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Screening for Type 2 Diabetes in Obese Youth

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KEY WORDS

fasting blood glucose, HOMA-IR, oral glucose-tolerance test, 1,5-anhydroglucitol, hemoglobin A1c, receiver operator characteristic analysis

ABBREVIATIONS

ADA—American Diabetes Association

AUC—area under the curve

BG—blood glucose

HbA1c—hemoglobin A1c

HOMA-IR—Homeostasis Model of Assessment for Insulin Resistance

IGT—impaired glucose tolerance

OGTT—oral glucose-tolerance test

ROC—receiver operator characteristic analysis

T2DM—type 2 diabetes mellitus

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WHAT'S KNOWN ON THIS SUBJECT: Easily implemented screening tests for T2DM in children would facilitate early intervention. Although at least 3 such tests have been examined in adults (fasting BG, HbA1c, and 1,5-anhydroglucitol), they have not been systematically compared in obese children.



WHAT THIS STUDY ADDS: We compared HbA1c, 1,5-anhydroglucitol, fasting BG, and a measure of insulin resistance for effectiveness in identifying patients with diabetes in a large pediatric obesity clinic population, finding that the first 2 tests are potentially useful for screening purposes.

abstract

OBJECTIVE: To assess available blood tests as potential screening tools for impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM).

METHODS: We studied 468 obese (BMI mean: 34.4 kg/m²) children, including a subgroup with serum fasting insulin levels of >15 μIU/mL. Fasting laboratory tests included measurements of serum glucose and insulin, hemoglobin A1c (HbA1c), and 1,5-anhydroglucitol (insulin-resistant subgroup only) levels. An oral glucose-tolerance test was performed on each patient, and 2-hour postload serum glucose and insulin levels were obtained. Fasting blood glucose (BG), Homeostasis Model of Assessment for Insulin Resistance (HOMA-IR), HbA1c, and 1,5-anhydroglucitol values were used as predictors for exceeding various 2-hour BG cut-offs. Receiver operator characteristic curves were fitted to determine area-under-the-curve values as measures of screening efficacy.

RESULTS: In the insulin-resistant subgroup, 3 (2%) patients had T2DM and 23 (12%) had IGT. Optimal sensitivity and specificity to detect T2DM were, respectively, 99% and 96% at HbA1c ≥ 6.0%, and 96% and 88% at 1,5-anhydroglucitol < 17.0 μg/mL, with lower values for fasting BG and the HOMA-IR. In the entire study group, 9 (2%) patients had T2DM and 44 (9%) had IGT. Optimal sensitivity and specificity to detect T2DM were, respectively, 86% and 85% at HbA1c levels of 5.7%, 88%, and 93% at a fasting BG level of 104 mg/dL, and 62% and 70% at an HOMA-IR of 7.9.

CONCLUSIONS: HbA1c, 1,5-anhydroglucitol, and fasting BG levels are good predictors of T2DM in obese children, whereas HOMA-IR values are not. HbA1c and 1,5-anhydroglucitol are excellent predictors of T2DM in insulin-resistant obese children. *Pediatrics* 2009;124:573–579

The prevalence of overweight children and adolescents has tripled over the past few decades.¹ In addition, there has been a striking rise in the incidence of type 2 diabetes mellitus (T2DM), a disease once thought unique to the adult population. A recent evaluation of a National Health Survey estimates that 1 in 3 children born in the United States in the year 2000 will develop diabetes.² In some demographic groups, up to 45% of newly diagnosed diabetic children are classified as non-immune mediated.³ This epidemic has a staggering economic impact on society, with an estimated \$174 billion spent on diabetes care and diabetic-related complications in 2007 alone. Approximately \$1 in \$5 US health care dollars is spent caring for someone with diabetes.⁴

These overwhelming statistics highlight the importance of identifying at-risk individuals predisposed to developing diabetes and targeting them for early intervention. The American Diabetes Association (ADA) and World Health Organization recognize an intermediary or "prediabetic" classification comprising those with impaired fasting glucose levels and/or impaired glucose tolerance for whom earlier prevention methods and treatment are indicated. However, identifying these individuals requires fasting laboratory measurements that are cumbersome for both the primary care physician and patient to complete. In a recent study surveying pediatric practices, a majority of practitioners reported failing to follow ADA-established guidelines for diabetic screening (using the oral glucose-tolerance test [OGTT] or fasting glucose), with only 40% adherence for moderate-risk patients and 58% adherence for patients at high risk. Limited clinician time for appropriate screening counseling was reported as a major barrier to compliance. Moreover, the use of nonfasting

tests was preferred by the physicians surveyed because of patient history of noncompliance with medical management and costs/limitations of transportation, thus avoiding the requirement of a second visit to obtain a fasting blood sample.⁵ Therefore, there is potential utility in finding a more convenient stratification tool for identifying these high-risk patients.

