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Insulin Resistance

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Continuing Education Activity

Insulin resistance, identified as an impaired biologic response to insulin stimulation of target tissues, primarily involves liver, muscle, and adipose tissue. Insulin resistance impairs glucose disposal, resulting in a compensatory increase in beta-cell insulin production and hyperinsulinemia. The metabolic consequences of insulin resistance can result in hyperglycemia, hypertension, dyslipidemia, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and a prothrombotic state. The predominant consequence of insulin resistance is type 2 diabetes(T2D). Insulin resistance is thought to precede the development of T2D by 10 to 15 years. Lifestyle modifications should be the primary focus when treating insulin resistance. Nutritional intervention with calorie reduction and avoidance of carbohydrates that stimulate excessive insulin demand is a cornerstone of treatment. Physical activity helps to increase energy expenditure and improve skeletal muscle insulin sensitivity. Medications also can improve insulin response and reduce insulin demand. Most of the complications from insulin resistance are related to the development of vascular complications and nonalcoholic fatty liver disease. This activity reviews the etiology, pathogenesis, epidemiology, presentation, treatment, and potential complications of insulin resistance and highlights the crucial role of the interprofessional team in its management.

Objectives:

- Articulate the acquired and genetic causes of insulin resistance.
- Explain the pathophysiology of insulin resistance.
- Summarize the 3 arms in the management of insulin resistance.
- Apply effective processes to improve care coordination among interprofessional team members to improve outcomes and reduce complications for patients with insulin resistance.

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Introduction

Insulin resistance is identified as the impaired biologic response of target tissues to insulin stimulation. All tissues with insulin receptors can become insulin resistant, but the tissues that primarily drive insulin resistance are the liver, skeletal muscle, and adipose tissue. Insulin resistance impairs glucose disposal, resulting in a compensatory increase in beta-cell insulin production and hyperinsulinemia. Recent studies have debated whether hyperinsulinemia

precedes insulin resistance, as hyperinsulinemia itself is a driver of insulin resistance. This concept may be clinically valuable, suggesting that hyperinsulinemia associated with excess caloric intake may drive the metabolic dysfunction associated with insulin resistance. The metabolic consequences of insulin resistance include hyperglycemia, hypertension, dyslipidemia, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and a prothrombotic state. Progression of insulin resistance can lead to metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), and type 2 diabetes.[1][2][3][4][5]

Insulin resistance is primarily an acquired condition related to excess body fat, though genetic causes are also identified. The clinical definition of insulin resistance remains elusive, as there is no generally accepted test for insulin resistance. Clinically, insulin resistance is recognized via the metabolic consequences associated with insulin resistance as described in metabolic syndrome and insulin resistance syndrome.[6][7]

The gold standard for measurement of insulin resistance is the hyperinsulinemic-euglycemic glucose clamp technique. This research technique has limited clinical applicability; however, several clinically useful surrogate measures of insulin resistance include HOMA-IR, HOMA2, QUICKI, serum triglyceride, and triglyceride/HDL ratio. In addition, several measures assess insulin resistance based on serum glucose or insulin response to a glucose challenge.[8][9][10][11]

The predominant consequence of insulin resistance is type 2 diabetes (T2D). Insulin resistance is thought to precede the development of T2D by 10 to 15 years. The development of insulin resistance typically results in impaired glucose disposal into insulin-resistant tissues, especially skeletal muscle. Consequently, in the presence of excess calorie consumption, more insulin is required to traffic glucose into these tissues. The resultant hyperinsulinemia further contributes to insulin resistance. This vicious cycle continues until pancreatic beta-cell activity can no longer adequately meet the insulin demand created by insulin resistance, resulting in hyperglycemia. With a continued mismatch between insulin demand and insulin production, glycemic levels rise to those consistent with T2D. Weight gain usually occurs alongside hyperinsulinemia but may be related more to a chronic caloric excess than hyperinsulinemia. The anabolic effect of insulin decreases as tissues become more insulin-resistant, and weight gain eventually slows.[12][13][14][15]

Resistance to exogenous insulin has also been described. An arbitrary but clinically useful benchmark considers patients insulin-resistant when requiring more than 1 unit/kilogram/day of exogenous insulin to maintain glycemic control. Patients requiring greater than 200 units of exogenous insulin per day are considered severely insulin-resistant.[16]

