Insulin Resistance
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Suggested CDR Learning Codes: 5190, 5400, 5410, 5420; Level 2

Insulin resistance is a state of reduced cellular responsiveness to normal circulating concentrations of insulin in the blood. Much is unknown about the condition's etiology, but research has shown insulin resistance appears to play a role in the pathophysiology of prediabetes, type 2 diabetes, and cardiovascular disease (CVD). While much remains to be discovered about the exact causes of the condition, research has investigated and pinpointed several likely risk factors, including a sedentary lifestyle, central obesity, genetics and, most likely, diet.

To support dietitians in helping clients and patients address and possibly even reverse insulin resistance, this continuing education article reviews the current theory and research regarding the condition's etiology and major risk factors as well as the role it may play in the development of type 2 diabetes and CVD.

History
Research leading to the discovery of what's known today as insulin resistance dates back to the late 1950s, when research scientists Solomon Berson and Rosalyn Yalow developed the radioimmunoassay, a technique used to measure circulating levels of hormones and other substances in the blood. In later research using this technique, Berson and Yalow found that people with type 2 diabetes exhibited higher-than-average levels of circulating insulin than did individuals with normal glucose tolerance.[1]

This finding led to the first speculation that patients with type 2 diabetes may not adequately respond to insulin and thus require more insulin than normal to maintain healthy blood glucose levels. Later studies corroborated these findings, and researchers eventually coined the term "insulin resistance" to describe this condition.[2-4]

In the book *How Fat Works*, author Philip A. Wood defines insulin resistance as a condition in which the body's cells require more and more insulin to achieve normal levels of glucose uptake.[5] According to Wood, a professor of genetics, nutrition science, physiology, and biophysics as well as an experimental pathologist and director of genomics at the University of Alabama at Birmingham, insulin resistance typically develops over many years and eventually can lead to overt diabetes when the pancreas no longer can keep up with a chronically excessive insulin demand.

Pathophysiology
The development of insulin resistance and reduced glucose tolerance may be linked to altered fatty acid metabolism. In normal metabolism, liver and muscle tissue take in circulating plasma fatty acids derived from dietary fats and/or adipose tissue and convert them to fatty acid metabolites such as acyl coenzyme A (acyl-CoA). Molecules of acyl-CoA are then either oxidized in the mitochondria for energy or converted to triglycerides and stored in adipose tissue for later use.[5]

Excess quantities of circulating fatty acids commonly are associated with obesity, insulin resistance, and type 2 diabetes.[6] According to Wood, an overabundance of fatty acids also may result in the abnormal deposition of fat in both liver and muscle tissues.[5] Indeed, studies have shown a strong positive relationship between the accumulation of fat in muscle tissue and insulin resistance.[7] In addition, a positive relationship has been observed between fasting plasma fatty acid concentrations and insulin resistance in muscle.[8] In other words, insulin resistance in muscle diminishes as circulating fatty acids are reduced.

According to Gerald Shulman, MD, PhD, a professor of medicine and cellular and molecular physiology at Yale University School of Medicine, excess fatty acids appear to interfere with a very early step in insulin stimulation of glucose transport across cell membranes. Moreover, Shulman's research suggests that fatty acid metabolites, including acyl-CoA, may be some of the most important biochemical triggers of insulin resistance.[9-11]

Both Shulman and Wood describe the normal biochemical pathway for the transfer of glucose across a cell membrane as follows[5,9]:

• Insulin binds with an insulin receptor on the cell membrane, which activates a protein known as insulin receptor substrate molecule 1 (IRS-1).

• IRS-1 activates the enzyme phosphatidylinositol-3 (PI-3) kinase.

• PI-3 activates a cascade of reactions that ultimately stimulate the translocation of glucose transporter 4 (GLUT4) to the cellular membrane.

• GLUT 4 allows the movement of glucose across the membrane and into the cell.

