Significance of HbA\textsubscript{1c} and its measurement in the diagnosis of diabetes mellitus: US experience

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Abstract: The 2014 American Diabetes Association guidelines denote four means of diagnosing diabetes. The first of these is a glycosylated hemoglobin (HbA\textsubscript{1c}) >6.5%. This literature review summarizes studies (n=47) in the USA examining the significance, strengths, and limitations of using HbA\textsubscript{1c} as a diagnostic tool for diabetes, relative to other available means. Due to the relatively recent adoption of HbA\textsubscript{1c} as a diabetes mellitus diagnostic tool, a hybrid systematic, truncated review of the literature was implemented. Based on these studies, we conclude that HbA\textsubscript{1c} screening for diabetes has been found to be convenient and effective in diagnosing diabetes. HbA\textsubscript{1c} screening is particularly helpful in community-based and acute care settings where tests requiring fasting are not practical. Using HbA\textsubscript{1c} to diagnose diabetes also has some limitations. For instance, HbA\textsubscript{1c} testing may underestimate the prevalence of diabetes, particularly among whites. Because this bias differs by racial group, prevalence and resulting estimates of health disparities based on HbA\textsubscript{1c} screening differ from those based on other methods of diagnosis. In addition, existing evidence suggests that HbA\textsubscript{1c} screening may not be valid in certain subgroups, such as children, women with gestational diabetes, patients with human immunodeficiency virus, and those with prediabetes. Further guidelines are needed to clarify the appropriate use of HbA\textsubscript{1c} screening in these populations.

Keywords: diabetes mellitus, diagnosis, glycosylated hemoglobin, USA

Introduction

The Centers for Disease Control and Prevention estimate that 18.8 million people in the USA over the age of 20 years have been diagnosed with diabetes and that another 7 million have diabetes but remain undiagnosed.\textsuperscript{1} The number of people with diabetes in the USA recently rose by 3 million over a 2-year period. Undiagnosed diabetes is particularly concerning, because careful management of diabetes, in terms of eating healthy, remaining active, and taking appropriate medications, has been shown to reduce the risk of adverse events, including myocardial infarction, cerebrovascular accident, end-stage renal disease, blindness, foot ulceration, and amputation.\textsuperscript{2}

Until recently, the diagnosis of diabetes mellitus was determined solely by glucose concentration on the basis of the results of two tests: two fasting plasma glucose (FPG) tests, two oral glucose tolerance tests (OGTTs), or one of each performed on separate days close together in time. In 1993, the Diabetes Control and Complications Trial established the importance of HbA\textsubscript{1c} as an indicator of risk for microvascular complications of diabetes, such as blindness, kidney disease, and nerve damage; however, it was not until 2009 that the International Expert
Committee recommended use of HbA1c for diagnosis of diabetes.3

The rationale for the use of HbA1c for diagnostic purposes is largely based upon data showing that the microvascular complications of diabetes (retinopathy, nephropathy, and neuropathy) tend to occur in patients with HbA1c ≥6.5%. The strength of the relationship between HbA1c and these complications is as strong as other definitions of diabetes, including FPG or OGTT. The consensus of the committee was that HbA1c screening should be used whenever possible to diagnose diabetes, in part due to its convenience.

The committee determined that an HbA1c ≥6.5% was the most reliable indicator of the presence of diabetes. Patients with an HbA1c between 6% and 6.4% were considered to be at high risk for developing diabetes. The committee acknowledged, however, that HbA1c cannot be used in patients with certain conditions, such as hemolytic anemia or in those with a recent blood transfusion. Moreover, as HbA1c screening may be considered costly in some settings, the FPG and OGTT tests can still be used in certain cases. The goal of this manuscript is to review existing literature on the role of HbA1c in diagnosing diabetes in the USA.

