REVIEW ARTICLE

Could glycated hemoglobin be used as a diagnostic tool in diabetes mellitus?

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KEY WORDS

diabetes mellitus, diagnostic tests, glycated hemoglobin

ABSTRACT

The diagnosis of carbohydrate metabolism disturbances is often delayed in a number of individuals due to unsatisfactory reliability and inconvenience of the currently available diagnostic tests. Clinical and economic benefits of an early diagnosis of diabetes are generally acknowledged. However, it is estimated that almost 30% of subjects with diabetes are not aware of the disease, and moreover, they already have long-term complications of chronic hyperglycemia at diagnosis. That is why, an International Expert Committee recommended considering the use of glycated hemoglobin (HbA_{1c}) testing in the diagnosis of this deleterious disease in nonpregnant individuals. This paper discusses the advantages and disadvantages of current methods used in the diagnosis of diabetes.

Introduction The prevalence of diabetes, mainly type 2, has been increasing rapidly over the past decades, thus becoming a major clinical and public health concern. It is estimated that approximately 250 million people suffer from diabetes worldwide and by 2025, the number will reach 300 million.[1] This common and serious condition is associated with reduced life expectancy and considerable morbidity. Moreover, several lines of evidence suggest that the prevalence of undiagnosed diabetes is similar to that of diagnosed diabetes.[2]

Diabetic retinopathy or microalbuminuria are observed in a substantial proportion of patients with newly diagnosed type 2 diabetes. Vascular complications of hyperglycemia are sometimes present even in individuals with impaired fasting glycemia (IFG) or impaired glucose tolerance (IGT). It is well known that these 2 stages of glucose intolerance, called prediabetes, are associated with a high probability of progression to type 2 diabetes.[3]

The greatest clinical challenge in subjects with glucose metabolism abnormalities is the prevention of chronic, hyperglycemia-related, cardiovascular complications, many of which can be life-threatening. This goal can only be achieved when the impaired glucose regulation is diagnosed at an early stage and intensive management of hyperglycemia is implemented as soon as possible.[4] Therefore, the American Diabetes Association (ADA) recommends that testing to detect type 2 diabetes is considered in adults without symptoms who are overweight or obese and have 1 or more additional risk factors for diabetes. In those without the above risk factors, testing should begin at the age of 45.[5]

Type 1 diabetes is usually easy to diagnose because of a typical clinical onset with relatively acute, extreme elevations in glucose concentrations accompanied by typical signs and symptoms. Unlike type 1, type 2 diabetes is usually diagnosed relatively late, when many patients already have evidence of chronic complications.[6]

Lower detection of diabetes is associated with the inconvenience of the currently available diagnostic tests, both for patients and clinicians. Therefore, these tests are often not optimally used in everyday clinical practice. That is why, the ADA, the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes have recommended to consider the use of glycated hemoglobin (HbA_{1c}) testing in the diagnosis of diabetes. It is believed that this marker will help not only in the clinical assessment of metabolic control of diabetes but also in identifying new cases of this disease, especially in asymptomatic subjects.[6]

Diagnosis of diabetes and prediabetes according to the current standards

At present, there are

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several methods used in the diagnosis of diabetes established by the ADA in 1997 and updated in 2003. Individuals with severe thirst, polyuria, weight loss, and with a random blood glucose level ≥200 mg/dl (≥11.1 mmol/l) can be easily diagnosed as already having diabetes.

In those with a random plasma glucose level of ≥100 mg/dl (≥5.6 mmol/l) and without typical clinical symptoms of chronic hyperglycemia, the oral glucose tolerance test (OGTT) or the fasting plasma glucose (FPG) test should be used in the diagnosis of diabetes and prediabetes (IFG and IGT).

FPG is determined largely by the ability of β-cells to secrete sufficient insulin in the basal state to inhibit hepatic glucose production. However, the plasma glucose concentration achieved 2 h after a 75 g OGTT depends not only on FPG but also on the ability of β-cells to respond to a sudden rise in plasma glucose levels. Therefore, these 2 tests reflect different physiological measures of glucose metabolism. This might at least in part explain the lack of a close association between FPG and OGTT results.

