Insulin Resistance Syndrome

GOUTHAM RAO, M.D., University of Pittsburgh Medical Center–St. Margaret, Pittsburgh, Pennsylvania

Insulin resistance can be linked to diabetes, hypertension, dyslipidemia, cardiovascular disease and other abnormalities. These abnormalities constitute the insulin resistance syndrome. Because resistance usually develops long before these diseases appear, identifying and treating insulin-resistant patients has potentially great preventive value. Insulin resistance should be suspected in patients with a history of diabetes in first-degree relatives; patients with a personal history of gestational diabetes, polycystic ovary syndrome or impaired glucose tolerance; and obese patients, particularly those with abdominal obesity. Present treatment consists of sensible lifestyle changes, including weight loss to attain healthy body weight, 30 minutes of accumulated moderate-intensity physical activity per day and increased dietary fiber intake. Pharmacotherapy is not currently recommended for patients with isolated insulin resistance. (Am Fam Physician 2001;63:1159-63,1165-6.)

A patient information handout on insulin resistance syndrome, written by the author of this article, is provided on page 1165.

Obesity, type 2 diabetes mellitus (formerly known as non–insulin-dependent diabetes), hypertension, lipid disorders and heart disease are common in most Western societies and are collectively responsible for an enormous burden of suffering. Many people have more than one—and sometimes all—of these conditions, leading to the hypothesis that the coexistence of these diseases is not a coincidence, but that a common underlying abnormality allows them to develop. In 1988 it was suggested that the defect was related to insulin, and the insulin resistance syndrome was first described.[1] It is estimated that this syndrome affects 70 to 80 million Americans.[2]

Insulin stimulates glucose uptake into tissues, and its ability to do so varies greatly among individual persons. In insulin resistance, tissues have a diminished ability to respond to the action of insulin. To compensate for resistance, the pancreas secretes more insulin. Insulin-resistant persons, therefore, have high plasma insulin levels. The syndrome can be defined as a cluster of abnormalities, including obesity, hypertension, dyslipidemia and type 2 diabetes, that are associated with insulin resistance and compensatory hyperinsulinemia. However, a cause-and-effect relationship between insulin resistance, these diseases and the mechanisms through which insulin resistance influences their development has yet to be conclusively demonstrated.

Insulin resistance syndrome is characterized by hyperinsulinemia and an increased prevalence of obesity, hypertension, dyslipemia and type 2 diabetes mellitus.

Components of Insulin Resistance Syndrome

TYPE 2 DIABETES

Type 2 diabetes is the condition most obviously linked to insulin resistance. Compensatory hyperinsulinemia helps maintain normal glucose levels—often for decades—before overt diabetes develops. Eventually the beta cells of the pancreas are unable to overcome insulin resistance through hypersecretion. Glucose levels rise, and a diagnosis of diabetes can be made.[3] Patients with type 2 diabetes remain hyperinsulinemic until they are in an advanced stage of disease. Only in severe cases, in patients with fasting glucose levels above 180 to 198 mg per dL (10 to 11 mmol per L), are low plasma levels of insulin present.

HYPERTENSION

One half of patients with essential hypertension are insulin resistant and hyperinsulinemic.[4] There is evidence that blood pressure is linked to the degree of insulin resistance.[5]

Insulin resistance syndrome may be related to atheromatous arterial disease, both directly and through its associated conditions.

Exactly how insulin resistance influences blood pressure, however, is controversial.[5,6] Furthermore, a strong relationship between insulin resistance and blood pressure may not occur in many patients, especially black patients.[7]

HYPERLIPIDEMIA

The lipid profile of patients with type 2 diabetes includes decreased high-density lipoprotein cholesterol levels (a significant risk factor for heart disease), increased serum very-low-density lipoprotein cholesterol and triglyceride levels and, sometimes, a decreased low-density lipoprotein cholesterol level.[8] Insulin resistance has been found in persons with low levels of high-density lipoprotein.[9] Insulin levels have also been linked to very-low-density lipoprotein synthesis and plasma triglyceride levels.[10]

