain and nervous system are not dependent on insulin; they regulate their glucose needs through other mechanisms.)
- 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 two to four 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*.

## Type 2 Diabetes

Type 2 diabetes is the most common form of diabetes, accounting for 90% of cases. An estimated 16 million Americans have type 2 diabetes and half are unaware they have it. The disease mechanisms in type 2 diabetes are not wholly known, but some experts suggest that it may involve the following three stages in most patients:

- The first stage in type 2 diabetes is the condition called *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 type 2 diabetics 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 right after a meal (called *postprandial hyperglycemia*). This effect is now believed to be particularly damaging to the body.
- Eventually, the cycle of elevated glucose further impairs and possibly destroys beta cells, thereby stopping insulin production completely 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 disease process is more severe and onset is usually in childhood:

- 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 *Well-connected Report # 9 , Diabetes: Type 1.*]

## Diabetes Secondary to Other Conditions

Conditions that damage or destroy the pancreas, such as pancreatitis, 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. Rare genetic disorders (Klinefelter's syndrome, Huntington's chorea, Wolfram's syndrome, leprechaunism, Rabson-Mendenhall syndrome, lipotrophic diabetes, and others) and hormonal disorders (acromegaly, Cushing's syndrome, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma) are associated with or increase the risk for diabetes.

## Causes

Type 2 diabetes is caused by a complicated interplay of genes, environment, insulin abnormalities, increased glucose production in the liver, increased fat breakdown, and possibly defective hormonal secretions in the intestine. The recent dramatic increase indicates that lifestyle factors (obesity and sedentary lifestyle) may be particularly important in triggering the genetic elements that cause this type of diabetes.

## Insulin Abnormalities

The characteristic features of most patients with type 2 diabetes are the following:

- Insulin resistance in muscle cells.
- Normal or even excessive levels of insulin (to compensate for this resistance), eventually followed by a drop in insulin production.

In addition, researchers are trying to determine the factors that might promote insulin resistance:

- Both obesity and insulin resistance at different phases are marked by elevated levels of free fatty acids and the hormones resistin and leptin. It is not known yet if elevated levels are simply a product of obesity or play some causal role in diabetes.
- Insulin resistance is associated with a chronic low inflammatory response, which involves a number of immune factors, such as TGH-beta 1 and C-reactive protein. Such factors can cause damage over time and may be responsible for the association between insulin resistance and heart disease.

## Genetic Factors

Genetic factors play an important role in type 2 diabetes, but the pattern is complicated, since both impairment of beta cell function and an abnormal response to insulin are involved. Researchers have identified a number of genetic factors that may be responsible for selected or more general cases of diabetes:

- Researchers have identified genes responsible for maturity-onset diabetes in youth (MODY), a rare genetic form of type 2 diabetes that develops only in Caucasian teenagers. (This is not the diabetes associated with obesity that is now being seen increasingly in young people.)
- A defective fatty-acid binding protein 2 (FABP2) gene may result in higher levels of unhealthy fat molecules (particularly triglycerides), which may be critical in the link between obesity and insulin resistance in some people with type 2 diabetes.
- Alterations in five genes that beta cell and pancreas function have been identified that may play an important role in inherited cases of type 2 diabetes.
- Variations in a gene that regulates a protein called calpain-10 is proving to affect insulin secretion and action and may play a role in type 2 diabetes in certain populations. There is some disagreement, however,

about its significance. Calpains are enzymes that play a wide role in many essential cellular functions. Evidence is now strongly suggesting that genetic activation of these enzymes may be important in many aging-related diseases.

- Defective genes that regulate a molecule called peroxisome proliferator-activated receptor (PPAR) gamma may contribute to both type 2 diabetes and high blood pressure in some patients.
- A defective gene has been detected that reduces activity of a protective substance called beta<sub>3</sub>-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 Thrifty Gene.* 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.

## Risk Factors

At this time, about 15.6 million Americans have diabetes; up to 95% of these cases are type 2. The prevalence of type 2 diabetes increased from 4.9% in 1990 to nearly 7% in 1999. Historically, type 2 diabetes usually developed after the age of 40, but it is now also increasing in children. Given the current epidemic of obesity, experts are now estimating that over a third of all people born in 2002 will eventually develop diabetes. Furthermore, the dramatic increase in diabetes is occurring worldwide as American lifestyles become global. Evidence strongly suggests that healthy lifestyles can prevent most cases of type 2 diabetes.

## Obesity and Metabolic Syndrome

Obesity is the number one risk factor for type 2 diabetes. It is estimated that 80% to 95% of the current dramatic increases in type 2 diabetes are due to obesity. 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 with these conditions.) Of note: 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.

*Metabolic Syndrome.* 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 levels, high blood pressure, and insulin resistance. A 2002 study estimated that nearly a quarter of the U.S. population now has this condition. Even worse, according to a 2003 study, nearly a million American teenagers have this syndrome.

## Family History

Between 25% and 33% of all type 2 patients have family members with diabetes. Having a first-degree relative with the disease poses a 40% risk of developing diabetes. One study reported that people with positive family histories have a higher risk for developing the disease at an earlier stage with more severe features. Because families share many lifestyle features (eating and exercise habits) it is difficult to determine when genetics or environment play the major role. When clusters of diabetes type 1 and 2 appear within families, genetic factors should be strongly suspected.

## Ethnicity

The risk for type 2 diabetes varies among population groups. Diabetes also seems to pose higher or lower risks for specific complications among ethnic groups. Genetic, socioeconomic factors, or both seem to be involved in some ethnic differences, but in most cases the observed increase in ethnic groups in Americans is due to changes in traditional lifestyles.

- *African Americans.* African American men have one and a half times the risk of developing type 2 diabetes

and African American women have twice the risk as their Caucasian peers. African Americans with diabetes are also at higher risk for amputations than diabetic Caucasians. This is most likely due to a higher incidence of high blood pressure and smoking as well as poorer health care in African Americans. Genetic factors also play a role. For example, there is some evidence that African Americans process insulin in the liver differently from Caucasians, which may make them more susceptible to diabetes when other risk factors are present.

- **Native Americans.** The Pima tribe in Arizona has an incidence of type 2 diabetes that is 19 times higher than that of the white population. The risk for diabetic complications among young Pima adults is also very high. Other Native American tribes in North America are also at high risk for type 2 diabetes. The association between diet and diabetes among this population remains critical, however, in assessing the reason for their higher risk. For example, in one study, Pimas who lived in Mexico exercised more and ate less fat (but consumed more calories) than Pima tribes in Arizona. Mexican Pimas have a prevalence of diabetes of only 6%, while half of their Arizona Pima neighbors had diabetes.
- **Hispanic Americans.** The rate of type 2 diabetes is also very high among Mexican Americans, approximately double that for Caucasians. This group may also be at higher risk for heart problems than other ethnic groups with diabetes.

## Low Birth Weight

Low birth weight is now a recognized risk factor for type 2 diabetes and heart disease in adulthood. The reasons are unclear, although recent studies are suggesting it may represent a genetic factor. Studies in 2002 and 2003 observed that babies of fathers with type 2 diabetes and of women who later developed type 2 diabetes tended to weigh less than babies of parents without diabetes. Such studies suggest that such parents may have some specific gene that affects insulin factors, putting both themselves and their children at risk for future diabetes. Theoretically, such a gene might also affect insulin factors in the developing fetus, causing low birth weight. (Of note, mothers of very high-weight babies are also at risk for diabetes -- although in these cases it is most often associated with gestational diabetes.)

