INSULIN RESISTANCE

At the Root of Type 2 Diabetes

By Robert S. Dinsmoor

Insulin resistance is one of the most important underlying causes of high blood sugar in Type 2 diabetes. Yet many people with diabetes do not know what insulin resistance is. In fact, a nationwide survey released by the American Association of Diabetes Educators in November of 1999 found that nearly two-thirds of the more than 1,000 people with Type 2 diabetes surveyed did not understand – or had never heard of – insulin resistance.

What is more, the survey found that the respondents who couldn't define insulin resistance had less control over their blood glucose and were less likely to be taking one of the newer diabetes drugs that specifically work against insulin resistance. These drugs, called thiazolidinediones (TZD's), include rosiglitazone (brand name Avandia) and pioglitazone (Actos).

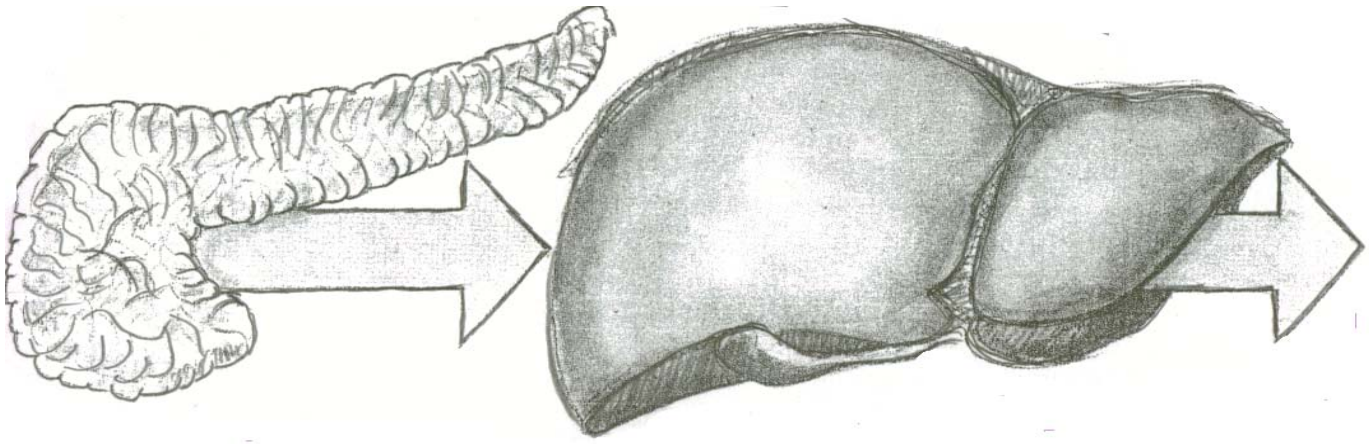
While the most obvious consequence of insulin resistance is high blood sugar, it is believed to have other effects on the body, as well. For example, it may play a major role in the high rate of cardiovascular disease among people who have it. As scientists learn more about insulin resistance, they also learn more about how to combat it. Among the tools already shown to reduce insulin resistance are weight loss, exercise, and a growing arsenal of drugs, including the TZD's. Since greater knowledge of insulin resistance seems to be related to improved diabetes control, let's take a look at the basics of insulin resistance and its treatment.

What is insulin resistance?

Simply stated, insulin resistance is a condition in which insulin can't do its job effectively, so a given amount of insulin lowers blood sugar less than would be expected. To understand this in more depth, it is helpful to understand what insulin normally does in the body.

Insulin is a hormone secreted by the beta cells of the pancreas that helps to regulate the way the body uses glucose. Its main job is to allow glucose in the blood to enter the cells of the body, where it can be used for energy. Insulin also controls the rate at which glucose is produced and secreted by the liver. Glucose is stored in the liver in a for called *Glycogen*. When blood glucose levels drop, the liver converts glycogen to glucose and releases it into the bloodstream. When there is enough glucose in the blood stream, insulin secreted by the pancreas signals the liver to shut down glucose production. In people who don't have diabetes, the pancreas continually measures blood glucose levels and responds by secreting just the right amount of insulin.

In a person with insulin resistance, the cells of the body are unable to take up as much glucose from the bloodstream as they should, even when there's a lot of insulin in the bloodstream. That is, the cells *resist* the insulin. On top of that, the liver may continue to secrete a lot of glucose into the bloodstream even when it isn't needed and despite the presence of lost of insulin. By some estimates, some 10% to 25% of the general population may be insulin resistance, but there are no real statistics on how many people have the condition.



What causes insulin resistance?

The short answer is that insulin resistance appears to be a product of both our genes and our environment. Certain genes predispose certain people to develop insulin resistance, but other factors such as inactivity, weight gain, and chronically high blood sugar levels trigger insulin resistance in susceptible individuals.

