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USE OF GLYCATED HEMOGLOBIN (HBA1C) TESTING IN THE DIAGNOSIS OF DIABETES: A SYSTEMATIC REVIEW

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ABSTRACT Early detection of diabetes is of great clinical importance in order to prevent or delay its micro- and macrovascular complications. That is why, the largest diabetes associations continue their search for the most accurate, sensitive and specific, reliable and reproducible diagnostic assay.ADA, the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes have recommended to consider the use of glycated hemoglobin (HbA1c) testing in the diagnosis of diabetes.

KEYWORDS : ADA, IDF, OGTT, NGSP, WHO

INTRODUCTION:

The formation of Hb A1c occurs in humans at a slow rate as posttranslational modification of Hb throughout the life of the red cell Hb A1c is formed by the nonenzymatic reaction of glucose with the amino-terminal valine residues of the - chains of Hb A Glucose binds reversibly to Hb as an aldimine, or Schiff base. This adduct then undergoes an Amadori rearrangement to form a stable ketoamine. The formation of the stable ketoamine is irreversible. The concentration of Hb A1c depends on several factors. The major determining factors are the life span of the red blood cell (RBC) and how long the Hb molecule is exposed to glucose. It is also thought that the permeability of the RBC to glucose influences the amount of glycation. In general, it is accepted that Hb A1c concentrations represent average glucose levels over the preceding 8 to 12 weeks.

Hemoglobin A1c Assays

Immunoassay and HPLC: Quantified by Antibody specific for the glycation epitope of A1c (turbidimetry) Spectro photometric measurement of HbA1c calculated A1c/Total Hb. It was noticed shortly after the DCCT and UKPDS trials that Hb A1c results reported in clinical laboratories for the same blood sample could differ considerably among methods. Therefore, standardization efforts were established on both the national and international levels. In 1996, the NGSP was initiated to standardize test results among laboratories to DCCT equivalent values. In 1997, the International Federation of Clinical Chemistry (IFCC) formed a committee to develop a higher-order reference method and reference materials for Hb A1c analysis. Although the clinical values obtained with assays standardized with the reference IFCC method correlate well (r = 0.999) with NGSP values, the absolute Hb A1c values reported differ by 1.5%–2.0% Hb A1c. The relationship between the NGSP network and IFCC networks was evaluated and a master equation was developed to document this relationship (NGSP = [0.9148 * IFCC] + 2.152). Because of this, emphasis has been placed on manufacturers to improve the accuracy and precision of Hb A1c assays. Almost all Hb A1c methods in clinical laboratories in the United States are certified by the NGSP. These standardization efforts have helped to lead the ADA and the World Health Organization (WHO) to include Hb A1c as the preferred test for the diagnosis of diabetes.

DISCUSSION

Advantages of A1C testing:

No need for fasting or timed samples. Relatively unaffected by acute (e.g., stress or illness related) perturbations in glucose levels Currently used to guide management and adjust therapyA1C is a more stable biological index than FPG, as would be expected with a measure of chronic glycemia levels compared with glucose concentrations that are known to fluctuate within and between days. *Disadvantage of HbA1c*: This is precluded, however, in patients who have underlying anemias, hemolysis, vitamin B12 or folate deficiencies, hemoglobinopathies, or Hb variants, all of which may alter the lifespan of the RBC and therefore the accumulated concentration of Hb A1c in the RBC Main Non-Glycemic Factors Affecting HbA1c Measurement the A1C test should not be used to diagnose type 1 diabetes, gestational diabetes, cystic fibrosis related diabetes. The A1C test may give false results in people with certain conditions the glucose challenge test or the oral glucose tolerance test (OGTT) are used to check for gestational diabetes usually between 24 and 28 weeks of pregnancy. Most cases of type 1 diabetes, particularly in children and adolescents, are diagnosed by the classical symptoms of polyuria, polydipsia, polyphagia, unexplained weight loss, and a casual glucose >200 mg/dl. *Elevates HbA1c*: Iron deficiency anemia, Chronic kidney disease, Vitamin B12deficiency, Severe hypertriglyceridemia, Aging, Black race, Asian race, Hispanic ethnicity, Hemoglobinopathies, Genetic factors. Reduces HbA1c**:** Pregnancy, Hemolytic anemia, Erythropoietin therapy, Iron/vitamin B12 replacement, Chronic liver disease, Antiretrovirals, Hemoglobinopathies Genetic factors. *Low HbA1c:* Nor is there a single, clear definition of what value of Hb A1c is considered low. In two studies, <4.0% is used as a cutoff In these three population-based studies, a low Hb Ab1 was associated with increased risk of mortality and liver disease, despite the fact the low values are more often observed in young, healthy individuals. A stronger association has been shown between low Hb A1c and liver disease, presumably due to aberrant glucose and insulin metabolism, decreased erythropoiesis and protein synthesis, and/or decreased red cell survival. Addition to liver disease, a low Hb A1C may be the result of any cause of increased red cell turnover/decreased survival, such as hemoglobinopathy, excessive bleeding, or red cell membrane defect. Consistent hypoglycemia is also a cause of how Hb A1c, either through extreme dietary control or overuse of antidiabetic medications. Finally, lab error may also result in inappropriately low Hb A1c. In cases where Hb A1c is suspected to be unreliable, alternatives include fructosamine, 1,5-anhydroglucitol, or oral glucose tolerance tests. *Diagnosing diabetes: American Diabetes Association (ADA)*Hemoglobin A1c (HbA1c): > or =6.5%.*Therapeutic goals for glycemic control (ADA)*Adults: Goal of therapy: < 7.0% HbA1c. Action suggested: > 8.0% HbA1c.Pediatric patients: Toddlers and preschoolers: < 8.5% (but >7.5%) School age (6-12 years): < 8%.Adolescents and young adults (13-19 years): < 7.5%.