Methodology
A hybrid of a systematic and truncated review was implemented for the literature due to the relatively recent adoption of HbA1c as a diagnostic tool for diabetes mellitus. The systematic review worksheet created by the Memorial Sloan-Kettering Cancer Center was utilized to establish the parameters for this review, using the following parameters:

- Patients/population or condition (diabetes mellitus patients in the USA)
- Intervention or exposure (diagnosis test using HbA1c)
- Comparison(s) (against other diagnostic tests for diabetes mellitus)
- Outcome(s) (validity of HbA1c as a diagnostic tool for diabetes mellitus)
- Sex (both)
- Age groups (all)
- Literature time frame (current year +10)
- Language (English)
- Publication types (clinical trials, comparative study, controlled clinical trial, evaluation study, government publications, guidelines, historical article, meta-analysis, observational study, pragmatic clinical trial, randomized controlled trials, research support retraction of publication, review, scientific integrity review, systematic review, technical report, validation studies)
- Document types (primary research articles, review articles, editorials/opinion/commentary/perspectives, meetings or conference abstracts, white papers, gray literature, article comments [formal, reviewed], dissertations/thesis, technical papers)
- Citation management tool (RefWorks)
- PubMed search terms and strategies (diabetes mellitus/)
- Literature time frame (current year)
- Patients/population or condition (diabetes mellitus)

Related citations were also investigated for their relevance. The MeSH search strategy resulted in 521 articles within the National Center for Biotechnology Information, US National Library of Medicine databases. The additional filters of 10 years and humans reduced the results to 391. Similar search strategies were run through Clinical Queries and the above-mentioned databases, increasing the relevant articles to 408 for review. HWS performed the initial literature searches. HWS and DTJ then removed articles that did not seem relevant after reading the abstracts (n=361). The remaining 47 articles were divided between DTJ, RG, KMD, and CLM for review and article summary. The bibliographic manager RefWorks was utilized to maintain control of all citations and their abstracts for tracking, reconsideration, and dissemination. The selection and retention strategy is depicted in Figure 1.

Measurement and standardization
HbA1c testing measures average blood glucose levels over the past 2–3 months in terms of the concentration of hemoglobin molecules that have glucose attached to them. It is reported as a percentage. The use of HbA1c for screening and diagnosis of patients with diabetes offers advantages in terms of ease of use over other tests as it does not require patients to fast overnight or for 2 hours after the administration of oral glucose.

In the past, a limitation of HbA1c screening in diagnosing diabetes was that diverse methods had been used in HbA1c assays and there was no standardization of the test. Hence, identifying a cut-off diagnostic HbA1c value was difficult to achieve. This shortcoming was addressed by the establishment of the National Glycohemoglobin Standardization Program (NGSP). NGSP standards stated that any local
HbA1c in the diagnosis of diabetes mellitus

Existing guidelines

The American Diabetes Association first published guidelines for diagnosing diabetes in 1997; however, they did not include HbA1c as a screening tool until 2010. Figure 2 summarizes the four recommended alternatives for diagnosing diabetes. The guidelines emphasized that HbA1c assays be standardized to the Diabetes Control and Complications Trial HbA1c assay, and certified by the NGSP.

Screening criteria for diabetes remained unchanged. All patients with factors that put them at high risk should be screened regardless of age. For those without risk factors, screening should begin at age 45 years and be repeated every 3 years. The new American Diabetes Association guidelines also introduced a new category of intermediate dysglycemia, called the “increased-risk” group (HbA1c 5.7%–6.4%), to describe individuals with what is also known as “prediabetes.”

Usefulness of HbA1c as an effective diagnostic tool

Validity

Results of the National Health and Nutrition Examination Survey (NHANES) supported the recommendation by the International Expert Committee as well as the American Diabetes Association to implement use of HbA1c to diagnose diabetes, as HbA1c and FPG similarly classified diabetes 97.7% of the time.

In another study, Eid and Pottala used a receiver operating curve to determine that an HbA1c ≥ 6.3% provided the most accurate cut-off measurement for diagnosing diabetes within a chronic disease management system, particularly within high-risk populations. This cut-off measurement was associated with a sensitivity of 70% and a specificity of 85%, showing strong diagnostic evidence for diabetes. Although measurement of HbA1c has the advantage of not being subject to the preanalytical variations that affect other blood glucose measurements, such as acute illness, short-term lifestyle modifications, food ingestion, or variations in the handling of samples, there are factors that may affect the validity of HbA1c measurements, including iron deficiency, altered hemoglobin structure or erythrocyte lifespan, and interracial variability in hemoglobin.