In addition to T2D, the disease spectrum associated with insulin resistance includes obesity, cardiovascular disease, NAFLD, metabolic syndrome, and polycystic ovary syndrome (PCOS). These are all of great consequence in the United States, with a tremendous burden on the healthcare system to treat the direct and indirect conditions associated with insulin resistance. The microvascular complications of diabetes, such as neuropathy, retinopathy, and nephropathy, as well as the associated macrovascular complications of coronary artery disease [CAD], cerebral-vascular disease, and peripheral artery disease (PAD), will eventually consume the lion's share of the healthcare dollar as the disease progresses in severity.[17][18][19][20][21][22][23]

Lifestyle modifications should be the primary focus when treating insulin resistance. Nutritional intervention with calorie reduction and avoidance of carbohydrates that stimulate excessive insulin demand is a cornerstone of treatment. Physical activity helps to increase energy expenditure and improve skeletal muscle insulin sensitivity. Medications also can improve insulin response and reduce insulin demand.[24][25][26]

Etiology

The etiologies of insulin resistance may be acquired, hereditary, or mixed. The great majority of people with insulin resistance fall have an acquired etiology.[25]

Acquired Etiologies of Insulin Resistance

- Increased visceral adiposity related to ectopic fat deposition and overflow from subcutaneous fat stores
- Aging process
- Physical inactivity
- Nutritional imbalance
- Medications (glucocorticoids, anti-adrenergic, protease inhibitors, selective serotonin reuptake inhibitors, atypical antipsychotics, and some exogenous insulins)
- High-sodium diets
- Glucose toxicity
- Lipotoxicity from excess circulating free fatty acids

In addition to the heritable components of the above etiologies of insulin resistance, there are several unrelated genetic syndromes with associated syndromic insulin resistance.[27]

Genetic Etiologies of Insulin Resistance

- Myotonic dystrophy
- Ataxia-telangiectasia
- Alstom syndrome
- Rabson-Mendenhall syndrome
- Werner syndrome
- Lipodystrophy
- Polycystic ovarian syndrome
- Type-A insulin resistance: Characterized by severe insulin resistance (abnormal glucose homeostasis, ovarian virialization, and acanthosis nigricans) caused by abnormalities of the insulin receptor gene
- Type-B insulin resistance: Characterized severe impairment of insulin action triggered by the presence of insulin receptor autoantibodies with resultant abnormal glucose homeostasis, ovarian hyperandrogenism, and acanthosis nigricans

An alternative classification of insulin resistance exists and is based on the site of dysfunction with respect to the insulin receptor. This classification system includes pre-receptor, receptor, and post-receptor etiologies.

Epidemiology

Epidemiologic assessment of insulin resistance is typically measured in relation to the prevalence of metabolic syndrome or insulin resistance syndrome. Criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III national survey data suggest insulin resistance syndrome is widespread.

An analysis from 2003 of the National Health and Nutrition Examination Survey (NHANES) data showed insulin resistance affects about 22% of United States (US) adults older than 20

years. A more recent analysis of NHANES data from 2021 found that 40% of US adults aged 18 to 44 are insulin-resistant based on HOMA-IR measurements. While obesity rates have increased considerably over the past 2 decades, this rapid increase in prevalence was not only associated with increased adiposity. Hypertension, dyslipidemia, and limited physical activity also increased insulin resistance.

While there has been a rapid rise in pediatric obesity and type 2 diabetes, no consensus has been reached on the pediatric population's diagnostic criteria for insulin resistance. From a demographic standpoint, insulin resistance affects all races and ethnicities, with limited data on comparison between groups.[28][29]

Pathophysiology

The 3 primary sites of insulin resistance are the skeletal muscle, liver, and adipose tissue. In a state of chronic caloric surplus, the tissues in the body become resistant to insulin signaling. Skeletal muscle is a large reservoir for circulating glucose, accounting for up to 70% of glucose disposal as measured by the hyperinsulinemic-euglycemic clamp. The direct result of muscle insulin resistance is decreased glucose uptake by muscle tissue. Glucose is shunted from muscle to the liver, where de novo lipogenesis (DNL) occurs. With increased glucose substrate, the liver develops insulin resistance as well. Higher rates of DNL increase plasma triglyceride content and create an environment of excess energy substrate, which increases insulin resistance throughout the body, contributing to ectopic lipid deposition in and around visceral organs. [25]

