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Screening Obese Children and Adolescents for Prediabetes and/or Type 2 Diabetes in Pediatric Practices: A Validation Study

Preneet C. Brar, MD[1], Lisa Mengwall, BA[1], Bonita H. Franklin[1], and Arthur H. Fierman, MD[1]

Abstract

Background. Increased prevalence of type 2 diabetes mellitus (T2DM) makes it important for pediatricians to use effective screening tools for risk assessment of prediabetes/T2DM in children. *Methods*. Children (n = 149) who had an oral glucose tolerance test (OGTT) and glycated hemoglobin (HbA1c) were studied. American Diabetes Association recommended screening criteria—HbA1c ≥5.7% and fasting plasma glucose (FPG) ≥100 mg/dL—were compared against OGTT. The homeostatic model assessment of insulin resistance (HOMA-IR), a mathematical index derived from fasting insulin and glucose, was compared with OGTT. We studied whether combining screening tests (HbA1c and fasting glucose or HbA1c and HOMA-IR) improved accuracy of prediction of the OGTT. *Results*. HbA1c of ≥5.7% had a sensitivity of 75% and specificity of 57% when compared with the OGTT. Combining screening tests (HbA1c ≥5.7% and FPG ≥100 mg/dL; HbA1c ≥5.7% and HOMA-IR ≥3.4) resulted in improved sensitivity (95.5% for each), with the HbA1c-FPG doing better than the HbA1c-HOMA-IR combination in terms of ability to rule out prediabetes (likelihood ratio [LR]) negative. 0.07 vs 0.14). *Conclusions*. HbA1c of ≥5.7% provided fair discrimination of glucose tolerance compared with the OGTT. The combination of HbA1c and FPG is a useful method for identifying children who require an OGTT.

Keywords

obesity, children & adolescents, insulin resistance, prediabetes/ Type 2 diabetes, screening tools

Background

The childhood obesity epidemic has led to an exponential increase in type 2 diabetes in children and youth.[1] Population studies in children have shown that rates of prediabetes/type 2 diabetes mellitus (T2DM) are rising.[2] Early detection of prediabetes in particular is key to restoring normal glucose tolerance (NGT) because use of either lifestyle modification[3] and/or medications such as metformin,[4] or both, have proven to be effective in reversing prediabetes. Therefore, defining effective screening tools for pediatricians is an important task, and validating these measures against a diagnostic standard such as OGTT is warranted.

The American Diabetes Association (ADA) recommends screening at-risk children using fasting plasma glucose (FPG) or oral glucose tolerance test (OGTT) every 2 years starting at 10 years of age or at the onset of puberty,[5] although the ADA statement acknowledges that further investigation is still needed to identify the best screening method.

The current ADA screening recommendation, which requires the child to be fasting, presents a challenge to the practicing pediatrician. Even though the FPG may be preferred for practical reasons (one blood draw), it is less sensitive than the OGTT because it cannot identify individuals with impaired glucose tolerance (IGT-defined by the ADA as a blood glucose ≥140 mg/dL 2 hours post–oral glucose challenge), which has been identified as the strongest predictor of type 2 diabetes in youth.[6]

OGTT, considered the clinical diagnostic standard for diagnosing prediabetes/T2DM, requires scheduling and involves at least 2 blood draws (0 and 120 minutes), which can be a logistical challenge in busy pediatric

[1]New York University School of Medicine, New York, NY, USA

Corresponding Author:
Preneet C. Brar, Department of Pediatrics, New York University School of Medicine, 462 First Avenue, NBV 8S4-8S11, New York, NY 10016, USA.
Email: Preneet.brar@nyumc.org

practices.[7] A 2006 survey revealed that most pediatricians followed screening practices that differed from ADA recommendations.[8] Similarly, a chart review of 7710 children and adolescents who met the ADA criteria for screening found that only 21.3% underwent the recommended screening for diabetes.[9] These studies highlight barriers to effective screening for prediabetes/T2DM.

Several alternatives to the ADA screening recommendations have been considered, the most recent being glycated hemoglobin (HbA1c). In 2011, the ADA specified using HbA1c measurements in the range of 5.7% to 6.4% and ≥6.5% for diagnosing prediabetes and diabetes, respectively.[10] HbA1c is a non-fasting test, which makes it a more convenient test for screening purposes. Though recommended for adults, many in the pediatric community have used these cutoffs without obtaining pediatric data to confirm their relevance in children and adolescents.