In an insulin-resistant individual, excess acyl-CoA and other fatty acid metabolites may inhibit IRS-1 activation of PI-3 and the subsequent transfer of glucose into the cell by GLUT 4. Thus, glucose's transfer into the cell is diminished and glucose levels in the blood rise.[9]

In a research review published in 2004 in **Physiology**, Shulman speculated that defects in mitochondrial function that reduce the ability of liver and muscle tissue to adequately oxidize fatty acids may contribute to the intracellular accumulation of metabolites that trigger insulin resistance.[11] A recent review by Pagel-Langenickel and colleagues, published in **Endocrine Reviews**, also provides evidence that dysfunctional mitochondria play an important role in the development of both insulin resistance and type 2 diabetes.[12]

In this substantial research review, the authors cited evidence suggesting that lean insulin-resistant offspring of parents with type 2 diabetes and individuals with severe obesity commonly exhibit a reduction in skeletal muscle cell mitochondrial number and density; genes responsible for turning on mitochondrial metabolic functions are downregulated in patients with diabetes; and decreased levels of fatty acid and glucose oxidation are observed in patients who are obese and/or present with a strong family history of diabetes. According to the review, researchers also are debating whether mitochondrial dysfunction actually may be a cause or just a symptom of insulin resistance.[12]

Vicious Cycle

Once insulin resistance begins, it appears to stimulate a series of events that continue to increase levels of both glucose and insulin in the blood. Under normal circumstances, circulating levels of insulin rise after a meal and reduce gluconeogenesis (the production of glucose from noncarbohydrate substrates) in the liver.

Insulin-resistant liver cells, however, don't respond to this normal cue to stop creating new sources of energy. Thus, the liver continues to produce glucose from substrates such as glycerol (obtained from abundant circulating triglycerides). This continual release of glucose from the liver then stimulates the additional release of insulin from the pancreas and contributes to rising insulin levels in the blood.[5]

In addition, research shows insulin-resistant adipose tissue may not react to rising plasma insulin levels. Normally, insulin reduces the breakdown of adipose tissue (lipolysis) and promotes fat storage after a meal. In people with insulin resistance, lipolysis continues despite elevated levels of insulin. Adipose tissue therefore releases more fatty acids into circulation which, in turn, may aggravate and promote insulin resistance.[5]

Risk Factors

The risk factors for insulin resistance include central obesity, physical inactivity, and genetics.

Central Obesity

The location of fat stores in the body appears to be a strong determinant of insulin resistance. Research indicates that adipose tissue in the hips, buttocks, and thighs is less of a risk factor than is fat deposited centrally, or in the gut.[5,13-15] The specific location of central fat also may be important, as visceral abdominal fat (located deep and around organs) may be more likely to cause insulin resistance than subcutaneous abdominal fat.[15]

Several theories address the role abdominal fat plays in the pathogenesis of insulin resistance, but the exact mechanisms remain undefined. According to Wood, fat that's stored lower in the body is less likely to undergo lipolysis than centrally deposited, visceral fat. Thus, abdominal fat is more likely to contribute to elevated levels of fatty acids circulating in the blood, which, in turn, may promote insulin resistance.[5]

Researchers also have proposed that the endocrine function of adipose tissue influences the development of insulin resistance.[16] For example, adipose tissue contributes to circulating levels of the proinflammatory cytokine interleukin-6 (IL-6), and elevated levels of IL-6 have

been positively associated with obesity, impaired glucose tolerance, and insulin resistance.[17] However, the role IL-6 and other mediators of inflammation play in the development of both insulin resistance and type 2 diabetes hasn't been adequately determined, and researchers recommend further investigation.[17]

Sedentary Lifestyle
Many people who are insulin resistant are obese (though some who are lean also can suffer from insulin resistance), but not all obese individuals are insulin resistant.[18] Gerald Reaven, MD, an endocrinologist and professor emeritus of medicine at Stanford University who's considered an expert on insulin resistance, maintains that insulin's ability to stimulate cellular glucose uptake may vary more than sixfold among individuals.[19] In fact, Reaven and his colleagues estimate that only 25% to 35% of this variability in insulin action is related to being overweight.[20] Therefore, obesity is likely only one of several factors that modulate insulin action.