Skeletal Muscle Tissue

After intake of a caloric load and conversion to glucose, muscle is the primary site for glucose disposal, accounting for up to 70% of tissue glucose uptake. In chronic caloric excess, muscle tissue accumulates intramyocellular fatty acids. Diacylglycerol is an intramyocellular fatty acid that signals energy excess within the cell. Diacylglycerol activates protein kinase C theta (PKC-theta), decreasing proximal insulin signaling. The direct result is decreased glucose transporter type 4 (GLUT4) translocation to the cell membrane and reduced glucose uptake by the muscle tissue. The excess glucose in the blood is shunted to the liver to be metabolized or stored.[25][30]

Hepatic Tissue

The liver is responsible for processing energy substrates. It packages, recirculates, and creates fatty acids and processes, stores, and creates glucose. If the liver becomes insulin-resistant, these processes are severely affected, resulting in significant metabolic consequences. When skeletal muscle develops insulin resistance, excess glucose in the blood is shunted to the liver. When the liver tissue senses an excess of energy substrate, particularly in the form of diacylglycerol, a process similar to that in skeletal muscle occurs. In the liver, the diacylglycerol content activates protein kinase C epsilon (PKC-epsilon), which decreases proximal insulin signaling. Excess glucose enters hepatocytes via insulin-independent pathways stimulating DNL via substrate push, creating more fatty acids from the glucose surplus. The excess fatty acid is deposited in the liver or as ectopic lipid throughout the viscera. Additionally, immune-mediated inflammatory changes contribute to excess lipolysis from adipose tissue, which is re-esterified by the liver and further adds to circulating fatty acid and ectopic lipid deposition. Finally, normal insulin-mediated suppression of gluconeogenesis is defective, and the liver continues to create more glucose, adding to the circulating glucose surplus.[25][30]

Adipose Tissue

Using the hyperinsulinemic-euglycemic clamp technique, researchers determined that lipolysis is sensitive to insulin. The failure of insulin to suppress lipolysis in insulin-resistant adipose tissue, especially visceral adipose tissue, increases circulating free fatty acids (FFAs). Higher levels of

circulating FFAs directly affect both liver and muscle metabolism, further exacerbating insulin resistance in these tissues and contributing to lipotoxicity-induced beta-cell dysfunction.[25][30]

History and Physical

The clinical presentation of insulin resistance is variable concerning both history and physical examination findings. It depends on the subset of insulin resistance present, the duration of the condition, the level of beta-cell function, and the individual's propensity for secondary illnesses due to insulin resistance. Common presentations include:

Associated Diseases

- Non-alcoholic fatty liver disease (NAFLD)
- Metabolic syndrome
- Prediabetes or type 2 diabetes
- Polycystic ovarian syndrome (PCOS)
- Obesity
- Microvascular disease (retinopathy, neuropathy, or nephropathy)
- Macrovascular disease (stroke, PAD, and CAD)

Associated Symptoms

- Hypertension
- Hyperlipidemia
- Gender and ethnicity-specific increased waist circumference
- The stigmata of PCOS (menstrual irregularities, hirsutism, acne, and alopecia)
- Acanthosis nigricans (see **Image.** Acanthosis Nigricans)
- The stigmata of one of several genetic syndromes that include insulin resistance syndromes
- Type A or type B insulin resistance syndrome

Evaluation

The gold standard for measuring insulin resistance is the hyperinsulinemic-euglycemic glucose clamp technique. This is a research technique in which a fasting, non-diabetic patient is placed on a high-rate constant infusion of insulin to suppress hepatic glucose production; the blood glucose is frequently monitored while a concomitant 20% dextrose solution is given at varying rates to regulate the blood glucose in the euglycemic range. The amount of glucose required to reach a steady state reflects the exogenous glucose disposal needed to compensate for hyperinsulinemia. Insulin resistance calculation is based on whole-body glucose disposal and body size.[31]

