CLIN CARE/EDUCATION/NUTRITION/PSYCHOSOCIAL

HbA$_{1c}$ and the Prediction of Type 2 Diabetes in Children and Adults

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OBJECTIVE

Long-term data validating glycated hemoglobin (HbA$_{1c}$) in assessing the risk of type 2 diabetes in children are limited. HbA$_{1c}$, fasting plasma glucose (FPG), and 2-h post-load plasma glucose (2hPG) concentrations were measured in a longitudinal study of American Indians to determine their utility in predicting incident diabetes, all of which is thought to be type 2 in this population.

RESEARCH DESIGN AND METHODS

Incident diabetes (FPG ≥126 mg/dL [7.0 mmol/L], 2hPG ≥200 mg/dL [11.1 mmol/L], HbA$_{1c}$ ≥6.5% [8 mmol/mol], or clinical diagnosis) was determined in 2,095 children without diabetes ages 10–19 years monitored through age 39, and in 2,005 adults ages 20–39 monitored through age 59. Areas under the receiver operating characteristic (ROC) curve for HbA$_{1c}$, FPG, and 2hPG in predicting diabetes within 10 years were compared.

RESULTS

During long-term follow-up of children and adolescents who did not initially have diabetes, the incidence rate of subsequent diabetes was fourfold (in boys) as high and more than sevenfold (in girls) as high in those with HbA$_{1c}$ ≥5.7% as in those with HbA$_{1c}$ ≤5.3%—greater rate ratios than experienced by adults in the same HbA$_{1c}$ categories. Analyses of ROCs revealed no significant differences between HbA$_{1c}$, FPG, and 2hPG in sensitivity and specificity for identifying children and adolescents who later developed diabetes.

CONCLUSIONS

HbA$_{1c}$ is a useful predictor of diabetes risk in children and can be used to identify prediabetes in children with other type 2 diabetes risk factors with the same predictive value as FPG and 2hPG.

The prevalence of type 2 diabetes has increased among youth in the U.S.; between 2001 and 2009, there was a 30.5% rise in the overall prevalence of diagnosed diabetes (1,2). Many youth diagnosed with type 2 diabetes have poor glycemic control (2,3) and experience higher rates of cardiovascular disease risk markers, fatty liver disease, and early evidence of microvascular complications (2,4,5). This highlights the need for early detection of prediabetes to prevent the increase in diabetes and its associated cardiometabolic risk factors.

The American Diabetes Association (ADA) recommends glycated hemoglobin (HbA$_{1c}$) as a diagnostic test for diabetes. This guideline is based on adult epidemiological studies that show an association between increased HbA$_{1c}$ and the risk for microvascular complications (6–8). Longitudinal studies investigating the relationship between HbA$_{1c}$ in childhood and the risk of developing diabetes are lacking. In addition,

few pediatric studies have compared HbA$_{1c}$ with other measures of glycemia such as fasting plasma glucose (FPG) and 2-h postload plasma glucose (2hPG).

In the 2016 *Standards of Medical Care in Diabetes*, the ADA recognized that data supporting HbA$_{1c}$ as a diagnostic measure for diabetes are limited in children and adolescents (9) while noting that past short-term studies did not address the more pertinent relationship between HbA$_{1c}$ and long-term health outcomes. The ADA recommends screening for type 2 diabetes or prediabetes using HbA$_{1c}$ in asymptomatic children and adolescents aged ≥10 years with a BMI ≥85th percentile for age and sex, based on Centers for Disease Control and Prevention growth charts (10), and at least two additional type 2 diabetes risk factors (9). Risk factors include type 2 diabetes in a first- or second-degree relative, minority race or ethnicity, signs of insulin resistance, or maternal history of diabetes or gestational diabetes during the child's gestation (9).

Measuring HbA$_{1c}$ is convenient in children because it does not require fasting, and a single test can be used to both diagnose and monitor glycemic control, thereby facilitating sample collection and compliance in children. In addition, HbA$_{1c}$ reflects chronic glycemia and has less preanalytical and analytical variability than FPG and 2hPG (9,11).