A sedentary lifestyle may be a strong risk factor for developing insulin resistance. In a study of volunteers of both Pima Indian and European ancestry who didn't have diabetes, Bogardus and colleagues found that differences in physical fitness were as powerful as variations in adiposity in the modulation of insulin action.[21] The results of a large observational study by Risérus and colleagues (n = 770) indicated that physical activity and socioeconomic status both were strong predictors of insulin resistance, following BMI, in adult men observed for 20 years.[22]

Considering the available evidence, Bogardus and colleagues concluded that obesity, along with physical inactivity, may account for approximately one-half of the variability in insulin sensitivity in healthy individuals who don't have diabetes.[19]

Genetics
Since the completion of the Human Genome Project in 2003, genetics has played an increasingly important role in disease diagnosis and treatment. In fact, genetic scientists have come to believe that many, if not all, diseases have a genetic component. While some diseases develop directly from a single, inherited genetic mutation, others develop as a genetic response to environmental stressors such as poor diet, viruses, or toxins.[5]

Many common diseases, including type 2 diabetes, seem to be multifactorial in origin, meaning that genetics as well as environmental and behavioral factors combine to produce disease.[5] According to Wood, insulin resistance also may be one of those multifactorial diseases that result from a genetic domino effect: Genes that promote higher blood levels of triglycerides may be triggered by a poor diet and/or sedentary lifestyle and consequently may create the conditions for developing insulin resistance.[5]

In research that was part of the Tufts Twin Study, Elder and colleagues attempted to determine the genetic heritability of components of the metabolic syndrome, which includes insulin resistance.[23] Heritability is defined as the relative influence of genetic factors on the expression of a disease or disease trait. Elder and colleagues connected every component of the metabolic syndrome, including insulin resistance, with a genetic link and determined that

genetics had more of an influence on the development of the metabolic syndrome than did environmental influences.

The study's results suggest that, despite established relationships between environmental factors and the metabolic syndrome, genetic variation may be an important and possibly primary determinant of the expression of insulin resistance.

The Effect of Diet
Some research suggests that a diet high in total, trans, and saturated fat may promote insulin resistance.[24-26] Studies also indicate that replacing saturated fat with polyunsaturated or monounsaturated fat may improve insulin sensitivity, but only if total fat intake also is controlled.[25]

According to a recent review by Risérus and colleagues of literature examining the role of different types of fat on insulin resistance, studies comparing insulin sensitivity and fatty acid composition in skeletal muscle (a reflection of the fatty acid composition of the diet) have found a direct, positive relationship between the proportion of long-chain polyunsaturated fatty acids and insulin sensitivity.[26] In addition, evidence suggests the more saturated fatty acids in the muscle cell membrane, the more insulin-resistant the individual.[24]

In the KANWU study, a three-month controlled, parallel, multicenter study performed at five different centers: Kuopio, Finland; Aarhus, Denmark; Naples, Italy; Wollongong, Australia; and Uppsala, Sweden, 162 subjects from these countries received isocaloric diets that differed only in fat quality, not quantity.[25] Researchers found that insulin sensitivity was impaired in individuals on the higher saturated fat diet and improved in those on the higher monounsaturated fat diet. However, substituting monounsaturated fat for saturated fat improved insulin sensitivity only if total fat intake remained at no more than 37% of calories. The authors concluded that the type of fat in the diet impacted insulin resistance, but quantity of fat also was important.

In the SLIM study (Lifestyle Intervention on Postprandial Glucose Metabolism), researchers also demonstrated improved glucose tolerance and insulin sensitivity among participants who reduced their intake of both saturated fat and total fat.[27] Again, the benefits of reduced saturated fat intake were noted only in those with a total fat intake of less than 35% of calories.