The ADA, but not the World Health Organization (WHO), recommended that the FPG test rather than the OGTT should be the diagnostic test of choice for clinical and epidemiological purposes. The ADA recommendation was mainly based on the inconvenience of the OGTT in everyday clinical practice. The FPG test was expected to have better reproducibility. Many experts agreed that it was an ideal first step in screening for glucose intolerance due to its convenience and low cost. If the result of the FPG test performed on a separate day is also ≥126 mg/dl (≥7 mmol/l), the diagnosis of diabetes can be established. The FPG cut-off value for the diagnosis of diabetes is based on its association with microvascular disease, the incidence of which expotentially increases above currently defined normoglycemic thresholds.[7]

Gabir et al.[8] showed that the incidence of both retinopathy and nephropathy increases at the FPG level of 6 mmol/l.

Unfortunately, FPG itself is neither perfectly stable nor free of laboratory variability, its day-to-day variance was found to be between 12% and 15%.[9] This, in addition to the estimated 13.7% biological variability, yielded 95% confidence interval for FPG measured at 126 mg/dl to be 103–149 mg/dl.[10]

Although the use of the FPG test is simpler, cheaper, quicker, and more reproducible, in some cases the omission of a 2-hour plasma glucose (2h PG) assessment will miss a proportion of diabetic subjects who have normal FPG but elevated 2h PG. Of note, FPG is unstable at room temperature.[11] It should be mentioned that FPG concentrations of 6 mmol/l or lower, considered as normal in some patients, will also demonstrate abnormal glucose tolerance when subjected to an OGTT.[12] It was shown that OGTT diagnosis of IGT had high specificity (92%) but much lower sensitivity (51%) in identifying subjects at a high risk for type 2 diabetes. Thus, if one relies exclusively on the OGTT in the diagnosis of IGT for identifying high-risk individuals, about half of those who ultimately develop type 2 diabetes would not have been identified.[13]

Gomez-Perez et al. noted that 82% of IGT cases were classified as normal using the fasting criteria.[14] Jesudason et al.[15] found that only 4% of the examined subjects were diabetic using the FPG test based on the ADA criteria compared with 10.4% using the WHO criteria.

The ideal test should be both sensitive and specific. Our own experience indicates that in many individuals who are at an increased risk of glucose metabolism disturbances, the OGTT proved to be more sensitive than the FPG test to identify diabetes.[16]

The OGTT was proposed in 1979 as a gold standard test in the diagnosis of prediabetes and diabetes by the National Diabetes Data Group. It has been demonstrated that the OGTT is more sensitive than the FPG test in diagnosing prediabetes and diabetes, but it is time-consuming, laborious, less convenient to administer, and has poor intraindividual repeatability. It should be stressed that both the OGTT and FPG test require fasting for at least 8 h. Therefore, unless the patient is severely hyperglycemic and overtly symptomatic, the diagnosis cannot be made in most patients coming for afternoon appointments or if they ate before a morning visit.[5]

The plasma glucose level during the OGTT is measured immediately before and 2 h after a patient drinks a liquid containing 75 g of glucose dissolved in water. It is a standard practice to confirm the diagnosis only if both the first and repeat tests are above the diagnostic threshold. The solution of glucose is tasteless and in some patients may provoke nausea and vomiting. During the test, patient needs to lie or sit quietly and many high-risk patients are unwilling to undergo this time-consuming test on a repeat basis.[5,6,12]

Of note, several studies have found no evidence suggesting that the FPG test is superior to HbA_{1c} in screening for diabetes, with an OGTT being the gold standard. HbA_{1c} had a slightly higher specificity and slightly lower sensitivity than the FPG for the detection of diabetes.[17]

Advantages and disadvantages of HbA_{1c} measurements The current ADA recommendations for the diagnosis of diabetes reject the HbA_{1c} assay as a diagnostic tool. It was mainly due to the ongoing debate that this measurement is inadequately standardized and insensitive.[5]