## Diabetes in Children and Adolescents

**Obesity-Related Type 2 Diabetes in Children.** Until recent years, diabetes in children was almost always type 1 (an autoimmune disease). Between 1982 and 1994, however, the incidence of type 2 diabetes in children multiplied by ten, until in 1996, a study reported that a third of all new diabetes cases in children were type 2. This increase parallels the rising epidemic in childhood obesity that has occurred both in the US and worldwide, notably Europe and Japan. In some areas of Japan, type 2 diabetes has now become the dominant form of diabetes in children and adolescents. Obesity in children is also related to abnormalities in cholesterol, blood pressure, and insulin levels in adults. Administering glucose tolerance tests in overweight children may be helpful in identifying those at high risk for diabetes.

**Maturity-Onset Diabetes in Caucasian Youth.** Maturity-onset diabetes in youth (MODY) is a rare genetic form of type 2 diabetes that develops only in Caucasian teenagers. It accounts for 2% to 5% of type 2 cases. (This form of type 2 diabetes is not associated with obesity.)

## Diabetes in the Pregnant Woman (Gestational Diabetes)

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

### Gestational Diabetes

Gestational diabetes is a diabetic condition (nearly always temporary) that develops during the third trimester. After delivery, blood glucose levels generally return to normal, although between one-third and one-half of these women develop type 2 diabetes within 10 years.

#### Who Gets Gestational Diabetes?

Estimates for the prevalence of gestational diabetes are generally about 4%. Some studies, however, have suggested significantly higher rates. In one German study, 13% of pregnant women were diagnosed with this form of diabetes, including many who did not have any risk factors.

Risk factors include the following:

- Weight gain (11 to 22 pounds) during early adulthood.
- Family history of diabetes.

- Smoking.
- Belonging to African American, Hispanic, or Asian ethnic groups.
- Gaining weight before getting pregnant.
- Being an older mother.

It should be noted that some studies suggest that women who develop gestational diabetes during pregnancy and take progestin-only contraceptives while breast-feeding are at high risk for developing full-blown type 2 diabetes.

### Who Should Be Tested for Gestational Diabetes?

A number of expert groups now recommend that nearly all pregnant women be tested for gestational diabetes between their 24th and 28th week. Pregnant women at high risk for diabetes should be tested earlier. The only women who do *not* need to be tested are those at very low risk. Generally they have the following characteristics:

- Under 25 years old.
- Normal weight.
- No first-degree relatives with diabetes.
- Not belonging to the following ethnic groups: Native American, Hispanic, Asian or African-American.

### How Serious Is Diabetes During Pregnancy?

*Effect of Diabetes on the Fetus.* Because glucose crosses the placenta, a woman with diabetes can pass high levels of blood glucose to the fetus. In response, the fetus secretes high level of insulin. Studies indicate that such conditions may effect the developing fetus as soon as it is conceived, placing the unborn child at risk for the following:

- Birth defects. (It should be noted that the risk is significant only in women who had diabetes before they became pregnant. A 2002 study reported no excess risk for infant malformations in women with gestational diabetes.)
- Excessive growth of the fetus.
- Delayed lung development.
- Possibly a higher risk for future diabetes and obesity in the child.

*Effect of Diabetes on the Pregnant Woman.* In addition to endangering the fetus, diabetes also presents risks to the pregnant woman.

In one German study, 25% of women with gestational diabetes required a cesarean section. (The non-diabetic rate in the study was also high however, 19.6%.)

The most serious potential complications from diabetes are high blood pressure and preeclampsia, a potentially dangerous condition. In one study, blood pressure was abnormally high in 6.5% of women with gestational diabetes compared to 1.7% of pregnant women without diabetes. (Note that one study suggested mortality rates in pregnant women with gestational diabetes vary widely, and normal rates have been reported in some countries, suggesting that good prenatal care can be fully protective.)

### How Is Gestational Diabetes Managed?

Some suggestions for preventing complications include the following:

- In most cases, increases in glucose levels can be managed with diet and exercise. Aerobic exercise before and during pregnancy may lower glucose levels and may be protective for women at risk or who have gestational diabetes. (Any pregnant woman should check with her physician before embarking on a vigorous exercise regimen.)
- If a woman with gestational diabetes cannot keep her glucose under control with lifestyle measures, then she usually is given insulin.
- Oral agents commonly used for type 2 diabetes have not been routinely prescribed because of a higher risk for birth defects and severe hypoglycemia in the newborn. Studies suggest that newer agents, such as glyburide, however, may be effective and safe alternatives to insulin.

## Other Medical Conditions

*Polycystic Ovary Syndrome.* Polycystic ovary syndrome (PCO) is a condition that affects about 6% of women and

results in the ovarian production of high amounts of androgens (male hormones), particularly testosterone. It appears to be an important cause of many menstrual disorders. Women with PCO are at higher risk for insulin resistance, and about half of PCO patients also have diabetes.

*Hepatitis C.* Patients with hepatitis C have a higher incidence of type 2 diabetes. The reasons for this are unclear.

## Symptoms

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

- 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.
- Impotence 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 develop a skin problem called acanthosis, which is characterized by velvety, dark colored patches of skin.

## Emergency Complications

### Hypoglycemia

People with diabetes who need to intensively control glucose levels are at risk for hypoglycemia (also called insulin shock). The condition develops if blood glucose levels fall below normal and may also be caused by insufficient intake of food, excess exercise, or alcohol intake. 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 hypoglycemia is common among people with type 2 diabetes, but severe episodes are rare, even among those who are taking insulin. Still, all patients who are intensively controlling glucose levels should be aware of warning symptoms.

*Risk Factors for Severe Hypoglycemia.* People at highest risk for severe hypoglycemia are those who intensively control blood glucose and also have one or more of the following conditions:

- Long-term diabetes.
- Less education on their condition.
- A previous history of severe hypoglycemia.
- Hypoglycemia unawareness. This is a condition in which people become insensitive to hypoglycemic symptoms. It affects about 25% of those who use insulin, nearly always type 1 diabetics. 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, such patients can often regain the ability to sense the symptoms. Note that even very careful testing may fail to detect a problem, particularly one that occurs during sleep.

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

- Sweating.
- Trembling.
- Hunger.
- Rapid heartbeat.

Severely low blood glucose levels can precipitate neurologic symptoms:

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

*Preventive Measures.* The following tips may help avoid hypoglycemia or prepare for attacks.

- Patients are at highest risk for hypoglycemia at night. Bedtime snacks may be helpful.
- 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.
- Diabetic patients on therapies that put them at risk for hypoglycemia should always carry hard candy, juice, sugar packets, or commercially available glucose substitutes designed for diabetic individuals.

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 for diabetics.
- 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, in contrast to insulin, raises blood glucose.

## Diabetic Ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) is a life-threatening complication caused by insulin depletion. Until recently, it has been 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 type 2 diabetes, especially among Hispanic and African Americans. It is not clear, however, what causes total insulin depletion in these patients. Research is needed to find which individuals are at particular risk.

