The Ominous Link Between Obesity and Type 2 Diabetes

Americans are facing an epidemic of obesity and type 2 diabetes, according to epidemiologic studies. Type 2 diabetes, a devastating illness already afflicting 90 to 95 percent of the 16 million people who have diabetes,[1,2] can lead to serious complications including blindness, kidney failure, lower limb amputations, and heart disease. Although genetic factors may predispose a person to be overweight or develop diabetes, other factors must also be involved, because our genes could not possibly have changed quickly enough to account for the rapid increase in the prevalence of obesity and type 2 diabetes. Research indicates that the obesity problem essentially results from Americans' eating too much and exercising too little. But how is an increase in obesity related to an increase in diabetes? For a long time, scientists have known that obese or overweight people are far more likely to develop type 2 diabetes; in fact, 80 percent of patients with type 2 diabetes are overweight or obese. However, only recently have scientists begun to find the biological molecules that connect these two health problems.

Type 2 diabetes develops through a multi-stage process. First, the body becomes unable to use insulin effectively, a condition known as insulin resistance. Insulin is a protein made by cells in the pancreas called beta cells. Insulin normally helps the body maintain a healthy level of the sugar glucose in the blood by causing fat and muscle cells to store glucose and by reducing glucose production in liver cells. When insulin resistance develops, the beta cells try to compensate by making more insulin. For a while, this helps keep blood glucose levels relatively normal, but eventually the beta cells become exhausted and cannot produce enough insulin to overcome the insulin resistance. At this point, individuals develop a condition called impaired glucose tolerance, in which blood glucose levels are higher than normal but not as high as those in diabetes. Left untreated, however, this condition frequently progresses to full-blown type 2 diabetes. Unfortunately, people with insulin resistance and impaired glucose tolerance experience no outward symptoms and thus are unaware of this silent progression towards diabetes.

How is obesity connected to insulin resistance and diabetes? Clues are being found in unexpected places. Surprisingly, fat cells are not passive storehouses for fat, just keeping fat in case it is needed for energy. Instead, fat cells actively sense changes in energy availability and signal the brain and other tissues to regulate feeding and cellular processes. Scientists are learning that fat cells send out these signals in the form of special hormones, or signaling proteins, which the fat cells make and secrete. With the discoveries of novel signaling hormones, scientists are learning that the connection between fat and diabetes involves a complex balance of fat cell hormones.

Among the signaling proteins made by fat cells are leptin, resistin, and adiponectin (also known as Acrp30). After a meal, fat cells release leptin. This hormone signals the appetite-control center in the brain to stop eating. Scientists found that mice lacking the gene for leptin overeat and become obese. When given leptin, these mice lose weight—unfortunately, however, administering leptin to people does not effectively treat obesity. Thus, additional factors must also contribute to obesity.

Resistin, another fat cell signaling protein discovered recently, is so-named because too much of this hormone is thought to cause insulin resistance. When scientists gave mice a substance that inhibits resistin activity, their blood sugar level and insulin response improved. In fact, scientists initially discovered resistin as a result of some creative experiments to investigate how fat cells are affected by anti-diabetes drugs called TZDs, which are used to treat people. One of the results of adding a TZD drug to fat cells turns out to be decreased resistin production—and improved response to insulin. Thus, resistin itself might now be useful as a

target for the discovery of new anti-diabetes drugs.

Another protein produced by fat cells, adiponectin, appears to connect obesity and diabetes in a way opposite to that of resistin—while too much resistin apparently causes insulin resistance, too little adiponectin may also be problematic. Scientists working on mouse models of obesity and type 2 diabetes recently found that giving extra adiponectin protein (made in the laboratory) to the mice caused them to become less insulin-resistant, lowering their blood glucose levels to near normal. In other experiments, when scientists gave mice a TZD drug, the type of diabetes drug that lowers resistin levels, they found that the drug can also increase adiponectin levels. From other research in mice, it appears that adiponectin helps muscle cells burn more energy; it also reduces body weight. In people, studies suggest that overweight and diabetic patients do not produce enough adiponectin. Thus, adiponectin may also be a good target for new therapies. In light of these studies, the ominous link between obesity and diabetes may be a balance of the levels of several fat cell signaling proteins with different effects. As more is learned about fat-cell signaling proteins, new drug therapies can be developed for obesity and diabetes.

While basic scientists are learning about what causes obesity and type 2 diabetes at the molecular level, clinical researchers are developing other measures to combat these conditions. Results from an exciting new study give us a way to battle the epidemic of obesity and type 2 diabetes. A major clinical study demonstrated that patients at risk of developing type 2 diabetes can prevent disease onset and improve their blood sugar through modest improvements in diet and exercise. These results are particularly important to minorities, who made up 45 percent of the study participants and are at increased risk of developing diabetes.

This study, called the Diabetes Prevention Program (DPP), identified overweight individuals suffering from impaired glucose tolerance, a condition which, as discussed, increases the risk for type 2 diabetes. In the study, patients were assigned to one of three groups: intensive lifestyle intervention, medication, or placebo control. The latter two groups also received conventional information about diet and exercise. The intensive lifestyle intervention had a goal of reducing body weight and staying active with a minimum of 150 minutes of exercise a week. The lifestyle intervention worked the best; patients in this group reduced their risk of developing diabetes by 58 percent. Significantly, the intensive lifestyle intervention was highly effective for both genders and all ages and racial/ethnic groups in the study. Patients in the medication group, who received the diabetes drug metformin, were 31 percent less likely to develop diabetes than the control group, and they also lost weight. Metformin, while less effective overall in reducing the risk of diabetes, was effective in both genders and in all the racial and ethnic groups, which included African-Americans, Hispanic Americans, Asian Americans, and American Indians. In contrast to the lifestyle intervention, however, which was highly effective for all age and weight groups, metformin was not as effective among patients who were less overweight and was not effective in people over 60. This landmark study showed that with instruction and encouragement, patients at high risk for diabetes could be successful in improving their diet and activity—with these relatively modest changes having a major impact in reducing the onset of diabetes.

1. "National Institute of Diabetes and Digestive and Kidney Diseases." *Diabetes Statistics.* 19 December 2001 http://www.niddk.nih.gov/health/diabetes/pubs/dmstats/dmstats.htm#prev

2. "Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion." *Diabetes Public Health Resource: National Diabetes Fact Sheet.* 19 December 2001 http://www.cdc.gov/diabetes/pubs/facts98.htm#appendix