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Diagnosis of Diabetes Mellitus Using Glycated Hemoglobin (A1c): The Nigerian Perspective

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Background: Diabetes is an international public health issue. International Expert Committee recommended an alternative diagnostic index testing for diabetes using glycated (A1c).
Objective: This study aimed to determine whether A1c test should be used for diagnosing diabetes mellitus in Nigeria.
Methods: By assessing the strength of WHO recommendation and the feasibility and resources implication in Nigeria setting.
Results: The strength of the recommendation was rated as good by the quality of evidence but not applicable at population level due to high cost and scarce availability of A1c test.
Conclusion: The adoption of A1c test as a diagnostic test at present is problematic. Therefore plasma glucose measurements should still be adopted for the diagnosis of Diabetes Mellitus while the A1c assay could be used for monitoring diabetes.

Keywords: Diabetes; A1c test; plasma glucose measurement; Nigeria.

1. INTRODUCTION

Diabetes Mellitus is a metabolic disorder characterized by chronic hyperglycemia and disturbances of carbohydrates, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Diabetes has been declared an International Public health

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issue because it has a major and deleterious impact on both individual and national productivity [1].

Before 2009, the diagnosis of diabetes were based on plasma glucose values either casual plasma glucose value ≥ 200 mg/dL (11.1 mmoi/L) with classic symptoms of diabetes, fasting plasma ≥126 mg/dL (7 mmol/L) or 2hr postload plasma glucose ≥200 mg/dL during the oral glucose tolerance test (OGTT) [2].

Owing to the inconvenience of measuring fasting plasma glucose levels or performing an OGTT and day-to-day variability in glucose, an alternative to glucose measurements for the diagnosis of diabetes has long been sought. HbA1c has now been recommended by an international committee and by America Diabetes Association (ADA) as a means to diagnose diabetes [3].

A report published in 2009 by an international Expert Committee on the role of A1C in the diagnosis of diabetes recommended that A1C can be used to diagnose diabetes and that the diagnosis can be made if the A1C level is ≥ 6.5% [3]. The committee also recommendation that Diagnosis should be confirmed with a repeat A1C test unless clinical symptoms and plasma glucose level, ≥11.1 mmol/L (200 mg/dL) are present in which case further testing is not required. Expert committee recommended that persons with A1C level between 6.0 and 6.5 were at particularly high risk and might be considered for diabetes prevention interventions.

Furthermore, WHO agreed that each country should decide whether it is appropriate for its own circumstances. The aim of this article is to systematically review the recommendations by analyzing the advantages and disadvantages of using A1C to diagnose diabetes in a multiethnic population such as Nigeria.

2. GLYCATED HEMOGLOBIN (A1C)

Glycated hemoglobin was initially identified as abnormal hemoglobin in patients with diabetes over 40years [4]. After that discovery, numerous small studies were conducted correlating it to glucose measurements resulting in the idea that A1C could be used as an objective measure of glycemic control. The A1C -Derived Average Glucose (ADAG) study included 643 participants representing a range of A1C levels. It established a validated relationship between A1C and average glucose across a range of diabetes types and patients population [5]. A1C was introduced into clinical use in the 1980s and subsequently has become a cornerstone of clinical practice [6] A1C reflects average plasma glucose over the previous eight to twelve weeks [7]. It can be performed at any time of the day and does not require any special preparation such as fasting. These properties have made it the preferred test for assessing glycemic control in people with diabetes. More recently there has been substantial interest in using it as a diagnostic test for diabetes and as a screening test for persons at high risk for diabetes.

3. EVIDENCE FOR THE USE A1C

In conformity with introducing a new diagnostic assay, reliable estimates of clinical sensitivity and specificity have been obtained from both literature and clinical outcome studies. The relationship between A1C and prevalent retinopathy is similar to that of plasma glucose [8]. This relationship was originally reported in the Pima Indians [9] and has also been observed in several populations including Egyptians [10], in the NHANES study in the USA [11], and in Japanese [12]. Overall, the performance of A1C has been similar to that of fasting or 2h plasma glucose. For all three measures of glycemia, the value above which the prevalence of retinopathy begins to rise rapidly has differed to some extent between studies. Although A1C gives equal or almost equal sensitivity and specificity to glucose measurement as a predictor of prevalent retinopathy it is not available in many parts of the world and in general, it is not known which is better for predicting microvascular complications.

