



Diabetes Mellitus

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I. INTRODUCTION

Diabetes Mellitus, disease in which the pancreas produces insufficient amounts of insulin, or in which the body's cells fail to respond appropriately to insulin. Insulin is a hormone that helps the body's cells absorb glucose (sugar) so it can be used as a source of energy. In people with diabetes, glucose levels build up in the blood and urine, causing excessive urination, thirst, hunger, and problems with fat and protein metabolism. Diabetes mellitus differs from the less common diabetes insipidus, which is caused by lack of the hormone vasopressin, which controls the amount of urine secreted.

In the United States, some 21 million people (7 percent of the population) suffer from diabetes mellitus. Every year, some 1.5 million people learn they have the disease. Diabetes mellitus kills more than 73,000 U.S. residents each year, making it the sixth leading cause of all deaths resulting from disease. In addition, diabetes is a contributing factor in many deaths from heart disease, kidney failure, and other conditions. Overall, experts estimate that diabetes contributes to about 225,000 deaths annually in the United States. In Canada, approximately 2.5 million residents (about 6 percent of the population) have diabetes mellitus. The disease ranks as the seventh leading cause of death in Canada, where it kills about 6,000 people a year. Diabetes and its complications contribute to about 25,000 deaths in Canada annually.

Diabetes is most common in adults over 45 years of age; in people who are overweight or physically inactive; in individuals who have an immediate family member with diabetes; and in people of African, Hispanic, and Native American descent. The highest rate of diabetes in the world occurs in Native Americans. More women than men have been diagnosed with the disease.

In diabetes mellitus low insulin levels or poor response to insulin prevent cells from absorbing glucose. As a result, glucose builds up in the blood. When glucose-laden blood passes through the kidneys, the organs that remove blood impurities, the kidneys cannot absorb all of the excess glucose. This excess glucose spills into the urine, accompanied by water and electrolytes—ions required by cells to regulate the electric charge and flow of water molecules across the cell membrane. This causes frequent urination to get rid of the additional water drawn into the urine; excessive thirst to trigger replacement of lost water; and hunger to replace the glucose lost in urination. Additional symptoms may include blurred vision, dramatic weight loss, irritability, weakness and fatigue, and nausea and vomiting.

II. TYPE 1 DIABETES

Diabetes is classified into two types. In Type 1 diabetes, formerly called insulin-dependent diabetes mellitus (IDDM) and juvenile-onset diabetes, the body does not produce insulin or produces it only in very small quantities. Symptoms usually appear suddenly, typically in individuals under 20 years of age. Most cases occur around puberty—around age 10 to 12 in girls and age 12 to 14 in boys. In the United States Type 1 diabetes accounts for 5 to 10 percent of all diabetes cases. In Canada, Type 1 diabetes accounts for about 10 percent of all diabetes cases.

Type 1 diabetes is a disease in which the body produces too little insulin or no insulin at all. In most cases, Type 1 diabetes is an autoimmune disease, that is, a condition in which the body's disease-fighting immune system goes awry and attacks healthy tissues. In the case of Type 1 diabetes, the immune system mistakenly attacks and destroys insulin-producing cells, known as beta cells, in the pancreas. Scientists believe that a combination of genetic and environmental factors somehow triggers the immune system to destroy these cells. Scientists have so far identified 20 genes that play a role in Type 1 diabetes, although the exact function of these genes is still under

investigation. Environmental factors, such as certain viruses, may also contribute to the development of the disease, particularly in people who already have a genetic predisposition for the disease. Type 1 diabetes also can result from surgical removal of the pancreas.

In addition to causing a buildup of glucose in the blood, untreated Type 1 diabetes affects the metabolism of fat. Because the body cannot convert glucose into energy, it begins to break down stored fat for fuel. This produces increasing amounts of acidic compounds in the blood called ketone bodies, which interfere with cellular respiration, the energy-producing process in cells.

III. TYPE 2 DIABETES

In Type 2 diabetes, formerly known as non-insulin-dependent diabetes mellitus (NIDDM) and adult-onset diabetes, the body's delicate balance between insulin production and the ability of cells to use insulin goes awry. Symptoms characteristic of Type 2 diabetes include those found in Type 1 diabetes, as well as repeated infections or skin sores that heal slowly or not at all, generalized tiredness, and tingling or numbness in the hands or feet.

Of the nearly 21 million people in the United States with diabetes, 90 to 95 percent have Type 2 diabetes. About 90 percent of all diabetes cases in Canada are Type 2. The onset of Type 2 diabetes usually occurs after the age of 45, although the incidence of the disease in younger people is growing rapidly. Because symptoms develop slowly, individuals with the disease may not immediately recognize that they are sick. A number of genes are involved in Type 2 diabetes. In addition, there is a strong relationship between obesity and Type 2 diabetes. About 80 percent of diabetics with this form of the disease are significantly overweight.