All these studies suggest that a diet low in saturated fat but also moderate in total fat content improves insulin sensitivity.

Role in CVD
Insulin resistance is a central part of a cluster of metabolic abnormalities called the metabolic syndrome. Originally discovered and labeled by Reaven as syndrome X,[28] metabolic syndrome is described as the concurrence of conditions, including elevated triglycerides, central obesity, low levels of HDL cholesterol, hypertension, and impaired fasting glucose.[5,29]

According to Reaven, individuals with the metabolic syndrome also may experience impaired clearance of fat from the blood after meals; elevated levels of small, dense lipoproteins; and

hypercoagulation resulting from elevated levels of plasma fibrinogen.[28] Insulin resistance is directly implicated in the development of several of these abnormalities, all of which may be considered independent risk factors of CVD.[28,30]

For example, elevated levels of insulin resulting from insulin resistance stimulate the liver to increase its production of triglyceride-rich very-low-density lipoproteins, thus causing blood triglyceride levels to rise.[28,30] Insulin-resistant adipose tissue undergoes lipolysis in the fed and fasting state, also adding to the plasma triglyceride load.[5,28] Insulin resistance may reduce the body's ability to clear fat from the blood after a meal.[28] As Reaven's research demonstrates, all these factors contribute to the development of CVD and an increased risk of heart attack.

Some long-term studies have demonstrated that insulin resistance increases the risk of CVD. In the San Antonio Heart Study, individuals with insulin resistance had a twofold to 2.5-fold increased risk of CVD at eight years.31 Insulin-resistant individuals without diabetes in the Botnia Study also experienced a twofold increased incidence of CVD at seven years.[32]

In a 2010 review published in *Diabetologia*, DeFronzo summarized research that suggests additional links between insulin resistance and CVD. In vivo and in vitro animal and human studies have demonstrated that insulin, especially at high doses, promotes LDL cholesterol transport into cultured arterial smooth muscle cells, augments collagen synthesis and arterial smooth muscle cell proliferation (thus increasing carotid intimal media thickness and reducing vascular elasticity), and may turn on genes that promote inflammation, which is known to accelerate atherogenesis. According to DeFronzo, the increased risk of CVD in people with insulin resistance can't be completely explained by changes in plasma lipids and fibrinolysis; instead, insulin's effect on smooth muscle cell proliferation and inflammation likely may be a primary driver of the disease.[30]

Role in Prediabetes and Type 2 Diabetes
According to the National Institutes of Health, insulin resistance is a risk factor for developing both prediabetes and type 2 diabetes.[33] Prediabetes, also known as impaired glucose tolerance or impaired fasting glucose, currently is diagnosed when hemoglobin A1c (HbA1c) levels fall between 5.7% and 6.4%.[34] Individuals with prediabetes are known to have an increased risk of converting to type 2 diabetes.[34] According to the American Diabetes Association (ADA), the continuum of risk is curvilinear, indicating that as HbA1c rises, the risk of diabetes rises at a disproportionately greater rate.[34]

The Insulin Resistance Atherosclerosis Study is a large epidemiological investigation into the relationship between insulin resistance and cardiovascular risk factors among individuals of three ethnic groups (blacks, Hispanics, and whites). In this study, researchers measured insulin sensitivity and first-phase insulin response in 557 participants with normal glucose tolerance and 269 individuals with impaired glucose tolerance. At five years, both insulin sensitivity and first-phase insulin response predicted conversion to diabetes, regardless of ethnic group. While individuals with a family history of diabetes and those with a higher BMI and larger waist circumference also were more likely to develop diabetes, insulin sensitivity, and first-phase insulin response still were more significantly correlated.[35]

