Screening for Dysglycemia in Overweight Youth Presenting for Weight Management

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OBJECTIVE—To examine the performance of current screening recommendations for detecting dysglycemia in children and adolescents with obesity.

RESEARCH DESIGN AND METHODS—In a cross-sectional study, an oral glucose tolerance test and demographic (age, sex, family history of diabetes, and ethnicity), clinical (BMI z-score, waist circumference, and pubertal stage), and laboratory variables used in current pediatric screening criteria for type 2 diabetes mellitus were measured in 259 overweight or obese youth aged 5–17 years. Glycemic status was based on American Diabetes Association (ADA) thresholds. The performance (sensitivity and specificity) of current screening criteria and newly developed models to identify isolated IGT were compared.

RESULTS—Dysglycemia was present in 20.8% of the cohort. Of the 54 participants with dysglycemia, 68% had a normal fasting glucose and were identified with the 2-h glucose test. Current ADA criteria had low sensitivity (41.7% [95% CI 25.6–57.8]) and moderate specificity (69.5% [63.5–75.6]) to identify IGT. In receiver operating characteristic (ROC) analysis, the addition of hemoglobin A1c or FPG did not improve the ROC area under the curve (AUC). The performance of a cumbersome oral glucose tolerance test and demographic (age, sex, family history of diabetes, and ethnicity), clinical (BMI z-score, waist circumference, and pubertal stage), and laboratory variables used in current pediatric screening criteria for type 2 diabetes mellitus were measured in 259 overweight or obese youth aged 5–17 years. Glycemic status was based on American Diabetes Association (ADA) thresholds. The performance (sensitivity and specificity) of current screening criteria and newly developed models to identify isolated IGT were compared.

CONCLUSIONS—The prevalence of IGT is high among obese children and youth. Current screening criteria have low sensitivity to detect isolated IGT. Although adding nonfasting laboratory values to history and physical measures does not improve diagnostic accuracy, adding fasting lipid profiles improves predictive value.

Obesity-related metabolic abnormalities are common in children and adolescents with obesity. Impaired glucose tolerance (IGT), an important predictor of progression to type 2 diabetes mellitus (T2DM) in youth (1), is identified in overweight and obese children, although the prevalence varies considerably with the population studied. Although 20–25% of overweight youth presenting to a weight management program in the northeastern U.S. were diagnosed with IGT (2), clinical cohorts in other countries have had much lower prevalence (5–17%) (3–5). In adults, IGT is a strong predictor for progression to T2DM (6) and increased risk of cardiovascular disease, independent of the development of T2DM (7). Randomized controlled trials of lifestyle or medication interventions in adults with IGT have demonstrated that T2DM can be prevented (8,9). Because the detection of IGT requires the performance of a cumbersome oral glucose tolerance test (OGTT), strategies to minimize the number of people requiring such a test have been studied in adults (10,11). Few such studies have been done in children and adolescents.

Current American Diabetes Association (ADA) guidelines recommend screening high-risk populations with a fasting plasma glucose (FPG) test (12,13), although they acknowledge that the best screening test and the population of obese children and youth that should be screened require further investigation (14). The majority of children with IGT have a normal fasting glucose (2), suggesting that FPG alone may be inadequate to identify prediabetes and that an OGTT be considered for screening in at-risk youth. Because the OGTT is costly, it should be performed on those at highest risk only, but little evidence evaluating the risk prediction properties of current screening criteria is available.

This study examines the clinical usefulness of current screening recommendations in identifying dysglycemia (T2DM, impaired fasting glucose [IFG], or IGT) in a cohort of 259 children and youth (aged 5–17 years) presenting to a weight management program and identifies a potentially new screening tool for identification of obese youth with dysglycemia.

