Clinical Chemistry Trainee Council
Pearls of Laboratory Medicine
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Title: Diagnosis of Diabetes

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Slide 1: Title Slide

Slide 2: Categories of Diabetes

Diabetes is defined by the American Diabetes Association (ADA) as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Several pathogenic processes are involved in the development of diabetes, and the disease is classified into several categories. However, the vast majority of cases of diabetes fall into two broad etiopathogenetic categories, type 1 and type 2. Type 1 diabetes mellitus (T1DM), accounting for 5-10% of those with diabetes, is caused by an absolute deficiency of insulin secretion. It results predominantly from an autoimmune destruction of the islet cells of the pancreas with consequent insulin deficiency. Patients with Type 2 diabetes mellitus (T2DM), which accounts for ~90-95% of those with diabetes, have both insulin resistance and inadequate insulin action. Gestational diabetes mellitus, which resembles T2DM diabetes more than T1DM, develops during ~7% of pregnancies and usually remits after delivery and is a risk factor for the development of T2DM later in life. Other types of diabetes are rare and will not be discussed here.

Slide 3: Prevalence

Diabetes is a common disease. According to the ADA, 25.8 million children and adults in the United States, or 8.3% of the population, have diabetes. 18.8 million people carry the diagnosis of diabetes and 7.0 million are undiagnosed.

Slide 4: Hyperglycemia: Symptoms and Sequela

Symptoms of hyperglycemia include polyuria, polydipsia, sometimes with polyphagia, blurred vision, and weight loss, which is characteristic of T1DM but not T2DM. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or hyperosmolar hyperglycemic state (HHS). Other findings in T1DM can include extreme hunger, fatigue, irritability, while other findings in T2DM can include slow healing of cuts and bruises, and tingling or numbness in the hands and feet.

Long-term complications of diabetes include retinopathy with the potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy and vascular diseases with risk of foot ulcers and amputations, and macrovascular diseases, such as cardiac disease and stroke. Susceptibility to certain infections may accompany chronic hyperglycemia. And, although rare, Mauriac syndrome, or the impairment of growth observed in T1DM, may also be seen.

Slide 5: Diagnostic Criteria

The diagnosis of diabetes is established by identifying the presence of hyperglycemia. Over the last 30 years, the diagnostic criteria have been modified to better identify individuals at risk for diabetic complications. Currently, any one of the following criteria described on this slide is diagnostic for the presence of diabetes. According to the ADA, if any one of these 3 criteria is met, confirmation by repeat testing is necessary to establish the diagnosis. Repeat testing to confirm hyperglycemia must be carried out on a separate day. In the absence of unequivocal hyperglycemia with symptoms, two abnormal blood glucose levels on a single day do not constitute diabetes. Repeat testing is not required for patients who have unequivocal hyperglycemia, for example ≥200 mg/dL with symptoms consistent with hyperglycemia. The World Health Organization (WHO) and the International Diabetes Federation (IDF) recommend either a fasting plasma glucose test or a 2-hour postload glucose test that uses the same cutoffs as the ADA.

In 2009, an International Expert Committee, which comprised members appointed by the ADA, the European Association for the Study of Diabetes, and the IDF, recommended that diabetes be diagnosed by measurement of Hb A1c, which reflects long-term blood glucose concentrations. The test should be performed in a laboratory using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP). Almost all Hb A1c methods are certified by the NGSP. The ADA and the WHO have endorsed the use of Hb A1c for diagnosis of diabetes. Because of this, emphasis has been placed on manufacturers to improve the accuracy and precision of Hb A1c assays. The National Academy of Clinical Biochemistry (NACB) recommends for a single Hb A1c method, the goal should be an interlaboratory CV less than 3%.

Slide 6: Gestational Diabetes Mellitus

The new revised ADA recommendations for the diagnosis of gestational diabetes will significantly increase the prevalence of this condition, primarily because only one abnormal value, not two, is sufficient to make the diagnosis. Additional well-designed clinical studies are needed in order to determine the optimal intensity of monitoring and treatment of women that are diagnosed by these new criteria that would not have met the prior definition of gestational diabetes.

Slide 7: Increased Risk for Diabetes

It is recognized that there is an intermediate group of individuals whose glucose levels do not meet criteria for diabetes, yet are higher than those considered normal. These people are defined as having impaired fasting glucose which is demonstrated as glucose concentrations of 100 to 125 mg/dl, or impaired glucose tolerance, which is demonstrated as glucose concentrations of 140 to 199 mg/dl 2-hours post glucose challenge. It should be noted that impaired fasting glucose and impaired glucose tolerance have been termed "pre-diabetes." Pre-diabetes is not a diagnosis but is a descriptive term to indicate that an individual is at increased risk for T2DM.

In 2003, an ADA Expert Committee report reduced the lower fasting plasma glucose cut point to define impaired fasting glucose from 110 mg/dl to 100 mg/dl. However, the WHO and many other diabetes organizations did not adopt this change.

Compared to the fasting glucose cutpoint of 100 mg/dl, a Hb A1c cutpoint of 5.7% is less sensitive but more specific and has a higher positive predictive value to identify people at risk for later development of diabetes. It has been shown that a 5.7% cutpoint has a sensitivity of 66% and specificity of 88% for the identification of subsequent 6-year diabetes incidence. It should be noted that for all three measurements, risk is continuous, so that as Hb A1c rises, the risk of diabetes rises disproportionately.