It is unclear whether A1C or plasma glucose is better for predicting the development of retinopathy, but a recent report from Australia has shown that a model including A1C for predicting incident retinopathy is as good as or possibly better than one including FPG [13].

4. ANALYTICAL PERFORMANCE CONSIDERATION

In evaluation of the performance characteristics of a candidate method, precision, accuracy, analytical range, detection limit, and analytical specificity are of prime importance.

There are aspects of the measurement of A1C that are problematic. Although in some laboratories the precision of A1C measurement is similar to that of plasma glucose, global consistency with both assays remains a problem.

Whether it is the glucose or A1C assay that is used, consistent and comparable data that meet international standards are required. This is starting to happen in many countries but obviously is still not standard across Nigeria within the six geopolitical zones of Nigeria, it is expected that results for glucose and A1C should be consistent between laboratories. This is yet to be achieved across the country.

The National Glycohemoglobin Standardization Program (NGSP) [14] was established following the completion of the Diabetes complications and control Trait (DCCT) for many years it was the sole basis for improved harmonization of A1C assays. More recently, the International Federation of Clinical Chemists (IFCC) established a working group on A1C in an attempt to introduce an International Standardization Program [15]. An important part of this effort was establishment of reference method procedures for A1C. Currently, both the NGSP and the IFCC base their evaluations on reference method procedures that have further enhanced the harmonization of A1C assays across manufacturers. In USA, the college of American Pathologists (CAP) has mandated more stringent criteria for individual assays to assigned values for materials provided in CAP proficiency programme [16].

The WHO consultation reviewed the evidence on the relationship between A1C and prevalent incident microvascular complications. This shows that A1C and glucose cut-off points associated with prevalent and incident microvascular complications in available studies. In view of the outcome of this evidence and of the advances in technology over recent years, WHO agreed that A1C may be used to diagnose diabetes providing that appropriate conditions apply, i.e. standardized assay, low coefficient of variability and calibration against IFCC Standards.

5. ADVANTAGES AND DISADVANTAGES OF ASSAYS FOR GLUCOSE AND A1C

5.1 Advantages for A1C as Diagnostic Tool

A1C has a greater pre-analytical stability than blood glucose because glucose assays require some stringent requirements e.g. fasting for FPG and administration of glucose load before collection of specimen for 2hr-PG. Fasting is not needed for A1C assessment and no acute perturbations (e.g. stress, diet, exercise, and smoking) affect A1C. Indeed, A1C can be measured anytime, irrespective of fasting or feeding. Even when preparation to glucose testing is optional, plasma glucose values may still be misleading as a result of improper processing of blood. Stringent requirements are necessary for rapid processing, separation and storage of plasma or serum minimally at 4℃.

Biological variability of A1C is lower than that of FPG. When the same subjects have two assessments of the available glucose-related parameters, the correlation is stronger among the individual A1C measurements than among FPG or 2-h PG measurements. The coefficients of variation of A1C FPG and 2h.PG are 3.6, 5.7, and 16.6% respectively [17]. This reflects of course both biological and analytical variability. Studies have shown that two required assessments of FPG to diagnose diabetes can provide quite unreliable information, whereas A1C, especially if measured twice as recommended, provides more robust clinical information [18]. Standardization of A1C assay is not inferior to standardization of glucose assay. A great effort was made in the US and other countries to make reproducible A1C across laboratories with an effective standardization program. Such a programme is to provide more reliable information to physicians who monitor diabetic patients [19]. The standardization is expected to minimize laboratory biases and is a prerequisite to use A1C not only for monitoring but also for diagnosing diabetes. However, this level of standardization is yet to be achieved in our laboratories.

Although it is generally believed that glucose assay is highly reproducible across laboratories, this is not true. A recent survey conducted in 6,000 US laboratories clearly documented a significant bias of glucose assessment in as many as 4.1% of them, yielding a misclassification of glucose tolerance in 12% of subjects [20]. Therefore, the argument that A1C cannot be used for diabetes diagnosis because of poor standardization is no longer tenable.

A1C captures chronic hyperglycaemia better than two assessments of fasting or 2-h oral glucose tolerance test plasma glucose. Hyperglycemia is regarded as the biochemical hallmark of diabetes. However, FPG and 2-h PG indicate a moment of a single day. Therefore, a diagnostic tool gauging chronic rather than spot hyperglycemia is certainly preferable.

