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<http://diabetes.niddk.nih.gov/dm/pubs/pima/kiddis/kiddis.htm>

NIDDK research conducted on the Pima Indians for the past 30 years has helped scientists prove that obesity is a major risk factor in the development of diabetes. One-half of adult Pima Indians have diabetes and 95% of those with diabetes are overweight.

These studies, carried out with the help of the Pima Indians, have shown that before gaining weight, overweight people have a slower metabolic rate compared to people of the same weight. This slower metabolic rate, combined with a high fat diet and a genetic tendency to retain fat may cause the epidemic overweight seen in the Pima Indians, scientists believe.

Scientists use the "thrifty gene" theory proposed in 1962 by geneticist James Neel to help explain why many Pima Indians are overweight. Neel's theory is based on the fact that for thousands of years, populations who relied on farming, hunting and fishing for food, such as the Pima Indians, experienced alternating periods of feast and famine. Neel said that to adapt to these extreme changes in caloric needs, these people developed a thrifty gene that allowed them to store fat during times of plenty so that they would not starve during times of famine.

This gene was helpful as long as there were periods of famine. But once these populations adopted the typical Western lifestyle, with less physical activity, a high fat diet, and access to a constant supply of calories, this gene began to work against them, continuing to store calories in preparation for famine. Scientists think that the thrifty gene that once protected people from starvation might also contribute to their retaining unhealthy amounts of fat.

Dr. Eric Ravussin, a visiting scientist at the Phoenix Epidemiology and Clinical Research Branch at NIDDK, has studied obesity in the Pima Indians since 1984. He believes the thrifty gene theory applies to the Pimas.

The Pima Indians maintained much of their traditional way of life and economy until the late 19th century, when their water supply was diverted by American farmers settling upstream, according to Ravussin. At that time, their 2,000-year-old tradition of irrigation and agriculture was disrupted, causing poverty, malnutrition and even starvation. The Pima community had to fall back on the lard, sugar and white flour the U.S. government gave them to survive, says Ravussin.

However, World War II brought great social and economic change for American Indians. Those who entered military service joined Caucasian units. Many other American Indians migrated from reservations to cities for factory employment and their estimated cash income more than doubled from 1940 to 1944.

When the war and the economic boom ended, most Native Americans returned to the reservations, but contact with the larger society had profoundly affected the Pimas' way of

life. Ravussin says it is no surprise that the increase in unhealthy weight among the Pima Indians occurred in those born post-World War II.

During this century people world-wide experienced more prosperity and leisure time, and less physical work. Since the 1920s, all Americans have consumed more fat and sugar and less starch and fiber. The greatest changes have occurred in consumption of fat. In the 1890s, the traditional Pima Indian diet consisted of only about 15 percent fat and was high in starch and fiber, but currently almost 40 percent of the calories in the Pima diet is derived from fat. As the typical American diet became more available on the reservation after the war, people became more overweight.

"The only way to correct obesity is to eat less fat and exercise regularly," Ravussin says.

Recently, Ravussin visited a Pima community living as their ancestors did in a remote area of the Sierra Madre mountains of Mexico. These Mexican Pimas are genetically the same as the Pima Indians of Arizona. Out of 35 Mexican Pimas studied, only three had diabetes and the population as a whole was not overweight, according to Ravussin.

"We've learned from this study of the Mexican Pimas that if the Pima Indians of Arizona could return to some of their traditions, including a high degree of physical activity and a diet with less fat and more starch, we might be able to reduce the rate, and surely the severity, of unhealthy weight in most of the population," Ravussin says.

"However, this is not as easy as it sounds because of factors such as genetic influences that are difficult to change. Our research focuses on determining the most effective way to bring about permanent weight loss in light of these factors," Ravussin adds.

— *Lorraine H. Marchand*

Kidney Disease

"The Gila River Indian Community may be the smallest town in the United States with its own dialysis center," says Dr. Bill Knowler about this community of 11,000 people. Dr. Knowler and his colleagues at the NIH suspect that the Pima Indians share a gene or genes that made them more likely to develop the kidney disease of diabetes (KDDM) that frequently leads to kidney failure.

The researchers have found that Pima Indians have over 20 times the rate of new cases of kidney failure as the general U.S. population, and diabetes is the culprit over 90 percent of the time. Furthermore, kidney disease is the leading cause of death from disease among Pima Indians who have diabetes.

American Indians have the highest rates of diabetes in the world. About half of adult Pima Indians have diabetes, which they get at a relatively young age. On average, Pima Indians are a mere 36 years old when they get diabetes, compared with Caucasians, who get it at

about age 60. The longer a person has diabetes, the greater the risk for developing complications, such as kidney disease. However, recent research shows that keeping blood sugar as close to normal as possible can slow or even prevent complications.

Under normal conditions, the kidneys, nestled on each side of the body under the rib cage, maintains body fluid and salt balance and removes waste. They also help regulate blood pressure and release erythropoietin, a hormone that tells the bone marrow to make red blood cells.

