Diagnosis of Diabetes using Hemoglobin A1c: Should Recommendations in Adults Be Extrapolated to Adolescents?

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Objective To compare test performance of hemoglobin A1c (HbA1c) for detecting diabetes mellitus/pre-diabetes for adolescents versus adults in the United States.

Study design Individuals were defined as having diabetes mellitus (fasting plasma glucose [FPG] ≥126 mg/dL; 2-hour plasma glucose (2-hr PG) ≥200 mg/dL) or pre-diabetes (100 ≤ FPG <126 mg/dL; 140 ≤ 2-hr PG <200 mg/dL. HbA1c test performance was evaluated with receiver operator characteristic (ROC) analyses.

Results Few adolescents had undiagnosed diabetes mellitus (n = 4). When assessing FPG to detect diabetes, an HbA1c of 6.5% had sensitivity rates of 75.0% (30.1% to 95.4%) and 53.8% (47.4% to 60.0%) and specificity rates of 99.9% (99.5% to 100.0%) and 99.5% (99.3% to 99.6%) for adolescents and adults, respectively. Additionally, when assessing FPG to detect diabetes mellitus, an HbA1c of 5.7% had sensitivity rates of 5.0% (2.6% to 9.2%) and 23.1% (21.3% to 25.0%) and specificity rates of 98.3% (97.2% to 98.9%) and 91.1% (90.3% to 91.9%) for adolescents and adults, respectively. ROC analyses suggested that HbA1c is a poorer predictor of diabetes mellitus (area under the curve, 0.88 versus 0.93) and pre-diabetes (FPG area under the curve 0.61 versus 0.74) for adolescents compared with adults. Performance was poor regardless of whether FPG or 2-hr PG measurements were used.

Conclusions Use of HbA1c for diagnosis of diabetes mellitus and pre-diabetes in adolescents may be premature, until information from more definitive studies is available. *(J Pediatr 2011;158:947-52)*.

In 2009, an International Expert Committee consisting of experts from the American Diabetes Association (ADA), the European Association for the Study of Diabetes, and the International Diabetes Federation was convened to assess the role of the Hemoglobin A1c (HbA1c) for the diagnosis of diabetes mellitus.[1] Traditionally, for both adolescents and adults, a diagnosis of diabetes mellitus was determined on the basis of a fasting plasma glucose (FPG) level or a 2-hour plasma glucose (2-hr PG) level after a 75-gram load of glucose.[2] Both tests require that individuals be fasting, an inconvenience in the clinical setting that may lead to lower testing rates and possible under-diagnosis of diabetes mellitus in the population.[3] HbA1c is a measure of longer-term glycemia that does not require fasting, and at specific thresholds, it has been associated with increased rates of diabetes mellitus complications (ie, retinopathy).[2] Therefore, the ADA recommended that HbA1c be preferentially used for diagnosis of diabetes mellitus in the clinical setting, phasing out both the FPG and the 2-hr PG measurements. According to the new guidelines, individuals without symptoms would be classified as having diabetes mellitus when they had HbA1c values ≥6.5% on two separate occasions. Individuals with an HbA1c value ≥6.0% (International Expert Committee recommendations)[1] or HbA1c value ≥5.7% (ADA recommendations)[4] are considered to be at increased risk for diabetes mellitus and targeted for diabetes prevention interventions.

The committee recommended that HbA1c testing also be used for diagnostic purposes in adolescents without symptoms; however, it is unclear whether similar HbA1c cutoff points are appropriate for the pediatric and the adult populations. Both of the HbA1c thresholds selected were based on studies performed exclusively in adults,[5,6] without consideration of studies from the pediatric population. Therefore, the objective of our study was to assess the usefulness of the new HbA1c guidelines for diagnosis of diabetes mellitus among asymptomatic adolescents in the United States from a nationally representative sample.

Methods

Our data source was the National Health and Nutrition Examination Surveys (NHANES 1999-2006), a cross-sectional, nationally representative examination

2-hr PG	2-hour plasma glucose
ADA	American Diabetes Association
AUC	Area under the curve
FPG	Fasting plasma glucose
HbA1c	Hemoglobin A1c
NHANES	National Health and Nutrition Examination Surveys
OGTT	Oral glucose tolerance test
ROC	Receiver operator characteristic

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study of the US civilian non-institutionalized population. NHANES has a stratified multi-stage probability sampling design,[7] which over-samples adolescents, non-Hispanic black, and Mexican-American individuals to provide reliable statistical estimates.