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Study visit and parameters
The baseline study visit occurred in the morning, after an 8- to 12-h fast (allowing water), and comprised an evaluation of cardiometabolic risk factors (including an OGTT), anthropometric evaluation, and completion of questionnaires as described below. Standing height was measured using a Harpenden Stadiometer (London, UK). BMI (kg/m²) and BMI z score were calculated based on Centers for Disease Control and Prevention normative data, using NUTSTAT, a component of the Epi Info program (15). Waist circumference (WC) was measured halfway between the iliac crest and lower rib (16) using a nonstretching tape with an attached spring balance pulled to a tension of 250 g. WC z scores were calculated based on age- and sex-specific Canadian normative data (17,18). Blood pressure (BP) was measured three times on the right arm, using an oscillometric method (Omron Healthcare, Inc., Lake Forest, IL) with appropriate-sized cuff after the children had been sitting at rest for ~10 min (19). The average of the three measures was used for further analysis. Age, sex, and height cutoffs for defining hypertension were based on the 95th centile using U.S. normative data as recommended (19).

Parents reported the family history of premature coronary heart disease (defined as events in first- or second-degree male relatives <55 years and/or female relatives <65 years), T2DM, and obesity. Children aged ≥8 years completed a confidential questionnaire identifying their cigarette smoking history and self-assessed pubertal stage (20,21). Boys and girls aged <8 years were assumed to be prepubertal, based on normative data for pubertal onset.

An OGTT was conducted as follows: a baseline venous blood sample was taken and the patient consumed 1.75 g/kg glucose solution up to a maximum of 75 g orally. Venous blood samples were drawn 30, 60, and 120 min after baseline. Prediabetes was defined as IFG, IGT, or IFG + IGT using ADA criteria (IFG: fasting glucose level ≥5.6 mmol/L; IGT: 2-h glucose level ≥7.8 mmol/L). Dysglycemia included prediabetes or T2DM. Baseline laboratory analyses were conducted in the laboratory of Hamilton Health Sciences and included plasma glucose, total cholesterol (TC), HDL cholesterol (HDL-C), and triglyceride (TG); LDL cholesterol (LDL-C) was calculated using the equation of Friedewald (22). Glucose was measured using an enzymatic reference method with hexokinase, and cholesterol levels were measured with an enzymatic colorimetric method on a Roche INTEGRA analyzer. Dyslipidemia was defined as fasting TG >1.7 mmol/L and/or HDL-C <1.03 mmol/L and/or LDL-C >3.3 mmol/L, according to current recommendations (23).

Statistical analysis
Study participants with dysglycemia were compared with those without dysglycemia using an unpaired t test for continuous variables and χ² test for discrete variables. Laboratory variables (TC, HDL-C, LDL-C, TG, glucose, hemoglobin A1c (HbA1c) alanine aminotransferase [ALT], and aspartate aminotransferase [AST]) were log transformed to improve normality and are presented in Table 1 as geometric means and 95% CIs. All other continuous variables are presented as mean ± SD and discrete variables as n (%).

The ADA currently recommends criteria for screening for T2DM in children (Table 2). The sensitivity and specificity of these criteria for identifying dysglycemia (T2DM, IFG, and IGT) and isolated IGT in our population were calculated. To examine the association of risk variables with dysglycemia, logistic regression analysis was used and odds ratios (ORs) were calculated. The sensitivity and specificity of other risk strategies were also evaluated including 1) current Canadian Diabetes Association (CDA) guidelines (24), 2) a risk score developed by Reinehr et al. (4), and 3) fasting glucose >4.8 mmol/L (3). The CDA screening criteria are similar to the ADA criteria but somewhat less stringent. The CDA recommends screening all subjects in puberty or aged ≥10 years who have two of the following: BMI >95th centile, high-risk ethnic group or family history of T2DM, signs or symptoms of insulin resistance, and/or use of antipsychotic medications. Reinehr et al. (4) developed a simple risk score that includes parental history of T2DM (2 points), pubertal onset (1 point), and extreme obesity defined as BMI z score >2.58 (1 point) and recommended screening children or youth with ≥2 points. Maffeis et al. (3) recommended doing an OGTT to identify IGT in children or youth if the FPG exceeded 4.8 mmol/L.

