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CHOLESTECH LDX™

Glucose and Diabetes

The purpose of this System Brief is to provide information about diabetes, applications for glucose testing and proper glucose testing on the Cholestech LDX System.

DIABETES MELLITUS

Diabetes mellitus is a complex disorder of carbohydrate, fat and protein metabolism. It is primarily a result of a defect in the secretion or action of insulin, the hormone that facilitates and controls the use of glucose in the cells. Because of the deficiency of insulin, people with diabetes have an impaired tolerance to glucose that leads to a number of short-term and long-term complications.

The long-term complications of diabetes mostly involve vascular problems. Microvascular problems include peripheral neuropathy (nerve damage), nephropathy (kidney disease) and retinopathy (retinal damage, causing decreased vision and blindness). The macrovascular manifestations of diabetes involve accelerated arteriosclerosis that can result in both ischemic heart disease and peripheral vascular disease.

The short-term dangers of diabetes can be life-threatening. They are related to a difficulty controlling insulin and glucose levels and primarily occur in patients taking insulin. When there is insufficient insulin, which is needed for glucose metabolism, the body burns fat for energy. This results in ketoacidosis (accumulation of ketones and acid in the blood) that can lead to diabetic coma. Hypoglycemia (low blood sugar) is common in patients receiving insulin, because of difficulties in adjusting their insulin levels. Unless treated promptly by administering glucose, this hypoglycemia can result in coma and death.

THE DIFFERENT TYPES OF DIABETES

Type 1 (previously referred to as insulin-dependent diabetes mellitus [IDDM] or juvenile-onset diabetes) comprises about 5 percent of all cases.[1] Diagnosis of type 1 diabetes usually occurs when the patient is between 10 and 30 years, but the disease can occur at any age. Though the exact mechanism is unknown, in type 1 diabetes, an environmental, genetic or autoimmune trigger causes the individual's own immune system to attack the pancreas, resulting in destruction of the insulin-producing cells. As a result, patients with type 1 diabetes are dependent on treatment with insulin to control glucose and other energy metabolism. Because insulin is a potent hormone, type 1 patients often experience wide and unstable fluctuations in blood glucose concentrations. Control of type 1 diabetes is facilitated by frequent monitoring of blood glucose levels.

Type 2 (previously referred to as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes) comprises 90 to 95 percent of all cases.[1] Type 2 diabetes is thought to involve several distinct or combined defects that result in either insulin deficiency, where there is an insufficient amount of insulin to maintain "normal" glucose physiology, or insulin resistance, where the response to insulin by the cells of the body is blunted.

Diabetes during pregnancy, or gestational diabetes, is a condition where the affected woman's glucose impairment is detected for the first time during the pregnancy. Gestational diabetes occurs in 2% to 10% of all pregnancies and women who have had it have a 35% to 60% risk of developing diabetes within 10 to 20 years.[1] Careful monitoring of the diabetic pregnancy is critical, not only for the mother's well-being, but also because of the numerous complications involving the fetus, such as premature birth, high birth weight, fetal lung immaturity and hypoglycemia, that are known to occur with poor maternal glucose control.

One to five percent of diagnosed diabetes results from other conditions, including genetic causes, following surgery or due to infections, medications or other illnesses. These often resolve with successful treatment of the primary condition.

THE PUBLIC HEALTH IMPACT

The Centers for Disease Control and Prevention (CDC) estimated that 25.8 million Americans had diabetes in 2010.[1] This is a prevalence of 8.3% in the population overall. But diabetes disproportionately affected 26.9% of those who are ≥65 years. Prevalence and incidence of diabetes have been rising in the United States, and in 2010, 1.9 million people ≥20 years were newly diagnosed with diabetes. Diabetes was the seventh leading cause of death of Americans in 2007.

Prediabetes is a term that describes people whose blood sugar is higher than what is considered normal, but not high enough to be diagnosed with diabetes. People with prediabetes have an increased risk of developing type 2 diabetes, heart disease and stroke. The CDC estimated that 79 million Americans had prediabetes in 2010.[1]

DIAGNOSIS

The demonstration of significant hyperglycemia (high blood glucose) is the key to the diagnosis of diabetes mellitus. For type 1 diabetes, the diagnosis is usually simple, since hyperglycemia appears abruptly, is severe and is accompanied by serious metabolic derangements (e.g., metabolic ketoacidosis). It is in type 2 diabetes that early diagnosis becomes troublesome. The risk for the later development of microvascular disease makes it important to identify patients with type 2 diabetes early.

The American Diabetes Association (ADA) has three criteria for diagnosing diabetes by measuring blood glucose[2]:

1. Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.
2. 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test (OGTT).
3. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

Beginning in 2011, the ADA added an additional diagnostic criterion based upon measurement of hemoglobin A_{1c} (A1C), a test that is considered a measure of the average blood glucose level over the preceding 2–3 months. The diagnostic criterion is an A1C ≥ 6.5%.

In the absence of unequivocal hyperglycemia, results for any of these criteria should be confirmed by repeat testing.

