EDUCATIONAL COMMENTARY – INSULIN RESISTANCE AND 1,5-ANHYDROGLUCITOL

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Learning Outcomes

On completion of this exercise, the participant should be able to

• identify the causes of insulin resistance;
• list risk factors associated with insulin resistance/type 2 diabetes mellitus;
• describe complications associated with insulin resistance/type 2 diabetes; and
• explain the benefits and limitations of using 1,5 anhydroglucitol testing in the management of diabetes.

Introduction

With the worldwide prevalence of diabetes mellitus increasing at alarming rates during the past few decades, diabetes prevention, diagnosis, and management continues to be a leading public health concern. The Centers for Disease Control and Prevention estimates that the number of diagnosed cases of diabetes in the United States quadrupled between 1980 and 2014. In 2012, 29.1 million Americans, 9.3% of the US population, had diabetes. An additional 1.4 million Americans are diagnosed as having diabetes each year. Type 2 diabetes accounts for approximately 90% to 95% of all cases diagnosed in adults. In 2012, direct medical costs and loss of productivity as a result of diabetes and its complications totaled $245 billion. Diabetes was the seventh-leading cause of death in the United States in 2014, listed as the cause of death on 76,488 of the more than 2.6 million death certificates filed that year. Understanding the causes and risk factors for insulin resistance and type 2 diabetes is essential for prevention, and laboratory testing is necessary to manage glycemia and prevent chronic complications.

Insulin Resistance and Type 2 Diabetes

Insulin, a small protein produced by the beta (β) cells of the islets of Langerhans in the pancreas, is the principal hormone in carbohydrate metabolism and regulation of plasma glucose levels. In response to elevated plasma glucose concentrations, the pancreas releases insulin, which then binds to and activates cell membrane receptors. Activation increases uptake of glucose by fat, liver, and muscle cells, decreases glycogenolysis (breakdown of glycogen to glucose), and increases glycolysis, lipogenesis, and glycogenesis (conversion of glucose to glycogen). Insulin resistance is defined as the reduced biological response to normal concentrations of insulin. Studies have shown a strong association between insulin resistance and hypertension, elevated triglycerides, and increased free fatty acids. Insulin resistance
has commanded a substantial amount of attention in recent years owing to its relationship with obesity and the development of prediabetes, type 2 diabetes, and vascular disease.

Type 2 diabetes mellitus, previously referred to as non–insulin dependent or adult-onset diabetes, is the most common form of diabetes in adults. It is generally associated with adult onset, abdominal obesity, milder symptoms, and lower risk for ketosis than type 1 diabetes. Patients with type 2 diabetes exhibit classic symptoms of hyperglycemia: excessive thirst, polyuria, and blurred vision. In type 1 diabetes, immune destruction of the pancreatic β cells lowers production of insulin; type 2 diabetes is characterized by varying degrees of insulin resistance and loss of pancreatic β-cell function. In type 2 diabetes, insulin resistance causes increased plasma glucose concentrations, with the resulting stimulation of the pancreatic β cells. The β cells are unable to maintain normal glucose concentrations and become increasingly fatigued and eventually unresponsive, unable to produce enough insulin to prevent hyperglycemia. The resulting hyperglycemia exacerbates the degree of β-cell dysfunction, continuing the vicious cycle.5

Causes

There are numerous causes of insulin resistance. Many of these are believed to be influenced by both genetic and environmental factors, making the exact mechanism poorly understood. Upper-body obesity is considered the most common condition associated with insulin resistance. It is thought to contribute to insulin resistance via a decrease in the sensitivity of β cells to glucose concentrations and a decrease in glucose uptake by tissues. Enlarged adipose cells lead to high serum free fatty acid concentrations, which inhibit insulin secretion. Adipocytes secrete cytokines such as tumor necrosis factor, which stimulate inflammatory responses and also contribute to insulin resistance.