This study assesses several blood tests (for hemoglobin A1c [HbA1c] and fasting glucose levels and the Homeostasis Model of Assessment for Insulin Resistance [HOMA-IR]) and a newer marker recently introduced in the United States (1,5-anhydroglucitol), as potential screening tools for impaired glucose tolerance (IGT) and diabetes in obese insulin-resistant children.

METHODS

Design

The study protocol was reviewed and approved by the institutional review board of the University of Texas Southwestern Medical Center. Patients were referred by community physicians to the Center for Obesity and its Consequences in Health clinic, a subdivision of the Endocrinology Center at Children's Medical Center (Dallas, TX). For the insulin-resistant subgroup, patients were solicited for the study if they had fasting insulin levels of $>15 \mu\text{IU/mL}$. Written informed consent was obtained from the parent or guardian of each subject, and an assent to participate in the study was obtained from each subject >10 years of age. Criteria for excluding patients included known renal disease and those patients already taking medications for glycemic control and/or medications with known renal toxicity. A fasting blood sample was obtained from each new patient and tested for glucose, insulin, and HbA1c levels. All HbA1c tests were performed on a DCA2000+ analyzer (Bayer Corporation, Elkhart, IN) with

intraassay and interassay precision rates of 1.7% to 3.5% and 2.7% to 4.1%, respectively.⁶ An OGTT using 1.75 g/kg of glucose (maximum: 75 g) was performed on each new patient in the fasting state beginning at 8 AM, and 2-hour postload glucose (2-hour blood glucose [BG]) and insulin levels were measured. Glucose levels were determined in the laboratory at Children's Medical Center by using a 2-step enzymatic assay (hexokinase and glucose-6-phosphate dehydrogenase; Dade Behring Dimension analyzer [Siemens, Deerfield, IL]). Insulin levels were measured by a solid-phase, 2-site, chemiluminescent immunometric assay (Siemens Immulite 2000).

After informed consent, 1 mL of additional blood was obtained along with the initial blood draw. Samples were processed in the main hospital laboratory where serum was isolated and frozen at -80°C . If insulin levels were $>15 \mu\text{IU/mL}$, frozen serum samples were sent to Esoterix (Calabasas Hills, CA) to determine 1,5-anhydroglucitol levels (GlycoMark, The Biomarker Group, Winston-Salem, NC). Intraassay and interassay precision ranges were 1.3% to 3.8% and 0.8% to 3.8%, respectively.⁷

Data collected from the medical charts included age, gender, race, weight, height, fasting insulin and glucose levels, HbA1c level, and 2-hour postload insulin and glucose levels. 1,5-Anhydroglucitol values were reported directly to the study coordinator. HOMA-IR values were calculated from fasting insulin and glucose levels: $(\text{fasting insulin } [\mu\text{IU/mL}] \times \text{fasting glucose } [\text{mg/dL}]) / 405$.

Definitions

The OGTT was considered the gold standard in this study. A patient was classified as having IGT if the 2-hour BG value was $\geq 140 \text{ mg/dL}$ and $< 200 \text{ mg/dL}$. T2DM was diagnosed in patients with a 2-hour BG value of $\geq 200 \text{ mg/dL}$.

TABLE 1 Demographic Data of Study Patients

	Insulin-Resistant Subgroup			Entire Cohort		
	Girls (N = 130)	Boys (N = 63)	Total (N = 193)	Girls (N = 271)	Boys (N = 197)	Total (N = 468)
Age						
Mean, y	12.8	12.7	12.8	12.4	12.6	12.5
SE	0.2	0.4	0.2	0.2	0.2	0.2
BMI						
Mean, kg/m ²	34.1	35.4	34.4	34.8	33.8	34.4
SE	0.6	0.9	0.5	1.1	0.8	0.8
T2DM, n	—	—	3	—	—	9
IGT, n	—	—	23	—	—	44

Statistical Analysis

Descriptive statistics were compiled in Microsoft Excel (Microsoft, Redmond, WA). Receiver-operator-characteristic (ROC) curves were constructed with use of a Web-based program, JLAB-ROC4,⁸ which fits continuously distributed test data to a binary gold standard (eg, normal/affected) by using the maximum-likelihood fit to a binormal model.