Diabetic ketoacidosis often develop as follows:

- The process is usually triggered in insulin-deficient patients by a stressful event, most often pneumonia or urinary tract infections. Other triggers include alcohol abuse, physical injury, pulmonary embolism, heart attacks, or other illnesses.
- Severely low insulin levels cause excessive amounts of glucose in the bloodstream (hyperglycemia).
- Fat breakdown then accelerates and increases the production of fatty acids.
- These fatty acids are converted into chemicals called ketone bodies, which are toxic at high levels.

Symptoms and complications include the following:

- 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 DKA has decreased to about 2% of all cases.
- Other serious complications from DKA 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.

## Screening Tests

There are no clear-cut guidelines for when to screen for diabetes. Some experts recommend that everyone over age 45 be tested regularly for diabetes, although others do not feel this necessary in people without symptoms or

risk factors. In fact, early screening could identify some people with impaired glucose levels that would eventually normalize. Such people might be treated unnecessarily with medications that pose a risk for hypoglycemia.

Still, given the risk for serious complications with diabetes and the potential value of early treatments, most experts recommend that all adults over 45 be screened and that younger adults be screened if they have one or more of the following conditions:

- A weight that is 20% more than ideal body weight.
- Risk factors for heart disease (e.g., high blood pressure, unhealthy cholesterol levels and especially if individuals have low HDL cholesterol and high triglyceride levels).
- A close relative with diabetes.
- A high-risk ethnic group background.
- In women, having delivered a baby weighing over nine pounds or having a history of gestational diabetes.

Some experts recommend that any child over 10 should be tested for type 2 diabetes (even if they have no symptoms), if they are overweight and have at least two of the above mentioned risk factors. Determining the risks and benefits of such an approach is of particular importance, given the rise in childhood type 2 diabetes. Type 2 diabetes is still uncommon in children and adolescents.

## Testing for Diabetes

**Fasting Plasma Glucose.** The fasting plasma glucose (FPG) test is the standard test for diabetes. It is a simple blood test taken after eight hours of fasting. In general, results indicate the following:

- 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. They are only slightly above normal but are considered to be risk factors for type 2 diabetes and its complications.
- 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, 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. For example, people who take the test in the afternoon and show normal results may actually have abnormal levels that would be revealed if they are tested in the morning.

**Glucose Tolerance Test.** The glucose tolerance test is more complex than the FPG and may over-diagnose diabetes in people who do not have it. It is, then, not used as often anymore. Some experts recommend it follow-up after FPG, if the latter test results are normal but the patient has symptoms or risk factors of diabetes. The glucose tolerance test may be more accurate than the FPG in certain groups (e.g., women with a history of gestational diabetes or certain Asian populations). The test uses the following procedures:

- It first employs an FPG test.
- A blood test is then taken two hours later after drinking a special glucose solution.

The following results suggest different conditions:

- In people without diabetes, blood sugar increases modestly after drinking the glucose beverage and decreases after two hours.
- In diabetes, the initial increase is significant and the level remains high, 200 mg/dL (11.1 mmol/L) or more.
- Measurements that fall between 7.8 and below 11.1 mmol/l put a person at risk for diabetes and are referred to as impaired glucose tolerance. This condition is now strongly associated with a high risk for future diabetes and a higher than average risk for heart disease and poorer survival rates. (Studies suggest it is a much stronger predictor of diabetes than impaired fasting glucose.)

**Test for Glycated Hemoglobin.** Tests for blood levels of *glycated hemoglobin*, also known as hemoglobin A1c (HbA1c) are not currently used for an initial diagnosis, but they are useful for determining the severity of diabetes. Some experts think it should be used to help predict complications in people who have FPG levels between 110 and 139, which are above normal but do not indicate full-blown diabetes.

The basis for its use as a diagnostic measurement in diabetes is as follows:

- Hemoglobin is a protein molecule found in red blood cells. When glucose binds to it, the hemoglobin becomes modified, a process called *glycosylation*.
- Glycosylation affects a number of proteins, and elevated levels of glycolated hemoglobin is strongly associated with complications of diabetes.
- A glycated hemoglobin level of 1% above normal range identifies diabetes in 98% of patients. Normal HbA1c 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 affected by food intake so it can be taken at any time. A home test has been developed that might make it easier to measure HbA1c. In general, measurements suggest the following:

- Normal HbA1c levels should be below 7%.
- Levels of 11% to 12% glycolated hemoglobin indicate poor control of carbohydrates. High levels are also markers for kidney trouble.

*Testing for Insulin Resistance.* Investigators hope that some day a simple test for insulin resistance will be available that will be able to identify people at risk for diabetes. The presence of insulin resistance may also be a predictor of heart disease, independent of the presence of diabetes. Some research suggests that measuring insulin and triglyceride levels during a fasting period may predict a person's sensitivity to insulin.

## 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 warranted in patients with signs of heart disease.

*Screening for Kidney Damage.* The earliest manifestation of kidney damage is microalbuminuria, in which tiny amounts (30 to 299 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 typically shows up in type 2 diabetics who have high blood pressure.

*Screening for Thyroid Abnormalities.* Thyroid function tests should be administered.

## Treatment

The major treatment goals for people with type 2 diabetes are twofold:

- To treat all conditions that place the patients at risk for heart disease and stroke, which are the major killers of people with type 2 diabetes.
- To control blood glucose levels. The goal is to achieve fasting blood glucose levels of less than 110 mg/dl and glycolated hemoglobin (HbA1c) levels of less than 7%. The objective is to reduce complications in small blood vessels and the nerve damage associated with diabetes.

An intensive multi-pronged approach is critical for reducing complications and improving survival rates in diabetics. In one major study, patients with diabetes and early signs of kidney involvement embarked on an intensive preventive program. At the end of about seven years, their risk for heart, stroke, death, and other complications was 24% compared to 44% of patients who had conventional therapy. Intensive therapy involved the following:

- Healthy lifestyle changes: Exercise for 30 minutes three to five times a week; low-fat diet; smoking cessation; vitamins and mineral supplements (vitamin E and C, folic acid, and chrome picolinate).
- Controlling blood sugar levels. The use of an oral anti-hyperglycemic agent, such as a sulfonylurea or metformin (Glucophage), for patients whose HbA1c levels were over 6.5%. Of note, studies suggest that metformin significantly reduces mortality rates compared to other agents, including insulin. It should be considered as the first option in managing blood sugar for most patients with type 2 diabetes. Other oral anti-hyperglycemic agents (OHAs) are also available. Insulin may eventually be needed.
- Taking heart protective agents. Among anti-hypertensive agents angiotensin converting enzyme (ACE) inhibitors are first choice for diabetics, particularly those with evidence of kidney problems--even without high blood pressure. Controlling high blood pressure, in fact, is one of the few factors proven to reduce mortality rates. Among cholesterol-lowering agents, statins are the first choice alone or in combinations. They protect people with diabetes, even if cholesterol levels are not abnormal. Aspirin is important to prevent blood clots and heart attack.

Of note, most people with diabetes would find such intensive treatment difficult to comply with. Still, they should make every effort, especially to control blood pressure, cholesterol levels, and blood glucose levels.

## Treating Special Populations

Different goals may be required 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 now approved for children. Until recently, only insulin was approved for treating children with any diabetes.