However, an International Expert Committee has recently suggested to consider the use of the HbA_{1c} assay in the diagnosis of diabetes in nonpregnant individuals.[6] Several facts support this recommendation. The correlation between HbA_{1c} level and chronic complications of diabetes has been demonstrated both in type 1 and type 2 diabetes. It has also been found that HbA_{1c}

correlates with retinopathy better than the FPG. Apart from the relationship with retinopathy, HbA_{1c} level has also been linked to the development of neuropathy and nephropathy.[18]

HbA_{1c} was first separated from other forms of hemoglobin in 1958 using a chromatographic column and first characterized as a glycoprotein almost 10 years later. Its increase in patients with diabetes was first described in 1969, and the reactions leading to its formation were characterized in 1975.[19]

It has been established that HbA_{1c} reflects mean glycemia during the last 2 to 3 months prior to determination of this marker of metabolic control and is not meaningfully affected by glycemic instability after adjusting for mean blood glucose. The use of HbA_{1c} for monitoring the degree of glucose control in diabetic patients was proposed in 1976. By this time, HbA_{1c} had been shown to decrease as glycemic control improved, and periodical measurement of HbA_{1c} level has become a commonly used tool to monitor the effectiveness of hyperglycemia management.[20]

It has been found that HbA_{1c} level is not affected by short-time lifestyle changes, whereas a few days or weeks of dieting or increased exercise can significantly influence the FPG test or OGTT. Unlike glucose, HbA_{1c} is stable at room temperature.[6]

Determination of HbA_{1c} has several limitations. Clinical observations indicate that several conditions can markedly affect HbA_{1c} test results. It seems that age, sex, and ethnicity do not affect HbA_{1c} test results. However, it has also been suggested that HbA_{1c} increases with age and is influenced by racial disparities.[19,21]

The interpretation of the patient's HbA_{1c} result requires caution in subjects with hemoglobinopathies or other complicating illnesses, affecting the erythrocyte life-span (i.e., hemolytic anemias, acute or chronic blood loss, chronic kidney and liver diseases). In such settings, the value of HbA_{1c} may be falsely low. In contrast, iron-deficiency anemia has been reported to increase HbA_{1c} by 1% to 1.5%.[22] Hemoglobin S or C carriers may have both high and low results measured by either reference or other methods.[23] Chemically modified hemoglobin, such as carbamylated associated with uremia or acetylated formed after overdosing salicylates, can also falsely increase results.[24,25]

It should be noticed that the use of vitamins C and E can lower HbA_{1c} levels by inhibiting glycation of macromolecules.[26,27]

Of note, HbA_{1c} is relatively unaffected by acute perturbations in glucose levels during myocardial infarction, stroke, acute infections, or extensive trauma.[6] It is worth stressing that from day to day variability of HbA_{1c} is less than 2%.[10] Many reports confirmed that both 2h PG and FPG measurements had higher variability compared with HbA_{1c}.[28]

Interestingly enough, recent observations indicate that the variability of HbA_{1c} has been increasing in relation to the baseline renal status in subjects with type 1 diabetes. This variability was significantly higher in patients who progressed to cardiovascular events. It has also been shown that patients with signs of a disadvantageous lifestyle (low socioeconomic status, smoking, low physical activity) had higher HbA_{1c} variability. It is reasonable to investigate these findings, especially in patients with type 2 diabetes, before implementing the HbA_{1c} assay as a diagnostic procedure.[29]

An International Expert Committees suggested that the HbA_{1c} level of 6.5% is sufficiently sensitive and specific to identify people with diabetes. Diagnosis should be confirmed with a repeat test unless clinical symptoms and glucose levels exceeding 200 mg/dl are present.[6]

It is suggested that the cut-off value of HbA_{1c} should not be considered as an absolute value differentiating between normal glycemia and diabetes. It should be noticed that HbA_{1c} levels between 6% and 6.5% as well as the presence of IFG or IGT, or both, indicates a high risk of diabetes. It is strongly recommended that physicians who have knowledge on the abnormal carbohydrate metabolism implement intensive preventive strategies as soon as possible. Also, lifestyle modification has to be considered in people with HbA_{1c} below 6% with other coexisting risk factors, i.e., obesity, hipertriglycerydemia, and other components of metabolic syndrome.[6]