RESULTS

Two-hundred twenty pediatric patients were enrolled in the study between February 23, 2007, and January 11, 2008, with 193 patients (insulin-resistant subgroup) meeting study criteria for insulin resistance. Demographic data are presented in Table 1. There were no significant differences between girls and boys with respect to age, BMI, or ethnicity (~25% black, 50% Hispanic, 15% white, 7% other or mixed ethnicity). Although 1,5-anhydroglucitol levels have been reported to differ in boys and girls,⁷ we found no such differences and, therefore, combined data on boys and girls for all additional analyses.

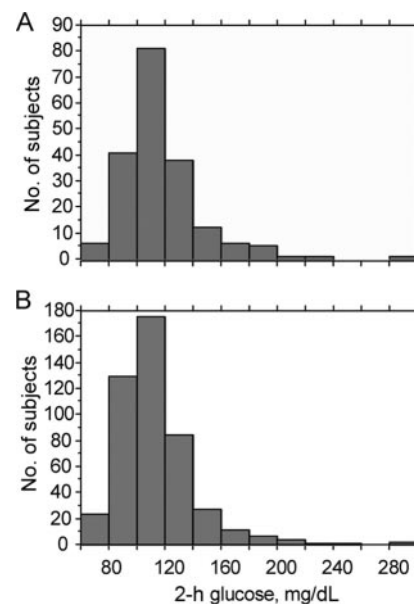
To confirm findings regarding screening efficacy of HbA1c, fasting BG, and HOMA-IR in a larger group of patients who had not been preselected for fasting insulin levels, records were reviewed of all obesity clinic patients from the start of the study until August 2008, yielding a group of 468 subjects.

This group (hereafter referred to as the entire cohort), included the insulin-resistant subgroup, patients (February 2007 to January 2008) who had not been recruited into, or failed to meet criteria for, the insulin-resistant subgroup (therefore most of these patients had been negatively selected to have fasting insulin levels of <15 μ U/mL), and all obesity clinic patients from January 2008 until August 2008. The entire cohort did not differ significantly in age, BMI, or prevalence of T2DM or IGT from those in the insulin-resistant subgroup (Table 1).

For the patients enrolled in the insulin-resistant subgroup, the BG values 2 hours after glucose load (2-hour BG) are shown in Fig 1. Three (1.6%) patients had frank T2DM (2-hour BG value > 200 mg/dL) and 23 (12%) had IGT (140 < 2-hour BG value < 200 mg/dL). One patient with IGT (2-hour BG value of 188 mg/dL) had a fasting glucose value above the T2DM threshold (134 mg/dL).

We evaluated relationships between 2-hour BG levels and each of the following: HbA1c, 1,5-anhydroglucitol, HOMA-IR, and fasting BG values. All 4 of these parameters were moderately correlated with 2-hour BG (R^2 : ~0.1 to 0.2 on log-transformed values, Fig 2), with fasting glucose being best correlated with 2-hour BG.

We used ROC analysis to determine which of these 4 parameters best predicted elevated levels of 2-hour BG. ROC

**FIGURE 1**

OGTT: BG values after oral glucose administration in the insulin-resistant subgroup (A) and the entire cohort (B).

curves (Fig 3) are plotted as the fraction of true-positives (or sensitivity) against fraction of false-positives (1-specificity) and screening efficacy expressed as area under the curve (AUC). A completely predictive test (ie, a critical value for the predictor exists such that all true-positives are detected before any false-positives) has an AUC of 1.0, whereas a predictor that does no better than random chance (equal proportions of true-positives and false-positives are detected at any critical value) has an AUC of 0.5. Because ROC analysis requires a binary gold standard, but 2-hour BG values are continuously distributed, we repeated the ROC analysis at 10 mg/dL intervals for all 2-hour BG threshold values from >80 mg/dL to >200 mg/dL (Figs 3 and 4).

