Diagnosis Modalities

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LEARNING OBJECTIVES

1. Discuss the use of fasting blood glucose, HbA1c and oral glucose tolerance testing for screening and diagnosis of diabetes mellitus.
2. Differentiate screening procedures for type 1 and type 2 diabetes mellitus.
3. Describe testing for gestational diabetes.
4. Identify various autoantibodies and their association with type 1 diabetes mellitus.

ABBREVIATIONS: HbA1c - Hemoglobin A1c, ADA - American Diabetes Association, OGTT - Oral glucose tolerance test, G6P - Glucose-6-phosphate ICA - Islet cell antibody, GADA - Glutamic acid decarboxylase antibody, IA-2A - Islet antigen-2 antibody, IAA- Insulin autoantibody

INDEX TERMS: Fasting Blood Glucose, HbA1c, Oral Glucose Tolerance Test, Screening for Type 1 Diabetes Mellitus, Gestational Diabetes Testing

Clin Lab Sci 2016;29(2):111-113

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INTRODUCTION

Proper testing for both type 1 and 2 diabetes mellitus is vital in the diagnostic process, monitoring the progression of the disease and determining the efficacy of treatment. According to the American Diabetes Association (ADA), in the absence of indisputable hyperglycemia, the diagnosis of diabetes mellitus should always be confirmed with repeat testing.[1] Timing of testing, as well as the specific tests ordered, may vary. The same basic tests, however, are utilized across most facilities.[2] Fasting plasma glucose, hemoglobin A1c (HbA1c) and oral glucose tolerance testing (OGTT) are all recommended for both screening and diagnosis of diabetes mellitus.[2]

Various Testing Procedures

The test often used to detect diabetes mellitus is a measurement of fasting blood glucose levels. After the patient has fasted overnight (at least 8 hours), blood sugar levels are measured using a methodology similar to that for random blood sugar levels. Fasting blood sugar levels of less than 100 mg/dL (~5.5 mmol/L) are normal. Levels between 100 and 125 mg/dL (~5.5-6.9 mmol/L) are considered prediabetic; levels above 125 mg/dL (~6.9 mmol/L) are considered diabetic in nature. Results hinge on the patient's compliance with fasting instructions prior to testing.[3]

HbA1c levels need to be measured as well. HbA1c is measured in percentages and reflects the average blood glucose levels over the past 3 months. HbA1c may be measured at any time, regardless of the last meal ingested.[4] An International Expert Committee and the American Diabetes Association have declared hemoglobin A1c measurements accurate enough to be used for the diagnosis of diabetes mellitus.[5] Normal HbA1c readings are below 5.7% (~39 mmol/mol). HbA1c readings between 5.7% and 6.4% (~39-46 mmol/mol) indicate prediabetes and the need for intervention to prevent the development of full diabetes mellitus. HbA1c readings of 6.5% (~48 mmol/mol) or above indicate diabetes.[4]

An OGTT for diabetes mellitus also may be ordered for confirmation of a diagnosis of diabetes mellitus. A high-glucose drink is ingested and blood sugar levels are measured at set time intervals. A blood sugar level of less than 140 mg/dL two hours after ingesting the high-glucose substance is considered normal, with levels

between 140 and 199 mg/dL indicating a prediabetic state. Blood sugar levels of 200 mg/dL or higher two hours after glucose ingestion is considered diabetic. OGTT, however, is rarely used anymore for the diagnosis of diabetes in non-pregnant individuals.[6]

Routine screening for type 1 diabetes mellitus is not suggested, as there are no treatment guidelines for patients who are not displaying symptoms yet.[7] Screening for type 2 diabetes mellitus, however, is critical for early detection in order to implement intervention strategies. Screening should begin at age 45 and be repeated every 3 years if results are within normal ranges. Screening for type 2 diabetes mellitus should begin earlier in overweight adults (body mass index equal to or above 25 kg/m^2) with one or more of the following symptoms: history of cardiovascular disease, physically inactive, first-degree family member with diabetes, high risk ethnicity including African American, Latino, Asian American, Native American or Pacific Islander, women who were diagnosed with gestational diabetes mellitus or delivered a baby over 9 lbs., hypertension, decreased HDL levels, increased triglyceride levels, suffer from another condition with insulin resistance, women with polycystic ovarian syndrome and those with HbA1c greater than or equal to 5.7% (~39 mmol/mol). The most appropriate tests for screening are fasting plasma glucose, HbA1c and a 2-hour 75 gram oral glucose tolerance test.[1]

