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Exercise and Insulin Resistance

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SUMMARY

INSULIN RESISTANCE (IR) IS A GROWING PROBLEM IN THE UNITED STATES. EXERCISE IS AN EFFECTIVE TREATMENT IN THE MANAGEMENT OF IR THROUGH ENHANCED INSULIN SENSITIVITY, INCREASED SKELETAL MUSCLE GLUCOSE UPTAKE, AND IMPROVED B-CELL FUNCTION. ADDITIONALLY, EXERCISE MAY POSITIVELY MODIFY COMORBIDITIES OFTEN ASSOCIATED WITH IR.

EXERCISE THERAPY AND INSULIN RESISTANCE

Type 2 diabetes mellitus (T2D) is a major health concern worldwide. According to the Centers for Disease Control, the number of Americans with diabetes more than tripled from 1980 to 2007 (12), primarily because of an increase in T2D. Insulin resistance (IR), or pre-diabetes, precedes the development of T2D and is often accompanied by many other metabolic abnormalities as shown in Table 1 (15). Particularly when combined with a healthy diet, exercise can be an effective tool in preventing and treating IR. However, conflicting exercise recommendations have complicated the exercise prescription. This column will briefly address the epidemiology and pathophysiology of T2D and summarize the role of exercise in IR. The accompanying One-on-One column will present guidelines for exercise testing and prescription in persons with IR.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

It is estimated that 25.8 million Americans (8.3% of the population) have diabetes (12). Additionally, 79 million Americans have prediabetes (fasting blood glucose between 100 and 125 mg/dL). Without change, nearly 30% of Americans will have T2D by the year 2050 (6). Numerous theories have attempted to explain the pathophysiology of IR. Perhaps, the most popular theory is that an accumulation of intramuscular triglycerides (IMTG) and fatty acid metabolites inhibits insulin signaling (2,14). However, endurance athletes demonstrate high levels of IMTG without resulting in IR. It is thought that the high turnover of IMTG in athletes prevents increased fatty acid metabolites (17). Other researchers have suggested that an increased fatty acid delivery to the mitochondria results in increased reactive oxygen species, shifting cellular redox potential and ultimately leading to IR (2). It is thought that excess calorie intake results in oversupply of electrons to the electron transport chain, formation of superoxide, and ultimately hydrogen peroxide that diffuses into the cytosol, altering the function of proteins and lipids.

Persons with IR are typically asymptomatic and may demonstrate normal fasting (<100mg/dL) and postprandial (<140 mg/dL at 2 hours) blood glucose. However, fasting and/or postprandial insulin levels will be significantly higher in IR (16). Because fasting insulin is not a common laboratory test, clinicians typically do not diagnose IR. Hyperinsulinemic-euglycemic clamps and oral glucose tolerance tests can be used to diagnose persons with IR but because of financial and time constraints are typically reserved for research settings. During the hyperinsulinemic-euglycemic clamp procedure, insulin is infused through a peripheral vein and glucose infusion is adjusted to maintain euglycemia. Higher glucose infusion rates are associated with increased insulin sensitivity. A brief interview with potential clients can be very useful for determining whether a client is at risk of IR. This interview should contain family

Table 1
Metabolic abnormalities commonly associated with insulin resistance (metabolic syndrome)

Risk factor	Measurement	Metabolic syndrome criterion
Impaired fasting glucose	Fasting blood glucose	≥100 to 125 mg/dL
		On hypoglycemic medications
Obesity	Waist circumference	Men > 40″
		Women > 35″
Triglycerides	Triglycerides	≥150 mg/dL
		On lipid lowering medications
HDL-C	HDL-C	Men < 40 mg/dL
		Women < 50 mg/dL
Hypertension	Blood pressure	Systolic ≥ 130 mmHg or
		Diastolic ≥ 85 mmHg
		On antihypertensive medications
Chronic Inflammation	N/A	N/A
Decreased fibrinolysis	N/A	N/A
Hyperuricemia	N/A	N/A

No consensus measure or criterion value for metabolic syndrome.

HDL-C = high density lipoprotein-cholesterol; N/A = not available.

Adapted from Reaven (15).

history, dietary and exercise habits, and current medications. Additionally, physical examinations (body mass index, waist circumference, body composition, blood pressure), and laboratory tests (fasting blood glucose, hemoglobin A1C, triglycerides, and high-density lipoprotein cholesterol) may aid in risk stratification of persons suspected to have IR. When comparing anthropometric parameters and aerobic fitness, elevated waist circumference seems to be the best predictor of IR (14).

Medical management of persons with IR typically consists of diet and exercise interventions, weight loss, and prescription of 1 or more insulin-sensitizing drugs (Table 2). Typical insulin sensitizers include metformin, rosiglitazone, and pioglitazone. These medications reduce the level of blood glucose by decreasing hepatic glucose output (metformin) and activating insulin-sensitizing genes and enzymes (rosiglitazone and pioglitazone). Because these medications do not directly affect the amount of circulating insulin, it typically is not necessary to adjust dosage in conjunction with exercise.

EXERCISE GOALS

There are several goals for exercise in IR (Table 3). The ultimate goal of exercise for persons with IR is to prevent the progression to T2D. Exercise helps accomplish this through several mechanisms (Table 4): improving insulin sensitivity of skeletal muscle and concomitant glucose uptake, preserving β-cell function, reducing dependence on pharmacological therapy, and managing associated comorbidities.