In our current study, HbA$_{1c}$, FPG, and 2hPG were measured in a longitudinal study of American Indian children, adolescents, and adults to assess the ability of these measurements to predict the development of diabetes, as defined by the ADA. This study examined the extent to which the ADA-recommended definitions of prediabetes in children and adolescents predicted who would develop diabetes and compared the sensitivity and specificity of HbA$_{1c}$, FPG, and 2hPG in predicting future diabetes.

RESEARCH DESIGN AND METHODS

A longitudinal study of diabetes and related conditions was conducted among residents of an American Indian community in the southwestern U.S. from 1965 to 2007. Children ≥5 years and adults underwent comprehensive clinical examinations, which included detailed medical histories, anthropometric measurements, and biochemical tests. These children and adults were invited to return for research examinations every 2 years. All laboratory

tests during the study period were performed at the National Institute of Diabetes and Digestive and Kidney Diseases laboratory located in Phoenix. HbA$_{1c}$ was measured from 1989 to 2000 by high-performance liquid chromatography using the Bio-Rad MDMS system; from 2001 to 2007, we used the A1C 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics, Inc.). A Bland-Altman analysis of 252 samples measured with each instrument indicated small systematic differences. Therefore, a linear regression equation was used to convert the older assay results to the newer assay: HbA$_{1c}$ new method = −0.1916 + (0.9829 × HbA$_{1c}$ old method). Our laboratory has followed the National Glycohemoglobin Standardization Program assay standardization recommendations since its inception. At each research examination, FPG and HbA$_{1c}$ were measured in fasting venous blood, and 2hPG was measured after a 75-g oral glucose tolerance test (OGTT).

The National Institute of Diabetes and Digestive and Kidney Diseases Institutional Review Board approved the study. Written informed consent was obtained from adults and from parents of the minors, and assent was obtained from the minors.

Criteria for inclusion in this analysis were HbA$_{1c}$, FPG, and 2hPG measures performed when the participant was 10 through 19 years of age at his or her first

examination without diabetes, and at least one follow-up examination before the 40th birthday, which yielded 2,095 children and adolescents. The adult comparison cohort consisted of those with a first baseline examination when they did not have diabetes from age 20 through 39 years with all three glycemic measures and a follow-up examination before the 60th birthday, which yielded 2,005 adults. A person could be counted in each cohort if seen at the appropriate ages. Subjects who gave a history of possibly taking metformin at baseline were excluded. Diabetes was defined at baseline and follow-up by the current ADA criteria: FPG ≥126 mg/dL (7.0 mmol/L), 2hPG ≥200 mg/dL (11.1 mmol/L), HbA$_{1c}$ ≥6.5% (48 mmol/mol) (9), or a previous clinical diagnosis. Prediabetes was defined as HbA$_{1c}$ levels between 5.7 and 6.4%, FPG between 100 and 125 mg/dL, or 2hPG between 140 and 199 mg/dL (9).

Statistical analyses were conducted using SAS 9.4 software (SAS Institute, Inc., Cary, NC). Diabetes incidence per 1,000 person-years was calculated using the number of incident cases of diabetes and person-years of follow-up through age 39 for the child cohort and through age 59 for the adult cohort. Sex-stratified areas under the receiver operating characteristic (ROC) curve (AUC) and standard errors for HbA$_{1c}$, FPG, and 2hPG predicting diabetes

Table 1—Baseline characteristics of child and adult cohorts, stratified by HbA$_{1c}$ level

	HbA$_{1c}$ (%)		
	≤5.3	5.4–5.6	5.7–6.4
Children			
Total (*n*)	1,795	238	62
Male (*n*)	831	97	13
Female (*n*)	964	141	49
Age (years)	14.1 (12.5–16.1)	13.8 (12–16)	14 (11.8–15.3)
Follow-up (years)	6.0 (3–10)	3.1 (2–6.1)	2.3 (1.9–4)
BMI (kg/m^2)	26.0 (22.0–31.0)	30.0 (25.0–35.0)	32.0 (28.0–38.0)
BMI (percentile)	94.9 (79.6–98.4)	98.2 (94.6–99.2)	98.7 (97–99.3)
HbA$_{1c}$ (%)	4.9 (4.6–5.1)	5.5 (5.4–5.5)	5.7 (5.7–5.9)
FPG (mg/dL)	89 (85–94)	91 (86–96)	93.5 (88–98)
2hPG (mg/dL)	101 (87–116)	107 (92–125)	116.5 (103–149)
Adults			
Total (*n*)	1,466	371	168
Male (*n*)	587	141	72
Female (*n*)	879	230	96
Age (years)	29.0 (24.1–33.3)	28.4 (23.6–34.1)	29.9 (23.8–34.2)
Follow-up (years)	5.2 (3.1–8.4)	3.6 (2.2–6.3)	3.2 (2.0–5.4)
BMI (kg/m^2)	33.0 (28.7–38.0)	36.6 (32.7–42.0)	39.1 (34.3–45.2)
HbA$_{1c}$ (%)	4.9 (4.7–5.1)	5.5 (5.4–5.6)	5.8 (5.7–5.9)
FPG (mg/dL)	90.0 (85.0–97.0)	95.0 (89.0–101.0)	98.0 (91.0–105.0)
2hPG (mg/dL)	106.0 (88.0–124.0)	114 (93–141.0)	120.0 (102.0–148.0)