HOMA-IR (homeostatic model assessment of insulin resistance) a mathematical index that uses fasting glucose and insulin to measure insulin resistance, is predictive of the development of T2DM in at-risk populations.[11] HOMA-IR has been validated in children against the gold standard hyperinsulinemic euglycemic clamp,[12] a test of insulin resistance typically performed in a clinical research setting. However, although validated as a measure of insulin resistance, there are no thresholds developed to use HOMA-IR as a risk predictor of prediabetes/T2DM in pediatrics.

We wish to contribute to the body of evidence that is being generated to answer how best to screen children and adolescents at greatest risk for prediabetes/T2DM.

Therefore, the goals of our study were as follows:

1. To evaluate the accuracy of HbA1c and HOMA-IR as single screening tests for prediabetes/T2DM in obese children and adolescents (compared with the OGTT criterion standard) and
2. To assess whether combining HbA1c with either fasting glucose or HOMA-IR increases the accuracy of diagnosing prediabetes/T2DM as confirmed by a positive OGTT result.

Methods

After institutional review board approval, a retrospective chart review of patients who had been referred to the pediatric endocrine clinic from 2005 to 2012 at Bellevue Hospital was performed. Obese patients who were referred to the clinic with a suspicion of diabetes, and/or related morbidities such as abnormal values of glucose, insulin, HbA1c, polycystic ovary syndrome, dyslipidemia, hypertension, acanthosis nigricans, and metabolic syndrome and who had both OGTT and HbA1c tests performed within 3 months of one another were included in the study. Fasting and 2-hour glucose and insulin values, HbA1c, height, weight, BMI, age, sex, ethnicity, and reason for referral were recorded.

Criterion Standard (Outcome Variable)

The OGTT was performed after an overnight fast. Oral glucose solution was consumed under supervision, at a dose of 1.75 g/kg of glucose to a maximum of 75 g, and blood samples for plasma glucose and insulin were collected at 0, 60 minutes, and 120 minutes. Based on ADA criteria for an OGTT, NGT was defined as fasting glucose ≤99 mg/dL and 2-hour glucose ≤139 mg/dL; impaired fasting glucose (IFG) was defined as a fasting glucose of 100 to 125 mg/dL; IGT was defined as a 2-hour glucose level of 140 to 199 mg/dL. Patients who met the definition for IFG and/or IGT were considered to have prediabetes. Those with fasting glucose ≥126 mg/dL and/or 2- hour glucose ≥200 mg mg/dL were considered to have diabetes.[10] Glucose analysis was performed by the glucose hexokinase II method (Seimens, Tarrytown, NY), and insulin analysis was performed by radioimmunoassay (Quest Diagnostics, Teterboro, NJ)

Predictor Variables

HbA1c assays were done between 2005 and 2010 using borate affinity chromatography (Belleveu Hospital) and then by immune turbidimetric calorimetry (Quest Diagnostics, Teterboro, NJ). Both these methods met the NGSP (National Glycohemoglobin Standardization Program) certification.

HOMA-IR, a validated measure of insulin sensitivity,[13] was calculated using the following values for fasting glucose and insulin: HOMA-IR = [Fasting plasma insulin (FPI; in μIU/mol) × FPG (in mmol/L)]/22.5. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. BMI percentiles and *Z* scores were obtained using age and gender-specific reference data.[14]

Statistical Analysis

Statistical analyses were performed using SPSS version 20. Those with diabetes and prediabetes (IFG and/or IGT) were considered together as a group for statistical analysis of test performance. The OGTT outcome was considered positive if fasting glucose was ≥100 mg/dL and/or 2-hour glucose was ≥140.

Analyses of test performance of HbA1c, HOMA-IR, FPG, and combinations of tests using OGTT as the gold

Table 1. Clinical Features of the Study Population According to Oral Glucose Tolerance Test (OGTT) Results (n = 149).[a]

	Normal, n = 125	Prediabetes,[b] n = 21	Diabetes,[b] n = 3
Age (years)	13.8 ± 3.1	13.0 ± 3.7	13.5 ± 0.1
Sex (%) M/F	38.4/61.6	33.3/66.7	33.3/66.7
Race/Ethnicity: H/W/B/A/O	74/2/8/7/9	57/5/5/14/19	33/0/0/67/0
BMI *Z* score	2.3 ± 0.5	2.1 ± 0.7	2.1 ± 0.5
Fasting glucose (mg/dL)	85.4 ± 7	100.4 ± 10	143.3 ± 60
2-Hour glucose (mg/dL)	98.0 ± 20	131.3 ± 29	266.3 ± 84
Fasting insulin (μIU/mL)	16.8 ± 12	23.2 ± 17	51.5 ± 40
2-hour insulin (μIU/mL)	74.1 ± 61	127.1 ± 108	290 ± 1
HbA1c	5.6 ± 0.3	5.9 ± 0.5	7.3 ± 0.9
HOMA-IR	3.6 ± 2.6	5.8 ± 4.5	13.1 ± 8.8