Usefulness in the community

Due to its ease of use, several studies have found that HbA1c testing can identify patients in the community who might...
otherwise go undiagnosed. A study by Grant et al found that community-based HbA\textsubscript{lc} screening can be used to identify many patients at risk for diabetes or with undiagnosed diabetes at churches, group homes, shelters, community centers, and street corners.\textsuperscript{8} Similarly, Nam et al found that community-based point-of-care (POC) testing of Korean Americans, with reference-based follow-up, was an effective means of identifying diabetes in an otherwise hard-to-reach population.\textsuperscript{9}

**Acute setting**

A number of other studies in the USA have found HbA\textsubscript{lc} screening to be a useful diagnostic tool in acute settings, which can be used to take advantage of the greater interest that some patients take in their health during times of acute illness. A study performed by Silverman et al found an HbA\textsubscript{lc} of 5.7\% as the optimal screening cut-off for prediabetes, and 6.0\% for optimal screening of diabetes in acute care settings. When used, these criteria effectively identified high-risk individuals who require referral for additional evaluation and management.\textsuperscript{10} A study examining usefulness of HbA\textsubscript{lc} screening in the emergency department found that assessment in the emergency setting did not differ substantially from that observed 45 days later in outpatient follow-up.\textsuperscript{11} Using POC HbA\textsubscript{lc} testing in an emergency department, Menchine et al found a high prevalence of undiagnosed diabetes in Hispanics (14\%), African Americans (27\%), and patients with body mass index $\geq$30 kg/m\textsuperscript{2} (22\%).\textsuperscript{12} Moreover, Magee and Nassar found that POC HbA\textsubscript{lc} testing in the emergency department enabled the treating physician and educator to manage patients appropriately.\textsuperscript{13} This resulted in improved glycemic control at 2 weeks post initiation of treatment at the emergency department visit. Another study, however, found that only 38\% of patients who screened positive on HbA\textsubscript{lc} tests for diabetes during an emergency department visit also tested positive on an OGTT during follow-up.\textsuperscript{14}

**As a predictor for future diabetes**

A Department of Veterans Affairs Medical Center study concluded that patients with high–normal HbA\textsubscript{lc} values may require follow-up sooner than 3 years, especially overweight or obese patients. In this outpatient population, HbA\textsubscript{lc} was a stronger predictor than obesity of a future diagnosis of diabetes.\textsuperscript{15}

Another historical analysis of data involving Veterans Affairs Medical Centers revealed that individuals with an elevated baseline HbA\textsubscript{lc} (\geq 5.0\%) had a significant risk of developing diabetes over an 8-year follow-up period. Investigators found that the risk of developing diabetes yielded an odds ratio exceeding 16 in those with an HbA\textsubscript{lc} of 6.0\%–6.4\%, with an 80\% cumulative incidence of diabetes.\textsuperscript{16} Moreover, Abdul-Ghani et al utilized the area under a receiver operating curve to determine that HbA\textsubscript{lc} was a significant predictor of a future diagnosis of diabetes, with an HbA\textsubscript{lc} cut-off of 5.65\% yielding the greatest sensitivity and specificity, although HbA\textsubscript{lc} had a smaller area under the curve than the 1-hour plasma glucose concentration in a multivariate logistic model that included anthropometric parameters, lipid profile, and FPG.\textsuperscript{17} Given these results, a combination of dual HbA\textsubscript{lc} and FPG may be a better predictor of future diabetes. A study performed by Selvin et al concluded that dual HbA\textsubscript{lc} and FPG levels are strong predictors of risk and diagnosis of diabetes, demonstrating that an HbA\textsubscript{lc} cut-off of 6.5\% was both highly specific and reasonably sensitive in linking HbA\textsubscript{lc} levels to the risk of long-term microvascular and macrovascular outcomes in nondiabetic adults.\textsuperscript{18}

A recent opinion piece in the *Journal of the American Medical Association* concluded that HbA\textsubscript{lc} remains the only test that can predict the microvascular complications of diabetes and for which there are generally accepted therapeutic targets. HbA\textsubscript{lc} can be measured accurately in the majority of patients and provides valuable information to help guide treatment decisions.\textsuperscript{19}