In the insulin-resistant subgroup, all 4 screening tests predicted IGT only moderately well, with AUC values of ~0.7. However, both HbA1c and 1,5-anhydroglucitol improved in their ability to predict high 2-hour BG levels as the threshold value of 2-hour BG

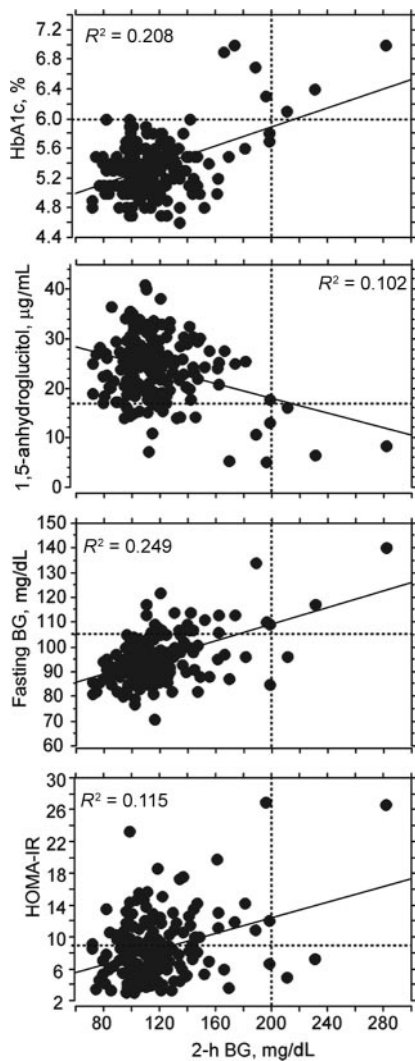


FIGURE 2

Correlations of each screening test as a function of the 2-hour postload glucose level (insulin-resistant subgroup only). Diagonal lines denote fitted linear regression equations. The dotted horizontal lines indicate critical values for each screening test for detecting T2DM (2-hour BG value of ≥ 200 mg/dL, the dotted vertical line) with minimum misclassification, as determined from ROC analysis (see Table 2). Note that there are no 2-hour BG values in the bottom-right quadrant of the HbA1c plot and the top-right quadrant of the 1,5-anhydroglucitol plot, which demonstrates discriminating capabilities of these 2 tests to detect T2DM (ie, all 2-hour BG values of ≥ 200 mg/dL had an HbA1c value of $> 6\%$ and a 1,5-anhydroglucitol value of < 17.0 $\mu\text{g/mL}$) despite modest linear correlation (R^2) of each screening test with the 2-hour BG level.

increased (Fig 4). These 2 tests had excellent ability to predict T2DM, with AUC values of 0.99 and 0.96, respectively (Table 2). On the basis of the fit-

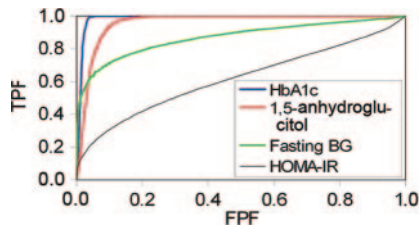


FIGURE 3

ROC curves for the screening tests to detect 2-hour postload glucose values of ≥ 200 mg/dL (insulin-resistant subgroup). ROC curves plot the sensitivity (or true-positive fraction) versus 1-specificity (or false-positive fraction) of the test. The theoretical best ROC curve has a square profile, yielding an AUC value of 1.0, indicating 100% sensitivity and specificity. A diagonal line from the lower left to the top-right corner (not shown) would yield an AUC value of 0.5, indicating no ability to discriminate between affected and unaffected individuals. TPF indicates true-positive fraction; FPF, false-positive fraction.

ted ROC curves, the optimal sensitivity and specificity for HbA1c were 99% and 96%, respectively, at a critical value of 6.0% (ie, HbA1c values $\geq 6.0\%$ predicted T2DM), and the optimal sensitivity and specificity for 1,5-anhydroglucitol were 96% and 88% at a critical value of 17.0 $\mu\text{g/mL}$ (values < 17.0 $\mu\text{g/mL}$ predicted T2DM). The 1 patient diagnosed with T2DM by elevated fasting glucose alone (134 mg/dL) was not included as an affected case in the ROC analysis, but would have been identified by either HbA1c or 1,5-anhydroglucitol screening tests (6.7% and 10.7 $\mu\text{g/mL}$, respectively).

Fasting BG and HOMA-IR values were less effective predictors of T2DM, with AUC values of 0.87 and 0.62, respectively.

In the entire cohort, HbA1c and fasting BG had similar screening efficacy for T2DM (Table 2), with AUC values of 0.94 and 0.97, and HOMA-IR remained a poor predictor with an AUC value of 0.71. Optimal sensitivity and specificity for predicting T2DM were 86% and 85%, respectively, at an HbA1c value of 5.7, and 88% and 93%, respectively, at a fasting BG value of 104 mg/dL.