Scientists are still trying to determine what causes insulin resistance on the cellular and molecular levels. Thanks to the tools of molecular biology, they have already learned a lot. Previously, considerable research focused on the insulin receptors found on muscle and fat cells throughout the body. Normally, insulin binds to these receptors, triggering a number of complex chemical reactions within cells. It used to be thought that diabetes resulted from abnormal binding to these receptors, but this is no longer believed to be the case. Most researchers now believe that insulin resistance is caused by abnormalities in the chemical reactions that happen within the cells themselves – so called "postbinding abnormalities." They have identified abnormalities in a number of different chemical pathways that could cause insulin resistance, as well as some of the genes that cause them. For example, researchers are now paying considerable attention to substances called *glucose transporters*, which move glucose into cells. Studies have shown that at least some insulin-resistant individuals are deficient in a glucose transporter called GLUT4, whose activity is normally regulated by the amount of insulin present.

Conditions associated with insulin resistance

Type 2 diabetes may be the most familiar condition associates with insulin resistance, but it isn't the only one. Two related conditions are impaired fasting glucose and impaired glucose tolerance. Insulin resistance is also associated with gestational diabetes, heart disease, and a condition known as polycystic ovary syndrome.

The exact role of insulin resistance in these medical conditions is unclear. While some researchers believe it to be the primary underlying cause, others believe it to be the result of some other disease process. Let's take a look at each condition individually.

Type 2 diabetes. The two main problems in Type 2 diabetes are insulin resistance and a defect in the way insulin is secreted: specifically, the pancreas doesn't secrete enough insulin fast enough in response to meals, when large amounts of glucose enter the bloodstream. This leads to long-term high blood sugar as well as to *hyperinsulinemia* (too much insulin in the bloodstream) as the pancreas tries to compensate for the high blood sugar by churning out extra insulin.

Medical researchers disagree as to whether the underlying cause of most cases of Type 2 diabetes is insulin resistance or a defect in insulin secretion, but either condition may lead to the other, and both conditions can worsen in a vicious circle. For example, insulin resistance can lead to higher blood glucose levels, especially following meals. This causes the pancreas to secrete more insulin to compensate. At first, this may keep blood sugar levels in the normal range. But eventually, the overworked beta cells become damaged and produce less and less insulin, and high blood sugar levels ensue.

Prediabetic states. Insulin resistance is also found in two "prediabetic states" called impaired glucose (IFG) and impaired glucose tolerance (IGT). Both of these conditions were recently defined by the American Diabetes Association in their updated Diagnosis and Classification of Diabetes Mellitus.

Both conditions are defined by blood glucose levels that are too high to be considered normal, but not high enough to be considered diabetic. Impaired fasting glucose is a diagnosed on the basis of a fasting plasma glucose level of greater than or equal to 110 mg/dl but less than or equal to 126 mg/dl. Impaired glucose tolerance is defined by plasma glucose levels greater than or equal to 140 mg/dl but less than 200 mg/dl two hours after ingesting 75 grams of glucose as part of an oral glucose tolerance test.

Both IFG and IGT are thought to put people at risk for Type 2 diabetes. In addition, studies suggest that people with these conditions, just like people with Type 2 diabetes, are at significantly greater risk for heart disease.

Gestational diabetes. Diabetes that starts during pregnancy is called gestational diabetes. It tends to occur in women who are already at greater risk for developing Type 2 diabetes by virtue of being over-weight, having a close family member with diabetes, or being a member of a high-risk ethnic group (African-American, Asian-American, Hispanic-American, or Native American).

Gestational diabetes most commonly occurs in the second or third trimester of pregnancy. Certain hormones released at that time work against the action of insulin to cause insulin resistance. According to some diabetes specialists, the hormones may serve as "the straw that breaks the camel's back," pushing these already susceptible women into the realm of diabetes. Although most women with gestational diabetes no longer have diabetes after the stress of pregnancy is over, all are at increased risk of developing Type 2 diabetes later in life.

Syndrome X. Sometimes referred to as "insulin resistance syndrome," Syndrome X refers to a cluster of conditions that all seem to run together. Those conditions are insulin resistance, hyperinsulinemia, high blood pressure, blood lipid abnormalities (increased triglyceride levels, decreased HDL cholesterol levels, and increased levels of small, dense LDL cholesterol particles), and obesity. Taken together, these conditions lead to dramatically increased risk of heart disease.

Some researchers believe that insulin resistance is the primary problem that leads to all the others. Some also believe that insulin resistance and hyperinsulinemia, even independent of their effect on blood glucose levels, can promote heart disease through insulin's effects on a blood vessel walls in the blood's tendency to clot, but this hypothesis remains somewhat controversial.

Polycystic ovary syndrome. Called PCOS for short, polycystic ovary syndrome affects only women and is characterized by elevated levels of male hormone, the absence of ovulation, irregular menstrual cycles, and infertility. About 30% of obese women with PCOS develop impaired glucose tolerance or Type 2 diabetes by age 40, and they appear to have increased risk of heart disease as well.