As we were primarily interested in reducing the number of OGTTs performed, while detecting patients with isolated IGT, several models for the prediction of isolated IGT were developed from least invasive to most complex. Variables that were significant in univariate analysis were included (age, sex, family history of T2DM, systolic BP [SBP], BMI z score, WC, HbA1c, FPG, elevated ALT, TC-to-HDL ratio, and TG). Model 1 included data available with history and clinical exam only; model 2 included data from history, clinical exam, and nonfasting blood work (HbA1c); model 3 included data from history, clinical exam, HbA1c, and fasting glucose; and model 4 added in the influence of fasting TG. To evaluate the predictive properties of current ADA and CDA screening criteria and each model to identify IGT, we performed receiver operating characteristic (ROC) analysis on the entire population with complete data. To estimate the discriminative value of the predictive models, we calculated the ROC area under the curve (AUC) for the outcome IGT. The AUC for the ADA and CDA screening criteria and each of the models was compared using a χ² test.

Although the models were developed using continuous variables, we sought to establish a user-friendly screening test using thresholds for each variable and to examine these in a logistic model. The applied thresholds considered were previously recommended, including BMI z score 2.58 (4) and HbA1c 5.7%, or were obtained using optimal discrimination on the ROC curve (TG >1.17 mmol/L).

RESULTS—The descriptive characteristics and risk variables of the cohort (n = 259) and of those with and without dysglycemia (prediabetes or T2DM) are presented in Table 1. Although the mean age was 11.8 years, participants ranged in age from 5 to 17 years. Of the participants, 1 (0.39%) had undiagnosed T2DM based on a 2-h glucose >11.1 mmol/L. Prediabetes was present in 20.5% of the cohort, and 4.2% had IFG, 13.9% isolated IGT, and 2.3% IFG + IGT. Thus, of the 53 participants with prediabetes identified using an OGTT, 36 (68.0%) had isolated IGT and would not have been identified if only fasting glucose had been measured. Furthermore, the 1 participant with T2DM also had a normal fasting glucose. We identified no difference in the prevalence of prediabetes in those <10 vs. ≥10 years (17.8 vs. 22.0%; P = 0.45).

The participants with dysglycemia (prediabetes or T2DM) did not differ in age, self-reported pubertal stage, ethnicity, BMI z score, WC z score, or percent body fat from those without dysglycemia (Table 1). A family history of T2DM was relatively common in the children in this cohort (50.2%), and the prevalence was not
different in those with and without dysglycemia. Diagnosed T2DM in at least one parent was less common (16.2%) but also did not differ between groups. Children with dysglycemia had higher SBP and diastolic BP (DBP), fasting TG, and ALT, but did not differ between groups. The ADA recommends screening children aged ≥10 years (or pubertal children) who are overweight or obese and have two associated risk factors as described in Table 2. A total of 83 children and youth (32%) met current screening criteria. Current screening criteria had a sensitivity of 38.9% (95% CI 25.9–51.9) and a specificity of 69.8% (63.5–76.0) to detect dysglycemia. In a similar manner, the sensitivity to detect isolated IGT was 41.7% (25.6–57.8) with specificity of 69.5% (63.5–75.6). Thus, in applying the current ADA screening criteria, less than half of those children with isolated IGT were identified. As noted in Table 3, the sensitivity and comparable specificity of dysglycemia included serum TG (1.87 [1.33–2.63]; P = 0.0003) and SBP (1.04 [1.01–1.07]; P = 0.01).

The ADA recommends screening children aged ≥10 years (or pubertal children) who are overweight or obese and have two associated risk factors as described in Table 2. A total of 83 children and youth (32%) met current screening criteria. Current screening criteria had a sensitivity of 38.9% (95% CI 25.9–51.9) and a specificity of 69.8% (63.5–76.0) to detect dysglycemia. In a similar manner, the sensitivity to detect isolated IGT was 41.7% (25.6–57.8) with specificity of 69.5% (63.5–75.6). Thus, in applying the current ADA screening criteria, less than half of those children with isolated IGT were identified. As noted in Table 3, the sensitivity and comparable specificity of dysglycemia included serum TG (1.87 [1.33–2.63]; P = 0.0003) and SBP (1.04 [1.01–1.07]; P = 0.01).
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Table 2—ADA recommended criteria for screening children and youth for T2DM