Although less common, several inherited conditions that contribute to insulin resistance have also been identified. Insulin resistance may be the result of mutations in insulin receptors (eg, Donohue syndrome [leprechaunism] and Rabson-Mendenhall syndrome) and mutations in postbinding signaling. Other major causes include anti-insulin antibodies, anti–insulin receptor antibodies, metabolic syndrome, stress, infection, hypertension, polycystic ovary syndrome, and excess counterregulatory hormones (eg, glucocorticoids, catecholamines, growth hormone, and placental lactogen).6

Associated Risk Factors

Several risk factors associated with insulin resistance, and the impending threat of type 2 diabetes, can be controlled or even eliminated through lifestyle changes. Obesity (body mass index [BMI] ≥ 30 kg/m²), hypertension, cigarette smoking, age, family history, and hyperlipidemia all increase risk for the
development of insulin resistance and type 2 diabetes. One of the most significant of these risk factors is obesity. Obesity is exacerbated by a sedentary lifestyle and a diet high in red meats, high-fat dairy products, sugary beverages, and sweets. Moderate exercise and a diet high in fruits, vegetables, and whole grains have been shown to reduce obesity and improve glycemic control, even in persons previously diagnosed as having type 2 diabetes. Several large studies have proven that cigarette smoking impairs insulin sensitivity and increases postprandial plasma glucose concentrations. Smoking has also been associated with an increase in the accumulation of abdominal fat. Risk for the development of type 2 diabetes increases with age, and individuals with a family history of type 2 diabetes have a much higher risk for developing it themselves. Prediabetes and type 2 diabetes are more prevalent among certain ethnic groups. Native Americans and Alaskan Natives have the highest prevalence of type 2 diabetes in the United States, followed by non-Hispanic blacks, Hispanics, Asian Americans, and, finally, non-Hispanic whites.

Complications

Complications of insulin resistance and type 2 diabetes can affect many parts of the body and can be severe. Chronic complications include both microvascular and macrovascular disorders. Microvascular disorders often present in the kidneys (nephropathy), eyes (retinopathy), and peripheral nerves (neuropathy). Diabetes is the leading cause of end-stage renal disease and adult-onset blindness in the United States. An increase in macrovascular atherosclerosis can result in gangrene, amputation, stroke, and myocardial infarction. More than 60% of all lower-limb amputations not associated with a traumatic event are the result of diabetes.

Treatment

The goal of treatment in patients with insulin resistance and/or type 2 diabetes is to prevent chronic complications that result from elevated plasma glucose concentrations. In patients whose insulin resistance is a direct effect of obesity, this is primarily done through diet and lifestyle modifications. Patients are encouraged to increase physical activity and lose weight to reduce abdominal fat and increase insulin sensitivity. When lifestyle changes are not successful in controlling hyperglycemia, oral hypoglycemic agents that enhance insulin action are often prescribed. Medications like metformin hydrochloride and thiazolidinediones can be used to limit the vascular complications associated with hyperglycemia.

Laboratory Testing

By assessing glycemia and glycemic control, the clinical laboratory plays a crucial role in the management of diabetes. Fasting and random plasma glucose testing show the clinician a patient’s
current glucose concentration, but they do not measure glycemic control, that is, how well the patient’s glucose concentrations have been maintained over a period of time. Several laboratory tests can be used to evaluate glycemic control by measuring time-averaged glucose concentrations. These assays include glycated hemoglobin (HbA1c), glycated albumin, fructosamine, and 1,5-anhydroglucitol (1,5 AG). Glycated hemoglobin is considered the gold standard for the measurement of glycemic control and is widely used in clinical laboratories. It is formed when glucose attaches nonenzymatically to the N-terminal valine of the β chain of normal adult hemoglobin. Its rate of formation reflects the mean plasma glucose concentrations that the erythrocytes have been exposed to over their life span and is therefore proportional to plasma glucose concentrations. Although HbA1c has no fasting requirements and is an excellent measure of long-term (2 to 3 months) control, it provides an average of plasma glucose concentrations and does not reflect short-term changes, fluctuations in glycemic control, or postprandial plasma glucose concentrations. HbA1c measurements can also be problematic in persons with decreased red blood cell life span, as in those with hemoglobinopathies and anemias. Glycated albumin and fructosamine measurements can be useful alternatives to HbA1c in the presence of decreased red blood cell life span. Similar to HbA1c, glycated albumin and fructosamine assays measure glucose that has attached nonenzymatically to plasma proteins. These tests are useful for obtaining a more short-term picture of glycemic control, as they reflect glucose control over the previous 2 to 3 weeks. Although useful in patients with abnormal red blood cell turnover, fructosamine and glycated albumin are unsuitable for use in some patient populations. Significant changes in plasma protein concentrations as a result of liver disease, malnutrition, malabsorption, acute disease states, and protein loss in the kidneys or gastrointestinal tract can lead to erroneous results.5