The usefulness of HbA_{1c} in the screening and diagnosis of diabetes has been widely debated for several years.[30] It was criticized primarily for its lack of sensitivity, the confounding aspects of the assay and reference-range standardization, and inadequate quality control.[31]

There are many commercial methods available for routine HbA_{1c} measurement. These methods are based on different analytical approaches, such as immunoassays, ion-exchange chromatography, and affinity chromatography. Currently, almost 99% of laboratories in the United States use certified assays that are traceable to the DCCT (Diabetes Control and Complications Trial) glycohemoglobin reference (ion-exchange high-performance liquid chromatography) with a total imprecision of 4% or less. It should be stressed that reliable standardization of the assay has been increasing worldwide.[19]

Rohlfing et al.[32] concluded that HbA_{1c} was a specific and convenient screening test for diabetes, with a value of 6.1% as a diagnostic threshold, whereas Wiener et al.[33] found that HbA_{1c} above 6.2% had 100% specificity for the diagnosis of diabetes. Buell et al.[34] demonstrated that the lower value of HbA_{1c} (5.8%) would be an appropriate cut-off value above which further evaluation is needed. High specificity of HbA_{1c} measurement (>97%) in order to diagnose diabetes was also noted during the Third National Health and Nutrition Examination Survey.[35]

Perry et al. observed that the combined measurement of HbA_{1c} greater than 6.1% and the FPG more than 100 mg/dl, compared with the determination of FPG alone, improved the sensitivity of screening for diabetes from 45% to 61%.[36]

Moreover, data from the DCCT and UK-PDS (United Kingdom Prospective Diabetes Study) demonstrated that at an HbA_{1c} level of 6%, there is a 75% increased risk of microvascular complications of type 2 diabetes.[37,38]

It was found that when FPG is inconclusive (110–125 mg/dl), an HbA_{1c} value more than 3 standard deviations above the mean (>5.94%) might suggest diabetes and the need for implementing proper treatment.[39]

Little et al. reported that a significantly greater percentage of the Pima Indians with IGT and elevated HbA_{1c} at baseline (68%) developed diabetes compared with those with normal HbA_{1c} (28%). HbA_{1c} was shown to be highly specific and moderately sensitive in identifying subjects with diabetes (as diagnosed by the OGTT).[40]

It seems that HbA_{1c} measurement is of limited value in differentiating isolated IFG, IGT, and diabetes in subjects with IFG. This marker cannot be used to identify subjects with IFG who do not require an OGTT.[41]

A large study that involved nondiabetic adults in the United States revealed the overall prevalence of HbA_{1c} above 6% in 3.8% of Americans, which corresponds to 7.1 million individuals. Approximately 90% of these people had FPG ≥100 mg/dl. Older age, male sex, non-Hispanic black ethnicity, hypercholesterolemia, higher body mass index, and lower education level were significantly associated with having a higher HbA_{1c} level even among individuals with normal FPG (<100 mg/dl).[42]

Ko et al.[11] showed that nondiabetic Chinese subjects with FPG ≥6.1 mmol/l and HbA_{1c} ≥6.1% had a rate of progression to diabetes almost 5.4 times higher than those with FPG <6.1 mmol/l and HbA_{1c} <6.1% (44.1% vs. 8.1% per year, respectively).

Greci et al.[43] found that HbA_{1c} measurement can also play a major role in diabetes case finding in hospitalized patients with random hyperglycemia. Admission HbA_{1c} level is a quick and convenient tool for the diagnosis of diabetes, and in ca 50% of cases it could eliminate the need for further diagnostic testing. It has been demonstrated that HbA_{1c} >6% and <5.2% reliably diagnosed and excluded diabetes, respectively. This provides an opportunity for identifying new cases of diabetes and initiating appropriate treatment during hospitalization.

