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Hemoglobin A1C and diabetes diagnosis: The Rancho Bernardo Study

Running Title: Hemoglobin A1c and diabetes

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Objective: To examine the sensitivity and specificity of hemoglobin A1c (HbA1c) as a diagnostic test for type 2 diabetes mellitus (T2DM) in older adults.

Research design and methods: Cross-sectional study of community-dwelling adults without known diabetes who had an oral glucose tolerance test and HbA1c measured on the same day.

Results: Mean age of the 2107 participants was 69.4±11.1 yrs; 43% were men. Based on ADA criteria, 198 had previously undiagnosed T2DM. The sensitivity/specificity of HbA1c cut point of 6.5% was 44/79%. Results were similar in age and sex-stratified analyses. Given the HbA1c cut point of 6.5%, 85% of participants were classified as non-diabetic by ADA criteria.

Conclusion: The limited sensitivity of the HbA1c test may result in delayed diagnosis of T2DM, while the strict use of ADA criteria may fail to identify a high proportion of individuals with diabetes by HbA1c ≥6.5% or retinopathy.

The current criteria for type 2 diabetes mellitus (T2DM) diagnosis (1) requires a fasting plasma glucose (FPG) and/or 75g-oral glucose tolerance test (OGTT), a diagnostic method that is time consuming, requires fasting, and is affected by acute perturbations in glucose levels and short-term lifestyle changes. Even though the time for onset has been shortened in the last decades, the onset of T2DM occurs years before clinical diagnosis (2; 3).

Hemoglobin A1c (HbA1c) has been suggested as a useful tool for T2DM screening and diagnosis (4-6); it does not require fasting, reflects the usual 3-4 months prior glycemia, has less intra-individual variability, and may better predict diabetes-related complications (7; 8). Recent reports have stated that the cut point of ≥6.5% would be diagnostic if confirmed by a repeated test; (4; 5). Further investigation of HbA1c diagnostic performance in specific age and sex groups is still lacking.

We designed the present study to determine the sensitivity and specificity of HbA1c for T2DM diagnosis, compared to the current OGTT gold standard as well as diabetic retinopathy (DR) in a cohort of older adults from the Rancho Bernardo Study.

METHODS

Participants included 2107 adults without known T2DM or anemia who had an OGTT and HbA1c test between 1984-1987. Glucose tolerance status was defined by ADA OGTT criteria as 1) normoglycemia: FPG <100 mg/dL and 2-h post-challenge glucose <140 mg/dL; 2) pre-diabetes: FPG ≥100 mg/dL and <126 mg/dL or 2-h post-challenge glucose ≥140 mg/dL and <200 mg/dL; and 3) T2DM: FPG ≥126 mg/dL or 2-h post-challenge glucose ≥200 mg/dL (1). Anemia was assessed by history.

All participants provided written informed consent. The study protocol was approved by the University of California, San Diego Human Research Protection Program.

Laboratory and anthropometric data were performed as previously described (9). HbA1c was measured by high-performance liquid chromatography using an automated analyzer (Smith Kline, Van Nuys, CA; normal range: 4.5-6.5%). Ophthalmologic evaluation was performed by nonmydriatic retinal photography (10).

All analyses were performed using SPSS (version 13.1, SPSS, Inc., Chicago, IL). Receiver-operating characteristic (ROC) curves were constructed to calculate sensitivity/ specificity of HbA1c cut points for T2DM diagnosis. Kappa coefficients were used to test for agreement between HbA1c values and DM status.

RESULTS

Mean age was 69.4±11.1 years; 43% were men. There were 198 participants with previously undiagnosed diabetes who had T2DM by ADA criteria. At the time of DM diagnosis, mean HbA1c was 6.5±1.07%; compared with 5.9±0.73% and 6.06±0.75% in participants with normal glucose and prediabetes, respectively (P<0.001).

Overall, the HbA1c cut point of 6.5% had a sensitivity/specificity of 44/79% (area under ROC curve 0.65; Figure 1A). The HbA1c cut point of 6.15% yielded the highest combination of sensitivity (63%) and specificity (60%), but would miss one-third of those with T2DM by ADA criteria and misclassify one-third of those without. Results in sex-stratified analysis were similar (Figure 1B). In analysis stratified by quartiles of age, the sensitivity/specificity of HbA1c cut point of 6.5% was up to 52/95% (Figure 1C).

Using the HbA1c cut point of 6.5%, the agreement with T2DM diagnosis was low (the kappa coefficient was 0.119), and 85% of participants with HbA1c ≥6.5% were classified as non-T2DM by OGTT ADA

criteria, of whom 34% were normoglycemic. When compared to T2DM diagnosis based only on FPG ≥126 mg/dL, the agreement was also low (kappa coefficient 0.061). The same pattern was observed considering T2DM diagnosis based only on post-challenge glucose ≥200 mg/dL (kappa coefficient 0.112).

In order to compare HbA1c and ADA criteria with a T2DM complication, we considered their prevalent retinopathy. Only 1.8% (n=38) of these individuals without known diabetes had any degree of DR; of those, 40% had HbA1c ≥6.5%, and none had T2DM by ADA criteria.

CONCLUSION

In this cohort of older adults, the suggested HbA1c cut point of 6.5% had relatively low sensitivity and specificity for T2DM diagnosis in all age groups and both sexes. There was low agreement between T2DM diagnosis made by HbA1c and the ADA criteria. However, HbA1C criteria were met in 40% of the participants with prevalent DR, while OGTT criteria were met in none.

In a recent systematic review of 9 studies, Bennett and colleagues reported that the HbA1c cut point of ≥6.1% had sensitivity of 78-91% and specificity of 79-84% compared to OGTT (5). In contrast, data from NHANES III showed that a HbA1c ≥6.5% had sensitivity/specificity of 44/99% (11). The present study showed similar sensitivity with the NHANES reports; however, our specificity of 79% for HbA1C ≥6.5% was much lower than previously reported. This is likely because these studies included much younger populations.

The recently published International Expert Committee Report on the role of HbA1c for T2DM diagnosis states that there is no single assay for hyperglycemia that can be considered the gold standard (6). In the present study, 85% of participants with HbA1c ≥6.5% were not classified as diabetic by ADA criteria and one-third of the participants with DM by ADA criteria would be classified as normoglycemic by HbA1c, that is, a significant proportion of misclassification. These observations raise two concerns. First, it would not be desirable to miss those with high HbA1c, considering that the burden of DR correlates better with HbA1c than with FPG or OGTT and that the prevalence of DR increases substantially when HbA1c values exceed 7% (6; 8). On the other hand, performing HbA1c instead of OGTT would miss 30% of those who are already diabetic and those with prediabetes. Failing to identify prediabetes would miss interventional opportunities to prevent or delay T2DM (12).

To our knowledge, this is the first report of HbA1c diagnostic performance in the elderly. Our findings are important, because the elderly in the U.S. have the greatest current burden and expected increase in the prevalence of T2DM (13; 14).

We conclude that the limited sensitivity of the HbA1c test may result in missed or delayed diagnosis of T2DM, whereas the use of current OGTT criteria will fail to identify a high proportion of individuals with HbA1c >6.5%. Further studies and discussion are needed before revising guidelines for T2DM diagnosis.

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Figure 1. HbA1C receiver-operating characteristic curve for T2DM diagnosis. A) Whole cohort; B) Men (—) and women (---); C) By quartiles of age: first quartile (—), second quartile (---), third quartile (---) and fourth quartile (----).