## Lifestyle Changes

A simple heart-healthy diet with weight control may be sufficient for people with type 2 diabetes. In fact, a 2002 study reported that successful lifestyle changes were more effective than metformin -- a major drug used in type 2 diabetes -- in preventing type 2 diabetes in high-risk individuals. On the other hand, the so-called Western diet (higher consumption of red meat, processed meat, French fries, high-fat dairy products, refined grains, and sweets and desserts) poses a high risk for type 2 diabetes. Lifestyle changes are difficult to initiate and sustain, however. Patients should be certain to surround themselves with a solid network of doctors, dietitians, family, and friends who understand both their condition and their needs.

### Heart-Healthy Diet

Currently, there is much controversy over the best balance of carbohydrates, fats, and protein. A number of dietary approaches for improving the heart are available:

- Therapeutic Lifestyle Changes (TLC) from the National Cholesterol Education Program.
- The Mediterranean Diet.
- Very low-fat diets, particularly the Ornish Program.
- The Dietary Approaches to Stop Hypertension (DASH) diet. This diet has been designed specifically to help people reduce blood pressure.
- Restricted calorie diets.

Although all the major dietary approaches differ in important aspects, they have some recommendations in common:

- Choose fiber-rich food (whole grains, legumes).
- Choose fresh fruits and vegetables.
- Choose unsaturated fats (found in vegetable and fish oils) over saturated fats (found mostly in animal products) and trans-fatty acids (found in hydrogenated fats and many commercial products and fast-foods).
- In selecting proteins, choose soy protein, poultry, and fish over meat.
- Weight control and exercise are essential companions of any diet program.
- After embarking on any heart-healthy diet, it generally takes an average of three to six months before any noticeable reduction in cholesterol occurs, although some people have reported better levels in as few as four weeks.

[For detailed information, see *Well-Connected Report #43 Heart-Healthy Diet*]

### Weight Loss

*The Diabetic Diet.* 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:

- Limit fats (particularly saturated fats and trans-fatty acids).
- Limit dietary cholesterol.
- Consume plenty of fiber-rich foods in the form of whole grains and fresh fruits and vegetables.
- Limit protein.
- Reduce salt.

[For detailed information, see *Well-Connected Report #42 Diabetes Diet*]

*Weight Loss with Diet and Medications.* 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. 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 (Xenical) or sibutramine (Meridia), may be beneficial. Orlistat may have specific benefits for people with diabetes. It may not only achieve weight but also improved glucose, cholesterol, and lipid levels. Surgical procedures are proving to be

extremely beneficial in selected cases. [For detailed information, see *Well-Connected Report #53, Obesity.*]

## Exercise

Sedentary habits, especially watching television, 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. An important study reported a 58% lower risk for type 2 diabetes in adults who performed moderate exercise for as little as 2.5 hours a week.

In 2002, a well-conducted study on overweight adults confirmed previous research that reported beneficial changes in cholesterol and lipid levels, including lower LDL levels (the so-called bad cholesterol), even when people performed low amounts of moderate or high intensity exercise (e.g., walking or jogging 12 miles a week). However, more intense exercise is required to significantly change cholesterol levels, notably increasing HDL (the so-called good cholesterol). An example of such a program would be jogging about 20 miles a week. Such benefits in the study occurred even with very modest weight loss, suggesting that overweight people who have trouble losing pounds can still achieve considerable heart benefits by exercising.

**Aerobic Exercises.** Aerobic exercise is proving to have significant and particular benefits for people with both type 1 and type 2 diabetes. Regular aerobic exercise, even of moderate intensity, improves insulin sensitivity. People with diabetes are at particular risk for heart disease, so the heart protective effects of aerobic exercise are very important for this patient population. Moderate exercise, in fact, protects the heart in people with type 2 diabetes, even if they have no risk factors for heart disease other than diabetes itself. (In general, when exercising people with diabetes, should aim for a heart rate target of 55% to 75% of their maximum heart rate.)

**Strength Training.** Strength training, which increases muscle and reduces fat, may be particularly helpful for people with diabetes, but evidence is needed to confirm this.

**Yoga.** One study reported that yoga helped patients with type 2 diabetes reduce their need for oral medications. Studies have indicated that yoga and Tai Chi (an ancient Chinese exercise involving slow relaxing movements) may lower blood pressure almost as well as moderate-intensity aerobic exercises.

**Some Precautions for People with Diabetes Who Exercise.** The following are precautions for *all* people with diabetes, whether type 1 or 2:

- Because people with diabetes are at higher than average risk for heart disease, they should always check with their physicians before undertaking vigorous exercise. For the best and fastest results, frequent high-intensity (not high-impact) exercises are best 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.
- 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 embarking on a workout program.

- Glucose levels swing dramatically during exercise; people with diabetes should monitor their levels carefully before, during, and after workouts.
- Patients should probably avoid exercise if glucose levels are above 300 mg/dl or under 100 mg/dl.
- To avoid hypoglycemia, diabetics should inject insulin in sites away from the muscles they use the most during exercise.
- They should also drink plenty of fluids. Before exercising, they should also avoid alcohol, which increases the risk 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; in non-diabetics insulin is released to control this. The diabetic therefore needs to test their blood sugar and take an extra dose as instructed by their diabetes healthcare provider.
- Anyone with existing hypertension should discuss an exercise program with their physician. Before starting to exercise, people with moderate to severe hypertension should lower their pressure and be able to control it with medications. They should avoid caffeinated beverages, which increase heart rate, the workload of the heart, and blood pressure during physical activity. Everyone, and especially people with high blood pressure, should breathe as normally as possible through each exercise. Holding the breath increases blood pressure.
- Good, protective footwear is essential to help avoid injuries and wounds in the feet.

## Monitoring Glucose (Blood Sugar) and Hemoglobin A1C

In 2002, the American Heart Association revised its guidelines for preventing heart disease and recommended that people with diabetes should aim for fasting blood glucose levels of less than 110 mg/dl and hemoglobin A1C or less than 7%.

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

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. For patients who have become insulin-dependent, more intensive monitoring is necessary. 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.

*Measuring Hemoglobin A1C.* Hemoglobin A1c (HbA1c), or glycated hemoglobin, is measured periodically to determine the average blood-sugar level over the life span of the red blood cell, which is about eight to 10 weeks. Home tests (DRx, Metrika A1c Now) are available for measuring HbA1c that may allow even better monitoring of glucose levels.

## 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.

## Medications

The American Heart Association now recommends that patients should aim for the following test results for intensive control of glucose levels:

- Fasting plasma glucose concentrations below 110 mg/dL.
- Glycolated hemoglobin (HbA1c) levels of less than 7%. Controlling HbA1c is the most important factor for reducing the risk of complications in patients with diabetes. According to one 2000 study, a 1% reduction in people with elevated glycolated hemoglobin levels lowers the risk for complications by 21%.

Evidence clearly supports strict glycemic control for reducing complications in the nervous system and blood vessels that occur in both type 1 and type 2 diabetes. Although to date tight control of blood glucose has not proven to reduce mortality rates from all causes or cardiovascular diseases in patients with type 2 diabetes, evidence is increasing that intensive control has benefits for the heart as well--although they may not be evident as rapidly.

It may be difficult for patients with type 2 diabetes to control their blood sugar levels--particularly if they are overweight. On the positive side, metformin (Glucophage), an oral anti-hypoglycemic agent, has many benefits--it helps control blood glucose levels, does not produce weight gain, and also has heart benefits. In comparison with other diabetic agents, including insulin, it is the only proven drug to improve survival rates. A number of oral agents are also available that are beneficial, alone or in combinations. Insulin therapy is often eventually required as natural insulin reserves become depleted.