The primary mechanism for decreased IR with exercise is increased skeletal muscle insulin sensitivity (18). Skeletal muscle accounts for approximately 75–95% of whole-body glucose disposal (4). Therefore, maintaining insulin sensitivity of skeletal muscle is crucial to prevent IR from progressing to T2D. Insulin sensitivity typically is greatly enhanced after a single exercise bout (3). However, a recent study in rodents showed that 29–53 hours after exercise, insulin sensitivity reverts to levels similar to sedentary controls (11). Even in non-exercising humans, 2 weeks of reduced physical activity has been shown to result in reduced insulin sensitivity (10). The quick reversal of insulin sensitivity after exercise cessation indicates the need for consistent exercise. This is a major reason why exercise guidelines for T2D suggest a maximum of 48 hours between exercise bouts (1). However, another study showed that after 8 months of exercise training, a 2-week hiatus resulted in insulin sensitivity that was still 30% higher than sedentary controls (3). Therefore, consistent exercise training may have some long-term benefits. This could potentially include increased muscle mass and therefore increased glucose uptake.

Table 2
Common medications for insulin resistance and mechanism of action

Class	Generic name	Trade name	Mechanism of action	Side effects/complications
Biguanides	Metformin	Glucophage	Decrease hepatic glucose output	Lactic acidosis: extreme weakness, muscle pain, difficulty breathing, palpitations
		Riomet		
Glucosidase inhibitors	Acarbose	Precose	Inhibit intestinal carbohydrate absorption	Abdominal pain, diarrhea
	Miglitol	Glyset		
Meglitinides	Nateglinide	Starlix	Stimulate pancreatic β-cells to release insulin	Back pain, diarrhea, dizziness, flu-like symptoms, joint infection, upper respiratory infection
	Repaglinide	Prandin		
Sulfonylureas	Glipizide	Glucotrol	Stimulate pancreatic β-cells to release insulin	Constipation, diarrhea, drowsiness, headache, itching, sensitivity to light, stomach pain, tremors
	Glyburide	DiaBeta		
		Glynase		
		Micronase		
	Glimepiride	Amaryl		
Thiazolidinediones	Pioglitazone	Actos	Increase insulin sensitivity	Anemia, cold symptoms, headache, sinus infection, muscle soreness, sore throat
	Rosiglitazone	Avandia		

In persons with insulin resistance, the need for medication can be obviated by adherence to comprehensive therapeutic lifestyle changes, including regular exercise (9).

In addition to increased insulin sensitivity, exercise increases glucose uptake through muscle contraction. One potential mechanism of contraction-mediated glucose uptake involves adenosine monophosphate–activated protein kinase (AMPK). Adenosine monophosphate is elevated during low cellular energy state causing an increase in AMPK activity, ultimately leading to translocation of glucose transporters to the cell surface (8). Under basal conditions, insulin-dependent glucose transporters (GLUT4) reside intracellularly. On stimulation, GLUT4 is translocated to the membrane to facilitate glucose uptake. After exercise, glucose transporters remain at the cell surface for several hours, contributing to an increased glucose disposal during this time (7). Insulin and muscle contraction have an additive effect on lowering blood glucose, suggesting that these pathways act independently (7,8). Therefore, exercise may increase glucose disposal in persons with IR.

Another goal of exercise training is to preserve pancreatic β-cell function. β-Cells are responsible for making and releasing insulin. The elevated blood insulin level associated with IR results in premature loss of β-cell function. The Studies of Targeted Risk Reduction Interventions through Defined Exercise (STRRIDE) study indicated that overweight individuals with dyslipidemia had only approximately 50–70% β-cell function of healthy individuals in other studies (16). Fortunately, β-cell function can be enhanced through exercise. Participants in 1 studied experienced a 31% improvement in β-cell function after only 7 days of moderate-intensity aerobic exercise (5). The fact that these changes occurred in the absence of changes in body weight, body composition, or dietary habits suggests that exercise alone is effective in improving β-cell function. With regard to exercise intensity, it has been suggested that moderate-intensity exercise is actually slightly more effective than vigorous exercise in rescuing β-cell function (5), possibly because of an increased

Table 3
Goals of exercise in insulin resistance

Prevent progression to type 2 diabetes mellitus
Reduce dependence on medications
Positively modify associated comorbidities (see Table 1)

Table 4
Mechanisms of exercise modification of insulin resistance

Improved insulin sensitivity (whole body and skeletal muscle)
Increased muscle mass (increased glucose uptake)
Contraction stimulated glucose uptake
Improved β-cell function

lipolytic activity associated with this intensity.

Exercise works in combination with insulin-sensitizing drugs to improve insulin sensitivity. In some cases, exercise can restore insulin sensitivity and eliminate the need for medication. In fact, some studies have shown that lifestyle interventions (exercise and diet) can be more effective than pharmaceutical therapy in preventing progression to T2D (9).

Another major goal of exercise in IR is to positively modify associated comorbidities. As mentioned earlier, IR is often compounded by additional metabolic abnormalities. Although nearly all associated comorbidities are positively modified through exercise, obesity is the most prevalent and thought to be a major determinant of IR (13,14). Often, it is advised for overweight and obese individuals with IR to lose 5–10% of body weight (1). However, subjects in a recent study experienced a 31% increase in insulin sensitivity after only a 3% reduction in body weight (12). Therefore, virtually any improvement in body weight and/or composition is likely to improve insulin sensitivity.

SUMMARY

Insulin resistance is a complicated pathological condition. Although T2D remains a major health concern, exercise training provides a multifaceted approach to treating IR and potentially preventing progression to T2D. Exercise professionals should know the health concerns associated with IR and the mechanisms by which exercise improves IR. Additionally, it is important for exercise professionals to implement exercise strategies and educate clients to maximize health outcomes. The accompanying One-on-One article discusses specific exercise programming for persons with IR.

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