The associated risks and complexity of the glucose clamp method limit its clinical usefulness. As a result, multiple surrogate markers for insulin resistance have been developed and tested. The homeostatic model assessment for insulin resistance (HOMA-IR), based on fasting glucose and fasting insulin levels, is a widely utilized measure of insulin resistance in clinical research. Other measures based on fasting insulin include HOMA2, the Glucose to Insulin Ratio (GIR), and the Quantitative Insulin Sensitivity Index (QUICKI). The McAuley Index utilizes fasting insulin and triglycerides. Post-glucose challenge tests, done after an overnight fast, measure insulin and

glucose response to a 75-gram glucose load. Methods include the Matsuda Index and Insulin Sensitivity Index (ISI).[8][9][10][32][33][34][35][36]

Other surrogate markers involve triglycerides alone or in relation to HDL cholesterol. Patients with prediabetes and triglycerides greater than or equal to 150 g/dL were more likely to have insulin resistance. The triglyceride/HDL ratio is correlated with insulin resistance in individuals who identify as White. In general, a ratio greater than 3.0 is associated with insulin resistance. More specifically, a ratio greater than or equal to 3.5 in males and greater than or equal to 2.5 in females indicates insulin resistance. These correlations do not hold up in individuals who identify as Black.[11][37]

Measures of insulin resistance have not been integrated into clinical guidelines. As a result, the presence of insulin resistance is generally inferred from the clinical presentation. Metabolic syndrome (MetS) and insulin resistance syndrome (IRS) are considered to be clinical indicators of insulin resistance.

Multiple criteria for metabolic syndrome (MetS) exist. In 2009, a joint scientific statement harmonizing criteria for MetS was released.[38] MetS is identified by the presence of 3 or more of the following diagnostic cut points:

- A waist circumference of 32” to 40” based on gender and ethnicity
- Elevated triglycerides greater than or equal to 150 mg/dL or on medication to treat hypertriglyceridemia
- Reduced HDL less than 40 mg/dL in males or less than 50 mg/dL in females
- Elevated blood pressure greater than or equal to 130 mm Hg systolic or greater than or equal to 85 mm Hg diastolic or on antihypertensive medication
- Elevated fasting glucose greater than or equal to 100 mg/dL or on a glucose-lowering agent

The American College of Endocrinology identifies specific physiologic abnormalities that increase IRS risk.[39] These abnormalities include:

- Impaired glucose tolerance or impaired fasting glucose
- Abnormal uric acid metabolism
- Dyslipidemia (increased triglycerides, decreased HDL-C, or small, dense LDL)
- Hemodynamic changes such as elevated blood pressure
- Prothrombotic factors (PAI-1, fibrinogen)
- Markers of inflammation (eg, C-reactive protein, white blood cell count)
- Endothelial dysfunction

Other factors include the following:

- Body mass index (BMI) greater than or equal to 25 kg/m^2
- Diagnosis of CVD, PCOS, NAFLD, or acanthosis nigricans
- A family history of T2D, hypertension, or CVD
- Sedentary lifestyle
- Non-white ethnicity
- Age older than 40 years

Treatment / Management

Intensive Lifestyle Intervention

Lifestyle intervention represents the cornerstone of treatment for insulin resistance. Dietary intervention should include a combination of calorie restriction and high glycemic index carbohydrate reduction. Physical activity improves both calorie expenditure and insulin sensitivity in muscle tissue.[40][41][42]

Individuals with insulin resistance are at high risk of developing T2D. The Diabetes Prevention Program and its Outcomes Study (DPP & DPPOS) demonstrated that lifestyle intervention was a significant and cost-effective intervention for diabetes prevention in high-risk adults.[24][26] These interventions include:

- Dietary therapy with sodium reduction, fat reduction, calorie restriction, and attention to the glycemic index of foods
- Education, support, and personalized programs
- A 7% weight loss reduced the onset of T2D by 58%
- DPP included a metformin arm which reduced the onset of T2D by 31%

Specific Pharmacological Interventions for Blood Glucose Management

While no medications are FDA approved for the treatment of insulin resistance, general approaches include the following:

- Metformin is a common first-line therapy for medication treatment of T2D and is approved for use in PCOS. The DPP & DPPOS study showed that the combination of metformin and lifestyle interventions was medically useful and cost-effective. Despite the concerns about using metformin in mild to moderate renal dysfunction, several organizations, including the American Geriatric Society and the Kidney Disease Improving Global Outcomes guidelines, endorse use as long as the GFR exceeds 30.[24][26][43][44][45]
- Glucagon-like peptide one (GLP-1) receptor agonists stimulate the GLP-1 receptors in the pancreas, thereby increasing insulin release and inhibiting glucagon secretion. The use of GLP-1 agonists is associated with weight loss, which may reduce insulin resistance. Liraglutide and semaglutide are FDA-approved for the treatment of T2D and obesity. Another agent, tirzepitide, is a dual GLP-1 and gastric inhibitory polypeptide (GIP) agonist, has effects similar to semaglutide, and is also FDA-approved for treating T2D.[46][47][48]
- Sodium-glucose cotransporter 2 (SGLT2) inhibitors increase urinary glucose excretion, thereby reducing plasma glucose levels and exogenous insulin requirements. The use of SGLT2 inhibitors has also been associated with weight loss, which may reduce insulin resistance.[49][50]
- Thiazolidinediones improve insulin sensitivity and glucose control by increasing insulin-dependent glucose disposal in skeletal muscle and adipose tissue and decreasing hepatic glucose output. Though effective, associated secondary weight gain and fluid retention, with associated cardiovascular concerns, limit their use.[51][52]
- Dipeptidyl peptidase-4 (DPP-4) inhibitors prolong the activity of endogenous GLP-1 and GIP by preventing their breakdown.[4]

Surgery

Surgical intervention in the form of gastric sleeves, banding, and bypass is available for qualified individuals with obesity. The excess fat loss associated with bariatric surgery improves insulin

sensitivity. The results of the STAMPEDE trial provide good evidence of the benefit of bariatric surgery on T2D.[53][54][55]

Differential Diagnosis

- Lipodystrophy (acquired, localized or generalized): Loss of adipose tissue that results from either genetic or acquired causation and can result in the ectopic deposition of fat in either hepatic or muscular tissue[56]
- Polycystic ovarian syndrome (PCOS)
- Obesity: Excess body weight is categorized as overweight (BMI of 25 to 29.9), class I obesity (BMI of 30 to 34.9), class II obesity (BMI 35.0 to 39.9), and class III obesity (BMI greater than 40)[57]
- Hypertension: The most recent ACC/AHA guidelines for the diagnosis of hypertension include systolic pressure greater than or equal to 130 mm Hg or diastolic pressure greater than or equal to 80 mm Hg[58]
- Hypertriglyceridemia: Elevated triglyceride levels (greater than or equal to 150 mg/dL)
- Type 1 diabetes
- Type 2 diabetes
- Other forms of glucose intolerance (impaired fasting glucose, impaired glucose tolerance, and gestational diabetes)

Prognosis

The prognosis of insulin resistance depends on the subset of the disease, the severity of the disease, underlying pancreatic beta-cell function, the heritable susceptibility of the patient to the secondary complications from insulin resistance, and individual response to appropriate therapy. The outcomes range from mildly insulin-resistant, asymptomatic individuals to those with catastrophic cardiovascular or cerebrovascular events and their resulting morbidity and mortality.

Statistically, coronary artery disease is the leading cause of mortality in the US, with diabetes as seventh. The common basis for diabetes and much of the resultant vascular disease is insulin resistance. Additional mortality from insulin resistance occurs in the less common manifestations of the disease, including genetic syndromes and fatty deposition diseases. Finally, substantial morbidity manifests with the loss of reproductive function and associated features of PCOS.

Mitigation for the disease exists. Increased clinical awareness enables early diagnosis and treatment. Improved understanding of the disease process has resulted in more targeted, multi-faceted therapies. Efforts to attain and maintain a healthy weight through improved dietary intake and increased physical activity can reduce insulin resistance and prevent associated complications. More generalized lay recognition can increase the efficacy of preventative care, with the hope of an eventual downturn in epidemic obesity and resultant insulin resistance.[59]

Complications

Most of the complications from insulin resistance are related to the development of vascular complications.

The microvascular disease manifests as retinopathy, nephropathy, and peripheral neuropathy. In the central nervous system, dementia, stroke, mood disturbance, and gait instability may occur. Cardiac microvascular disease can manifest as angina, coronary artery spasm, and cardiomyopathy. Renal microvascular disease is a significant cause of chronic kidney disease, renal failure, and dialysis. Ophthalmological small vessel disease is a leading cause of

retinopathy and visual impairment. Macrovascular disease, secondary to insulin resistance, causes PAD, CAD, and CVA.