Slide 8: Preananalytical Considerations

If a fasting glucose is used, the patient must fast for at least eight hours, an unattractive choice because of the challenge for a physician or a laboratory to enforce or for a patient to adhere to. In addition, there is both intra- and inter-individual biologic variability that confound glucose-result interpretation. This observed variability demonstrates that the concentration of a fasting individual's glucose is not the same when measured on different days. Further, because fasting plasma glucose is higher in the morning than in the afternoon, this measurement may show even greater variability if samples are obtained at different times of the day after the patient's eight-hour fast. There is also the issue of sample stability. Decreases in glucose concentrations in whole blood ex vivo are due to glycolysis. The rate of glycolysis, reported to average 5- 7% per hour, varies with the glucose concentration, temperature, leukocyte count, and other factors. Such decreases in glucose concentration will lead to missed diabetes diagnoses in the large proportion of the population who have glucose concentrations near the cutpoints for diagnosis of diabetes. Some important variables that may influence the results of bedside glucose monitoring include changes in hematocrit, altitude, environmental temperature or humidity, hypotension, hypoxia and high triglyceride concentrations, as well as various drugs. Furthermore, most glucose meters are inaccurate at very high or very low glucose concentrations. Another important factor is variation in results among different glucose meters.

Hb A1c results can be either falsely increased or falsely decreased, depending on the particular hemoglobinopathy and Hb A1c assay method used. However, if an appropriate method is used, Hb A1c can be measured accurately in the vast majority of individuals heterozygous for Hb variants. For a summary of published studies, visit the NGSP website. If altered erythrocyte turnover interferes with the relationship between mean blood glucose and Hb A1c values, or if a suitable assay method is not available for interfering Hb variants, alternative non–Hb-based methods for assessing long-term average glycemia, such as the fructosamine assay, may be useful. Hb A1c results are not affected significantly by acute fluctuations in blood glucose concentrations, such as those occurring with illness or after meals; however, age and race reportedly influence Hb A1c. These effects on Hb A1c values remain to be determined.

Slide 9: Discordant Results between Different Tests

Just as there is less than 100% concordance between the fasting plasma glucose and 2-hour plasma glucose tests, there is not full concordance between Hb A1c and either glucose-based test. Further research is needed to better characterize those patients whose glycemic status might be categorized differently by two different tests obtained close together in time. Such discordance may arise from

measurement variability, change over time, or because Hb A1c, fasting plasma glucose, and postchallenge glucose each measure different physiological processes. When two different tests are available in an individual and the results are discordant, the test whose result is above the diagnostic cut point should be repeated and the diagnosis made on the basis of the confirmed test.

Slide 10: Point-of-Care Testing for the Diagnosis of Diabetes

Although most portable meters use whole blood and have been programmed to report a plasma glucose concentration, the imprecision of the current meters precludes their use from the diagnosis of diabetes. Although attractive because of convenience, ease, and accessibility, testing with portable meters would generate many false positives and false negatives.

For Hb A1c, the ADA cautions that point-of-care devices for measuring Hb A1c should not be used for the diagnosis of diabetes. Although several point-of-care HbA1c assays are NGSP certified, the test is waived in the United States, and proficiency testing is not necessary. Therefore, no objective information is available concerning their performance in the hands of those who measure Hb A1c in patient samples. A recent evaluation revealed that few point-of-care devices that measure Hb A1c met acceptable analytical performance criteria. Currently, only NGSP-certified Hb A1c methods performed in clinical laboratories should be used to diagnose diabetes.

Slide 11: Genetic and Autoimmune Markers

Genetic markers are currently of limited clinical value in the diagnosis of diabetes; however, mutational analysis is rapidly emerging for classifying diabetes in the neonate and in young patients with a dominant family history of diabetes. Type 1, or autoimmune diabetes, is strongly associated with HLA-DR and HLA-DQ genes. While specific HLA haplotypes, alone or in combination, may account for up to 90% of children and young adults with T1DM, these haplotypes may be present in 30%–40% of the Caucasian population, and may therefore be necessary but not sufficient for disease. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers.

Markers of the immune destruction of the insulin producing β-cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to GAD65, and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β. One and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected. However, when used it is recommended that antibody assays should have a specificity >99%, proficiency testing should be documented, multiple autoantibodies should be assayed, and sequential measurement should be performed. These strategies will reduce false-positive and false-negative results. While the presence of multiple islet cell autoantibodies is associated with a >90% risk of T1DM, the positive predictive value of a single islet cell autoantibody is low. Although autoantibody testing is currently of limited clinical value in the diagnosis of diabetes, islet autoantibody testing may be beneficial when T1DM and T2DM cannot readily be distinguished. Distinguishing T1DM and T2DM is very important as aggressive insulin replacement therapy at onset may prolong beta-cell function in T1DM (Shah SC, Malone JI, Simpson NE. A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. N Engl J Med 1989;320:550-4).

Slide 12: Points to Remember

There are several key points to remember about the diagnosis of diabetes. Diabetes can be diagnosed using measurement of plasma glucose and Hb A1c concentrations. Satisfying a single diagnostic criterion does not confirm a diagnosis unless it is repeated on a separate day or coincides with unequivocal hyperglycemia. Interpretation of glucose and Hb A1c results may be affected by analyte instability and alteration of erythrocyte turnover, respectively. Currently, point-of-care assays are not sufficiently precise or accurate enough to be used for diagnostic purposes. Lastly, genetic markers and autoantibody testing are currently of limited clinical value in the diagnosis of diabetes.

Slide 13: References