

HCV & Type 2 Diabetes: An Introduction

By Liz Highleyman

Diabetes is a condition in which blood sugar levels are too high. This can occur when the body does not produce enough insulin or when cells do not use insulin properly. Over time, high blood sugar levels can lead to many complications, including nerve damage and loss of vision.

Sugar and Insulin

Your body needs a type of sugar called **glucose** as a fuel to provide energy. When the foods you eat are digested and broken down, glucose is released into the bloodstream. In order for your cells to use this sugar, they require a hormone called **insulin**. Insulin acts as a “key” that allows glucose to enter cells. Insulin is produced by **beta cells** located in the **Islets of Langerhans** of the **pancreas**.

Blood glucose levels fluctuate over the course of the day. In most people, blood sugar rises after eating, but soon returns to normal levels. But if there is not enough insulin -- or if the body cannot properly use insulin -- glucose cannot enter the cells and builds up to high levels in the blood (a condition known as **hyperglycemia**). When this happens, body and brain cells are starved for energy, and prolonged high blood sugar can lead to a variety of health problems.

Types of Diabetes

There are two major types of diabetes:

- **Type 1 diabetes** is also known as juve-

nile diabetes (because it usually develops in children) or **insulin-dependent diabetes mellitus**. In people with Type 1 diabetes, the pancreas produces little or no insulin (often because beta cells have been destroyed by the body’s immune system). Symptoms typically develop rapidly, and may include increased thirst and appetite, frequent urination, and rapid weight loss. People with Type 1 diabetes must inject insulin.

- **Type 2 diabetes** is also known as adult-onset diabetes or **non-insulin-dependent diabetes mellitus**. It usually develops in older, overweight people. In people with Type 2 diabetes, either the pancreas does not produce enough insulin, the body cannot properly use the insulin that is produced (**insulin resistance**), or both. Some people with this type of diabetes can control their condition with diet and exercise modification, but others must take oral medications or insulin.

In addition, women may develop a condition called **gestational diabetes** during pregnancy. Blood sugar levels usually return to normal once the baby is born. However, women who develop gestational diabetes while pregnant are at higher risk of later developing Type 2 diabetes.

Type 2 Diabetes: the Basics

An estimated 16 million people in the U.S. (about 6% of the population) have Type 2 diabetes; many of these people are un-

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aware that they have the condition. Type 2 diabetes is much more common than type 1, accounting for over 90% of diabetes cases.

Type 2 diabetes is more common among Latino/Hispanic-Americans, African-Americans, Asian/Pacific Islander-American, and Native Americans. According to the National Institute of diabetes and Digestive and Kidney Diseases (NIDDK), Type 2 diabetes rates for Latinos and African-Americans are about twice the rate for non-Hispanic whites; rates among certain Native American tribes and Pacific Islander groups are even higher. Some studies suggest that certain racial and ethnic groups suffer higher rates of various long-term conditions related to diabetes. For example, Mexican-Americans appear to have higher rates of retinopathy (eye disease) and kidney disease than other people with diabetes.

Risk Factors for Type 2 Diabetes

Type 2 diabetes most often develops in adults over 40 years of age, but it may also occur in children and younger adults. Some experts now recommend that all people age 40 and older should be screened for diabetes. People who are overweight and have a sedentary lifestyle (that is, they get little exercise) are at greatest risk of developing the condition; in fact, about 80% of people with Type 2 diabetes are overweight. High blood pressure and high levels of blood lipids (fats) and cholesterol are also associated with Type 2 diabetes. Another risk factor is family history; if you have a parent or sibling with Type 2 diabetes, there is a greater chance that you will also develop the disease.

HCV and Type 2 Diabetes

In the mid-1990s, researchers began to report that rates of Type 2 diabetes were higher in people with hepatitis C virus (HCV) infection, and vice versa. For exam-

ple, in the September 1996 issue of *Diabetes Care*, Rafael Simo and colleagues reported that study participants with diabetes had a 11.5% rate of HCV infection, compared to a HCV rate of 2.5% in a matched population of non-diabetic blood donors.

More recently, Nizar Zein and colleagues from the Mayo Clinic examined the prevalence of Type 2 diabetes in people undergoing liver transplants. They reported in the February 2000 issue of the *Journal of Hepatology* that the rate of diabetes was higher in people who had end-stage cirrhosis (liver scarring) related to HCV (25%) or alcoholism (19%) than in those with liver failure due to cholestatic (bile duct blockage) liver disease (1.3%). Interestingly, the success rate for liver transplants was not adversely affected by diabetes.