Non-alcoholic fatty liver disease (NAFLD) is intricately related to insulin resistance and T2D. Patients with T2D have a 2-fold increased risk for NAFLD. With an increasing worldwide prevalence and incidence in children, NAFLD should be of great concern to clinicians treating patients with insulin resistance.[19][20]

Deterrence and Patient Education

Primary, secondary, and tertiary prevention have distinct roles in managing insulin resistance.

Primary prevention promotes public education regarding the importance of regular health monitoring. A healthy diet and increased activity level can prevent or delay the onset of insulin resistance, metabolic syndrome, and diabetes, along with the associated complications. The emphasis on behavior modification and a sustainable lifestyle is critical for long-term weight management.

Secondary prevention includes laboratory screening for insulin resistance, diabetes, and further subspecialist referral to manage the early intervention for insulin resistance. The DPP & DPPOS studies demonstrate the benefits of lifestyle change and the use of metformin to prevent progression from pre-diabetes to T2D. [24][26]

Public acceptance of tertiary prevention, such as intensive medical intervention and bariatric surgery for weight reduction, can lead to decreased morbidity and mortality associated with the consequent complications of insulin resistance.

Pearls and Other Issues

Intensive lifestyle intervention should be the first line of therapy for patients with metabolic syndrome or insulin resistance syndrome. The benefits of exercise cannot be understated in treating patients with insulin resistance. Barriers to exercise should be discussed, and a well-formulated plan, including moderate-intensity cardiovascular exercise like walking, should be provided in accordance with the physical activity guidelines. Discussion of dietary modification following the dietary guidelines should also be provided with individualization to the patient's preferences, with particular attention to reducing sugar, refined grain products, and high glycemic index carbohydrates.

For patients with T2D, insulin resistance, and hyperinsulinemia, consider treatment with agents to improve insulin sensitivity or contribute to weight loss, like metformin, GLP-1 receptor agonists, GLP-1/GIP receptor agonists, and SGLT2 inhibitors. [60][61][62]

Enhancing Healthcare Team Outcomes

Over the past few decades, the incidence of insulin resistance has skyrocketed primarily due to our lifestyle and the rising incidence of obesity. Without treatment, the condition is associated with numerous complications, including fatal cardiac events. Therefore, the management of insulin resistance is best done with an interprofessional team. The consultations and coordination of care most indicated for the treatment of insulin resistance include:

- Obesity medicine specialist: medical management for obesity treatment
- Bariatric surgeon: bariatric surgery is effective for obesity treatment in individuals who satisfy the criteria for surgery
- Endocrinology: early and aggressive management of T2D, hyperlipidemia, and PCOS
- Cardiology and cardiac surgery: management of the cardiovascular complications of insulin resistance

- Gastroenterology: early detection and treatment of NAFLD
- Neurology: management of the cerebrovascular and peripheral neurologic complications of insulin resistance
- Vascular surgery: surgical management of both carotid artery disease and PAD
- Nurse diabetic educator: assists the clinician in educating the patient on diabetes prevention
- Dietitian: educates the patient on a healthy diet, including low-carbohydrate approaches
- Physical therapist: educates the patient on how to increase physical activity safely
- Pharmacist: educates the patient on the importance of medication adherence, instructing the patient on the proper use of medications, potential drug-drug interactions, and side effects
- Social worker: assist the patient with the necessary support and finances to obtain treatment
- Psychologist: provide behavioral therapy support

There is limited evidence in favor of continuous glucose monitoring (CGM). Remote monitoring for healthcare teams shows benefits in the management of T2D. More research is needed to show the effects of CGM on those with prediabetes or insulin resistance without T2D.

The key to the management of insulin resistance is encouraging lifestyle changes. Dietary intervention should include a combination of calorie restriction and reduction of high glycemic index carbohydrates. Physical activity improves both calorie expenditure and insulin sensitivity in muscle tissue.[63][64]

Outcomes

The outcomes of well-managed insulin resistance are good for those who remain adherent to therapy. Unfortunately, many patients struggle with adherence to therapy, with consequential progression to T2D and subsequent risk of adverse cardiac or CNS events. Early identification and intervention with an interprofessional team approach are essential in managing these patients.[62][65]

Review Questions

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Figure

Acanthosis Nigricans Contributed by Scott Dulebohn, MD

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