Similarly, results from the Diabetes Prevention Program (DPP) showed that participants who improved insulin sensitivity and insulin secretion through lifestyle change or treatment with metformin experienced a reduction in the conversion to type 2 diabetes. The DPP Research Group concluded that "analysis of the changes in plasma glucose and insulin during the first year of the study suggests that development of diabetes … resulted from continued decreases in insulin sensitivity and beta-cell function, whereas reduction in the incidence of diabetes observed in the two active interventions was due to their ability to increase insulin sensitivity and improved beta-cell function." In other words, lifestyle change alone as well as treatment with metformin appeared to reduce insulin resistance and improve insulin secretion. The researchers drew no conclusions regarding the exact physiologic mechanisms involved.[36]

Although it's commonly accepted that insulin resistance usually precedes the development of type 2 diabetes by many years, the physiologic mechanisms that promote the progression of insulin resistance to type 2 diabetes in some individuals are still under investigation. Unger and Grundy were the first to postulate that continuous overstimulation of pancreatic beta cells resulting from insulin resistance and hyperglycemia eventually could lead to beta-cell failure.[37] These investigators also were the first to introduce the terms "glucotoxicity" and "lipotoxicity," which describe the deleterious effects of chronically elevated blood glucose and triglyceride levels on beta-cell function. Researchers have continued to implicate the direct toxic effects of hyperglycemia and hyperlipidemia on beta-cell function as well as the effects of whole-body oxidative stress resulting from hyperglycemia in the conversion of insulin resistance to overt diabetes. However, the exact physiologic processes involved haven't been determined and are still under scientific debate.[38]

Reversing Insulin Resistance
Research shows that weight loss and physical activity can play an important role in improving insulin resistance.

Weight Loss and Improved Insulin Sensitivity
Several studies have demonstrated the importance of weight loss, especially when resulting from a reduction in visceral fat mass, on the reversal of insulin resistance. A four-year intervention involving participants in the Finnish Diabetes Prevention Study demonstrated a strong correlation between changes in insulin resistance and weight. Although this study was small (researchers could follow only 52 people for the entire length of the study), the results were remarkable. In the entire group, insulin sensitivity improved by up to 64% among participants with the highest degree of weight loss (up to 17.2% of body weight) and deteriorated by 24% in those who gained weight (up to 10%). Participants who lost weight generally followed a diet plan that was low fat (fewer than 30% of calories from fat and fewer than 10% of calories from saturated fat) and high fiber (15 g fiber/1,000 kcal).[39]

Interestingly, some research also suggests that caloric restriction promoting visceral fat loss may reduce or even override the impact of dietary fat type on insulin resistance. Researchers in a randomized controlled study compared the effects of a low-carbohydrate diet (20% of energy from carbohydrate and 60% of energy from fat) with a low-fat diet (60% of energy from carbohydrate and 20% of energy from fat) on weight reduction and insulin resistance in adults who were overweight or obese.[40]

In this study, diets were designed on an individual basis to facilitate a weekly 0.5-kg weight loss. At the end of eight weeks, both groups lost an average of 7% of their initial body weight and demonstrated similar reductions in both waist circumference and percent body fat. Both groups experienced comparable improvements in insulin sensitivity, and researchers attributed this improvement to weight loss alone, not to the specific macronutrient makeup of the diets. Because this study implies that dietary fat levels may not be as important as weight loss for reducing insulin resistance, it's evident that questions remain regarding the relative contributions of macronutrients and weight loss to the reversal of insulin resistance.

Effect of Exercise

There's substantial literature showing improved insulin sensitivity after exercise, both with and independent of weight loss.[41-47] There's debate about the best exercise prescription to maximize insulin sensitivity in different populations, but both regular aerobic exercise and resistance training seem to confer beneficial results.