Abbreviations: M, male; F, female; A, African-American, H, Hispanic; W, white; B, black; O, other; BMI, body mass index; HbA1c, glycated hemoglobin; HOMA-IR, Homeostatic Model of Assessment for insulin resistance.
[a]Values represent mean ± standard deviation, except as otherwise noted.
[b]Prediabetes is defined as fasting plasma glucose (FPG) ≥100 mg/dL and/or 2-hour OGTT glucose 140 to 199 mg/dL; diabetes is defined as FPG ≥126 mg/dL and/or 2-hour OGTT glucose ≥200 mg/dL.

standard included sensitivity, specificity, positive predictive value, and negative predictive value and likelihood ratio (positive and negative) at various thresholds. Receiver operating characteristic (ROC) curves were used to provide the area under the curve (AUC) as a measure of diagnostic accuracy and also serve to illustrate the variation of sensitivity and specificity with changes in the threshold value of the screening test.

Results

Individual Tests as Predictors of Prediabetes/T2DM

Data from 149 obese patients meeting the study criteria were collected and analyzed. HbA1c and OGTT were measured on the same day in 55% of patients and within 1 month in 75%. The mean (standard deviation) number of days between tests was 13 (19) days. Table 1 summarizes the demographic, anthropometric, and laboratory data of the study group organized by their OGTT diagnoses: normal (n = 125), prediabetes (n = 21), diabetes (n = 3). Of the 21 patients with prediabetes, 12 had IFG alone, 5 had IGT alone, and 4 had both IFG and IGT. The majority of the patients (71.1%) were Hispanic, and 62.4% of the patients were female.

Table 2. Screening Tests to Predict Prediabetes/T2DM.[a]

	OGTT Diagnosis		
	Prediabetes or T2DM	Normal Glucose Tolerance	Total
HbA1c			
Positive[b]	18	53	71
Negative[c]	6	72	78
Total	24	125	149
HOMA-IR			
Positive[b]	13	42	55
Negative[c]	5	65	70
Total	18	107	125
FPG			
Positive[b]	18	0	18
Negative[c]	6	125	131
Total	24	125	149
HbA1C and HOMA-IR in combination			
Either or both positive[b]	21	77	98
Both negative[c]	1	38	39
Total	23	115	137
HbA1c and fasting glucose in combination			
Either or both positive[b]	23	53	76
Both negative[c]	1	72	73
Total	24	125	149

Abbreviations: T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin; OGTT, oral glucose tolerance test; HOMA-IR, homeostatic model assessment of insulin resistance; FPG, fasting plasma glucose; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; CI, confidence interval.
[a]Subject total is lower for HOMA-IR and FPG because fasting insulin results were not available in all cases. The sensitivity, specificity, PPV, NPV, LR negative, LR positive, and AUC (95% CI), respectively, for various tests are as follows: HbA1c: 75.0%, 57.6%, 25.4%, 92.3%, 0.43, 1.77, 0.74 (95% CI = 0.61-0.87); HOMA-IR: 72.2%, 60.7%, 23.6%, 92.9%, 0.46, 1.84, 0.71 (95% CI = 0.57-0.84); PG: 75%, 100%, 100%, 95%, 0.25, indeterminate, 0.904 (95% CI = 0.81-0.99); HbA1C and HOMA-IR in combination; 95.5%, 33.0%, 21.4%, 97.4, 0.14, 1.43, 0.64 (95% CI = 0.53-0.75); HbA1C and FPG in combination: 95.8%, 57.6%, 30.3%, 98.6%, 0.07, 2.26, 0.77 (95% CI = 0.68-0.85).
[b]Positive test results: HbA1C ≥5.7%, as defined by the American Diabetes Association (466 American Diabetes Association 2011); HOMA-IR ≥3.4 mg/dL (cut-point maximizing sensitivity and specificity in our study; see Table 3); fasting glucose ≥100 mg/dL (502 Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 2003).
[c]Negative test results: HbA1C <5.7%; HOMA-IR < 3.4 mg/dL; fasting glucose <100 mg/dL.