Managing risk factors for heart disease and stroke, particularly strict control of blood pressure, may more important for improving survival than strict control of blood glucose levels in these patients. Such goals also seem to be more attainable for many patients with type 2 diabetics.

*Oral Anti-hyperglycemic Agents (OHAs).* Many oral anti-hyperglycemic agents (OHAs) are now available to help patients with type 2 diabetes control their blood sugar levels. Most of these agents are aimed at using or increasing sensitivity to the patient's own natural stores of insulin. Metformin is the only agent to date that achieves lower mortality rates:

- Biguanides (metformin). Increase tissue sensitivity to available insulin. Metformin also has beneficial effects on cholesterol, blood pressure, and clotting factors. It does not cause weight gain or hypoglycemia. Metformin produces lower mortality rates than other drugs, including insulin, and should be considered as

first-line therapy for most type 2 patients who are insulin resistant.

- Sulfonylureas (examples include glyburide, glipizide, and glimepiride). Stimulate insulin secretion.
- Meglitinides (repaglinide, nateglinide). Stimulate insulin secretion. These newer agents are better than sulfonylureas in controlling glucose spikes after meals.
- Thiazolidinediones (pioglitazone and rosiglitazone). Reduce insulin resistance. These agents improve cholesterol levels and may reduce the risk for blood clots. However, they can cause swelling from fluid build-up, which can worsen heart failure or even possibly precipitate it. They also may injure the liver. The drugs have not been intensively studied, and some experts believe they should not be used except in clinical studies.
- Alpha-glucosidase inhibitors (acarbose and miglitol). Slow intestinal absorption of carbohydrates. Have only modest effects and have gastrointestinal side effects.

Combinations of these agents, particularly with metformin, are often used to increase effectiveness. For example, combinations of rosiglitazone and metformin (Avandamet) and glyburide and metformin (Glucovance) are proving to be very effective. Glucovance may be particularly beneficial for patients with unhealthy cholesterol levels and poor control of their blood sugar levels. Some experts recommend the combination as first-line treatment.

*Adding Insulin Replacement.* Insulin replacement is usually required as natural insulin reserves are depleted. It is typically started in combination with an oral agent. Eventually, some people may need to go on full insulin replacement.

## Metformin (a Biguanide)

Metformin (Glucophage) is a biguanide, which appears to work by reducing glucose production in the liver and by making tissues more sensitive to insulin. It is now be considered by many experts to be the first choice for most type 2 patients who are insulin resistant, particularly if they are overweight. Metformin achieves lower mortality rates from diabetes and all causes than other drugs. In one comparison study, it achieved the lowest mortality rates (8%) compared to insulin (28%), a sulfonylurea (16%), and a thiazolidinedione (14%). Combinations with insulin-secreting drugs, other insulin-sensitizing drugs, or insulin itself are 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 beneficial effects on cholesterol and lipid levels and may be heart protective. Some research, in fact, has suggested that it significantly reduces the risk for heart attack. It is also the first choice for children who need oral agents and is proving to be very effective for women with polycystic ovaries and insulin resistance.

*Side Effects.* Side effects include the following:

- A metallic taste.
- Gastrointestinal problems, including nausea, and diarrhea.
- It may also reduce absorption of vitamin B12 and folic acid, which are important for protection against heart disease.
- There have been some 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 congestive heart failure or kidney or liver disease. It is rarely suitable for adults over 80.

## Sulfonylureas

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

Most patients can take sulfonylureas for seven to 10 years before they lose effectiveness. Combinations with small amounts of insulin or with other drugs (such as metformin or a thiazolidinedione) may extend their benefits. In fact, a combination of glyburide and metformin in one pill (Glucovance) is now available. Glucovance may be particularly beneficial for patients with unhealthy cholesterol levels and poor control of their blood sugar levels. Some experts recommend the combination as first-line treatment.

Also encouraging was a 2000 study of patients with severe type 2 diabetes reporting that combinations of insulin with either chlorpropamide or glipizide (two different sulfonylureas) achieved better glucose control over the long term than insulin alone.

**Side Effects and Complications.** In general, sulfonylureas should not be used by women who are pregnant or nursing or by individuals who are allergic to sulfa drugs. Side effects include the following:

- 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 prolonged and dangerous. The newer sulfonylureas, such as glimepiride, appear to have about one tenth the risk of hypoglycemia than do older sulfonylureas.
- Some may pose a slight risk for cardiac events.

Sulfonylureas interact with many other drugs, and patients should be sure to inform their physician 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 agents are rapidly metabolized and short acting and 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. (Nateglinide appears to work more quickly and is shorter-acting than repaglinide). These agents may be particularly effective in combination with metformin or other agents. And they may be good agents 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 agents, such as nateglinide, may pose less of a risk.) People with heart failure or liver disease should use them with caution and be monitored.

## Thiazolidinedione

Thiazolidinediones include rosiglitazone (Avandia) and pioglitazone (Actos). 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 do not cause hypoglycemia when used alone, although they are usually taken in combination with oral agents or insulin.

In some studies, thiazolidinediones have produced favorable effects on the heart, including reducing blood pressure and preventing blood clots. Pioglitazone improves triglyceride and HDL levels. (Rosiglitazone has mixed effects on lipid levels.) Of importance, some evidence suggests that these agents may preserve beta-cell function and, if used early, may help prevent progression of diabetes. This effect has not been observed with other standard oral agents.

**Side Effects** Nevertheless, thiazolidinediones can have serious side effects. They tend to increase fluid-build up, which can cause or worsen heart failure in some patients. Combinations with insulin increase the risk. They should not be used at all in patients with existing heart failure and should be used cautiously in those with risk factors for heart failure. Any patient who experiences sudden weight gain, water retention, or shortness of breath should call their physicians immediately.

Thiazolidinediones can cause also anemia and, as with other oral agents, can cause moderate weight gain. There have been a few reports of liver injury. At this time some experts believe thiazolidinediones should not be used routinely for managing type 2 diabetes but only in the context of clinical studies.

## 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 agents may reduce heart risk factors, including high blood pressure. A 2002 study using acarbose also suggested that these agents might even delay the development of type 2 diabetes in high-risk individuals. 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.

## Insulin Replacement

*Issues Involves with Insulin Replacement.* Insulin replacement is the best treatment for strict control of blood glucose and is required as natural insulin reserves are depleted. Because type 2 diabetes is progressive, most patients eventually require insulin, typically starting it in combination with an oral agent. However, when a single oral agent fails to control blood sugar it is not clear whether it is better to add insulin replacement or to add a second or third oral agent. A 2003 study reported that three oral agents were as effective as insulin plus an oral agent, but the costs are significantly higher. Some experts advocate using insulin as early as possible for optimal control.

However, in patients who still have insulin reserves, there is some concern that extra natural insulin will have adverse effects, including hypoglycemia, weight gain, and heart complications. It is still not clear if insulin replacement will improve survival rates compared to oral agents, notably metformin.

One approach that might solve some of these problems is to combine insulin with metformin, which achieves blood glucose control without added weight gain. Newer forms of insulin analogues, such as glargine, may be specifically helpful for people with type 2 diabetes and reduce the risk for hypoglycemia.