ATHEROSCLEROTIC HEART DISEASE

Nearly 40 years ago, experiments[11] showed that infusion of insulin into one femoral artery of a dog resulted in atherosclerotic changes in the artery. The mechanism through which insulin resistance influences atherogenesis, however, is unclear. A recent study implicates thrombotic factors.[12]

The Author

GOUTHAM RAO, M.D., is a full-time faculty member of the family practice residency program at the University of Pittsburgh Medical Center–St. Margaret in Pittsburgh, Pa. A graduate of McGill University Faculty of Medicine, Montreal, Canada, Dr. Rao completed a residency in family practice at the University of Toronto and a faculty development fellowship at the University of Pittsburgh Medical Center–St. Margaret.

Address correspondence to Goutham Rao, M.D., University of Pittsburgh Medical Center–St. Margaret, 815 Freeport Rd., Pittsburgh, PA 15215 (e-mail address: raog@msx.upmc.edu). Reprints are not available from the author.

TABLE 1
Factors Associated with Increased Likelihood of Insulin Resistance

Strong family history of diabetes
History of gestational diabetes
Polycystic ovary syndrome
Impaired glucose metabolism: fasting glucose level between 110 and 125 mg per dL (6.1 and 7.1 mmol per L) or impaired glucose tolerance, with a two-hour post–75-g glucose load level between 140 and 199 mg per dL (7.8 and 11.1 mmol per L)[3]
Obesity: body mass index of 30 kg per m^2 or more
Increased waist-to-hip ratio: 1.0 in men and 0.8 in women

OBESITY

Many persons with one or more of the conditions listed above are obese. Obesity is a component of the syndrome, but it promotes insulin resistance rather than resulting from it. Weight loss can improve insulin sensitivity and reduce insulin levels.

OTHER ABNORMALITIES

Other abnormalities linked to insulin resistance include hyperuricemia, elevated levels of plasminogen activator inhibitor 1 and a preponderance of small-size, low-density lipoprotein particles. Higher plasminogen activator inhibitor 1 levels and decreased low-density lipoprotein particle diameter are thought to increase the risk of coronary heart disease.[13]

Diagnosis

Diagnosis of each of the diseases that comprise insulin resistance syndrome is usually straightforward and familiar. By the time a diagnosis of hypertension or diabetes is made, however, complications are often already present. Furthermore, insulin resistance and hyperinsulinemia often have been present for years, conferring an increased risk for the development of other compo-

nents of the syndrome, including coronary heart disease.

The precise way in which insulin resistance develops is unclear, although genetics, diet and level of physical activity are believed to play a role.[14] Identifying patients with insulin resistance and those who are likely to develop insulin resistance offers the hope that some or all of the components of the syndrome can be prevented.

Unlike the diagnosis of overt diabetes, the biochemical diagnosis of insulin resistance syndrome is fraught with difficulties. The most accurate way to measure insulin resistance is the euglycemic insulin clamp technique, in which insulin is infused to maintain a constant plasma insulin level. Glucose is then infused and, as the plasma level falls because of the action of insulin, more glucose is added to maintain a steady level. The amount of glucose infused over time provides a measure of insulin resistance.[15] This and similar methods are useful for research but are otherwise impractical. Use of fasting insulin levels has received some attention. Fasting insulin levels correlate well with the degree of insulin resistance.[15] Unfortunately, measurement of fasting insulin is not widespread. Standard methods for performing the test have yet to be adopted, and criteria for normal and abnormal values have not been established.

The lack of practical, inexpensive, reliable serum tests means that the diagnosis of insulin resistance can, at best, be made on the basis of strong clinical suspicion *(Table 1)*. This is reasonable because the goal is to identify a condition whose treatment is neither risky nor expensive because it involves sensible lifestyle modifications and careful monitoring for the component diseases of the syndrome.