HbA1c of ≥5.7% as used by the ADA was tested as a predictor of OGTT outcome: prediabetes (abnormal IFG and/or IGT) or T2DM versus NGT showing only fair predictive ability (Table 2). Sensitivity could be

Table 3. Test Characteristics of Various Thresholds of HbA1c and HOMA-IR for Predicting Prediabetes and Diabetes (Positive OGTT).

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
HbA1c threshold				
5.6	83.3% (61.8-94.5)	47.2% (38.3-56.3)	23.3% (15.0-33.8)	93.7% (83.7-97.9)
5.7[a]	75.0% (52.9-89.4)	57.6% (48.4-66.3)	25.4% (16.1-37.3)	92.3% (83.4-96.8)
5.8	66.7% (44.7-83.6)	65.6% (56.5-73.7)	27.1% (16.7-40.5)	91.1% (82.8-95.8)
5.9	66.7% (44.7-83.6)	77.6% (69.1-84.4)	36.4% (22.8-52.3)	92.4% (85.1-96.4)
HOMA-IR threshold				
2.7	77.8% (51.9-92.6)	45.8% (36.2-55.7)	19.4% (11.4-30.8)	92.5% (80.9-97.6)
3.1	72.2% (46.4-89.3)	56.1% (46.2-65.5)	21.7% (12.5-34.5)	92.3% (82.2-97.1)
3.4[b]	72.2% (46.4-89.3)	60.7% (50.8-69.9)	23.6% (13.7-37.3)	92.9% (83.4-97.3)
4.0	61.1% (36.1-81.7)	68.2% (58.4-76.7)	24.4% (13.4-39.9)	91.3% (82.3-96.1)

Abbreviations: HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; OGTT, oral glucose tolerance test; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.
[a]HbA1c threshold recommended by the American Diabetes Association.
[b]Optimal HOMA-IR threshold in this study.

increased by reducing the HbA1c cut-point, but at the expense of the already low specificity (Table 3).

Test performance of HOMA-IR for detecting prediabetes/T2DM at varying thresholds showed that a cut-point of 3.4 maintained the highest sensitivity without reducing specificity below 60% (Tables 2 and 3); overall test performance with AUC = 0.71 (95% CI = 0.57-0.84) was similar to HbA1c alone, with AUC = 0.74 (95% CI = 0.61-0.87). Using the ADA-defined cut-point of 100 mg/dL, FPG had a sensitivity of 75%, excellent specificity of 100% (Table 2), and the highest AUC (0.904; 95% CI = 0.81-0.99) when compared with HbA1c and HOMA-IR.

Combinations of Tests to Predict Prediabetes/T2DM

The combination of HbA1c (≥5.7%) and HOMA-IR (≥3.4) results in a substantially higher sensitivity than either test alone, but with resulting poor specificity (Table 2). Combining HbA1c (≥5.7%) with FPG (≥100 mg/dL) results in similarly high sensitivity while preserving the specificity seen with HbA1c alone (Table 2). The combination of HbA1c and FPG was superior to the combination of HbA1c and HOMA-IR in terms of ability to rule out prediabetes/T2DM (LR negative 0.07 vs 0.14) and in terms of overall accuracy (AUC = 0.77 [95% CI = 0.68-0.85] vs 0.64 [95% CI = 0.53-0.75]; Table 2).

Discussion

Because 1 out of every 3 children and adolescents in the US is overweight or obese, pediatricians are already counseling families about lifestyle modification, but now, they must also screen for diabetes risk.[5]

Published data on the prevalence of prediabetes in obese adolescents range from 19% (in our study) to 39%.[15] Our study investigated the usefulness of tests commonly performed in pediatric offices, including HbA1c, fasting glucose, fasting insulin, and the HOMA-IR index derived from fasting glucose and insulin values.

Because there were no false-positive FPG results in our study, this ADA-recommended test had a positive predictive value and specificity of 100%. However, 25% of those with prediabetes or T2DM were misclassified as normal using the FPG test. In this screening situation, a high sensitivity is of paramount importance, making FPG far from ideal as a screening test for prediabetes/T2DM. More important, FPG will miss patients with IGT (because IFG is absent in 70%-90% of cases of IGT), another component of prediabetes and one that is likely to precede the development of an abnormal FPG value.