The ADA Clinical Practice Recommendations now recommend using HbA1c to diagnose diabetes using a NGSP-certified method and a cutoff of HbA1c ≥6.5%. POC assay methods are not recommended for diagnosis. He National Diabetes Education Program and major clinical diabetes

organizations including the American Association of Clinical Endocrinologists, the American Society of Clinical Endocrinologists and the American Diabetes Association recommend use of the term A1C or "the A1C test" to describe HbA1c in clinical practice. Large volume of data from diverse populations has now established an A1C level associated with an increase in the prevalence of moderate retinopathy and provides strong justification for assigning an A1C cut point of 6.5% for the diagnosis of diabetes. This decision was aided by the parallel decision to recommend effective prevention strategies for the highest at-risk group with an A1C between 6.0 and 6.5%.The landmark nine-year Diabetes Control and Complications Trial (DCCT), completed in 1993, showed that the risk for development and progression of the chronic complications of diabetes is closely related to the degree of glycemic control, as measured by hemoglobin A1c (HbA1c).There was a 60% reduction in development or progression of diabetic retinopathy, nephropathy, and neuropathy between the intensively treated group where the mean Hb A1c achieved was approximately 7% and the standard group's mean Hb A1c of 9% over an average of 6.5 years. It has long been known that increasing amounts of Hb A1c correlate with diabetes complications. Regression models from the Diabetes Complication and Control Trial (DCCT), quantified these relationships. United Kingdom Prospective Diabetes Study (UKPDS), that ultimately placed the importance of a target Hb A1c value for diabetic patients in efforts to reduce their risk of complications as a result of the disease. If A1C testing is not possible owing to patient factors that preclude its interpretation (e.g., hemoglobinopathy or abnormal erythrocyte turnover) or to unavailability of the assay, previously recommended diagnostic measures (e.g., FPG and 2HPG) and criteria should be used.

In children and adolescents, A1C testing is indicated when diabetes is suspected in the absence of the classical symptoms or a plasma glucoseconcentration 200 mg/dl (11.1mmol/l).To avoid misdiagnosis or missed diagnosis, the A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) assay. Point-of-care A1C testing for diabetes screening and diagnosis should be restricted to U.S. Food and Drug Administration–approved devices at laboratories proficient in performing testing of moderate complexity or higher by trained personnel. Marked discordance between measured A1C and plasma glucose levels should raise the possibility of A1C assay interference and consideration of using an assay without interference or plasma blood glucose criteria to diagnose diabetes. In conditions associated with an altered relationship between A1C and glycemia, such as hemoglobinopathies including sickle cell disease, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes. The ADA guidelines recommend that A1C testing be performed at least twice yearly in patients who have achieved stable glycemic control. For those patients who are not at goal or for whom therapy recently changed, quarterly A1C testing is recommended. Additionally, A1C targets of $<7\%$ (compared with 8%) were not associated with decreased deaths (either all-cause or cardiovascular-related deaths) or reductions in macrovascular events over a 5- to 10-year treatment period.

CONCLUSION

International Expert Committee recommended the use of HbA1c test to diagnose diabetes with the threshold of $\geq 6.5\%$, and the ADA affirmed this decision. Patients who have an HbA1c between 5.7 and 6.4 are considered at increased risk for developing diabetes in the future. (The terms prediabetes, impaired fasting glucose, and impaired glucose tolerance will eventually be phased out by the ADA to eliminate confusion. The A1C assay is an accurate, precise measure of chronic glycemic levels and correlates well with the risk of diabetes complications.

Conflict of Interest: No conflict of interest

Abbreviations:

ADA - American Diabetic Association
IDF - International Diabetes Federation
OGTT -Oral Glucose Tolerance Test
NGSP – National Glycohemoglobin Standardization Program

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