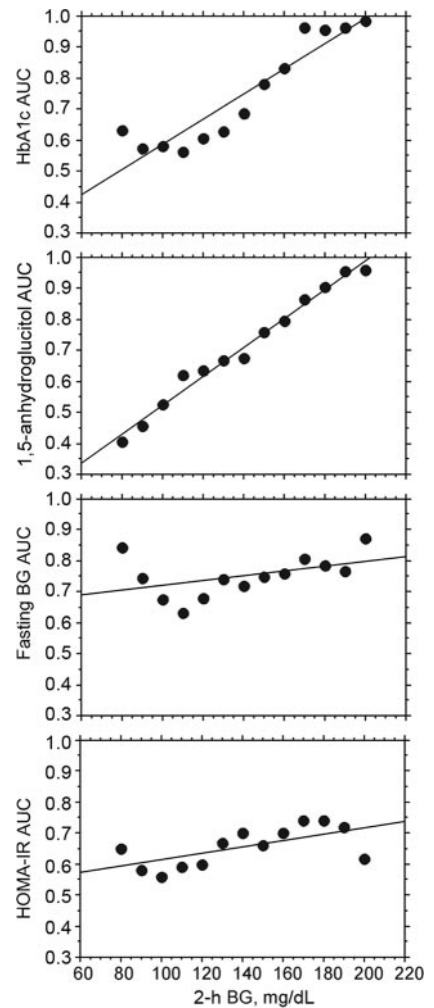


FIGURE 4

ROC AUC values for each screening test plotted against the 2-hour BG cutoff used to dichotomize the subjects into unaffected and affected groups (insulin-resistant subgroup). Note the linearity of the 1,5-anhydroglucitol AUC values, indicating that this test discriminates better as the 2-hour BG threshold increases.

DISCUSSION

Efficacy of Screening for T2DM

To the best of our knowledge, this study is unique in comparing different methods as screening tools for IGT and T2DM in the obese pediatric population. Our study demonstrates that HbA1c, fasting BG, and (at least in those who have elevated fasting insulin levels) 1,5-anhydroglucitol are able to discriminate those with and without T2DM among obese children. These findings are generally consistent with previous studies in adults.⁹⁻¹⁴

TABLE 2 Critical Values for Screening T2DM by Using Various Tests

	ROC AUC	SE	Minimize Misclassification			95% Sensitivity		95% Specificity	
			Critical Value	Sens %	Spec %	Critical Value	Spec %	Critical Value	Sens %
Insulin-resistant subgroup, <i>N</i> = 193 (3) ^a									
HbA1c	0.987	0.008	6.0%	99	96	6.0%	97	5.9%	100
1,5-anhydroglucitol	0.961	0.026	17.0 μg/mL	96	88	16.5 μg/mL	89	14.3 μg/mL	74
Fasting BG	0.871	0.148	105 mg/dL	74	87	90 mg/dL	28	110 mg/dL	64
HOMA-IR	0.618	0.204	9.5	50	70	3.5	3	14.7	23
Entire cohort, <i>N</i> = 468 (9) ^a									
HbA1c	0.935	0.042	5.7%	86	85	5.5%	66	6.0%	67
Fasting BG	0.968	0.036	104 mg/dL	88	93	99 mg/dL	80	106 mg/dL	86
HOMA-IR	0.709	0.098	7.9	62	70	3.0	12	14.3	27

Sens indicates sensitivity; Spec, specificity.

^a For number of subjects included in each analysis, the number of patients with T2DM is listed in parentheses.

Current standards for identifying IGT and T2DM in children are the same as those in adults. The ADA recommends screening overweight patients who possess at least 2 of the following risk factors: family history of T2DM including maternal history of gestational diabetes, race/ethnicity (Native Americans, blacks, and Hispanic Americans), and/or other conditions associated with insulin resistance (such as polycystic ovarian syndrome and metabolic syndrome). The recommended screening methods include either fasting plasma glucose or 2-hour OGTT.¹⁵ Identifying IGT and intervening with therapies such as lifestyle modification and/or drug treatment reduces the incidence of T2DM in adults (reviewed by Nathan et al¹²). In addition, IGT in adults predicts hospitalization¹⁶ and death¹⁷ independently of progression to T2DM.