At the 10th International Symposium on Viral Hepatitis and Liver Disease held in April 2000, Shruti Mehta and colleagues from Johns Hopkins University examined the medical records of nearly 10,000 people taking part in the National Health and Nutrition Examination Survey. All were assessed for diabetes and hepatitis C; 1,242 (8.4%) had diabetes (type 1 or type 2) and 230 (2.1%) had HCV. After controlling for race, injection drug use, and other factors, the researchers found that in people age 40 and older, those with HCV were nearly four times more likely to have Type 2 diabetes than those without HCV; a similar association was not seen in people under age 40. There was no association between HCV and Type 1 diabetes, nor between hepatitis B virus (HBV) infection and either type of diabetes.

Several hypothesis have been put forth to explain Type 2 diabetes appears to be more common in people with HCV. Two early suggestions were that people with diabetes might have been more likely to contract HCV due to frequent medical proce-

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dures, and that since people with Type 2 diabetes often have elevated liver enzyme levels, they might have been more often tested for HCV. However, studies that have controlled for these factors have still shown increased rates of diabetes in people with HCV, leading researchers to suggest that HCV itself may contribute to diabetes. One possibility is that HCV may infect and damage the insulin-producing beta cells of the pancreas. Since HCV is known to be associated with autoimmune conditions, another possibility is that the immune systems of people with HCV may attack and damage insulin-producing cells. In addition, liver inflammation or damage due to HCV may affect the production of glucose or the metabolism of insulin by the liver, thus altering blood sugar levels. Studies have shown that cirrhosis of the liver, regardless of cause, increases the risk of insulin resistance, although it is not known why. James Everhart, MD, has suggested that HCV may not cause Type 2 diabetes directly, but may rather have a “permissive” effect, acting with other factors to cause the condition. Clearly more research is needed in this area.

Insulin Resistance

In many people with Type 2 diabetes, muscle, fat, and liver cells do not use insulin properly, a condition known as *insulin resistance*. The cause of insulin resistance is not known, but scientists believe it may be related to defects or deficiencies in the cells’ insulin receptors, or problems with signaling inside the cell. Being overweight is known to trigger insulin resistance. A recent study by Claire Steppan and colleagues from the University of Pennsylvania published in the January 18, 2001 issue of *Nature* suggested that a recently discovered hormone called *resistin*, which is secreted by fat cells and may be present at higher

levels in overweight people, might impede the action of insulin.

Insulin resistance may precede the development of Type 2 diabetes. Some studies suggest that diet and exercise modification and early treatment with antidiabetic drugs can help prevent or delay the development of full-blown diabetes. However, the body’s ability to produce insulin may diminish over time in people with insulin resistance, so the condition may progressively worsen.

Symptoms of Types 2 Diabetes

The symptoms of Type 2 diabetes typically develop slowly over time (that is, it is a *chronic* rather than an *acute* condition). Some people with mild Type 2 diabetes have no symptoms and may be unaware that they have the condition. Symptoms of diabetes may include increased hunger and thirst, frequent urination, fatigue, blurred vision, and dry, itchy skin.

Long-Term Complications of Diabetes

Over time, high blood sugar levels can lead to serious damage to many parts of the body, especially the blood vessels and nerves. Long-term consequences of diabetes (both Type 1 and type 2) include heart disease, atherosclerosis (hardening of the arteries), stroke, kidney disease, diabetic neuropathy (nerve damage), gastroparesis (damage to nerves that control the emptying of the stomach), diabetic retinopathy (eye damage that can lead to blindness), and gum disease. Blood vessel and nerve damage can lead to a variety of problems, including tingling, pain, or numbness in the hands and feet, sexual dysfunction, and ulcers or sores that are slow to heal. Complications due to severe nerve damage sometimes necessitate amputation of the lower limbs. According to the NIDDK, diabetes is the most common cause of blindness, kidney failure, and am-

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putation in U.S. adults.

Diagnosing Type 2 Diabetes

Various tests are used to diagnose diabetes. The most common is the **fasting plasma glucose test**. In this test, the blood sugar level is measured after a person has fasted (no food or beverages except water) for eight hours. According to current American Diabetes Association standards, a fasting plasma glucose level of over 126 mg/dL indicates diabetes (a normal level is 80-120 mg/dL).