Traditionally, women with PCOS have been treated with oral contraceptives to lower the male hormone levels and normalize menstruation. However, recent studies have shown that reducing insulin resistance through insulin-sensitizing drugs can alleviate some of the manifestations of PCOS and restore normal menstruation.

Type 1 diabetes. Insulin resistance may also occur in Type 1 diabetes, although it is not a hallmark of the disease. In fact, it is very rare. It is most commonly due to antibodies the body makes against insulin, but this rarely occurs with the advent of more purified insulins and human insulin, which tend to provoke less of an immune response.

Treating insulin resistance

Medical researchers say it would be helpful to be able to detect insulin resistance early, so that treatment could begin before any damage is done. Scientists have several ways of evaluating insulin resistance in research subjects, but the various methods are either too complicated, too expensive, too unreliable -- or all of the above -- to be practical for screening people in the clinic.

What doctors can do is use fasting plasma glucose levels and the oral glucose tolerance test to screen people who are at high risk for Type 2 diabetes (those who have close relatives with diabetes, or part of a high-risk ethnic group, or are overweight). Those who turn out to have impaired glucose tolerance or impaired fasting glucose are likely to be insulin-resistant, and they may benefit from the same lifestyle changes recommended for people with Type 2 diabetes.

Exercise. While new drugs for Type 2 diabetes specifically target insulin resistance, one equally effective and inexpensive therapy with virtually no side effects is often overlooked: exercise. Physical like to be has been found to increase the body's sensitivity to insulin, both during and for up to one day after the activity. In addition, over the past decade, a number of large studies carried out in the United States, Sweden, and China have shown conclusively that regular aerobic exercise (such as running, brisk walking, bicycling, and climbing stairs) can reduce a persons risk of developing diabetes by roughly one-third to one-half.

In recent years, exercise specialists have also become intrigued by the effects of resistance training. Resistance training refers to exercise such as weight lifting that uses muscle strength to work against a resistive load. As it turns out, many people with Type 2 diabetes have relatively low muscle mass for their body weight. Since it is primarily muscle tissue that burns up glucose, building muscle mass can help the body use glucose more effectively.

Diet. Two related measures are dietary changes and weight loss. Reducing one's caloric intake and losing even modest amounts of weight have clearly been shown to lower insulin resistance.

Drug therapy. Until the mid-1990's, the only drugs on the market for treating Tied 2 diabetes were insulin in the class of drugs called sulfonylureas, which prod the pancreas to secrete more insulin. Both types of drug treatments work by increasing the amount of insulin in circulation, which helps compensate for insulin resistance, but neither actually addresses the problem of insulin resistance itself.

Since then, a number of new drugs for Type 2 diabetes have come on the market, some of which specifically target insulin resistance. Metformin (brand name Glucophage) targets insulin resistance in the liver, decreasing the liver's production of glucose. Rosiglitazone (Avandia) and pioglitazone (Actos) reduce insulin resistance by making muscle and fat cells more sensitive to insulin.

Because these drugs reduce insulin resistance and people with Type 2 diabetes, it is natural to wonder one of the can help treat insulin resistance that hasn't yet developed into diabetes -- ideally, helping to prevent diabetes. To try to answer this question, a large study called the Diabetes Prevention Program (DPP) is now underway. It is designed to test whether lifestyle changes, with or without insulin-sensitizing drugs, can prevent or delay Type 2 diabetes in individuals who have impaired glucose tolerance.

Originally, there were four separate study groups: one group receiving instructions on diet and exercise, aimed at weight loss; one receiving standard dietary advice and metformin; one receiving standard dietary advice and troglitazone (Rezulin); and one control group receiving standard dietary advice and an inactive placebo. However, after numerous cases of liver dysfunction and several deaths were reported among people taking troglitazone -- and one person participating in the DPP died in the seventh month of taking it -- researchers felt that it was unethical to continue testing a potentially harmful drug in people who don't yet have diabetes. The troglitazone group was discontinued in 1998, and Rezulin was subsequently withdrawn from the market in March 2000. It will be several years before the results of the DPP become available.

Insulin resistance and you

Now that you know about insulin resistance, what can you do about it if you have Type 2 diabetes? Well, you can't change your genetic makeup, but you can investigate ways to become more physically active and to lose weight if you are overweight. You can also speak with your doctor about trying one of the newer diabetes drugs if your blood sugar is not being adequately controlled by your current drug regimen.

Keep in mind that there is no one-size-fits-all diabetes plan. Your plan for increased physical activity needs to be enjoyable and reasonable for you -- or you won't stick with it. Your weight-loss plan also needs to be reasonable for you. And your doctor can tell you which drugs he thinks would be useful for you and why. (Not all of the new drugs work for or are appropriate for all people.) Changing your lifestyle and finding a drug combination that controls your blood sugar requires time, patience, and persistence. But the rewards can be great: lowered insulin resistance and a healthier you. □

Robert Dinsmore is a Contributing Editor of Diabetes Self-Management *and a freelance writer based in Massachusetts.*