<table>
<thead>
<tr>
<th>Screening characteristic</th>
<th>Overweight (BMI &gt; 85th centile) and two of</th>
</tr>
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<tbody>
<tr>
<td>Screening criteria</td>
<td></td>
</tr>
<tr>
<td>Family history of T2DM in first- or second-degree relative</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)</td>
<td></td>
</tr>
<tr>
<td>Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension [SBP or DBP &gt; 95th centile], dyslipidemia [TG &gt; 1.7 mmol/L or HDL-C &lt; 0.013 mmol/L, polycystic ovary syndrome, or small for gestational age birth weight])</td>
<td></td>
</tr>
<tr>
<td>Maternal history of T2DM or gestational diabetes mellitus during the child’s gestation</td>
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Recommended test FPG
Age of commencement 10 years or in puberty
Frequency Every 2 years

(P = 0.49), pubertal (P = 0.52), parental T2DM (P = 0.15), HbA1c > 5.7% (P = 0.43), fasting blood glucose (P = 0.85), SBP > 95th centile (P = 0.82), and BMI z score > 2.58 were not significant and were not included in the final logistical model. Remaining in the model was TG > 1.17 mmol/L (OR 4.3; P < 0.0001). This variable alone had clinical usefulness (Table 3), and AUC that exceeded the ADA and CDA screening criteria was somewhat lower than continuous models 4A and 4B (Table 4).

CONCLUSIONS—Current ADA screening criteria had low discriminatory capacity for identifying dysglycemia in our cohort of overweight children presenting to a weight management program. Using a specific multilevel approach to applying screening criteria, we have identified a screening algorithm requiring history and physical examination only, with comparable discriminatory capacity (AUC in ROC analysis) to ADA recommendations but requiring less information (age, sex, parent history of T2DM, SBP, and BMI z score). The addition of a nonfasting blood test to measure HbA1c did not improve the predictive properties, but adding a fasting TG improved the discriminatory capacity. In fact, a fasting TG > 1.17 mmol/L had better discriminatory capacity and clinical usefulness than current ADA criteria in identifying isolated IGT.

Dysglycemia was common (20.8%) and IGT in identified in 16.2% of the participants, comparable to the findings of several American studies (2, 25). Silent T2DM was relatively rare in this population (1 of 259) but was identified on a 2-h blood glucose alone. As with previous studies, the prevalence of IFG was low, and 68% of children with elevated 2-h glucose levels had fasting glucose < 5.6 mmol/L (ADA cutoff point for IFG). Among our population of obese children and adolescents, important risk predictors for the presence of IGT included higher HbA1c and fasting serum TG. SBP, parental T2DM, and higher TC-to-HDL ratio were also predictive variables. Important variables without evident influence include age, pubertal stage, sex, body size (BMI), and WC, suggesting that among obese youth, these variables have little predictive potential for dysglycemia.

Current ADA screening criteria had low sensitivity and only moderate specificity to identify isolated IGT. Other previously recommended screening tools also had low sensitivity. Using ROC analysis, we identified a model using history, physical examination, and fasting laboratory data (glucose and TG) with better discrimination of IGT than current ADA and CDA screening criteria. This may enable reasonable identification of children with pre-diabetes while avoiding excessive use of OGTTs.

HbA1c thresholds recently have been recommended for identifying adults at high risk for T2DM and for diagnosis of T2DM in adults (26). This approach also has been recommended recently for adolescents, although the clinical usefulness in this age-group has since been challenged (27, 28). Using National Health and Nutrition Examination Survey data, HbA1c thresholds of 5.7 and 6.0% had poorer performance in identifying prediabetes in adolescents compared with adults. We found no added predictive benefit of including HbA1c with data from history and physical examination in identifying IGT. However, adding the fasting TG level improved the AUC.

When applying thresholds to develop a simple clinically applicable version of model 4, only fasting TG > 1.17 mmol/L remained in the model, and this alone had sensitivity of 70% and specificity of 64% to identify IGT. Furthermore, the AUC exceeded that of current ADA and CDA screening methods.