Data are shown as median (interquartile range) or as indicated.

were calculated by the method of Pencina and D'Agostino (12); the AUCs were compared by the method of DeLong et al. (13). AUCs allow for a quantitative comparison of the discriminatory power of the different tests. For graphical purposes, ROC curves were derived for each variable, based on predicting the cumulative incidence at 10 years. In brief, ROC curves for each test measure were drawn by modeling the survival probability with the PHREG procedure in SAS using successive detection thresholds for HbA_{1c} (incremented by 0.1%), FPG (incremented by 2 mg/dL), or 2hPG (incremented by 5 mg/dL) and calculating the 10-year cumulative incidence of diabetes in those above and below the threshold from the baseline hazard and the hazard ratio associated with being above the threshold. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at each threshold (at 10 years of follow-up) were calculated from these cumulative incidence values and the proportion exceeding the threshold at baseline.

RESULTS

Baseline Characteristics
Among 2,095 children and adolescents at baseline, 588 (28.1%) were categorized as normal weight (BMI <85th percentile for age and sex), 394 (18.8%) were overweight (BMI ≥85th to <95th percentile), and 1,113 (53.1%) were obese. In the adult cohort at baseline, 143 (7.1%) had BMI <25 kg/m^2, 383 (19.1%) had a BMI between 25 and 30 kg/m^2, and 1,479 (73.8%) were obese with a BMI ≥30 kg/m^2.

Adult and pediatric participants were classified into prediabetes (5.7–6.4%), intermediate (5.4–5.6%), or lower (≤5.3%) baseline HbA_{1c} categories. The prevalence of prediabetes by HbA_{1c} ≥5.7% was 3.0% in the children and adolescents and 8.4% in the adults, and by FPG ≥100 mg/dL, the prevalence was 9.2% in children and adolescents and 21.1% in adults. The prevalence of impaired glucose tolerance (2hPG ≥140 mg/dL) was 8.1% in children and adolescents and 17.3% in adults. Baseline characteristics are reported in Table 1 for the pediatric and adult cohorts, stratified by HbA_{1c}. FPG, 2hPG, and BMI values increased with HbA_{1c} strata in children and adults. Supplementary Table 1 lists the Spearman correlation coefficients between HbA_{1c}, FPG, and 2hPG in children and adults. Age-sex stratified Venn diagrams representing the overlap

in prediabetes definitions at baseline by HbA_{1c}, FPG, and 2hPG are presented in Supplementary Figs. 1 and 2.

Incidence of Diabetes by HbA_{1c}
Median follow-up time to the diagnosis of diabetes or the last examination before diabetes developed in the pediatric cohort was 5.2 years (interquartile range [IQR] 2.7–9.6). Median follow-up was 4.6 years (IQR 2.8–7.9) in the adults. Total person-years of follow-up were 13,528 in children and 11,520 in adults. The sex-stratified incidence of diabetes by baseline HbA_{1c} category in children and adults is shown in Fig. 1A. The incidence rates exhibited a similar pattern of risk increase in the higher HbA_{1c} categories in children and adolescents and in adults (Fig. 1A). Although the incidence rates were higher in adults, the rate ratios comparing higher HbA_{1c} categories with the lowest category of HbA_{1c} were the same or higher in children (Fig. 1B). Male children and adolescents in the highest HbA_{1c} category (5.7–6.4%) at baseline had a fourfold higher incidence of diabetes, and female

children and adolescents in the same HbA_{1c} range at baseline had a sevenfold higher incidence of diabetes during follow-up than their counterparts in the lowest HbA_{1c} category (Fig. 1B).