The filtering units of the kidney, called glomeruli, are made up of clusters of tiny blood vessels. They act "like a screen that normally lets water and waste products filter through but holds back most of the protein," Dr. Knowler explains. "Early in the course of diabetes, we are seeing changes in the size of the holes of the screen, so that more protein escapes into the urine," he added. Called micro-albuminuria, this excess protein may be one of the first clues that kidney damage has begun.

When the kidney's filters are damaged, the remaining ones have to work harder to make up for the loss. As more of the filters are damaged, the kidneys lose their ability to compensate. When the kidneys decline to only 5 or 10 percent of their original capacity, a person is diagnosed with end-stage kidney disease.

"The real tragedy of kidney disease is that it leads to kidney failure, which means that a person must go on dialysis or have a kidney transplant," Dr. Knowler says.

But recent studies bring hope that the years of collaboration between NIH, other scientists and the Pima community is beginning to bear fruit.

For example, the NIH researchers now know that Pima Indians are more likely to get kidney disease of diabetes if they have high blood pressure, even before onset of diabetes; if they have microalbuminuria, or a family history of protein in the urine or kidney disease; or if they have high blood sugar, or diabetes serious enough to require drug or insulin treatment. If the impact of these risk factors, such as high blood pressure, could be reduced, the onset of kidney disease might be prevented or slowed.

Even with this important information, investigators still needed to know what was happening inside the kidney before they could design treatment studies, according to Dr. Robert Nelson, a researcher from The Cleveland Clinic Foundation who works with Dr. Knowler.

Dr. Nelson explains that studies of patients with insulin-dependent, or Type I diabetes showed that the kidney filters blood faster and the blood moves faster within the kidney when diabetes sets in. It is the higher pressure that comes with those changes that may damage the sensitive filters and allow protein to leak into the urine.

Scientists thought that if the disease process worked the same in Pima Indians with Type II diabetes as in people with Type I diabetes, a special type of drug that reduces blood pressure within the kidney might help prevent or slow the kidney disease. Such a drug, an

angiotensin-converting-enzyme (ACE) inhibitor, was recently approved by the Food and Drug Administration for the treatment of kidney disease of Type I diabetes.

Encouraged by this information, the Diabetic Renal Disease Study group, with Dr. Nelson directing patient care, set out to discover whether the kidney in Type II diabetes behaves as it does in Type I diabetes. After measuring kidney function in over 200 Pima Indians, with and without diabetes or kidney disease, the researchers found that the amount of blood filtered within the kidney does increase at the onset of Type II, as it does in Type I diabetes. A large European study of kidney function in people with Type II diabetes found the same thing.

After several years of studying how kidney disease of diabetes occurs, Dr. Nelson now believes there is enough evidence to conduct clinical studies to try to prevent its development or progression. A trial using an ACE inhibitor is now under way. Dr. Nelson says that although it seems slow in coming, the research is a "deliberate process" designed to get the best information possible in order to give the best care possible.

In the meantime, the best defense against kidney disease of diabetes—in any group of people—is to try to prevent diabetes from developing at all by maintaining healthy weight, exercising, and following a healthy diet. This is the goal of a new NIH Diabetes Prevention Program in which the Pimas and other American Indians are participating.

Once a person has diabetes, kidney disease might be prevented or slowed by controlling blood sugar levels and blood pressure, and by maintaining healthy weight.

Doctors and the Pima Indians continue to work together toward the day when the Gila River Indian Community will no longer need a dialysis center.

— *Mary Harris*

Diabetic Eye Disease

Preventing diabetic eye disease, or retinopathy, is an important goal of the NIH Research Clinic at Sacaton. Long-term diabetes can cause blood vessels in the retina of the eye to break down, leading to loss of vision and even blindness. Doctors don't know the cause.

There are two things people with diabetes can do to slow, and perhaps prevent that complication, according to Dr. William Knowler: with the help of their doctors, he advises, they should try to keep their blood sugar and blood pressure as close to normal as possible. Secondly, they should have regular eye exams with eye drops to detect any early signs of eye disease, such as small problems in the blood vessels of the retina.

These early signs, called "background retinopathy," usually do not affect eyesight by themselves, but they can lead to a more dangerous stage, called proliferative retinopathy. In this second stage, new blood vessels build up in the retina and branch out into the vitreous

humor in the middle of the eye. These blood vessels break and bleed easily, causing a blood clot that steals sight.

The detailed eye exams that can help prevent blindness are available to all residents of the Gila River Indian Community at the NIH Clinic in Sacaton every two years. A patient with background retinopathy should have eye exams more often. The sooner retinopathy is found, the better, says Dr. Knowler.

If retinopathy advances and the changes are spotted soon enough, eye doctors do have treatments to prevent blindness in some cases. They can use lasers to seal damaged blood vessels, preventing them from forming the blood clots that can cause blindness. However, these treatments must be given at just the right time, before serious damage is done to the eye. Until researchers discover the causes of diabetic disease, Dr. Knowler says, "keeping appointments for eye exams can make the difference between keeping or losing eyesight."