We focused on individuals who had both FPG and HbA1c measures, and for a subanalysis of individuals with a 2-hr PG and HbA1c. Both FPG and the 2-hr PG have limitations for identifying diabetes mellitus because of poor concordance[8] and lack of reproducibility.[9,10] However, because FPG or 2-hr PG were the recommended tests for diagnosis of diabetes mellitus, we used them as the best method to compare with HbA1c. Procedures on the assessment of fasting status, blood collection, sample processing, and analysis of FPG and 2-hr PG in NHANES have been described in earlier publications.[11,12] HbA1c was measured with two high-performance liquid chromatography systems (Primus Corporation, Kansas City, Missouri, and Tosoh Medics, San Francisco, California), which were standardized to the reference method used for the Diabetes Control and Complications Trial.[13]

Of the 21 056 and 6873 subjects aged 12 to 79 years from NHANES 1999 to 2004 and NHANES 2005 to 2006, respectively, we examined individuals with both HbA1c and FPG measures during the morning examination after fasting for a minimum of 8 hours. We excluded subjects who were pregnant at the time of the exam (n = 1350) or who reported an earlier diagnosis of diabetes mellitus (n = 1824). We analyzed data on 1156 overweight and obese adolescents aged 12 to 18 years, because the ADA recommends that only overweight and obese adolescents be screened,[14] and compared them with data from 6751 adults aged 19 to 79 years.[4] Our adult population included normal weight and overweight/obese individuals because adults can be targeted for screening regardless of weight.[4] Furthermore, we also conducted our analyses on a subpopulation of adults aged 45 to 79 years because of the recommendation to screen adults ≥45 years old. Because these findings were similar to those for our entire adult population, the results are not shown. In addition, we analyzed data from a subsample of 267 adolescents and 1476 adults who had 2-hr PG measures from an oral glucose tolerance test (OGTT) during NHANES 2005 to 2006.

Our outcomes of interest were diabetes mellitus and pre-diabetes, on the basis of definitions using both FPG, which was available for all study years, and 2-hr PG, which was available for NHANES 2005 to 2006. Individuals were classified as having diabetes mellitus when they had an FPG ≥126 mg/dL or pre-diabetes when they had an FPG ≥100 mg/dL and <126 mg/dL. In the 2-hr PG subsample, individuals were classified as having diabetes mellitus when they had a 2-hr PG ≥200 mg/dL or pre-diabetes when they had a 2-hr PG ≥140 mg/dL and <200 mg/dL. To evaluate the International Expert Committee's and the ADA's new recommendations, we first calculated sensitivity, specificity, and positive and negative predictive values[15] at an HbA1c threshold of 6.5% for diabetes mellitus and thresholds of 6.0% (International Expert Committee) and 5.7% (ADA) for pre-diabetes separately for adolescents and adults.

We then created receiver operator characteristic (ROC) curves evaluating the test performance of various HbA1c level cutoff points for detecting diabetes mellitus and pre-diabetes for adolescents versus adults. ROC analysis is a formal method of assessing the trade-offs between sensitivity and specificity at various test cutoff points or thresholds,[16] providing a measure of diagnostic accuracy called area under the curve (AUC). Tests with an AUC close to 0.5 have very poor discrimination, whereas tests with an AUC close to 1.0 have excellent discrimination.[17] We also tested the equality of AUC for adolescents versus adults. For the ROC analyses for pre-diabetes, we combined the outcomes of pre-diabetes and diabetes mellitus.

Statistical analyses were performed with Stata software version 9 (Stata Corporation, College Station, Texas), which applies the appropriate sampling weights to adjust for the complex multicluster sample design. We used Taylor series linearization for variance estimation. For description of the sample that required the availability of survey weights, we reported demographics separately for NHANES 1999-2004 and 2005-2006. However, for assessing test performance, we combined individuals across all surveys. This study was considered exempt by the University of Mighigan Institutional Review Board.

Results

The demographic characteristics of the overall study population, which includes weighted estimates of the proportion of individuals with pre-diabetes and previously undiagnosed diabetes mellitus on the basis of FPG or 2-hr PG levels, are presented in **Table I**. Compared with adults, few adolescents had undiagnosed diabetes mellitus, and there were no cases identified with the 2-hr PG (**Table II**). Although there were substantially more adolescents with pre-diabetes (on the basis of either FPG or 2-hr PG measures) than with undiagnosed diabetes mellitus, adolescents who were pre-diabetic were still fewer in number than adults with pre-diabetes (**Table II**).

Table II shows estimates of test performance of an HbA1c cutoff point of 6.5% for detecting diabetes mellitus and cutoff points of 6.0% and 5.7% for detecting pre-diabetes as defined with FPG or 2-hr PG in adolescents and adults. For detecting diabetes mellitus, an HbA1c cutoff point of 6.5% resulted in a higher point estimate for sensitivity for adolescents compared with adults; however, the confidence intervals for sensitivity in adolescents were quite large, related to the small number with diabetes mellitus (n = 4). Estimates of specificity were similar for both groups, and the positive predictive value was lower and the negative predictive value was higher for adolescents because of their lower prevalence of disease.

For detecting pre-diabetes on the basis of FPG, an HbA1c cutoff point of 6.0% resulted in a lower estimate of sensitivity for adolescents compared with adults. As with diabetes mellitus, the specificity rate was similar for both groups, and again, the positive predictive value was lower and the negative predictive value was higher for adolescents compared with adults, because of the low prevalence of pre-diabetes in adolescents. For detecting diabetes mellitus on the basis