In light of these limitations, several studies have looked at 1,5 AG testing as an alternative to the aforementioned glycemic control measurements. Isolated from the Polygara amara plant in 1888 and chemically defined in 1943, 1,5 AG is a dietary monosaccharide similar in structure to glucose.8 It is freely filtered and reabsorbed by the kidneys and is found in high, stable concentrations in the blood of individuals with normal glucose levels. Renal reabsorption of 1,5 AG is competitively inhibited by urinary glucose. When plasma glucose concentrations exceed the renal threshold, the high amounts of glucose block tubular reabsorption of 1,5 AG, and plasma 1,5 AG levels fall, in inverse relation to the elevated plasma glucose concentrations. This relationship allows for the identification of rapid changes in hyperglycemia. Studies have shown that 1,5 AG accurately reflects glycemic control in patients with diabetes over the previous 48 hours to 2 weeks, correlates strongly with postprandial plasma glucose concentrations, and may be a useful alternative to HbA1c in diabetes management.

Commercial assays for 1,5 AG have been used clinically in Japan since 1991. In 2003, the United States Food and Drug Administration approved the use of 1,5 AG testing for short-term glycemic monitoring.
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under the trade name GlycoMark™. GlycoMark™ is an enzymatic, colorimetric assay for use on automated chemistry analyzers with either serum or EDTA plasma specimens. The assay first pre-treats the sample with glucokinase (GK) for the conversion of glucose to glucose-6-phosphate (G-6-P) to prevent glucose interference in the coupling reactions. Pyranose oxidase is added to oxidize 1,5 AG resulting in the generation of hydrogen peroxide. The addition of peroxidase allows for the colorimetric determination of hydrogen peroxide generation.

Although 1,5 AG testing is not affected by hemoglobinopathies like HbA1c testing, GlycoMark™ assays are not without limitations. Low 1,5 AG values can be seen with stage 4 or 5 kidney disease, advanced cirrhosis, severe hypertriglyceridemia, and steroid therapy. Low 1,5 AG concentrations are also seen in pregnancy due to varying renal thresholds and in diabetic patients undergoing treatment with INVOKANA® as it prevents reabsorption of 1,5 AG in the kidneys. Increased 1,5 AG concentrations are seen in patients receiving intravenous hyperalimentation and with the administration of several Chinese medications such as Polygala Tenuifolia and Senega syrup. Interest in 1,5 AG quantification is increasing but it remains a less commonly ordered laboratory test. GlycoMark™ is not routinely available in clinical laboratories at the present time but can be ordered from several large reference laboratories.

Summary

Rising rates of obesity and diabetes have prompted significant research to better understand the mechanisms associated with insulin resistance. Although genetic factors play a key role in insulin resistance, lifestyle modifications can have a positive impact on the prevention of type 2 diabetes. Laboratory tests play an important part in the diagnosis and management of the disease, but only when the ordering clinician understands their use and limitations. When used appropriately, laboratory tests can accurately monitor glycemia and glycemic control, lowering the risk for chronic microvascular and macrovascular complications.

References


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