HbA_{1c}, FPG, and 2hPG Predicting Diabetes in Children and Adults
Figure 2 shows the incidence of diabetes by different glycemic measures at baseline stratified by age and sex. Among children and adolescents in both sexes, all three glycemic measures were similarly predictive.

Supplementary Table 2 lists the AUCs for each of the three tests in boys, girls, men, and women. In boys, girls, and men, the AUC for HbA_{1c} did not differ significantly from that of FPG or 2hPG. Only in women did the HbA_{1c} have a lower AUC than 2hPG (0.63 vs. 0.70, $P = 0.0012$). Supplementary Table 3 reports the sensitivities and specificities from which these AUCs were derived. The lack of a significant difference in AUC between HbA_{1c} and the glucose measures suggests that all three tests have the potential to offer
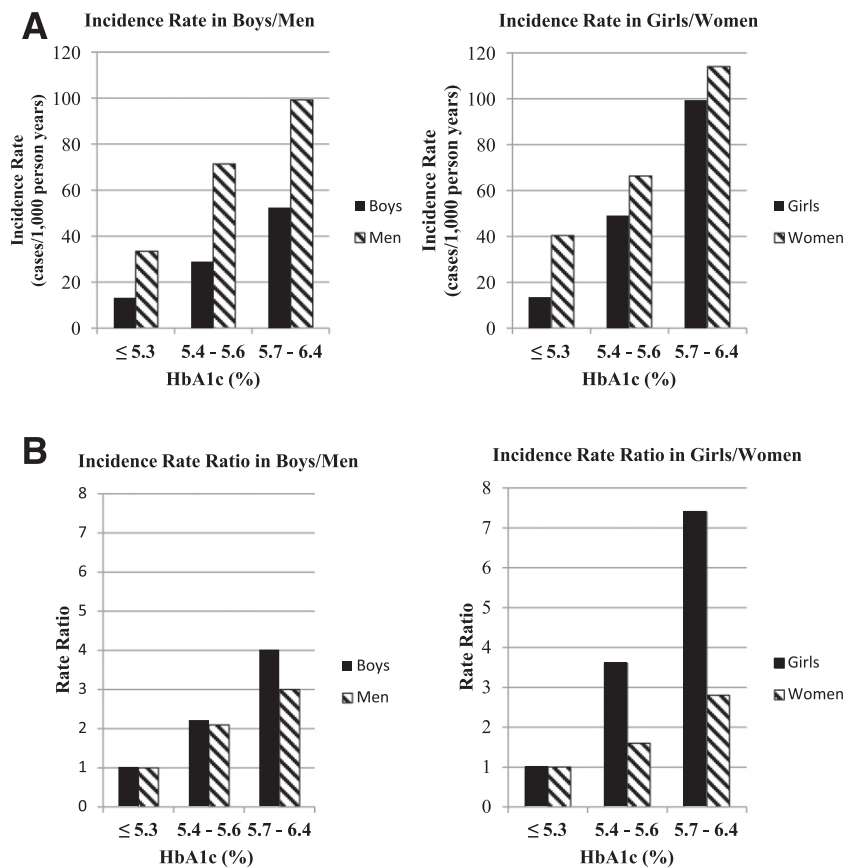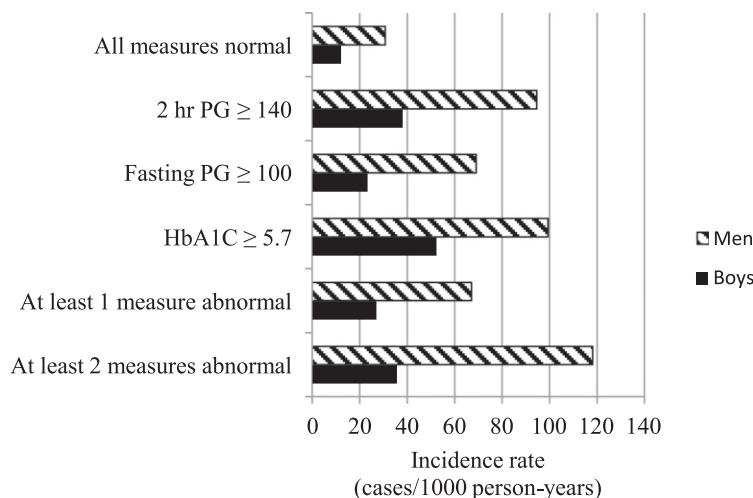

Figure 1—Incidence of type 2 diabetes by HbA_{1c} category stratified by sex. Data are presented as incidence rates (cases/1,000 person-years) (A) and as incidence rate ratios (using the incidence in the lowest HbA_{1c} category as the reference rate) (B).