PREDIABETES

Prediabetes is defined by measures of FPG, an OGTT or A1C.[2] Impaired fasting glucose (IFG) is an FPG of 100–125 mg/dL (5.6–6.9 mmol/L). Impaired glucose tolerance (IGT) is a 2-hour plasma glucose following an OGTT of 140–199 mg/dL (7.8–11.0 mmol/L). A1C of 5.7–6.4% is also identified as prediabetes.[2]

Healthy ("normal") levels are below those considered to be prediabetes: FPG <100 mg/dL (5.6 mmol/L), 2-hour plasma glucose following an OGTT <140 mg/dL (7.8 mmol/L), or an A1C <5.7%.

SCREENING

The ADA recommends testing to detect type 2 diabetes and assess risk for future diabetes in asymptomatic adults of any age who are overweight or obese (BMI ≥25 kg/m²) and who have one or more additional risk factors for diabetes.[2] Absent these risk factors, testing should begin at age 45 years:

- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Women who delivered a baby weighing >9 lb or were diagnosed with gestational diabetes
- Hypertension (≥140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
- Women with polycystic ovarian syndrome (PCOS)
- A1C ≥5.7%, IGT or IFG on previous testing
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- History of cardiovascular disease

The ADA recommends testing asymptomatic children for type 2 diabetes beginning at age 10 years or the onset of puberty if they are overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height) and have two of the following risk factors[2]:

- Family history of type 2 diabetes in first- or second-degree relative
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, PCOS or small-for-gestational-age birth weight)
- Maternal history of diabetes or gestational diabetes during the child's gestation

FPG, an OGTT or A1C are appropriate for screening. If tests are normal, repeat testing carried out at 3-year intervals is reasonable.[2]

GLUCOSE TEST METHODS

There are a variety of glucose testing methods. Most laboratory methods employ enzymes that react with glucose and ultimately form a colored product. The glucose concentration is proportional to the amount of color formed. The Cholestech LDX glucose (GLU) test uses a glucose oxidase enzyme that catalyzes the oxidation of glucose to gluconolactone and hydrogen peroxide. A second reaction produces color that is detected by the photometer inside the Cholestech LDX analyzer.

COLLECTING AND HANDLING OF SAMPLES

Capillary whole blood (i.e., fingerstick) samples should be tested on the Cholestech LDX System within eight (8) minutes of collection. Use venous whole blood (collected using heparin as the anticoagulant) within 30 minutes of collection. When blood is drawn and permitted to clot and stand uncentrifuged at room temperature, the average decrease in glucose is 5–7% (5–10 mg/dL) per hour.[3] This decrease is the result of glycolysis (metabolism of glucose by the red blood cells). Plasma removed from cells after moderate centrifugation still contains white blood cells that also metabolize glucose.

Glucose levels measured on the Cholestech LDX System may show significant differences from a capillary sample drawn at the same time and tested on a handheld glucose meter. On a handheld glucose meter, the glucose is measured in whole blood. The red blood cells have a solid phase that does not contain glucose and thus has a dilution effect on the glucose concentration, causing lower glucose results. Plasma glucose levels will be approximately 10–12% higher than whole blood glucose levels measured on a handheld glucose meter.[3]

Blood glucose concentration may vary depending on the source of the sample: arterial, capillary or venous. Arterial blood has the highest glucose levels, followed by capillary blood, then venous blood. In the fasting state, capillary glucose levels are 2–5 mg/dL higher than venous levels. After eating, glucose levels in capillary blood may be 20–70 mg/dL higher than levels in venous blood.[3] These differences must be taken into account when comparing non-fasting capillary
glucose results on the Cholestech LDX System with results from serum drawn at the same time and measured on a comparison method.

FPG AND OGTT WITH THE CHOLESTECH LDX SYSTEM

Measurement of glucose in a venous or fingerstick whole blood sample using any Cholestech LDX test cassette including GLU is done in plasma following separation of the red blood cells. It is therefore possible to adhere to ADA recommendations and test FPG in whole blood samples from a fasting individual using the Cholestech LDX System.

While there is no GLU-only Cholestech LDX test cassette, it is possible to use the GLU on a cassette such as TC•GLU to perform an OGTT using venous whole blood. Because glucose will rise more in capillary than in venous blood following the oral glucose load, an OGTT can only be conducted using a venous sample.

For further information on diabetes:

- American Diabetes Association
  www.diabetes.org
- Centers for Disease Control and Prevention
  www.cdc.gov/diabetes
- National Institute of Diabetes and Digestive and Kidney Diseases
  http://diabetes.niddk.nih.gov/

1. CDC. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, CDC, 2011.
2. ADA. Standards of medical care in diabetes–2011. Diabetes Care 2011; 34(Suppl 1):S11-S61.
3. Sacks DB. Carbohydrates. In: Burtis CA et al (ed). Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 4th ed. St. Louis, MO: Elsevier, Inc.; 2006 p. 868-869.

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