Lack of Agreement Between the Revised Criteria of Impaired Fasting Glucose and Impaired Glucose Tolerance in Children With Excess Body Weight

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OBJECTIVE — The aim of this study was to describe the agreement between impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) in children with excess body weight using the original and the revised definitions of IFG.

RESEARCH DESIGN AND METHODS — Obese and overweight children aged 4–17 years were included (n = 533). Anthropometric parameters and biochemical tests (fasting and 2-h glucose tests after an oral glucose load [1.75 g/kg]) were performed. Case subjects with a fasting plasma glucose ≥126 mg/dl were excluded. The diagnostic parameters of the original and the revised definitions of IFG for detecting IGT were estimated. The analysis of agreement between these categories was made using the κ test.

RESULTS — The prevalence of IFG increased from 6.2 to 13.3% using the new criteria. The prevalence of IFG became closer to the prevalence of IGT (14.8%). The revised criteria increased the sensitivity from 26.6 to 36.7%. However, the new IFG definition was not useful for identifying IGT cases. Of the 71 case subjects with IFG, only 29 (40.8%) had IGT. In addition, 50 case subjects with IGT (9.4%) and 13 with diabetes (2.4%) had a fasting glycemia <100 mg/dl. A poor agreement was found between the 2003 IFG definition and abnormal 2-h postchallenge plasma glucose (κ = 0.359). The proportion of false-positive cases increased (36.3–59.1%) under the new definition.

CONCLUSIONS — The new definition modestly increases the sensitivity of IFG for detecting IGT in children with excess body weight. Despite this, more than one-half of these cases are not detected. In addition, the false-positive rate was increased by 61%.

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Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; ROC, receiver operator curve.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Impaired fasting glucose (IFG) is associated with an increased risk for having type 2 diabetes and cardiovascular events (1–3). It was originally conceived to be an analogous condition to impaired glucose tolerance (IGT) (4). However, multiple reports have proved that there is a lack of agreement between IGT and IFG (5–8). The prevalence of IGT was two times higher, and 40% of the IGT cases were considered normal using the fasting glycemia criterion. Based on this, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus of the American Diabetes Association recently changed the definition of IFG (9). The lower limit was changed from 110 to 100 mg/dl. This change is intended to get a similar prevalence of IGT and IFG.

Childhood obesity is now a problem of epidemic proportions worldwide (10). In the U.S., 20% of children ages 6–17 years are obese, and an additional 22% of them are overweight. The prevalence is greater in Mexican Americans and African Americans compared with Asian Americans or Caucasians. Childhood obesity is associated with an increased likelihood for having either IGT or IFG. In referral centers, the prevalence of IGT has been reported close to 25% in obese children 4–10 years of age (11) and up to 4.1% in population-based surveys (12). Our purpose is to describe the agreement between IGT and IFG in children with excess body weight.

RESEARCH DESIGN AND METHODS

— Overweight or obese boys and girls, aged 4–17 years (n = 533), were included in the study. They were recruited from seven primary care units (n = 168) and from one elementary school located in a middle-income area of Mexico City (n = 365). Physicians of the primary care units were asked to routinely identify children with excess body weight, who were invited to participate in a research program designed to evaluate

Table 1—*Characteristics of the participants*

	Overweight	Obesity	Total	*P*
n (%)	105 (19.7)	428 (80.3)	533 (100)	—
Age (years)	9.44 ± 2.3	9.78 ± 2.4	9.71 ± 2.3	0.2
Sex (boys/girls)	35/70	226/202	261/272	<0.001
Weight (kg)	37.8 ± 11.8	52.1 ± 17	49.3 ± 17.1	<0.001
Height (cm)	132 ± 12	140 ± 14	138 ± 14	<0.001
BMI (kg/m^2)	20.8 ± 4.1	25.6 ± 4.2	24.7 ± 4.6	<0.001
Waist circumference (cm)	71.6 ± 9.8	78.5 ± 13	77.2 ± 13.3	<0.001
Hip circumference (cm)	81.4 ± 10.3	86.7 ± 13.2	85.7 ± 12.9	<0.001
Systolic blood pressure (mmHg)	100 ± 10	103 ± 12.9	102.4 ± 12.4	0.03
Diastolic blood pressure (mmHg)	69.6 ± 8.5	72.6 ± 9.1	72 ± 9	0.003
Fasting plasma glucose (mg/dl)	92.4 ± 7.9	93.7 ± 8.2	93.4 ± 8.2	0.16
2-h plasma glucose (mg/dl)	105 ± 34	112 ± 37	111 ± 36	0.10