Another test is the **oral glucose tolerance test**. In this test, a person drinks a sugar-water solution after fasting overnight, and their plasma glucose level is measured to determine if glucose levels rise and fall normally; a glucose level of 200 mg/dL or higher after two hours indicates diabetes. If a person has symptoms such as excessive thirst or frequent urination, a diagnosis of diabetes may be made if a random non-fasting blood test reveals a glucose level of 200 mg/dL or higher.

Other tests are done to monitor the progress of diabetes. The hemoglobin A1c test measures how much sugar adheres to red blood cells, and is used to determine average blood glucose levels over the course of three months. A desirable hemoglobin A1c test result is 7% or lower. This laboratory test should be repeated every 3-6 months to help determine if a person's diabetes is under ; however, it is not a substitute for regular home blood glucose monitoring.

Finally, urine tests may also be used to diagnose and monitor diabetes. In people with uncontrolled diabetes, metabolic by-products called **ketones** are excreted in the urine when the body burns fat instead of glucose for fuel; this usually occurs in people with Type 1 diabetes. Since simple and reliable home blood tests are now widely

available, urine testing is no longer considered a reliable way to monitor blood sugar levels.

Managing Type 2 Diabetes

People with Type 2 diabetes can live long and relatively symptom-free lives if they take good care of their health and carefully manage their disease. This involves diet modification, exercise, regular blood glucose monitoring, and treatment which may include oral medications or injected insulin.

Diet and Exercise

A healthy diet and adequate exercise are the first steps in managing – and preventing -- Type 2 diabetes. Just as being overweight can trigger Type 2 diabetes, weight loss can improve the condition. People with Type 2 diabetes should eat a balanced diet that is low in fat, salt, and refined sugar, and high in complex carbohydrates; such a diet should contain plenty of fruits, vegetables, and grains. Maintaining a healthy diet can promote weight loss, keep blood glucose levels within a healthy range, and reduce the risk of cardiovascular disease. Your doctor or a dietitian can help you develop a good personalized eating plan.

Exercise can also help control weight and improve cardiovascular health; in addition, studies suggest that regular exercise can help the body use insulin more efficiently. The NIDDK recommends exercising three times per week for 30-45 minutes each session. Check with your doctor before starting any new exercise plan.

Eating adds fuel to the body and usually raises blood sugar levels, while exercise burns fuel and tends to lower blood glucose levels. Maintaining an awareness of when and how much you eat and exercise can help you keep your blood sugar within a healthy range. It may be helpful to eat and

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Diabetic Emergencies

Insulin shock is caused by extreme low blood sugar (hypoglycemia) that occurs when a diabetic's insulin level becomes too high. This can happen if a person injects too much insulin, misses a meal, or exercises too strenuously. An insulin reaction usually comes on quickly. Symptoms include hunger, mental confusion, irritability, rapid pulse, shakiness, weakness, sweating, pale skin, fatigue, seizures, and loss of unconsciousness. Insulin shock can be fatal. First aid for insulin shock is rapid administration of sugar. If the person is conscious, help them eat or drink something like hard candy, jam, honey, fruit juice, or non diet soda. Glucose tablets and gel are also available. Do not try to give food or drink to an unconscious person; however, glucose gel or honey can be applied directly to the inner lip or under the tongue of a person who is unable to swallow. If the person loses consciousness, call 911. Emergency personal can inject glucagon, a rapidly acting hormone that increases blood glucose levels. If symptoms don't improve in 10-15 minutes, administer more sugar. Once acute symptoms are relieved, the person should eat a snack or meal that contains carbohydrates.

Diabetic coma is a life-threatening condition associated with extreme high blood sugar (hyperglycemia). It occurs when the body lacks insulin and burns fat instead of glucose for fuel, releasing a ketones into the blood. A high level of ketones can alter the chemistry of the blood, a condition called ***ketoacidosis***. Dangerous hyperglycemia may occur if a person lacks access to insulin or is ill; it almost always occurs in people with Type 1 diabetes. Unlike an insulin reaction, symptoms of ketoacidosis usually come on slowly, sometimes over several hours or even days. Symptoms include nausea, vomiting, abdominal pain, weakness, drowsiness, dehydration (characterized by sunken eyes and dry mouth and skin), deep rapid breathing, and finally loss of consciousness. In addition, the person's breath will often have a fruity or acetone smell. A person experiencing ketoacidosis or diabetic coma needs immediate medical attention. Call 911 or take the person to an emergency room.