A **Incidence Rate in Boys (10-19 years) and Men (20-39 years)**

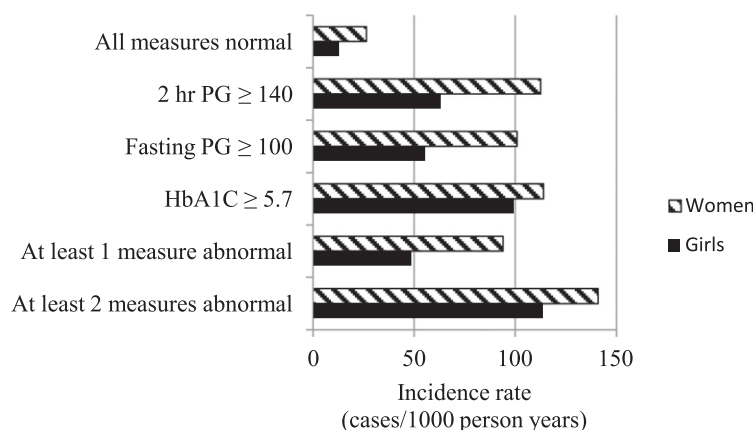**B** **Incidence Rate in Girls (10-19 years) and Women (20-39 years)**

Figure 2—Incidence of type 2 diabetes by various glycemic measures at baseline stratified by age and sex. PG, plasma glucose. Data are presented as incidence rates (cases/1,000 person-years)

the same level of sensitivity and specificity, depending on the threshold chosen.

Clinical Utility of HbA$_{1c}$

Although adults may undergo HbA$_{1c}$ screening regardless of weight, the ADA recommends testing children and adolescents ≥10 years only if their BMI is in the overweight or obese range and if they have two additional risk factors. All children and adolescents in this study had at least one risk factor, American Indian ethnicity. We classified the pediatric subjects as having parental diabetes if at least one parent was diagnosed with diabetes before the age of 45 years. The ROC curves in Fig. 3A represent the sensitivity

and specificity of HbA$_{1c}$, FPG, and 2hPG within this already higher-risk population of American Indian children and adolescents who were overweight or obese and had at least one parent with diabetes. Figure 3B depicts the same curves for the full child cohort. Among the children and adolescents who met the recommended screening criteria (overweight or obese with two additional risk factors), the estimated 10-year cumulative incidence of diabetes in those with HbA$_{1c}$ ≥5.7% was 78% (i.e., PPV) and the 10-year cumulative incidence in those with HbA$_{1c}$<5.7% was 23% (i.e., NPV = 100% − 23% = 77%). For FPG ≥100 mg/dL, the PPV was 36% and the NPV was 78%, and for 2hPG ≥140 mg/dL,

the PPV was 52% and the NPV was 80%. Differences among these values generally reflect that the specific thresholds for each test differ in specificity and sensitivity; comparable PPV and NPV could be obtained by changing the thresholds.

The current ADA thresholds for prediabetes for each of the three tests have been depicted using circular points on the ROC curves in Fig. 3, and their proximity to each other indicates that these thresholds offer a similar sensitivity and specificity. Thus, the testing method used does not affect the sensitivity and specificity with which we are able to predict diabetes in children and adolescents. An arbitrary HbA$_{1c}$ threshold of 5.4% is marked with a diamond point in Fig. 3, with a higher sensitivity (40% in the high-risk group) but a lower specificity (89% in the high-risk group). The square points in Fig. 3 represent the sensitivity and specificity offered by different combinations of current ADA thresholds. These combinations do offer a higher sensitivity than any one ADA threshold alone at the expense of lower specificity.