IV. COMPLICATIONS

If left untreated, diabetes mellitus may cause life-threatening complications. Type 1 diabetes can result in diabetic coma (a state of unconsciousness caused by extremely high levels of glucose in the blood) or death. In both Type 1 and Type 2 diabetes, complications may include blindness, kidney failure, and heart disease. Diabetes can cause tiny blood vessels to become blocked; when this occurs in blood vessels of the eye, it can result in *retinopathy* (the breakdown of the lining at the back of the eye), causing blindness. Diabetes mellitus is the leading cause of new cases of blindness in people aged 20 to 74. In the kidneys, diabetes can lead to *nephropathy* (the inability of the kidney to properly filter toxins from the blood). About 40 percent of new cases of end-stage *renal disease* (kidney failure) are caused by diabetes mellitus. Blockages of large blood vessels in diabetics can lead to many cardiovascular problems, including high blood pressure, heart attack, and stroke. Although these conditions also occur in nondiabetic individuals, people with diabetes are two to four times more likely to develop cardiovascular disorders.

Diabetes mellitus may also cause loss of feeling, particularly in the lower legs. This numbness may prevent a person from feeling the pain or irritation of a break in the skin or of foot infection until after complications have developed, possibly necessitating amputation of the foot or leg. Burning pain, sensitivity to touch, and coldness of the foot, conditions collectively known as neuropathy, can also occur. Other complications include higher-risk pregnancies in diabetic women and a greater occurrence of dental disease.

V. DIAGNOSIS AND TREATMENT

Diabetes is detected by measuring the amount of glucose in the blood after an individual has fasted (abstained from food) for about eight hours. In some cases, physicians diagnose diabetes by administering an oral glucose tolerance test, which measures glucose levels before and after a specific amount of sugar has been ingested.

Once diabetes is diagnosed, treatment consists of controlling the amount of glucose in the blood and preventing complications. Depending on the type of diabetes, this can be accomplished through regular physical exercise, a carefully controlled diet, and medication.

Individuals with Type 1 diabetes must receive insulin, often two to four times a day, to provide the body with the hormone it does not produce. Insulin cannot be taken orally, because it is destroyed in the digestive system.

Consequently, insulin-dependent diabetics have historically injected the drug using a hypodermic needle or a beeper-sized pump connected to a needle inserted under the skin. In 2006 the United States Food and Drug Administration approved a form of insulin that can be inhaled and then is absorbed by blood in the lungs.

The amount of insulin needed varies from person to person and may be influenced by factors such as a person's level of physical activity, diet, and the presence of other health disorders. Typically, individuals with Type 1 diabetes use a meter several times a day to measure the level of glucose in a drop of their blood obtained by pricking a fingertip. They can then adjust the dosage of insulin, physical exercise, or food intake to maintain the blood sugar at a normal level. People with Type 1 diabetes must carefully control their diets by distributing meals and snacks throughout the day so as not to overwhelm the ability of the insulin supply to help cells absorb glucose. They also need to eat foods that contain complex sugars, which break down slowly and cause a slower rise in blood sugar levels.

Although most persons with Type 1 diabetes strive to lower the amount of glucose in their blood, levels that are too low can also cause health problems. For example, if a person with Type 1 diabetes takes too much insulin, it can produce low blood sugar levels. This may result in hypoglycemia, a condition characterized by shakiness, confusion, and anxiety. A person who develops hypoglycemia can combat symptoms by ingesting glucose tablets or by consuming foods with high sugar content, such as fruit juices or hard candy.

In order to control insulin levels, people with Type 1 diabetes must monitor their glucose levels several times a day. In 1983 a group of 1,441 Type 1 diabetics aged 13 to 39 began participating in the Diabetes Control and Complications Trial (DCCT), the largest scientific study of diabetes treatment ever undertaken. The DCCT studied the potential for reducing diabetes-related complications, such as nerve or kidney disease or eye disorders, by having patients closely monitor their blood sugar levels four to six times a day, maintaining the levels as close to normal as possible. The results of the study, reported in 1993, showed a 50 to 75 percent reduction of diabetic complications in people who aggressively monitored and controlled their glucose levels. Although the study was performed on people with Type 1 diabetes, researchers believe that close monitoring of blood sugar levels would also benefit people with Type 2 diabetes.

For persons with Type 2 diabetes, treatment begins with diet control, exercise, and weight reduction, although over time this treatment may not be adequate. People with Type 2 diabetes typically work with nutritionists to formulate a diet plan that regulates blood sugar levels so that they do not rise too swiftly after a meal. A recommended meal is usually low in fat (30 percent or less of total calories), provides moderate protein (10 to 20 percent of total calories), and contains a variety of carbohydrates, such as beans, vegetables, and grains. Regular exercise helps body cells absorb glucose—even ten minutes of exercise a day can be effective. Diet control and exercise may also play a role in weight reduction, which appears to partially reverse the body's inability to use insulin.