**Limitations of HbA\textsubscript{lc} as a diagnostic tool**

**Results differ from other tests**

When diagnosing prediabetes, a recent study by Gosmanov and Wan found that HbA\textsubscript{lc} testing had a low positive predictive value of 39\% using a 75 g OGTT as the gold standard.\textsuperscript{20} In another study, Lipska et al compared HbA\textsubscript{lc} screening with FPG in an elderly cohort from the Health, Aging, and Body Composition study.\textsuperscript{21} Only 80 patients were found to have undiagnosed diabetes, and an equal number were identified solely by one method or simultaneously by both: 27.5\% (n=22) only by FPG, 36.3\% (n=29) only by HbA\textsubscript{lc}, and 36.3\% (n=29) by both methods. They also found that elderly blacks and women were significantly more likely to be identified with diabetes by HbA\textsubscript{lc} than by FPG. Moreover, NHANES data revealed that the use of HbA\textsubscript{lc} in screening resulted in a one-third lower prevalence of undiagnosed diabetes than FPG or 2-hour glucose testing.\textsuperscript{22}

In another study comparing HbA\textsubscript{lc} screening with both FPG and 2-hour glucose, HbA\textsubscript{lc} had low sensitivity and high specificity for identifying diabetes and prediabetes, and the
authors concluded that the data supported greater use of the OGTT and both FPG and 2-hour glucose values for diagnosis of diabetes and prediabetes.\textsuperscript{23} Another study enrolled patients in a clinic-based diabetes prevention program and found that reliance on HbA\textsubscript{lc} alone to screen and enroll patients in the program would have missed one-third of eligible high-risk patients (HbA\textsubscript{lc} defined as 6.0\%–6.4\%) as compared with the OGTT.\textsuperscript{24} Similarly, Fajans et al reported that nearly one-third of subjects found to have prediabetes and impaired glucose tolerance via plasma glucose concentrations had an HbA\textsubscript{lc} < 5.7\%, indicating that HbA\textsubscript{lc} lacks sensitivity and reliability for diagnosing prediabetes or impaired glucose tolerance.\textsuperscript{25}

Investigators wishing to determine the distribution of normal versus increased HbA\textsubscript{lc} levels in individuals who had undergone a 2-hour OGTT found that nearly two-thirds diagnosed with diabetes via OGTT had normal HbA\textsubscript{lc} levels.\textsuperscript{26} An analysis of Native American (46\%) subjects from the Strong Heart Study demonstrated that HbA\textsubscript{lc} alone detected fewer cases of prevalent diabetes compared with FPG in the initial screening; however, neither test done alone will effectively identify diabetes, and the authors concluded that using both FPG and HbA\textsubscript{lc} together will identify a larger group at risk, since HbA\textsubscript{lc} might detect subjects who are missed by FPG and vice versa.\textsuperscript{27} A study that tested same-visit HbA\textsubscript{lc} at a family practice center compared with three laboratory HbA\textsubscript{lc} methods demonstrated that same-visit HbA\textsubscript{lc} results were significantly lower than those found with the three laboratory methods.\textsuperscript{28}

**Racial disparities**

Not only do estimates of the prevalence of diabetes depend on which screening test is used, administering HbA\textsubscript{lc} instead of FPG affects estimates of the prevalence of diabetes differently in different racial or ethnic groups. In 2011, Getaneh et al found substantial discrepancies in prevalence by race and ethnicity when using HbA\textsubscript{lc} compared with FPG as a screening tool. Of patients diagnosed as having diabetes by FPG, HbA\textsubscript{lc} screening did not identify diabetes in 64.5\% of white, 46.1\% of Dominican, 44.0\% of African-American, and 41.9\% of Hispanic subjects.\textsuperscript{29} Similarly, a study by Vable et al using NHANES data found that the estimated prevalence of diabetes in non-Hispanic whites was halved when using HbA\textsubscript{lc} instead of FPG. In contrast, for Hispanics and non-Hispanic blacks, there was no significant change in the estimated prevalence.\textsuperscript{30}