CONCLUSIONS

Few large longitudinal studies have assessed the predictive value of HbA$_{1c}$ measured in childhood and adolescence in predicting incident diabetes. The prevalence of prediabetes defined by impaired fasting glucose (IFG) and IGT among 12–19 year old adolescents in the U.S. based on the 2005–2006 National Health and Nutrition Examination Survey (NHANES) was 12.7% and 3.4% respectively (14). In our current study among subjects aged 10 to 19 years, the IFG prevalence at baseline was 9.2%, and the IGT prevalence, 8.1%, was higher than in NHANES. In the current study, HbA$_{1c}$ was a useful predictor of future diabetes in all age and sex categories, performing as well as or better than other measures of glycemia, except in adult women, among whom 2hPG had a significantly higher AUC than HbA$_{1c}$. HbA$_{1c}$, FPG, and 2hPG also had very similar discriminatory power within the subset of high-risk children identified by ADA criteria.

The reason for the poorer performance of HbA$_{1c}$ in adult women is uncertain. Women participants were not pregnant at baseline but of reproductive age. Iron deficiency is common in women of reproductive age, and depleted iron stores affect glycation rates and elevate HbA$_{1c}$. A study from the NHANES (1999–2006)
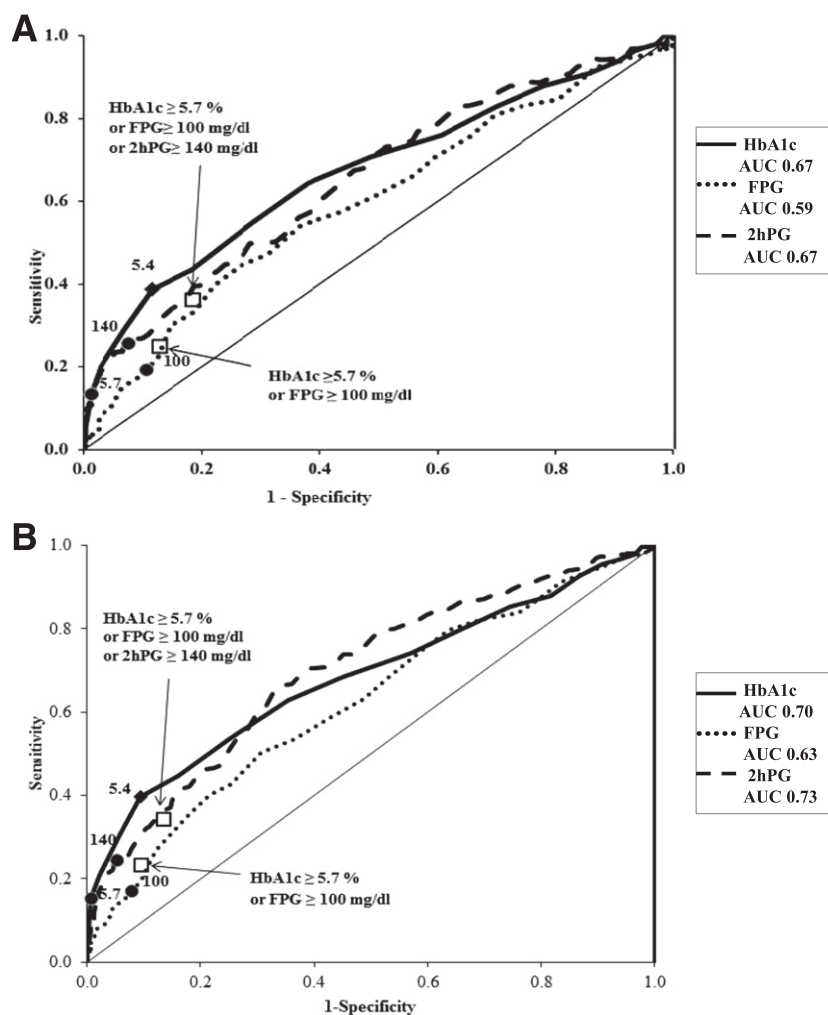
Figure 3—Sensitivity and specificity of HbA_{1c}, FPG, and 2hPG in identifying persons who developed diabetes within 10 years of screening among children and adolescents meeting ADA recommended criteria for screening (A) and among all children and adolescents in the study (B). The black circles indicate the current ADA thresholds for prediabetes for each of the three tests. The squares represent the sensitivity and specificity offered by different combinations of current ADA thresholds. The diamond indicates the arbitrary HbA_{1c} threshold of 5.4%.

showed iron deficiency was common among women (13.7%) and was associated with higher HbA_{1c} primarily at the lower end of the HbA_{1c} distribution (15). In the absence of iron studies in our cohort, we are unable to evaluate whether iron deficiency altered the HbA_{1c} at baseline among the women.