Data are means ± SD.

the effect of metformin on inflammatory markers in IGT children. In addition, all regular students from the first to sixth grade were evaluated for excess body weight and invited to participate in the same research program. Informed consent was obtained from both the children and their parents or guardians. The Ethics and Research Committee of the Hospital de Pediatria of the Centro Médico Nacional approved the study.

All case subjects came to the clinic after a 12-h overnight fast for a clinical examination (body weight, height, and waist-to-hip circumference) and biochemical tests (fasting and 2-h glucose measurement after an oral glucose load [1.75 g/kg maximum, 75 g in water]). All tests were done between 8:00 and 10:00 A.M. A fasting plasma glucose ≥126 mg/dl was considered an exclusion criterion. A structured interview was conducted. A questionnaire was used to obtain information on demographic and socioeconomic aspects. Anthropometric measurements were done. Participants removed their shoes and upper garments. Body weight was measured on a 140-kg capacity floor scale with the child standing in the center of the scale. Height was obtained using the floor scale's stadiometer with the child standing in the center of the scale. Height was measured to the nearest 0.5 cm. Body weight was measured to the nearest 0.1 kg. The BMI was calculated as weight (kg) divided by height (m^2). Abdominal circumference was measured to the nearest 0.1 cm at the level of the greatest frontal extension of the abdomen between the bottom of the rib cage and the top of the iliac crest. The equipment was regularly calibrated using reference samples provided by the manufacturer.

Definitions

Overweight was defined as a BMI >85th percentile for children of the same age and sex, according to the tables of the Center for Disease Control and Prevention. Obesity was defined as a BMI >95th percentile (13).

IFG was defined using either the 1997 (110–125 mg/dl) or the 2003 definitions (100–125 mg/dl). IGT was defined as a 2-h plasma glucose concentration between 140 and 199 mg/dl during the oral glucose tolerance test (OGTT).

Statistical analysis

Data are presented as means ± SD or percentages. Sensitivity, specificity, positive predictive value, false-negative rate, and false-negative rate for the original and the revised definitions of IFG for detecting IGT were estimated as described by Daly and Geoffrey (14). The analysis of agreement between these conditions was made using the κ test (15). The resultant coefficient gives values between −1 and 1. The nearest value to 1 indicates a perfect agreement. A value <0.6 is indicative of a nonsignificant agreement between two variables. The negative likelihood ratio was calculated to estimate the odds of missing an abnormal glucose response during the OGTT with the original and the revised definitions of IFG (13). It is defined as (1 − sensitivity)/specificity. Multiple regression analysis was made to identify factors associated with abnormal 2-h postchallenge plasma glucose. Receiver operator curve (ROC) analysis was used to identify the threshold values of the factors associated with IGT, with the higher likelihood to be found in IGT cases. The selected cutoff points were those closest to the left corner of the ROC graph. The analysis was done using the SPSS program version 10 for Windows (SPSS, Chicago).

RESULTS — The clinical characteristics of the participants are shown in Table 1. Children who were either overweight (n = 105, 19.9%) or obese (n = 428, 81.1%) composed the study sample. Eighty-one percent (n = 435) were aged between 6 and 11 years. All case subjects completed the 2-h OGTT (n = 533). Case subjects with a fasting plasma glucose ≥126 mg/dl were not included in this report.

The prevalence of IFG using the 2003 criterion was 13.3% (n = 71). This rate is significantly higher compared with that obtained with the 1997 definition (6.2%, n = 33, P < 0.001). The prevalence of IFG using the new definition was closer to the percentage of case subjects with IGT (14.8%). Despite this, the new criterion missed 63 case subjects (11.6%) who had an abnormal glucose tolerance test.