Population-based screening for IGT among children and adolescents may be advantageous. Children with IGT or T2DM potentially face many years of hyperglycemia and, thus, may have an increased lifetime risk of developing complications. Thus, intervention may be particularly beneficial in this population. In addition, most children are enrolled in school and could be readily ascertained by school-based screening programs.

With these considerations in mind, many school districts in Texas have

mandated screening for acanthosis nigricans,¹⁸ a skin condition that is often a sign of insulin resistance. However, this has a low positive predictive value for T2DM¹⁹ (and the present study, data not shown). Such screening programs can prompt relatively low-yield medical evaluations of many children, overwhelming both primary care practices and endocrinologists.²⁰ The present study suggests that available screening methods have only modest power to predict IGT, consistent with previous observations in adolescents²¹ and adults.^{9–11} This probably reflects the different pathophysiology underlying impaired fasting glucose and impaired glucose tolerance.¹⁴ However, there are several potential strategies for more effective screening of obese children for T2DM. Although fasting BG is a good screening test for T2DM, it may be cumbersome to implement in routine pediatric practice.⁵ One straightforward alternative would be to obtain blood for 1,5-anhydroglucitol assays in primary physicians' offices, which should identify most children with T2DM (at least those with elevated fasting insulin levels). 1,5-Anhydroglucitol is maintained in the serum at a constant rate. In normoglycemia, renal absorption of 1,5-anhydroglucitol is almost 100%. However, renal absorption is competitively inhibited by glucosuria, causing the serum 1,5-anhydroglucitol level to de-

crease. This level is reflective of glycemic control over the previous 2 weeks.²² This test does not require patients to be fasting, but it may not be reliable in children with impaired renal function.

Although our findings suggest that HbA1c is a good predictor of T2DM, there are drawbacks that make it potentially unreliable as a uniform screening tool. HbA1c is biochemically heterogeneous and is assayed by widely divergent methodologies with differing sensitivities to interfering factors such as hemoglobin variants (eg, sickle cell disease), chemically modified hemoglobin derivatives (eg, carbamyl-hemoglobin), and conditions that alter red blood cell processing and disposal (transfusion, hemolysis).¹⁰ At present, there is a lack of consensus regarding assay standardization with the most recent method relying on a tandem mass spectroscopy approach that is not practical to implement in clinical laboratories. The lack of consistency makes it difficult to set critical values and compare studies evaluating this test as a screening tool.^{10,23} This problem could be addressed by mandating a single HbA1c assay method for a screening program, whether based in primary physicians' offices or schools.

To best target interventions to prevent T2DM, it might be most useful to identify individuals with more severe IGT who are close to passing, but have not yet passed, the glycemic threshold for

diabetes. Although methods for ROC analysis with a continuous gold standard have been recently published,²⁴ to the best of our knowledge, the simultaneous optimization of threshold values for both a screening test and a gold standard has not previously been attempted. The plots of ROC AUC values against different 2-hour BG thresholds (Fig 4) suggest that, at least in children with elevated fasting insulin levels, both 1,5-anhydroglucitol and HbA1c may be very good screening tests for severe IGT (eg, 2-hour BG levels of >180 mg/dL).

Limitations of This Study

Because 1,5-anhydroglucitol levels were measured only in the subjects in the insulin-resistant subgroup (fasting insulin levels >15 μ IU/mL), we cannot yet determine if 1,5-anhydroglucitol levels effectively predict severe IGT or

T2DM in the general obese pediatric population. There were relatively few cases of T2DM in the study groups; however, the SEs for the estimates of AUC for 1,5-anhydroglucitol and especially for HbA1c were quite small (Table 2), providing a high degree of confidence for these measures of screening efficacy. HbA1c assays were run on 2 machines that were calibrated daily, and 1,5-anhydroglucitol assays were run in a single batch in a single reference laboratory. It is thus uncertain whether the screening efficacy we obtained with these methods can be replicated in practice. Because of the difficulty with standardization of HbA1c assays discussed previously, particular caution is urged in using the data in the present study to guide therapeutic decisions on the basis of HbA1c values obtained in the community.

CONCLUSIONS

HbA1c, fasting BG, and 1,5-anhydroglucitol levels are all good predictors of T2DM in obese children, whereas HOMA-IR values are not. HbA1c and 1,5-anhydroglucitol are excellent predictors of T2DM in prescreened, insulin-resistant, obese children.

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