Additional NHANES data showed disproportionate differences using HbA\textsubscript{lc} criteria with respect to race; there was a two-fold increase in non-Hispanic blacks and Mexican-Americans versus non-Hispanic whites for diagnosed, undiagnosed, and both types of diabetes.\textsuperscript{32} However, a recent study by Tsugawa et al concluded that even though HbA\textsubscript{lc} levels are higher in blacks than in whites at any given glycemic level, the fact that the risk of retinopathy starts to increase at a lower HbA\textsubscript{lc} level in blacks than in whites suggests that the cut-off does not need to be changed for blacks.\textsuperscript{31}

Another study found that factors associated with a diabetes diagnosis differed by type of screening. In a multiethnic middle-school cohort, high-risk HbA\textsubscript{lc} (5.7\%–6.4\%) was associated with non-Hispanic black race, a family history of diabetes, and higher measurements of body mass index, waist circumference, and fasting insulin levels, whereas impaired fasting glucose was associated with Hispanic ethnicity, and increased body mass index, waist circumference, and fasting insulin levels, as well as increased frequency of hypertension and hypertriglyceridemia.\textsuperscript{32} A study performed by Olson et al found discrepancies within white and black racial groups with regard to both the International Expert Committee and American Diabetes Association diagnostic criteria. Both criteria demonstrated limitations in their use in screening, as both had high specificity but low sensitivity.\textsuperscript{33} Among Filipino-Americans, Japanese-Americans and native Hawaiians, the use of HbA\textsubscript{lc} resulted in lower sensitivity and was estimated to have missed a diagnosis in 60\% of those newly diagnosed with diabetes when compared with the OGTT.\textsuperscript{14}

**Gestational diabetes**

Diagnosing gestational diabetes using HbA\textsubscript{lc} tests also raises some concerns. In a review article, Malkani and DeSilva noted that consensus on diagnostic criteria for gestational diabetes is sorely needed.\textsuperscript{35} While HbA\textsubscript{lc} is not routinely used to diagnose gestational diabetes, it has been used to determine the need for medication in expecting mothers. Clayton et al found that a POC HbA\textsubscript{lc} of 5.72\% significantly indicated a need for medication; however, a very close mean POC HbA\textsubscript{lc} of 5.4\% was associated with no need. A slight correlation was seen between POC HbA\textsubscript{lc} and FPG. Based on overlap of results, the large standard deviations, and the small sample size of their study, the authors were unable to determine a cut-off for POC HbA\textsubscript{lc} and concluded that larger trials are needed.\textsuperscript{36}

**Children**

One retrospective study analyzed 206 children with diabetes and found that, in 10\% of cases, the initial diabetes diagnosis
was misclassified, with HbA \textsubscript{1c} being significantly higher in those initially misclassified as type 1 versus type 2. The authors concluded that the initial classification of diabetes on the basis of HbA \textsubscript{1c} may not be a reliable predictor of classification in children.\textsuperscript{17}

Children are more frequently afflicted with type 1 diabetes, which is associated with more rapidly developed and transient hyperglycemia that might go undetected with an HbA \textsubscript{1c} test. A study performed by Vehik et al found that the diagnostic criterion of HbA \textsubscript{1c} > 6.5% was not a sensitive indicator of type 1 diabetes in high-risk subjects younger than 21 years of age due to the sensitivity of the test. Decreasing the threshold and checking for an HbA \textsubscript{1c} increase over time may be a more appropriate indicator for type 1 diabetes.\textsuperscript{32}

Another study performed by Sharma and Fleming comparing HbA \textsubscript{1c} with other prediabetic diagnostic tests in diagnosing prediabetes in high-risk African-American children concluded that HbA \textsubscript{1c} is not sensitive enough at a cut-off of 5.7% for prediabetes screening in children, when compared with either FPG or HOMA-IR (calculated homeostasis model assessment of insulin resistance). Additionally, no correlation was seen in HbA \textsubscript{1c} levels between obese and overweight children, nor any difference in HbA \textsubscript{1c} levels between boys and girls.\textsuperscript{39}