Testing for gestational diabetes is not completely standardized and varies among various testing facilities. Those with a high risk for developing gestational diabetes (possessing several risk factors) may be tested at the first prenatal visit. Those of average risk often are tested between weeks 24 and 28 of the second trimester of the pregnancy.[8] The 2-hour OGTT is used for both screening and diagnostic purposes. Following an 8-hour fast, a plasma glucose level is drawn. A fasting level of 92 mg/dL or higher is considered diagnostic of gestational diabetes. Next, a drink containing 75 grams of glucose is ingested and plasma glucose levels are measured at 1 and 2 hours. A 1-hour plasma glucose level of greater than or equal to 180 mg/dL or a 2-hour level of 153 mg/dL or higher are both considered indicative of gestational diabetes. Only one of the three plasma glucose levels mentioned needs to be elevated to make a diagnosis of gestational diabetes mellitus. [3] Blood glucose levels of the mother will be checked again at six to twelve weeks post-delivery. If blood glucose levels have returned to normal, no further monitoring is required. If blood glucose levels are still elevated, further testing may be considered to determine whether the diabetes has persisted in the mother post-pregnancy.[8]

Glucose may be monitored using one of two common methodologies which are glucose oxidase or hexokinase method. Glucose oxidase uses glucose oxidase enzymes to oxidize glucose to gluconate and subsequent formation of hydrogen peroxide. The hydrogen peroxide that is formed is used to measure the use of oxygen in the reaction. Peroxidase is used by hydrogen peroxide to oxidize a chromogenic indicator. This colored complex will cause changes in absorbance that will be directly proportional to the amount of glucose contained in the sample.[3]

The hexokinase methodology is also known as the glucose-6-phosphate dehydrogenase method. Hexokinase is used to catalyze the reaction between ATP and glucose in the sample resulting in glucose-6-phosphate (G6P) and ADP. G6P is then oxidized to 6-phosphogluconate by converting glucose-6-phosphate dehydrogenase NAD^+ to NADH and H^+. Similar to the glucose oxidase methodology, absorption is used to determine final glucose measurements, as the amount of NADH produced is directly proportional to the amount of glucose in the original sample.[9]

Various autoantibodies have been associated with type 1 diabetes mellitus. The presence of these autoantibodies may offer an explanation for the presentation of type 1 diabetes mellitus. The four most common autoantibodies include islet cell antibodies (ICA), glutamic acid decarboxylase antibodies (GADA), islet antigen-2 antibodies (IA-2A) and insulin autoantibodies (IAA). Autoantibody testing is performed when ascertaining the cause of type 1 diabetes mellitus as being autoimmune or due to another cause.[10] The presence of ICA is commonly tested by indirect immunofluorescence. Radioimmunoassay methodologies are used to test for IAA, GADA and IA-2A autoantibodies. The presence of any of the autoantibodies indicates that the cause of type 1 diabetes mellitus is autoimmune in nature. If an asymptomatic individual possesses the autoantibodies listed previously, an increased risk for developing type 1 diabetes mellitus exists. [11] The presence of a family history of type 1 diabetes in conjunction with

the autoantibodies IAA, GADA, IA-2A show a positive correlation with the occurrence of type 1 diabetes. The rate of progression to diabetes in multiple islet autoantibody-positive relatives, however, shows significant variation among individuals.[12]

Other autoimmune disorders occur with higher frequency in individuals with type 1 diabetes mellitus. For this reason, it is vital to test patients with type 1 diabetes mellitus for additional autoimmune disorders. Complications from these disorders often lead to significant decrease in the quality of life for patients and in some cases may be fatal. Type 1 diabetics are at an increased risk for other autoimmune disorders such as Hashimoto thyroiditis, Grave's disease, Addison's disease, pernicious anemia and celiac disease, the presence of which can be determined by proving the existence of particular autoantibodies.[13]

Utilizing proper testing is critical to properly diagnose both type 1 and 2 diabetes mellitus. Screening is crucial for early detection of type 2 diabetes mellitus, but it is not recommended for type 1 diabetes mellitus.[14,15] HbA1c test, fasting plasma glucose testing, and OGTT are all utilized for both screening and diagnosis of type 2 diabetes mellitus.[2] OGTT also can be useful in the diagnosis of gestational diabetes mellitus. Overall, HbA1c is the most favorable test and is now the gold standard for the diagnosis of diabetes mellitus.[3]

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