Some recent studies have expressed skepticism about using adult HbA_{1c} threshold values for diagnosing prediabetes and diabetes in children and adolescents. These studies tend to rely on cross-sectional comparisons of HbA_{1c} with previously established measures of glycemia and showed poor correlation of HbA_{1c} with FPG or 2hPG. Our current study differs, however, because we examined the value of HbA_{1c} in predicting diabetes, not in associating with

IFG or IGT. Clearly, there is little overlap among the three categorical definitions of prediabetes based on HbA_{1c}, FPG, and 2hPG, as is well recognized in adults and as we found in children and adolescents as well as in adults (Supplementary Figs. 1 and 2). We suggest the goal of screening is to identify those at high risk of developing diabetes (or who already have it) rather than detecting those who have prediabetes by different criteria. In this respect, the HbA_{1c} performs as well as the other tests.

The ADA includes HbA_{1c} as a diagnostic measure for diabetes because of its association with long-term microvascular complications in adults, including retinopathy and diabetic nephropathy. This recommendation included adult participants from the same study population we describe here,

and we reported previously that HbA_{1c} and FPG measurements in adults were just as useful as 2hPG in predicting the risk of microvascular complications (16). Another study in this population found that a sharp rise in incidence of these complications occurred at the same level of glycemia in youth and adult cohorts; however, that study compared only FPG and 2hPG (17).

In the current study, we also stratified by ADA-recommended risk factors (9). All of the subjects had at least one risk factor, American Indian ethnicity. We further stratified the cohort based on those who had at least one parent with diabetes onset before age 45 years, those who were overweight or obese, or both. We used the parental onset age of 45 years because we previously showed that the prevalence of type 2 diabetes is particularly high in offspring whose parents both had diabetes before age 45 in this population (18). We find that the current prediabetes definition of $HbA_{1c} \geq 5.7\%$ had a sensitivity of ~13% and a specificity of ~99% in overweight children with two additional risk factors (one risk factor unique to our study being American Indian ethnicity) for predicting the 10-year incidence of diabetes. Of course, the sensitivity would be increased by using a lower threshold; for example, sensitivity was 39% and specificity 88% at an $HbA_{1c} \geq 5.4\%$ (Fig. 3).

Our study was conducted in a specific population group with a high prevalence of diabetes that is almost exclusively type 2 diabetes (18). Past studies have established that mutations in the maturity-onset diabetes of the young genes are not a major cause of diabetes among youth in this population (19). Though variation in HbA_{1c} reliability has been reported among African, Mediterranean, and Southeast Asian populations, hemoglobinopathies prevalent in these populations that could interfere with the HbA_{1c} interpretation have not been commonly reported in American Indians (20). HbA_{1c} results also vary with red cell dynamics and assay methods (21–23). Thus, the generalizability of our results to populations with a lower prevalence of type 2 diabetes, a higher prevalence of type 1 diabetes, or a higher prevalence of hemoglobinopathies or disorders affecting hemoglobin turnover is uncertain.

The strengths of our study include both a large pediatric and adult cohort, examinations with all three glycemia tests performed at the same time, and an

extensive longitudinal follow-up period. Also, all of our laboratory tests, including HbA_{1c} assays, were performed at the same laboratory using standardized methods.

In summary, higher HbA_{1c} at baseline predicted a higher incidence of diabetes in both children and adults. Although the absolute incidence rates were greater in adults, the incidence rate ratios were the same or greater in children. When incidence rates were compared with various abnormalities in glycemic measures (HbA_{1c}, FPG, and 2hPG) at baseline, individually or combined, HbA_{1c} performed as well as FPG and 2hPG in boys, girls, and men, but not as well as 2hPG in adult women. We therefore conclude that HbA_{1c} can be used to assess risk for diabetes in children or to identify children with prediabetes with the same confidence as FPG or 2hPG.

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