Fortunately, studies to date have not reported any adverse cardiac effects in patients with type 2 diabetes who are taking 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.* Experts are working toward administering insulin so that it closely mimics the daily pattern of insulin, which responds to blood sugar levels by surging after meals and then falling to a steady base level afterward. To achieve this, physicians may use two insulin types:

- **Fast-Acting Insulins for Surges.** Insulin lispro and insulin 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 (insulin glargine, ultralente insulin) have been 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.

Noninjected forms of insulin are under investigation and may be particularly beneficial for type 2 diabetes. For example, preprandial inhaled insulin, or INH, is used with an inhaler, and Oralin is administered using an oral spray that is absorbed in the cheek lining. In one study, INH was added to oral agents administration and inhaled before meals. After 12 weeks it was more effective in controlling blood glucose, although patients gained weight and had a great incidence in hypoglycemia.

[For more detailed information on insulin therapy, see *Well-Connected Report #9, Diabetes: Type 1.*]

## Investigative Agents

*Incretins.* Incretins are hormones that are released from the intestine and enhance insulin secretion. Glucagon-like insulinotropic peptide, or GLP-1 (Betatropin), is an incretin under investigation. It appears to help metabolize glucose and reduce appetite. Betatropin is administered using injections. Early studies report that it is effective in controlling blood glucose levels and has also been associated with weight reduction. A transmucosal tablet (placed between the lip and gum) is also under investigation and is 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. It therefore prevents the surge in blood sugar that typically occurs after meals. Some studies indicate that in combination with insulin it helps control glucose levels, importantly after meals, without increasing the risk for hypoglycemia or increasing weight when added to insulin regimens. It is being considered for approval for both type 1 and type 2 insulin-dependent diabetes. One possible adverse effect is a delay in stomach emptying, which is already a complication of diabetes in some patients with neuropathy.

*D-Chiro-Inositol.* D-chiro-inositol (INS-1) is an investigational agent that increases sensitivity to insulin. It is showing promise in treating people with less severe diabetes and women with polycystic ovary syndrome. More research is underway.

**Ciliary Neurotrophic Factor.** An agent derived from ciliary neurotrophic factor (Axokine) signals the brain to suppress appetite. It is proving to be effective in achieving weight loss, and also improves cholesterol, lipid, and glucose levels regardless of food intake. The agent, then, may be particularly helpful for people with type 2 diabetes. It is currently in late trials.

**Exenatide.** Exenatide (Heloderma) is derived from the venom of the Gila monster. Animal and laboratory studies suggest that it enhances insulin secretion and slows stomach emptying. It may also have some protective effects on beta cells. Early studies are reporting reductions in HbA1C when used in combination with metformin, sulfonylureas, or both.

## Long-Term Complications

Patients with diabetes have higher mortality rates than nondiabetics regardless of sex, age, or affluence. Heart disease and stroke are the leading causes of death in these patients. All life-style and medical efforts should be made to reduce the risk for these conditions.

People with type 2 diabetes are also subject to 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. People with diabetes should aim for fast blood glucose levels of less than 110 mg/dl and hemoglobin A1C or less than 7%.

The impact of these multiple health problems are of great concern, particularly with the dramatic increase in diabetes. Experts now estimate that over a third of people born in 2002 will eventually develop diabetes.

There are two important approaches to preventing complications from diabetes:

- Intensive control of blood glucose and keeping glycosylated hemoglobin (HbA1c) levels below 7.0. This is proving to prevent complication due to vascular (blood vessel) abnormalities and nerve damage (neuropathy) that can cause major damage to organs, including the eyes, kidneys, and heart.
- Managing risk factors for heart disease. Evidence is increasing that control of blood glucose also helps the heart, but its benefits most likely occur over time. It is very important that people with diabetes control blood pressure, cholesterol levels, and other factors associated with heart disease.

## Complications of Heart and Circulation

Heart attacks account for 60% and strokes for 25% of deaths in all diabetics. Diabetes effects the heart in many ways:

- Both type 1 and 2 diabetes accelerate the progression of atherosclerosis (hardening of the arteries). This can lead to coronary artery disease, heart attack, or stroke.
- In type 1 diabetes, high blood pressure usually develops if the kidneys become damaged. High blood pressure is another major cause of heart attack, stroke, and heart failure. Children with diabetes are also at risk for hypertension.
- Impaired nerve function (neuropathy) associated with diabetes also causes heart abnormalities. And some experts estimate that the mortality rates from neuropathy-related heart conditions ranges between 15% and 53%.

Intensive blood sugar control may help protect blood vessels and reduce the risk for blood clotting. It is still not known whether intensive control will have a major protective effect on the heart, however. People with diabetes must be sure to use other measures as well to protect the heart.

**Aspirin for Reducing the Risk for Blood Clots.** Taking a daily aspirin reduces the risk for blood clotting and has been shown to be protective against heart attacks. In one 2000 study, low-dose aspirin was associated with a 30% lower risk for death from heart disease in adults with type 2 diabetes. Of note: people who are at risk for retinopathy should discuss the possible benefits of high-dose aspirin with their physician.

**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). (Controlling systolic pressure may be especially important for reducing the risk for kidney complications.)

Anti-hypertensive agents that block angiotensin are the first option for many people with diabetes. Angiotensin is a natural chemical that influences all aspects of blood pressure control and also interferes with insulin's normal

metabolic signaling. In fact, angiotensin may be the common factor linking diabetes and high blood pressure. Drugs that block them are ACE inhibitors and ARBs:

- Angiotensin-converting enzyme (ACE) inhibitors are the standard agents for people with diabetes and hypertension. They include captopril (Capoten), enalapril (Vasotec), quinapril (Accupril), benazepril (Lotensin), ramipril (Altace), perindopril (Aceon), and lisinopril (Prinivil, Zestril). These agents have remarkable benefits for people with diabetes, including reducing the risks of heart attack, stroke, and death. ACE inhibitors also delay the onset and progression of kidney disease. In many cases, however, combinations are required to achieve blood pressure goals. In such cases, low-dose diuretics or calcium-channel blockers are added as needed.
- Angiotensin-receptor blockers (ARBs), also known as angiotensin II receptor antagonists, are newer drugs that are similar to ACE inhibitors in effectiveness. They may have fewer side effects. Brands include losartan (Cozaar, Hyzaar), olmesartan (Benicar) candesartan (Atacand), telmisartan (Micardis), eprosartan (Teveten), irbesartan (Avapro), and valsartan (Diovan). In one study, ARBs appeared to reduce the risk of developing diabetes. Other studies have also reported protection against kidney disease even in people with normal blood pressure, making them particularly beneficial for people with diabetes.

Combinations of the two are under investigation, and studies suggest such combinations may be beneficial for people with diabetes and kidney disease.

Other anti-hypertensive agents may be important for specific groups. Diuretics appear to be more beneficial than ACE inhibitors for African Americans with diabetes. In one major study, these patients had lower rates of stroke and heart failure than those taking ACE inhibitors. Beta blockers, another group of anti-hypertensive agents, may have more benefits for patients with existing heart disease, although more research is needed to confirm this.