Both extreme hypoglycemia and extreme hyperglycemia can lead to loss of consciousness. If you are unsure which condition a diabetic person is experiencing, treat for insulin shock, since this is a more immediate danger (and since such treatment will not make a person with hyperglycemia appreciably worse). If the person does not respond to first aid, call 911.

If you have diabetes, wear a MedicAlert tag so you can be treated properly if you are unconscious. Inform your doctor if you experience either type of diabetic emergency. If these happen frequently, your insulin or medication dose may have to be adjusted.

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exercise at similar times each day. Some doctors recommend several small meals over the course of the day instead of 2-3 large meals, to help keep blood sugar levels more consistent. Skipping meals, engaging in unusually prolonged or strenuous exercise, and illness can all affect blood sugar levels. When exercising, keep a snack or sports drink on hand in case your blood sugar level falls too low.

Blood Glucose Monitoring

The key to managing diabetes is keeping a consistent, healthy blood glucose level. Therefore, it is important to test your blood sugar level regularly. To perform this simple test, draw a drop of blood using a sharp tool called a *lancet*. Place the blood on a test strip, which will change color depending on how much glucose the blood contains. You can determine your glucose level by comparing the colors on your test strip to those on a color chart, or you can use a glucose monitoring machine which reads the test strip. Be sure to properly dispose of used lancets in an appropriate “sharps” container. New noninvasive glucose monitors that measure glucose levels through the skin are currently being developed.

Your doctor may recommend that you test your blood sugar before and after eating and exercising. This is especially important for people who are newly diagnosed and are learning how to keep their blood sugar at a healthy level. Regular testing can help your doctor determine correct dosages for medication or insulin. Keeping daily records of your blood glucose test results -- and how they are related to meals, exercise, illness, and symptoms -- is an important step in keeping your diabetes under control.

Treatment for Type 2 Diabetes

Diabetes is a chronic manageable condition. Although there is no cure, several treat-

ments are available that can keep the condition under control and allow people with the disease to live a long and healthy life.

Unlike people with Type 1 diabetes, people with Type 2 diabetes usually produce some insulin. Thus, treatment is usually focused on helping the body use insulin as efficiently as possible. As noted above, the first steps in controlling Type 2 diabetes involve changes in diet and exercise levels. In some cases, changes in diet and exercise alone -- especially if they lead to weight loss -- can control mild Type 2 diabetes.

Oral Antidiabetic Drugs

If diet and exercise changes are not sufficient to keep blood glucose levels within a healthy range, oral *antidiabetic* medications are usually tried next. These medications only work in people whose bodies produce some insulin (thus, they are not effective in people with Type 1 diabetes).

There are several major types of drugs used to treat Type 2 diabetes. The oldest class of drugs are called sulfonylureas. These drugs stimulate the production of insulin and help the body use insulin more efficiently. This category includes chlorpropamide (Diabinese), glimepiride (Amaryl), glipizide (Glucotrol), glyburide (Micronase, Glynase), tolazamide (Tolinase), and tolbutamide (Orinase). These drugs are typically taken once or twice per day immediately before meals.

Metglitinides also stimulate the production of insulin by the pancreas. The only currently used drug in this class is repaglinide (Prandin). This drug is taken before each meal.

Alpha-glucosidase inhibitors retard the digestion of starches and certain sugars by blocking an enzyme. This causes a slower increase in blood sugar after eating. Drugs in this class are acarbose (Precose) and

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migliitol (Glyset). These drugs are taken with the first bite of a meal.

Biguanides help lower blood glucose levels by decreasing the amount of sugar produced by the liver. The only currently used drug in this class is metformin (Glucophage). It is taken 2-3 times per day with meals.

Finally, thiazolidinediones (“glitazone”) drugs make the body’s cells more sensitive to insulin. These drugs include pioglitazone (Actos) and rosiglitazone (Avandia). They are typically taken once or twice per day with food.

Because the various antidiabetic drugs work differently, your doctor may prescribe a combination treatment regimen. Sometimes an initial drug is tried first and other medications added if it does not work alone. Often doctors will try different combinations and dosages to find the regimen that works best for you.