The agreement between tests is shown in Table 2. The new IFG definition is not useful to identify IGT cases. Of the 71 case subjects with IFG, only 29 (40.8%) had IGT; diabetes was diagnosed in 11 case subjects (15.5%), and a normal glucose response during the OGTT was observed in the remaining 31 case subjects (43.7%). In addition, 63 case sub-

Table 2—*Agreement between either the 1997 or the 2003 definitions of IFG and abnormal glucose response during the OGTT*

	OGTT			
	Normal	IGT	Diabetes	Total
1997 definition (fasting plasma glucose 110–125.9 mg/dl)				
Normal	423 (79.4)	58 (10.9)	19 (3.6)	500 (93.8)
IFG	7 (1.3)	21 (3.9)	5 (0.9)	33 (6.1)
Total	430 (80.7)	79 (14.8)	24 (4.5)	533 (100)
2003 definition (fasting plasma glucose 100–125.9 mg/dl)				
Normal	399 (74.9)	50 (9.4)	13 (2.4)	462 (86.6)
IFG	31 (5.8)	29 (5.4)	11 (2.1)	71 (13.3)
Total	430 (80.7)	79 (14.8)	24 (4.5)	533 (100)

Data are *n* (%).

jects with abnormal 2-h postchallenge plasma glucose (IGT [$n = 50$, 9.4%] or diabetes [$n = 13$, 2.4%]) had a fasting glycemia <100 mg/dl. The κ index was 0.359 for the revised version; this rate was slightly better than that found with the original criteria ($\kappa = 0.319$). However, both estimates indicate a poor agreement between the IFG definitions and abnormal 2-h postchallenge plasma glucose. This was a consistent observation even when analyzing subsets of the population (overweight and obese case subjects or between sexes).

The 2003 definition of IFG increased the likelihood of detecting cases with abnormal 2-h postchallenge plasma glucose. As stated previously, lowering the threshold from 110 to 100 mg/dl almost doubled the prevalence of IFG; 38 additional abnormal cases were detected. The revised IFG criteria allowed the detection of 14 cases with abnormal glucose tolerance (8 with IGT and 6 with diabetes). However, 24 of the 38 additionally detected case subjects had a normal 2-h postchallenge glycemia. The sensitivity, specificity, positive predictive rate, false-positive rate, and false-negative rate for the diagnosis of either abnormal 2-h postchallenge plasma glucose or IGT for the original or the revised IFG criteria are shown in the Table 3. The revised criteria increased the sensitivity from 25.2 to 38.8% for the diagnosis of abnormally high 2-h postchallenge plasma glucose. This change reduced the odds of leaving undiagnosed a case with abnormal glucose tolerance (negative likelihood ratio) from 0.75 to 0.69. Thus, the revised criteria of IFG lowered by 13% the number of cases with abnormal 2-h postchallenge plasma glucose missed by the 1997 definition, but this is far from the negative likelihood ratio that assures that, by diagnosing IFG, we can be sure that the presence of IGT is not missed (i.e., <0.1).

Finally, we assessed if the information from other clinical data could help to improve the diagnostic proficiency of the new criteria. Conditions associated with abnormal 2-h postchallenge plasma glucose were identified using a multiple regression analysis. The BMI and the diastolic blood pressure were the only significant variables included in the model ($r^2 = 0.16$, $P = 0.002$). ROCs were constructed to identify the BMI and diastolic blood pressure values most likely to identify a case with abnormal 2-h postchallenge plasma glucose. The corresponding values were 26 kg/m^2 for the BMI and 70 mmHg for the diastolic blood pressure. However, the inclusion of these factors did not improve the diagnostic proficiency of the revised IFG definition (specificity 18.6%, positive likelihood ratio 1.15, and negative likelihood ratio 0.313).