[For more information, see *Well-Connected Report #14 High Blood Pressure.*]

*Improving Cholesterol and Lipid Levels.* Abnormal cholesterol and lipid levels are common in diabetes. High LDL cholesterol should always be lowered, but people with diabetes also often have additional harmful imbalances--low-HDL cholesterol and high triglycerides. Patients should aim for LDL levels below 100 mg/dl, HDL levels over 60 mg/dL and triglyceride levels below 150 mg/dL.

Statins are currently the best cholesterol-lowering agents for people with diabetes. They include pravastatin (Pravachol), simvastatin (Zocor), fluvastatin (Lescol), and atorvastatin (Lipitor). These agents are very effective for lowering LDL cholesterol levels. In addition, evidence suggests that statins reduces the risk for adverse heart events in people with even mild diabetes and in those with normal cholesterol levels. Furthermore, in one study, a statin was shown to reduce the risk by 30% of developing diabetes in people with high cholesterol. (Statins, however, do not appear to have any effect on blood vessel inflexibility in diabetes, which is an important risk factor for heart disease in these patients.) The primary safety concern with statins in people with diabetes 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 is beneficial, statins are not as effective as other medications, such as fibrates or niacin, in addressing HDL and triglyceride imbalances--a common problem in type 2 diabetes.

Combinations of statins with one these agents, then, may be important in people with diabetes. 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 fenofibrate (Tricor) and bezafibrate (Bezalip), are usually the first choice. Niacin has the most favorable effect on HDL and triglycerides of all the cholesterol drugs. However, about 30% of patients who take niacin experience elevated blood glucose levels. On the positive side, some studies have reported that diabetics who use niacin had little trouble with glucose control. In addition, niacin-statin therapy reduces the progression of heart disease. Some experts believe it now may be used as an alternative to or in combination with statins. Combinations with a new agent ezetimibe (Zetia) may also be beneficial. Ezetimibe inhibits the absorption of cholesterol in the intestines and is proving to be a very useful adjunct to statins for lowering LDL levels.

[For more information, see *Well-Connected Report #23 Cholesterol, Other Lipids, and Lipoproteins.*]

## 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.

*Treatment and Prevention of Nephropathy.* Long-term studies are now reporting a 60% reduction in new cases of nephropathy with strict blood glucose control and a delay in progression of the disease. Targeting specific preventive measures may especially protect against kidney disease. They include maintaining glycolated hemoglobin levels at 7% or below, controlling blood pressure--particularly systolic pressure, and lowering not only LDL cholesterol but also triglycerides.

The antihypertensive drugs ACE inhibitors are proving to protect against progression of kidney disease even in people with normal blood pressure. They are now the agents of choice for both preventing and managing nephropathy in type 1 diabetes. Newer agents called angiotensin-II-receptor blockers (ARBs), such as losartan (Cozaar) and irbesartan (Avapro), are also helpful for both conditions.

Sulodexide is an agent based on a natural substance called a glycosaminoglycan, which helps reduce blood clotting. Studies are suggesting that it may help prevent nephropathy with few side effects. (It also may be helpful for foot ulcers.)

If the kidneys fail, the patient will need to go on dialysis. Symptoms of kidney failure may include swelling in the feet and ankles, itching, fatigue, and pale skin color.

## Neuropathy

Diabetes reduces or distorts nerve function causing a condition called neuropathy. It particularly affects sensation. It is a common complication that affects nearly half of both type 1 and type 2 diabetics after 25 years. Neuropathy usually starts in the fingers and toes and moves up to the arms and legs (called a stocking-glove distribution). Symptoms include the following:

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

The most serious consequences of neuropathy affect the legs and feet and pose a risk for ulcers and, in very severe cases, amputation. In some cases, neuropathy may mask 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.

*Neuropathy Pain and its Treatment.* 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 .

A number of agents are used for neuropathy depending on its effects. Some used for neuropathy pain include the following:

- Topical medications, particularly capsaicin (the active ingredient in hot peppers), are commonly used for local neuropathy pain. One study reported that a spray containing isosorbide dinitrate, which helps open blood vessels, was helpful in reducing burning and pain in about half of patients.
- Alpha lipoic acid dramatically improved neuropathy in one study when administered intravenously to a group of patients with diabetes. Animal studies suggest that this potent antioxidant may have nerve-protective properties. Alpha lipoic acid is available over-the-counter. However, this substance is not regulated in the US and, as with all natural remedies, the safety and effectiveness of over-the-counter supplements cannot be guaranteed.
- Tricyclic antidepressants, such as amitriptyline (Elavil) or doxepin (Sinequan), are effective in reducing pain from neuropathy in up to 75% of patients. A combination of doxepin and capsaicin (applied to the skin) may be particularly beneficial. Unfortunately, tricyclics may have adverse effects on heart rhythm, which make them problematic for many patients, particularly elderly ones.
- Anti-seizure drugs, such as gabapentin (Neurontin) or valproate, may prove to be an effective alternative for treating painful neuropathy.
- Transcutaneous electrostimulation involves administering mild electrical pulses to painful areas. Some evidence suggests this procedure may help reduce pain, particularly in combination with a tricyclic.
- Tramadol (Ultram), a painkiller that is similar to opioids, achieved moderate pain reduction in one study and may have fewer side effects than anti-seizure drugs or tricyclics. It carries a slight risk for addiction.

Nausea, headache, and constipation are common.

*Other Complications of Neuropathy.* Neuropathy also affects other functions and treatments are needed to reduce their effects as well. 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.

Impotence in men is also associated with neuropathy. Sildenafil (Viagra), vardenafil (Levitra, Nuviva, and tadalafil (Cialis)) are proving to be effective treatments for impotence in about half of the men with either type 1 or type 2 diabetes. Side effects are usually minimal.

*Foot Ulcers and Amputations.* Perhaps the most serious consequences of diabetic neuropathy occur in the lower limbs. An estimated 15% of diabetics experience serious foot problems. They are the leading cause of hospitalizations for these patients.

Diabetes is responsible for more than half of all the lower limb amputations performed in the U.S. Each year there are about 88,000 non-injury amputations and between 50% to 75% of them are due to diabetes. Worse, the number is increasing as the prevalence in diabetes type 2 rises. About 85% of amputations start with foot ulcers, which develop in about 12% of people with diabetes.

In general, foot ulcers develop from infections, such as those resulting from blood vessel injury. 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.

According to a 2003 government survey, those at higher risk for foot ulcers tend to be people with diabetes who are overweight, smokers, and those with a long history of diabetes. People who had had the disease for more than 20 years and were insulin-dependent were at the highest risk. Related conditions that put people at risk include peripheral neuropathy, peripheral arterial disease, foot deformities, and a history of ulcers.

*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 like an infection, with the foot becoming swollen, red, and warm. A seriously 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 to 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. A 2001 study in the U.K. concluded that a single dose of pamidronate, a bisphosphonate, reduces bone turnover, symptoms, and disease activity. When the acute phase has passed, patients usually need lifelong protection of the foot using a brace initially and custom footwear.