It has been reported that the measurement of FPG and HbA_{1c} in first-degree relatives of patients with type 2 diabetes is extremely useful to identify those subjects in whom an abnormal OGTT result is highly probable.[44]

Determination of HbA_{1c} could also be a useful test in the screening, diagnosing, and assessing the prognoses of the gestational abnormal glucose metabolism. However, this issue merits further investigation.[45]

Shah et al. noticed that in contrast to the homeostasis model assessment of insulin resistance, HbA_{1c}, 1,5-anhydroglucitol, and FPG levels are good predictors of type 2 diabetes in obese children. It is worth mentioning that HbA_{1c} and 1,5-anhydroglucitol proved to be excellent predictors of type 2 diabetes in insulin-resistant obese children. It is extremely important to diagnose diabetes as early as possible in the pediatric population because the lifetime risk for the development of this disease is estimated to be 1 in 3 children born in the United States in 2000.[46]

To be useful in clinical practice, a diagnostic test should be accurate, specific, standardized, handy, and inexpensive. It has been observed that both currently available screening strategies detected only about 30% (OGTT alone) and 25% (fasting glucose + OGTT) of subjects with previously undiagnosed diabetes. It should be stressed that HbA_{1c} testing followed by OGTT in those subjects who proved to have elevated HbA_{1c} yielded the highest rate of detected type 2 diabetes (more than half of all cases). However, this strategy incurred the highest costs. Further studies are warranted in order to determine which screening procedure is most appropriate in terms of cost-effectiveness. On the other hand, the seemingly vital issue is to evaluate the effectiveness of early intervention in diabetic subjects.[47]

Conclusions 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.

Clinical experience indicates that since the FPG, 2h PG, and HbA_{1c} levels are related to diabetic retinopathy to a similar extent, it might be reasonable to assign equal importance to each of these tests, in terms of diagnosis and screening. The choice of the optimal test for diagnosis of diabetes should be based upon clinical characteristics of the subject and availability of various tests in a particular clinical setting.

On the other hand, some primary care physicians have already been using the HbA_{1c} measurement unofficially to diagnose diabetes because other tests are viewed as inconvenient.[48]

The International Expert Committee Report on the Role of the A_{1C} Assay in the Diagnosis of Diabetes is controversial, mainly due to the ongoing concerns about the test's sensitivity and the lack of a definitive randomized controlled trial demonstrating that early intervention based on HbA_{1c} levels may improve long-term outcomes in at-risk individuals.[49]

To summarize, it is still questionable whether HbA_{1c} assay should be considered as a new tool among the currently available methods used in the diagnosis of diabetes. Bloomgarden[50] analyzed the results of the 69th ADA Scientific Sessions and concluded that HbA_{1c} assay may not be sufficiently accurate in everyday clinical practice to identify subjects with diabetes in populations of varying age and ethnic background and with illnesses affecting erythrocyte turnover. Therefore, further analyses are needed before the International Expert Committee proposal of using the HbA_{1c}

assay in the diagnosis of diabetes can be transformed into widely endorsed recommendations and guidelines. Soon after our article had been accepted for publication, an International Expert Committee recommended the use of HbA_{1c} test to diagnose diabetes with the treshold of ≥6.5%, and the ADA affirmed this decision.[51]

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ARTYKUŁ POGLĄDOWY

Czy pomiar hemoglobiny glikowanej może stać się narzędziem w diagnostyce cukrzycy?

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cukrzyca, hemoglobina glikowana, testy diagnostyczne

STRESZCZENIE

Rozpoznanie zaburzeń gospodarki węglowodanowej jest często opóźnione ze względu na niedoskonałości dostępnych metod diagnostycznych. Kliniczne i ekonomiczne znaczenie wykrywania zaburzeń metabolizmu glukozy na bardzo wczesnym etapie jest powszechnie doceniane. Zakłada się, że blisko 30% chorych na cukrzycę typu 2 nie ma świadomości występowania choroby. Prawidłowe rozpoznanie ustala się niejednokrotnie dopiero w momencie ujawnienia się narządowych powikłań przewlekłej hiperglikemii. Dlatego też Międzynarodowy Komitet Ekspertów zaproponował rozważenie wykorzystania oznaczania odsetka hemoglobiny glikowanej (HbA_{1c}) w diagnostyce cukrzycy osób z wyjątkiem kobiet w ciąży. W artykule omówiono zalety i wady metod obecnie stosowanych w celu wykrywania cukrzycy.

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