Despite being one of very few studies to critically examine the usefulness of current screening recommendations to identify prediabetes in obese youth, our study does have some limitations. Even though no influence of pubertal stage was identified on prevalence of prediabetes, it is noteworthy that puberty was not assessed by a physician but was self-reported by the study participants using a validated methodology. Although we identified no difference in prevalence of prediabetes in those aged < 10

Table 3—Sensitivity and specificity of current screening guidelines, published scores, and simple TG model for detecting isolated IGT

<table>
<thead>
<tr>
<th>ADA screening criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>(25.6–57.8)</td>
<td>41.7</td>
<td>69.5</td>
<td>18.1</td>
<td>88.1 (83.3–92.9)</td>
</tr>
<tr>
<td>(67.6–93.5)</td>
<td>80.6</td>
<td>36.8</td>
<td>17.1</td>
<td>92.1 (86.5–97.7)</td>
</tr>
<tr>
<td>FPG &gt; 4.8 mmol/L</td>
<td>50.0 (33.7–66.3)</td>
<td>62.8 (56.3–69.1)</td>
<td>17.8</td>
<td>88.6 (83.7–93.6)</td>
</tr>
<tr>
<td>Reinehr score ≥ 2</td>
<td>36.1 (20.4–51.8)</td>
<td>74.0 (68.2–79.8)</td>
<td>18.3</td>
<td>87.8 (83.1–92.5)</td>
</tr>
<tr>
<td>Simple TG &gt; 1.17 mmol/L</td>
<td>71.4 (57.8–85.1)</td>
<td>64.1 (57.7–70.4)</td>
<td>27.8</td>
<td>92.1 (87.7–96.4)</td>
</tr>
</tbody>
</table>

Data are percentage (95% CI). PPV, positive predictive value; NPV, negative predictive value.
Table 4: ROC analysis of models for prediction of isolated IGT using ADA criteria

<table>
<thead>
<tr>
<th>Model</th>
<th>Measures included</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>ADA screening criteria†</td>
<td>0.57</td>
<td>0.48–0.67</td>
</tr>
<tr>
<td>CDA</td>
<td>All ≥10 years (or pubertal) with two of the following: BMI &gt; 95th centile, high-risk ethnic group or family history of T2DM, signs or symptoms of insulin resistance, and/or use of antipsychotic medications</td>
<td>0.54</td>
<td>0.49–0.60</td>
</tr>
<tr>
<td>1A</td>
<td>Age, sex, parent history T2DM, SBP, and BMI z score</td>
<td>0.63#</td>
<td>0.53–0.72</td>
</tr>
<tr>
<td>1B</td>
<td>Age, sex, parent history T2DM, SBP, and waist z score</td>
<td>0.63#</td>
<td>0.53–0.72</td>
</tr>
<tr>
<td>2A</td>
<td>Model 1A + HbA1c</td>
<td>0.64#</td>
<td>0.55–0.73</td>
</tr>
<tr>
<td>2B</td>
<td>Model 1B + HbA1c</td>
<td>0.64#</td>
<td>0.55–0.73</td>
</tr>
<tr>
<td>3A</td>
<td>Model 1A + FPG</td>
<td>0.66#</td>
<td>0.57–0.75</td>
</tr>
<tr>
<td>3B</td>
<td>Model 1B + FPG</td>
<td>0.66#</td>
<td>0.57–0.74</td>
</tr>
<tr>
<td>4A</td>
<td>Model 1A + FPG + TG</td>
<td>0.72*</td>
<td>0.63–0.81</td>
</tr>
<tr>
<td>4B</td>
<td>Model 1 B + FPG + TG</td>
<td>0.71*</td>
<td>0.62–0.80</td>
</tr>
<tr>
<td>Simple TG</td>
<td>TG &gt; 1.7 mmol/L, BMI &gt; 30 kg/m², and waist z score</td>
<td>0.68*</td>
<td>0.59–0.77</td>
</tr>
</tbody>
</table>

†See Table 1 for ADA screening criteria. #AUC significantly different from CDA model (P < 0.05). *Model 4A and B AUC differ from CDA and ADA (P = 0.001), model 1 (P = 0.01), model 2 (P < 0.05), and model 3 (P = 0.01); simple TG AUC differs from ADA (P < 0.05) and CDA (P < 0.05).

References


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