A multiethnic cohort study conducted by Nowicka et al tested the sensitivity and specificity of HbA \textsubscript{1c} in the diagnosis of type 2 diabetes and prediabetes compared with the OGTT. Of the 1,156 obese children and adolescents without a diagnosis of diabetes, 77% had normal HbA \textsubscript{1c} (< 5.7%), demonstrating that HbA \textsubscript{1c} would understate the diagnosis of prediabetes and type 2 diabetes due to the specificity and sensitivity of the test.\textsuperscript{40}

In contrast with the previous studies, an analysis performed by Shah et al found that HbA \textsubscript{1c} was a good predictor of type 2 diabetes in obese children, particularly those with insulin resistance. HbA \textsubscript{1c} ≥ 6% demonstrated a sensitivity and specificity of 99% and 96%, respectively. However, the authors did acknowledge that the difficulties in standardizing HbA \textsubscript{1c} assays in the community may affect the applicability of their study.\textsuperscript{41}

Women

A study by Pradhan et al attempted to determine if an elevated HbA \textsubscript{1c} level would be a good predictor of cardiovascular disease and type 2 diabetes in women. A study of 26,563 women showed that baseline HbA \textsubscript{1c} is a good predictor for type 2 diabetes, but not for cardiovascular health, in middle-aged and older women. The study also showed that the risk for diabetes increases even when levels of HbA \textsubscript{1c} were considered to be in the normal range. The authors emphasized that these findings cannot be generalized to different groups (eg, adolescents and men).\textsuperscript{42}

Elderly

The NHANES data showed that when using the HbA \textsubscript{1c} test, the prevalence of undiagnosed diabetes or high-risk diabetes is strongly influenced by increasing age.\textsuperscript{22}

Other considerations

Data from NHANES showed that in patients with high or low hemoglobin concentrations, HbA \textsubscript{1c} should be used with caution to diagnose diabetes or prediabetes, since changes in erythrocyte turnover may alter test results. HbA \textsubscript{1c} was higher in patients with iron deficiency anemia, who had HbA \textsubscript{1c} levels similar to those with normal hemoglobin and iron status. When groups of anemic and nonanemic patients with and without iron deficiency were studied individually, there was no difference in the relationship between FPG and HbA \textsubscript{1c} in this population.\textsuperscript{43}

Human immunodeficiency virus

The usefulness of HbA \textsubscript{1c} as a screening tool for diabetes in patients with human immunodeficiency virus (HIV) is unclear. In one study of patients with HIV, HbA \textsubscript{1c} was a more accurate screening tool for diabetes than FPG, as without any confirmatory criterion, FPG was found to overestimate the incidence of diabetes in HIV patients.\textsuperscript{44} However, Eckhardt et al concluded that HbA \textsubscript{1c} values are insensitive, although highly specific, for diagnosing diabetes in patients with HIV. Additionally, HbA \textsubscript{1c} may be affected by current antiretroviral medications, with overestimation of HbA \textsubscript{1c} in those currently receiving protease inhibitors and underestimation in those currently receiving non-nucleoside reverse-transcriptase inhibitors, with the exception of tenofovir.\textsuperscript{45}

Discussion

As the prevalence of diabetes continues to rise in the USA, means of screening high-risk and hard-to-reach populations has become increasingly important. Because HbA \textsubscript{1c} levels have been associated with an increased risk of diabetes-related complications, and HbA \textsubscript{1c} screening provides a convenient way to diagnose diabetes, guidelines have begun to advocate use of HbA \textsubscript{1c} to diagnose diabetes.\textsuperscript{46–48} Limitations include the prevalence of estimates based on HbA \textsubscript{1c} differing from those of other methods of diagnosis, particularly among white patients. Moreover, the usefulness and validity of HbA \textsubscript{1c} screening in certain populations has been questioned. Hence,
for certain subgroups, multiple methods may be needed. For example, using FPG in addition to HbA1c may be the best method for screening for diabetes in HIV patients. Another disadvantage is that HbA1c screening has been found to be less cost-effective than a 2-hour OGTT, a 1-hour glucose challenge test, or random glucose testing. Hence, it might be useful to implement risk stratification, which has been shown to improve the predictive power of HbA1c screening for diabetes and may be more cost-effective than opportunistic screening.

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