In 2003, Goodpaster and colleagues demonstrated that a regular, moderate-to-high intensity exercise program (a 40-minute workout at up to 75% maximum heart rate, four to six times per week for 16 weeks) enhanced not only insulin sensitivity but also the capacity of obese, middle-aged individuals to burn fat, especially in those who also lost weight.[41] Since sedentary, obese individuals with insulin resistance exhibit a reduced capacity to burn both fat and glucose for energy, enhancing mitochondrial fat and glucose oxidation may reduce insulin resistance.[5] Evidence from this study suggests that exercise is a potential means to that end.[41]

In a randomized 12-week trial designed to examine the effect of exercise (EX group) or exercise combined with moderate caloric restriction (EX + CR group) on insulin resistance and other measurements of the metabolic syndrome, Yassine and colleagues found that exercise alone had a significant impact on insulin resistance in a population of older (65.5 ± 5 years) obese adults. A caloric restriction of 500 kcal/day in the EX + CR group didn't lead to any greater improvement in insulin resistance, despite greater weight loss (7.4% of initial body weight).[47]

The exercise intervention in this study was a simple walking program, although participants were gradually (at the end of four weeks) exercising at a relatively high level of intensity (80% to 85% of maximum heart rate) for 50 to 60 minutes per day, five days per week. Level of fitness, as measured by aerobic capacity, was strongly correlated with insulin sensitivity in this study group.

While dieting can reduce visceral fat mass and improve insulin sensitivity, caloric restriction also results in the loss of some lean body mass. In fact, a recent review estimates that reduced muscle mass can account for 14% to 23% of total weight lost.[48] Results from the Healthy Aging and Body Composition Study indicate that older adults experience greater loss of muscle mass with intentional caloric restriction than do younger individuals.[49] Because skeletal muscle plays an important role in glucose metabolism, muscle wasting from dieting or aging may have a significant impact on the development of insulin resistance.[50] Researchers suggest that the

effect of exercise on muscle mass may be an important modulator of insulin sensitivity, especially in older adults.[50,51]

Additional Dietary Considerations

The following are additional dietary considerations in relation to their impact on insulin sensitivity:

Fat: Research shows possible insulin sensitivity improvements with a reduction in saturated, trans, and/or total fat.[24-27]

Vegan diet: One study by Barnard and colleagues demonstrated the effects of a 14-week, low-fat vegan diet on weight loss and insulin sensitivity. In this study, 64 overweight, postmenopausal women were randomly assigned to a low-fat vegan diet group or a control diet group following National Cholesterol Education Program guidelines. Neither group had calorie restrictions. Participants who ate the vegan diet lost 5.8 ± 3.2 kg compared with 3.8 ± 2.8 kg among controls. Insulin sensitivity improved in both groups, with no significant difference between the two.[52]

In a separate study, researchers at the Imperial College School of Medicine in London showed the positive effects of a vegan diet on lowering plasma triglycerides, fasting glucose, and systolic blood pressure compared with controls who ate an omnivorous diet.[53]

With results similar to those of Barnard, these researchers also discovered a nominal improvement in insulin sensitivity in the vegan diet group. However, the vegan group demonstrated significantly improved pancreatic beta-cell function and a reduction in intramuscular fat deposits, both indirect indicators of improved glycemic control and insulin sensitivity.

Carbohydrates: Choosing carbohydrate-dense foods that are low on the glycemic index also may have beneficial effects, especially when combined with a reduction in calories and regular exercise. A study by Kirwan and colleagues demonstrated that combining a low-glycemic diet with exercise resulted in a greater decrease in insulin resistance in older obese adults than did exercise and calorie reduction without regard to glycemic index.[54]

Phytochemicals: In a study that considered the impact of dietary components other than macronutrient content, Minich and Bland recommend examining the diet's phytochemical content for clues to the etiology of insulin resistance.[55] These researchers postulated that a plant-based diet containing significant levels of phytochemicals effectively may prevent insulin resistance. They cited evidence from clinical trials supporting the beneficial effects of fruit and vegetable pigments, bitter melon, green tea, cinnamon, and hops on maintaining normal cellular insulin signaling function, the key to preventing insulin resistance.[55]