Among patients who have not yet developed diabetes, hypertension, dyslipidemia or coronary heart disease, insulin resistance should be suspected if there is a history of type 2 diabetes in first-degree relatives or a personal history of gestational diabetes, polycystic ovary syndrome or impaired glucose metabolism. The condition is also common among persons with obesity (defined as a body mass index [BMI] of 30 kg per m^2 or more).[16] The pattern of obesity is also extremely important. There is a strong relationship between abdominal obesity and the degree of insulin resistance independent of total body weight.[17] The degree of abdominal obesity can be estimated by use of waist circumference or the waist-hip ratio. The waist is usually measured at its narrowest point and the hips at the fullest point around the buttocks. A waist-hip ratio of greater than 1.0 in men or 0.8 in women is strongly correlated with abdominal obesity and insulin resistance, and confers an increased risk of associated diseases.[18]

In the absence of a practical diagnostic test, the diagnosis of insulin resistance syndrome depends on clinical suspicion.

Management

The American Diabetes Association emphasizes that the causal link between insulin resistance and the components of the syndrome is not conclusive and that there is currently no sound evidence showing that the treatment of insulin resistance reduces morbidity or mortality.[2] Nevertheless, treatment of insulin resis-

TABLE 2
Nonpharmacologic Approach to Insulin Resistance Syndrome

Exercise
Encourage patients to accumulate 30 minutes of moderate-intensity physical activity most—or, preferably, all—days of the week
Weight reduction
Assist patients in dietary modification to attain a healthy body weight
Dietary fiber
Encourage patients to include foods high in fiber in their diet

Effective interventions, such as weight reduction, regular physical activity and an increase in dietary fiber, should be initiated in patients suspected of having insulin resistance syndrome.

tance involves lifestyle changes from which everyone can benefit *(Table 2)*. Because insulin resistance often precedes the development of its consequences by years, if not decades, identifying and treating it encourages patients to develop good habits at a young age.

EXERCISE

Exercise training improves insulin sensitivity.[19] Patients with suspected insulin resistance should be advised to increase their level of physical activity. Even regular, sustained, moderate increases in physical activity, such as daily walking, can substantially decrease insulin resistance.[20] This is compatible with the standard recommendation that everyone should accumulate at least 30 minutes of moderate-intensity physical activity on most or, even better, all days of the week.[21]

HYPOCALORIC DIET AND WEIGHT REDUCTION

Insulin sensitivity improves within a few days of caloric restriction, before any significant weight loss occurs.[13] Weight reduction leads to further improvement. The amount of weight loss needed for sustained decreases in insulin resistance is still unclear. In obese women without diabetes, weight loss of approximately 15 percent has been linked to significantly lower insulin levels.[22] Regaining even a modest amount of the lost weight, however, with a body weight that was still 10 percent below starting values, resulted in an increase in insulin levels to baseline. The women in this study were very obese (mean BMI: 36.4 kg per m^2) and remained obese even with the loss of 15 percent of body weight (mean BMI: 30.5 kg per m^2). The implication is that all obese patients should be encouraged to attain a healthy body weight. This can be accomplished and sustained through dietary modification and exercise—a recommendation that is easy to make, of course, but difficult to follow.

DIETARY FIBER

The amount of dietary fiber consumed is inversely related to insulin levels.[23] This observation may explain the lower incidence of hypertension, hyperlipidemia and cardiovascular disease among people with diets high in fiber. A diet high in natural sources of fiber (e.g., whole grains and vegetables) helps combat insulin resistance.

PHARMACOTHERAPY

Metformin has been successfully used for some time to treat diabetes. It increases insulin sensitivity,[24] as does the new thiazolidinedione class of drugs.[25] These drugs are not labeled for treatment of isolated insulin resistance. Pending more evidence, the American Diabetes Association does not recommend drug therapy for the treatment of insulin resistance in the absence of diabetes.[2]

Future Directions

Metformin, diet and exercise are being studied in the National Institutes of Health–sponsored Diabetes Prevention Program.[26] Although the outcome being studied is type 2 diabetes, these interventions clearly improve insulin sensitivity. At this time, clinicians should make it a priority to aggressively identify patients with possible insulin resistance and assist them in making appropriate lifestyle modifications.

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