CONCLUSIONS — Screening for dyslipidemias, arterial hypertension, and abnormal glucose metabolism has become a routine procedure in children and adolescents with excess body weight (16). The most common abnormality of carbohydrate metabolism is IGT. However, its diagnosis is frequently missed in children because of the labor-intensive nature of the OGTT. In 1997, the concept of IFG was created as an analogous category to IGT based on fasting plasma glucose. However, multiple reports have shown that these categories are not equivalent; IFG had a lower sensitivity for predicting diabetes than IGT, and the prevalence of IFG was almost one-half that of IGT (17). Our results are a clear example of these limitations. The prevalence of IFG was remarkably lower (6.1 vs. 14.8%, $P < 0.001$), and the agreement between IFG and IGT was poor. Our results are similar to those reported in Mexican adults (5); thus, the unsatisfactory diagnostic proficiency of IFG to detect IGT cases is ob-

Table 3 —*Sensitivity, specificity, positive predictive value, negative predictive value, false-positive ratio, false-negative ratio, positive and negative likelihood ratios, and precision for the diagnosis of either abnormal glucose tolerance during the OGTT or IGT for the 1997 or the 2003 IFG criteria*

	Abnormal 2-h postchallenge plasma glucose (diabetes and IGT)		IGT	
	1997 criteria	2003 criteria	1997 criteria	2003 criteria
Sensitivity (%)	25.2	38.8	26.6	36.7
Specificity (%)	98.3	92.8	97.3	90.7
Positive predictive value (%)	78.7	56.3	63.6	40.8
Negative predictive value (%)	84.6	86.3	88.4	89.1
False-negative test (%)	15.4	13.6	11.6	10.8
False-positive test (%)	21.2	43.6	36.3	59.1
Positive likelihood ratio	14.8	5.38	9.84	3.96
Negative likelihood ratio	0.76	0.65	0.75	0.69
Precision (%)	84.2	82.3	86.8	82.7

served in both children and adults. Several recent reports show that treatment of IGT reduces the incidence of diabetes and cardiovascular complications; these new data (18–20) support the need for a more accurate method for detecting IGT.

In 2003, the IFG definition was changed to overcome the limitations described above: the lower limit was decreased to 100 mg/dl. This threshold was selected based on an ROC analysis (9). The decision was also based on strong epidemiological data suggesting that case subjects with fasting plasma glucose 100–109 mg/dl may be at a higher risk for developing diabetes than those with a level below 100 mg/dl and the need to equalize the prevalence of IGT and IFG (21). In our patients, the 2003 definition increases the sensitivity of IFG to detect cases with IGT. The revised criteria enhance the sensitivity from 26.6 to 36.7% for the diagnosis of IGT. Also, the prevalence of IGT and IFG was equalized (14.8 vs. 13.3%, respectively). However, some negative aspects of the new definition should be mentioned. The new criterion is still far from being equivalent to IGT. Only 40.8% of the IFG cases also had IGT. Also, the overall precision of IFG for detecting IGT was decreased because the proportion of false-positive cases increased (36.3–59.1%). Furthermore, the new IFG criteria still failed to detect 61.1% of the cases with abnormal 2-h postchallenge plasma glucose. Regretfully, information obtained from other clinical data did not help to improve the diagnostic proficiency of the test.

The new definition has received criticisms because the IFG prevalence rises from 6.7 to 24.1% in adults (22,23). Legitimate concerns have been expressed about detecting cases with a low likelihood of having diabetes sometime in their lives. The use of a second test (i.e., the OGTT) for confirming the presence of an abnormal glucose tolerance may overcome this criticism. This strategy has been discussed previously by several authors (24) and is recommended by European guidelines (25).

A limitation of this study is the assessment of the OGTT only once. The variability of the OGTT results may cause random misclassification of some cases. In a study with a small group of obese children, Sinha et al. (11) reported that the reproducibility of the OGTT is acceptable. If this finding is confirmed in additional studies, the OGTT can reliably detect the presence of IGT. The diagnosis may be of greater importance in children and adolescents than in other age-groups. Because type 2 diabetes is the tip of the iceberg of insulin resistance in pediatric populations, studying IGT is necessary for the detection of affected cases.

In conclusion, the new definition modestly increases the sensitivity of IFG for detecting cases with either IGT or abnormal postchallenge plasma glucose in children with excess body weight. However, more than one-half of those cases are not detected despite the lower threshold. In addition, the false-positive rate was increased by 61%. Thus, fasting plasma glucose and the 2-h postchallenge plasma glucose may be considered complementary tests for diagnosis of diabetes and glucose intolerance in children with fasting plasma glucose <126 mg/dl.

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