Oral antidiabetic drugs alone do not work for everyone. Even if they reduce blood glucose levels somewhat, the drugs may not bring levels within the normal range that is optimal for good health. Oral drugs are most effective in people who have recently developed Type 2 diabetes and in those whose blood sugar levels are not too far above normal.

Like all drugs, oral antidiabetic medications may cause side effects. Sulfonylurea drugs can cause upset stomach, skin rash, and weight gain. Meglitinides may cause weight gain. Sulfonylurea and meglitinide drugs, which stimulate the production of insulin, can cause blood sugar levels to drop too low (hypoglycemia), potentially leading to insulin shock; this does not occur with the other drug classes. Alpha-glucosidase inhibitors can cause intestinal gas, bloating, and diarrhea (especially when the drug is first started). Biguanides may cause weakness, fatigue, nausea and/or diarrhea

(especially when the drug is first started), and may worsen existing kidney problems; on the other hand, they may have the beneficial effect of decreasing fat and cholesterol levels. Both sulfonylurea and biguanide drugs can adversely interact with alcohol, causing gastrointestinal upset and skin flushing and occasionally more serious illness.

Thiazolidinediones can cause liver damage, indicated by elevated liver enzymes and symptoms such as nausea, abdominal pain, lack of appetite, fatigue, and jaundice. One drug in this category, troglitazone (Rezulin), was taken off the market last year because it caused fatal liver failure. Because of their potential adverse effect on the liver, pioglitazone and rosiglitazone should be used with extreme caution in people with HCV or other liver disease.

Antidiabetic drugs can interact with drugs for other conditions, affecting how well they work and potentially increasing side effects. Interactions with drugs used to treat HCV have not been well studied. However, in a 1998 case report from Italy, a 29-year-old man with chronic HCV developed diabetes during treatment with interferon, leading a researcher to speculate that interferon may enhance autoimmune damage to insulin-producing cells. Tell your doctor about any drugs you are using, including over-the-counter (non-prescription) medications, herbal remedies, and recreational drugs.

Insulin

In some people with Type 2 diabetes, oral drugs do not adequately control blood sugar levels. In others, medications work for awhile, but then stop working over time. Studies have shown that in people with Type 2 diabetes, the body’s ability to produce insulin may decline with time. If oral medication alone is not adequate, people

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with Type 2 diabetes must inject insulin, as do people with Type 1 diabetes. Sometimes oral drugs and insulin are used together. The longer a person has type 2 diabetes, the more likely he or she will need insulin injections. When people with Type 2 diabetes have an infection or undergo surgery, or when women with Type 2 diabetes become pregnant, they may need to use insulin temporarily.

Because current formulations of insulin are broken down by the digestive system, they cannot be taken by mouth; attempts to make an effective oral insulin have been underway for years. Some formulations of insulin work rapidly, while others are more long-acting. People may inject insulin once or twice a day, or may use a wearable pump that delivers a steady amount of insulin. Do not reuse or share injection needles, and dispose of them safely in an appropriate “sharps” container.

Control is Key

Controlling your blood sugar level is the key to good health. Maintain a healthy weight, eat right, and get adequate exercise. Monitor your blood glucose regularly. Take antidiabetic drugs and/or insulin as directed. Try to eat and take medications at about the same time each day. Let your doctor know if you are having trouble maintaining a consistent, healthy blood sugar level.

Poorly controlled diabetes is associated with numerous long-term complications. Have your blood pressure, kidney function, and vision checked regularly. Brush and floss your teeth daily, and get regular dental checkups and cleanings. Avoid smoking to reduce the risk of cardiovascular disease. Learn about proper foot and skin care, which are especially important for people with diabetes. Make sure to inform your healthcare providers about any unusual symptoms. People with Type 2 diabetes can

live long and healthy lives if they educate themselves about their condition and take good care of their health.

Resources

American Diabetes Association: www.diabetes.org

National Institute of Diabetes and Digestive and Kidney Diseases: www.niddk.nih.gov/health/diabetes/diabetes.htm (includes specific information for African-Americans, Latinos, Asian/Pacific Islanders, and Native Americans)

Canadian Diabetes Association: www.diabetes.ca
Centers for Disease Control and Prevention: www.cdc.gov/diabetes

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