5.2 Disadvantages for A1C as Diagnostic Tool

Diabetes is clinically defined by high blood glucose and not by glycation of proteins. If A1C is considered the primary diagnostic tool, this will lead to a major change in the pathophysiological consideration defining diabetes. Subsequently, A1C is a poor marker of important pathophysiological abnormalities featuring diabetes.

Humans spend most of their time in postprandial or post absorptive states that are deranged in diabetes. A1C is a poor indicator of what occurs in the postprandial state. A1C captures only chronic hyperglycemia, but it will miss acute hyperglycemia. Normal blood glucose levels 2hr after glucose load indicates a good β-cell capacity, whereas high 2-h OGTT glucose levels document an impairment of β-cell function [21]. Recent study has shown that A1C is a weaker correlate of insulin resistance and insulin secretion in studies of metabolism compared with FPG and 2-h PG [22]. Diabetes diagnosis based on A1C misses a large proportion of asymptomatic early cases of diabetes that can only be identified by the OGTT. A1C sensitivity is inferior compared with fasting blood glucose at the population level. Also people with impaired glucose tolerance (IGT) in whom the efficacy of diabetes prevention has been unequivocally proven [23] cannot be detected by A1C.

A1C is better associated with chronic complications than FPG. Research findings have shown that in the general population, FPG is a poor marker of future cardiovascular disease (CVD) events, whereas 2-h OGTT and A1C are good predictions [24,25]. Therefore, mciroangiopathic complications (retinopathy) are associated with A1C as strongly as with FPG and A1C is better related to cardiovascular disease than FPG. Individual susceptibility to glycation might be an additional benefit of A1C assessments. In addition, A1C can be used concomitantly for diagnosing and initiating diabetes monitoring. Using the same biomarker for diagnosing and monitoring diabetes might be an advantage.

Epidemiological studies carried out in the general population showed that A1C and plasma glucose (FPG and/or 2-h OGTT) identify partially different groups of diabetic subjects [26]. A1C ≥6.5% identifies approximately 30-40% of previously undiagnosed patients with diabetes [27]. A larger percentage is detected by FPG (approximately 50%) and 2-h PG (approximately 90%). The ethnic differences in A1C compared with glucose measurements were also well demonstrated in the diabetes prevention program population [28]. Nigeria is a multiethnic nation which is at a disadvantage of using A1C as a diagnostic assay. A1C -based diagnosis for diabetes has substantially different consequences for diabetes prevalence across ethnic groups and populations. A1C has significant differences in various ethnic groups which are poorly understood and characterized.

A1C is affected by several interferences; severe illness may shorten red-cell life and artificially reduce A1C values. Abnormal hemoglobins significantly interfere with A1C assay [29]. Abnormal hemoglobins are not uncommon in many regions of the world including Nigeria. Also there are several clinical conditions that influence erythrocyte turnover (e.g., malaria, chronic anemia, major blood loss, hemolysis, urea, pregnancy, smoking and various infections) that are responsible for misleading A1C data.

Standardization of A1C assay is poor, even in Western Countries, and standardization of glucose assay would be easier to implement. Using the same biomarker for diagnosing and monitoring diabetes might have negative effects. In Nigeria, A1c is still not readily available and its cost is so high that is unprofitable to prefer A1c over simple and inexpensive glucose measurements in diagnosing of diabetes.

6. CONCLUSION

The overall performance of A1c has been similar to that of fasting or 2-h plasma glucose. A1c gives equal or almost equal sensitivity and specificity to glucose measurement as a predictor of prevalent retinopathy. In addition, the use of A1c can avoid the problem of day-to-day variability of glucose values and importantly avoids the need for the person to fast and to have preceding dietary preparations. Obviously these are advantages for early identification and treatment of diabetes which have been strongly advocated over the years.

Despite the utility and convenience of A1c compared with measures of plasma glucose for diagnosing diabetes, there is the need to balance these against its drawbacks in Nigeria situation. In Europe and USA, HbA1c is a common tool for the diagnosis of diabetics. However, in Nigeria,

HbA1c is not widely used because of the cost and unavailability of the assay. Despite being recognized as a valuable tool in diabetes management. In addition the A1c assay is not currently well enough standardized in laboratories for its use to be recommended at this time. Considering our own circumstances, based on cost, availability of equipment, population characteristics, lack of national quality assurance system and affordability of individuals, it is inappropriate to recommend the use of A1C for diagnosing diabetes in Nigeria at this time.

Instead, we should ensure that reliable blood glucose measurements are generally available at all levels of our health care while A1C should be reserved for monitoring purpose.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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