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

- 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.
- 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.
- Well-fitting footwear is very important. People should be sure the shoe is wide enough; according to a 2001 study, 30% of diabetic patients wear shoes that are too narrow. Patients should also avoid high heels, sandals, thongs, and going barefoot. Shoes with a rocker sole (e.g., LucRo) reduce pressure under the heel and front of the foot by 35% to 65% and may be particularly helpful. Custom-molded boots (e.g., Conformer Diabetic Boot) increase the surface area over which foot pressure is distributed. This reduces stress on the ulcers and allows them to heal.
- Shoes should be changed often during the day.
- Wear socks, particularly with extra padding (which can be purchased).
- Patients should avoid tight stockings or any clothing that constricts the legs and feet.
- Foot pain, numbness, or tingling is worse at night; diphenhydramine (Benadryl) may help.
- A specialist in foot care should be consulted for any problems.

*Treating Foot Ulcers in Diabetes.* About one-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, which is the removal of injured tissue until only healthy tissue remains. Debridement may be accomplished using chemical (enzymes), surgical, or mechanical (e.g. irrigation) means.
- Hydrogels (Nu-Gel, Intrasite Gel, Scherisorb, Clearsite, Duoderm, Geliperme) are helpful in healing ulcers and are noninvasive and soothing.
- Felted foam appears to be helpful in healing ulcers on the sole of the foot.

*Investigative Agents for Treating Foot Ulcers.* A number of recent investigative agents and procedures for treating foot ulcers include the following:

- Cultures of human skin cells or human skin equivalent (HSE) (e.g., Dermagraft, Apligraf, or Regranex) stimulate new cell growth and help heal skin ulcers. Studies are showing that HSE promotes healing and the risk for rejection of such grafts is low. Adverse effects include infections at other sites.
- Administering hyperbaric oxygen (oxygen given at high pressure) is showing promise in promoting healing. In one study, for example, patients who had had ulcers that had not responded to treatment for over three months received daily treatments that lasted 90 minutes for two weeks. About 15 days after completion, patients who received oxygen had significant reduction in ulcers, sometimes with complete healing. Other studies are also demonstrating good results.
- Sulodexide is an agent based on a natural substance called a glycosaminoglycan, which helps reduce blood clotting. Studies are suggesting that it may be helpful for treating foot ulcers but improving blood flow.
- Granulocyte-colony stimulating factor, or G-CSF (filgrastim, Neupogen, Amgen) has accelerated healing and significantly reduced the need for surgery in some studies. A 2003 study, however, indicated that offered no additional advantages compared with antibiotics and bed rest.
- Low-molecular weight heparin, which is a blood thinner, is being investigated for treating foot ulcers.
- Monochromatic near-infrared photo energy (MIRE) uses light therapy to improve sensation in the feet of patients with peripheral neuropathy.

*Devices to Heal Ulcers and Protect the Foot.* Researchers are also using or investigating various devices to heal or prevent ulcers. The following are some examples:

- 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 is useful for ulcer healing and for Charcot foot. Although it is very effective in healing ulcers, recurrence is common.
- Noncontact normothermic wound therapy (Warm-UP) uses a unit that applies infrared radiant heat for an hour three times a day. In one study, 70% of the wounds treated were healed compared to 40% that received standard gauze treatments. More research is needed to determine if this approach has any advantages over other measures.
- Felted foam uses a multi-layered foam pad over the bottom of the foot with an opening over the ulcer. Small studies have suggested that it is effective in healing ulcers in this area.

## Retinopathy and 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. 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. [For more information, see *Well-Connected Report #26 Cataracts* or *Report #25 Glaucoma*.]

*Description of Retinopathy.* Retinopathy is a condition in which the retina 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, however. 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. The sensation of seeing flashing lights may indicate retinal detachment.

According to a 2003 study, about 40% of young adults with type 1 diabetes had developed retinopathy within 10 years of diagnosis. (Although this rate is high, it is significantly lower than in previous years when blood glucose control was not as strict.) The risk is lower in patients with type 2, although in one study over 20% had signs of retinopathy six years after diagnosis. Any patient on insulin or who has had diabetes for more than 20 years should have a yearly eye examination. Patients with no signs of retinal damage or risk factors for retinopathy may only require screening every three years.

*Prevention of Retinopathy.* Fortunately, severe and even moderate vision loss is largely preventable with intensive control of blood glucose levels. (Note: intense glucose control can cause early worsening of retinopathy, although this is nearly always counterbalanced by long-term benefits.) Measures for reducing risks to the heart (e.g., ACE inhibitors for lower blood pressure and drugs that improve cholesterol) may also have protective benefits for the eyes. Whereas low-dose aspirin is used to prevent heart disease, high doses may prevent retinopathy. Patients at risk for retinopathy should discuss this therapy with their physicians.

*Treatment of Retinopathy.* 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.

## 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 age 55 who have had diabetes for a number of years. In one study of people with type 1 diabetes, high glucose levels (hyperglycemia) were associated with slower brain function, including less verbal fluency and slow ability to do mental arithmetic.

## 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. In fact, deaths among people with diabetes increase by 5% to 15% during flu epidemics and they are six times more likely to be hospitalized with complications from flu than nondiabetics who have flu. Everyone with diabetes should have influenza vaccinations annually 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. Furthermore, according one study, depression, in turn, increases the risk for hyperglycemia and complications of diabetes. Restoring mental health, both through medication and psychotherapy, not only improves quality of life but also helps patients control their blood sugar levels.

## Changes in Bone Quality

Diabetes changes bone quality and density, but the effects differ depending on type:

- Type 1 diabetes is associated with a slightly reduced bone density, putting patients at risk for osteoporosis and possibly fracture. The best medications for bone loss in patients with diabetes may be the bisphosphonates, such as alendronate (Fosamax) and risedronate (Actonel). They not only help prevent bone loss but may even reduce daily insulin requirements in patients taking insulin. [ See *Well-Connected Report #18 Osteoporosis.*]
- Type 2 diabetes, on the other hand, is associated with an increased bone density but is also associated with fractures. In such cases, the bone quality itself may be impaired.

Older patients with either type are at risk for falling, which compounds the risk for fracture.

## Other Complications

Other complications of diabetes include the following:

- Diabetics have a slightly higher prevalence of hearing loss than nondiabetics.
- Up to half of people with diabetes are at risk for nonalcoholic fatty liver disease, also called nonalcoholic steatohepatitis (NASH). It is a particular danger in people who are obese.
- 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.
- Much evidence exists on the link between type 1 and type 2 diabetes and periodontal disease. People with these diseases have 15 times the risk of the nondiabetic population.

## Resources

- [www.diabetes.org](http://www.diabetes.org) -- American Diabetes Association (800-232-3472)
- [www.niddk.nih.gov](http://www.niddk.nih.gov) -- National Institute of Diabetes and Digestive and Kidney Diseases
- [www.nei.nih.gov](http://www.nei.nih.gov) -- National Eye Institute (800-869-2020)
- [www.medicalert.org](http://www.medicalert.org) -- Medic Alert (888-633-4298)
- [www.eatright.org](http://www.eatright.org) -- American Dietetic Association (800-366-1655)
- [www.insulinfree.org](http://www.insulinfree.org) -- Insulin-Free World Foundation
- <http://limaye.ecri.org> -- Limaye Center
- [www.diabetesincontrol.com](http://www.diabetesincontrol.com) -- Diabetes information
- [www.childrenwithdiabetes.com](http://www.childrenwithdiabetes.com) -- Information on children with diabetes
- [www.diabetesnet.com](http://www.diabetesnet.com) -- Diabetes products

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*Reviewed By:* Harvey Simon, MD, Editor-in-Chief, Associate Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital

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