Using the ADA criteria for prediabetes based on HbA1c (5.7%-6.4%), our study of pediatric patients found that the 5.7% cut-point value provided only fair discrimination of glucose tolerance, with 75.0% sensitivity and 57.6% specificity. The sensitivity we found is remarkably higher than that in other studies, which have reported sensitivities of 5%,[16] 32%,[17] and 30%[15] using the same HbA1c criteria as recommended by ADA. We can speculate that differences in patient population, such as the referral nature of the patients (to a pediatric endocrinology clinic), ethnicity (our population was >60% Hispanic), or other variables, could have affected the analysis of the relationship between HbA1c and OGTT outcomes.[18]

ROC curve analyses are typically used to determine the optimal cut-point value for a screening test by simultaneously optimizing both the sensitivity and specificity of the test. For this particular clinical situation, we assert that it is preferable to favor sensitivity over specificity because the priority is to identify all cases, and the consequence of labeling as a result of a false-positive result would be mitigated by prompt performance of a follow-up OGTT. Using this reasoning and based on our results, a HbA1c threshold of 5.6% may offer the best combination of sensitivity (83.3%) and specificity (47.2%) if this test is used alone. This is a cut-point that is similar to that suggested in the study by Nowicka et al, which recommended a HbA1c cut-point of 5.5%.[15] However, further evidence is needed before it can be suggested that the ADA cutoff for prediabetes/T2DM in children needs to lowered based on our as well as other pediatric studies.[19]

A HOMA-IR cut-point of 3.4 was similar to the HbA1c cut-point of 5.7% (Table 4) in terms of its sensitivity and specificity as a screening test for prediabetes. This HOMA-IR cutoff is lower than the value of 3.6 reported by Keskin et al[20] in Turkish children. Study differences, such as ethnicity (Hispanic and African American in our study) and higher BMI, might explain the difference in our results.

As shown in Table 2, combining fasting glucose and HbA1c as a single test (performed simultaneously or in sequence) yields excellent sensitivity (95%), with a specificity of 57%, and greatly improves the likelihood ratio of a negative test compared with either test alone. This combination was validated in 2298 adults. where combining FPG (>100 mg/dL) and HbA1c above 5.6% had a sensitivity of 87.9% of detecting prediabetes.[21] If both tests are normal according to ADA criteria (fasting glucose <100 mg/dL and HbA1c <5.7%), pediatricians managing a patient population similar to the one described in this study can be fairly certain that an OGTT is not indicated (LR negative = 0.07).

Over a 7-year period at our endocrine clinic, we analyzed the OGTT results of 149 individuals, and only 19% of the patients had prediabetes. Because ours is a referral population, it is likely that the prevalence of prediabetes would be lower in general pediatric practices, resulting in somewhat lower positive and negative predictive values. This variation of prediabetes prevalence according to ethnicity, type of recruitment, or environmental factors implies that screening tests have population-restrictive validity and/or predictive properties.

There are inherent limitations to using HbA1c and HOMA-IR as screening tests. HbA1c values may be low in children with hemoglobinopathies[22] and high in children with iron deficiency and states of decreased cell turnover.[23] There may be ethnic discrepancies in HbA1c in children that are not explained by glycemic status.[18] Also, interindividual differences in hemoglobin glycation may affect the predictive accuracy of HbA1c.[24] Optimal HOMA-IR cutoffs for diagnosis likely vary with pubertal status because physiological insulin resistance occurs during the course of puberty, but large-scale studies to develop these thresholds have yet to be done.[25] OGTT was used in our study as the comparator, and we recognize that the reproducibility of OGTT is only fair (66%).[26] However, until we define 1 screening test as a gold standard, OGTT has merit as a diagnostic standard currently used around the world.

Our investigation showed that HbA1c may not be ideal as a stand-alone screening tool to diagnose prediabetes. Although HOMA-IR has potential as a screening tool for prediabetes/T2DM, it too should not be used alone because it does not identify patients with IGT, another component of prediabetes.[27]

In conclusion, we have demonstrated in a modest-sized referral population of obese children and youth that the combination of HbA1c and fasting glucose is a potentially useful screening method to rule out prediabetes/T2DM and more accurately identify those children and adolescents who require follow-up diagnostic testing with an OGTT. Those with prediabetes should have a repeat OGTT after a reasonable interval because 30% of individuals can revert back to NGT.[6] By using HbA1c and fasting glucose in combination, pediatricians may increase case finding of prediabetes and have the opportunity to intervene earlier in the progression of the development of overt diabetes in children and youth. This screening strategy does require that patients present for fasting blood work, presenting a logistic challenge for practicing pediatricians and patients; further study might explore the utility of combining HbA1c with a random, nonfasting blood glucose. HbA1c, fasting glucose, and HOMA-IR tests alone are not accurate enough to recommend their use as single tests for prediabetes screening. Replication of our study results in larger, non–referral-based populations is warranted.

Declaration of Conflicting Interests

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