For some people with Type 2 diabetes, diet, exercise, and weight reduction alone may work initially, but eventually this regimen does not help control high blood sugar levels. In these cases, oral medication may be prescribed. If oral medications are ineffective, a person with Type 2 diabetes may need insulin doses or a combination of oral medication and insulin. About 50 percent of individuals with Type 2 diabetes require oral medications, 40 percent require insulin or a combination of insulin and oral medications, and 10 percent use diet and exercise alone.

VI. CURRENT RESEARCH

At present no cure exists for diabetes, and scientists are unsure of the exact cause, although researchers are investigating a combination of genetic and environmental factors. So far researchers have identified 20 genes involved in Type 1 diabetes, and they are working to determine each gene's role in causing the disease. The inheritance patterns of Type 1 diabetes are complicated, with many different genes influencing a person's risk. For instance, a gene known as DR plays a role in Type 1 diabetes. Two forms of this gene, called DR3 and DR4, are present in 95 percent of people with Type 1 diabetes. People who inherit DR3 alone develop diabetes at an older age and have antibodies that destroy insulin-producing beta cells. Those who inherit DR4 tend to develop diabetes earlier in life and have antibodies that destroy insulin. A person with both DR3 and DR4 typically develops diabetes at a very young age and has the highest level of insulin-destroying antibodies.

In 2000 researchers were surprised to find that a variation of a gene called Caplain-10, which is not involved in glucose metabolism, is associated with the development of Type 2 diabetes. One form of this gene produces a

small amount of protein, and researchers are studying how this decrease in protein increases a person's risk for diabetes. Other genetic studies indicate that certain genes cause a variation of Type 2 diabetes called maturity onset diabetes of the young (MODY), which develops in people under the age of 25. Although scientists do not yet understand how these genes cause MODY, the genes are known to be active in the liver, intestine, kidney, and pancreas.

Other scientists hope to identify the environmental factors that trigger Type 1 diabetes in people with a genetic predisposition for the disease. If they can determine what causes the immune system to attack the cells that produce insulin, they may discover how to prevent the condition from developing. For instance, studies suggest that certain viruses, such as coxsackie B, rubella, and mumps, may trigger an immune reaction against beta cells or in some cases directly infect and destroy these cells.

Researchers attribute most cases of Type 2 diabetes to obesity. Studies show that the risk for developing Type 2 diabetes increases by 4 percent for every pound of excess weight a person carries. Researchers are investigating the exact role that extra weight plays in preventing the proper utilization of insulin and why some overweight people develop the disease while others do not.

Research also focuses on transplanting a healthy pancreas or its insulin-producing beta cells into a person with Type 1 diabetes to provide a natural source of insulin. Some patients who have received pancreas transplants have experienced considerable improvements in their health, but positive, long-term results with beta-cell transplants have not yet occurred. In both types of transplants recipients must take drugs that suppress their immune systems so the body will not reject the new pancreas or cells. These drugs can cause life-threatening side effects because the patient's body can no longer protect itself from other harmful substances. In most people with diabetes, these drugs pose a greater risk to health than living with diabetes. Scientists are also studying the development of an artificial pancreas and ways to genetically manipulate non-insulin-producing cells into making insulin.

New methods for accurately measuring blood glucose levels may improve the quality of life for many individuals with diabetes. New techniques include the use of laser beams and infrared technology. For example, a tiny computer using infrared light can be used to measure a person's blood sugar level. The computer automatically delivers the reading to an insulin pump carried on the diabetic's body that injects the appropriate amount of insulin.

Other advances include new drugs that control blood sugar. In April 2000 the United States Food and Drug Administration (FDA) approved glargine, an insulin drug that needs to be injected only once a day. Sold under the brand name Lantus, this drug can be used by people with Type 1 diabetes, as well as by those with Type 2 diabetes who require insulin injections. And, as mentioned earlier, in 2006 the FDA approved a form of insulin that can be inhaled. Physicians have long known that some insulin-dependent diabetics fail to take the drug as often as needed because of the discomfort of injections. Doctors hoped the inhalant form of insulin would lead to better patient compliance.

A number of drugs have been developed to help people with Type 2 diabetes. Examples include acarbose, (sold under the brand name Precose), which controls blood sugar by slowing the digestion of carbohydrates; and metformin (sold under the brand name Glucophage), which controls liver production of sugar, causes weight loss, and reduces total cholesterol. Pioglitazone (brand name, Actos) and rosiglitazone (brand name, Avandia) are drugs that make the cells more sensitive to insulin. A study published in 2007 found that Avandia increases the risk of heart attacks. Soon afterward the FDA told the manufacturers of Avandia and Actos, which had also been shown to carry a heart risk, to add prominent safety warnings to the drugs' labels.

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