Bottom Line

Despite all this research, the ideal diet and lifestyle prescription for the treatment and prevention of insulin resistance is unknown. Moderate caloric restriction that facilitates the loss of abdominal fat seems to be important to improving insulin sensitivity, as does regular aerobic

exercise. Some evidence suggests that replacing saturated fat with polyunsaturated fat also may contribute to reduced visceral fat mass.[26]

The ADA has made no specific recommendations for treating insulin resistance, but recommends lifestyle modification for prediabetes, a known insulin-resistant state. In its 2013 Medical Standards of Care Position Statement, the ADA recommended a diet and exercise program that targets and supports a 7% loss of body weight and at least 150 minutes per week of moderate exercise.[34]

Resistance exercise to build muscle mass can be beneficial, especially for older adults. Helping patients devise a diet and exercise program that facilitates the loss of 1 to 2 lbs of body weight per week eventually may help improve their insulin sensitivity.

Saturated and trans fat seem to reduce insulin sensitivity more than poly- and monounsaturated fats, but total fat intake still needs to be controlled. A goal of 30% of calories from fat, mostly plant-based unsaturated fats, can be a reasonable and safe dietary goal for most patients with insulin resistance.

Encouraging patients to follow a plant-based diet featuring vegetables, fruits, beans, whole grains, nuts, and seeds also is a sensible approach. The USDA MyPlate guidelines can be an easy first step many patients can take toward including more phytochemical-packed plants and fewer foods containing saturated fats in their meals. The USDA guidelines also suggest limiting added sugars to no more than 10% of total calories and increasing intake of carbohydrate-dense foods that are also low on the glycemic index, including unrefined grains and grain products. In general, foods that are less processed tend to rate lower on the glycemic index scale. For example, rolled oats have a lower glycemic index than instant oats. However, to more accurately assess glycemic index, it's useful to refer to a glycemic index database, such as the one found at GlycemicIndex.com.

Overall, however, current research seems to indicate that the exact macronutrient balance of the diet may be less important than sustained activity, maintaining a healthy body weight and, perhaps, the micronutrient content of the foods patients consume in preventing and treating insulin resistance.

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Examination

1. Which of the following may trigger insulin resistance at the cellular level?
A. Insufficient mitochondrial fatty acid oxidation
B. Insulin deficiency
C. Excessive pancreatic beta-cell insulin production
D. Decreased levels of fatty acid and glucose oxidation

2. Which of the following is a risk factor for insulin resistance?
A. Hypertension
B. Excess fat in the hips, buttock, and thighs
C. Excess visceral fat
D. Excessive exercise

3. Exercise appears to improve insulin sensitivity and reduce insulin resistance only when individuals lose weight.
A. True
B. False

4. Insulin resistance is defined as the cells' reduced ability to respond to normal circulating levels of insulin.
A. True
B. False

5. In which of the following ways may central obesity contribute to the development of insulin resistance?
A. Reducing pancreatic beta-cell activity
B. Increasing the amount of glucose circulating in the blood
C. Raising blood pressure
D. Releasing excess fatty acids into the blood

6. Exercise may reduce insulin resistance by influencing how well cells use which of the following for energy?
A. Glucose
B. Fat
C. Both glucose and fat
D. Lean mass

7. Insulin resistance is a major component of the metabolic syndrome. Another component of this syndrome includes which of the following?
A. Facial hair growth in women
B. Fatigue
C. Elevated levels of HDL cholesterol
D. Elevated levels of small, dense lipoproteins

8. Which of the following diet modifications does research suggest can reduce insulin resistance?
A. Reduced total caloric intake
B. Increased intake of protein
C. Reduced intake of polyunsaturated fat
D. Increased intake of fiber

9. Insulin resistance can trigger the liver to produce and release glucose into the bloodstream in the fed state.
A. True
B. False

10. Insulin resistance ultimately can lead to the development of type 2 diabetes because the body eventually does which of the following?
A. Undergoes complete beta-cell failure and absolute insulin deficiency
B. Creates antibodies against insulin
C. Develops some beta cell failure and relative insulin deficiency
D. Loses all of its cellular insulin receptors