Decreased β-Cell Function in Overweight Latino Children With Impaired Fasting Glucose

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OBJECTIVE — To determine whether overweight Latino children with impaired fasting glucose (IFG) (≥100 mg/dl) have increased insulin resistance or decreased β-cell function compared with those with normal fasting glucose (NFG).

RESEARCH DESIGN AND METHODS — We studied 207 healthy overweight Latino children, aged 8–13 years, with a family history of type 2 diabetes. Fasting and 2-h glucose and insulin were assessed by oral glucose tolerance test. Insulin sensitivity (S_i), the acute insulin response to glucose (AIRg), and the disposition index (DI; an index of β-cell function) were determined using the insulin-modified intravenous glucose tolerance test and minimal modeling. Body composition was determined by dual-energy X-ray absorptiometry.

RESULTS — There were no differences in body composition between NFG ($n = 182$) and IFG ($n = 25$) children. Compared with children with NFG, children with IFG had higher fasting and 2-h glucose values and higher fasting insulin. After adjusting for covariates, children with IFG had no difference in S_i but 15% lower DI than NFG children (2,224 ± 210 vs. 2,613 ± 76, $P < 0.05$). Multivariate linear regression showed that AIRg and DI, but not S_i, were significant predictors of fasting blood glucose.

CONCLUSIONS — In overweight Latino adolescents with a family history of type 2 diabetes, IFG is associated with impaired β-cell function and therefore may identify children likely to be at risk for progression to type 2 diabetes. The actual risk of progression of IFG to type 2 diabetes remains to be determined by prospective longitudinal studies.

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In 1997, the American Diabetes Association (ADA) defined impaired fasting glucose (IFG), a new category of altered glucose homeostasis, as a fasting plasma glucose 110–125 mg/dl (1). Recently, the ADA lowered this clinical cut point for IFG to 100–125 mg/dl (2). The rationale for lowering this cut point was to optimize the sensitivity and specificity of a fasting glucose measurement for predicting future type 2 diabetes in individuals at risk.

Studies in adults using the previous cut point of 110 mg/dl confirm that IFG has physiological significance with respect to underlying insulin/glucose dynamics. Weyer, Bogardus, and Pratley (3) demonstrated that Pima Indian adults with IFG have diminished insulin secretion for the degree of insulin resistance they manifest. Others have similarly shown that adults with IFG have increased insulin resistance and decreased insulin secretion relative to those with normal glucose homeostasis (4–6). To date, little data are available regarding the significance of IFG in children at increased risk of type 2 diabetes.

The relevance of the IFG cut point to disease risk in children is unknown, both in terms of the predictive value for future type 2 diabetes and with respect to the underlying pathophysiology of IFG. We have previously shown that overweight Latino adolescents with impaired glucose tolerance (IGT = 2-h glucose ≥140 mg/dl) have decreased β-cell function compared with those with normal glucose tolerance, as indicated by a lower disposition index (DI) using the frequently sampled intravenous glucose tolerance test (i.e., impaired acute insulin secretion relative to the degree of their insulin resistance) (7). However, it is unknown whether children with IFG have impaired insulin action (lower insulin sensitivity) or reduced β-cell function (lower disposition index) compared with children with normal fasting glucose (NFG). If insulin/glucose dynamics are indeed altered in IFG, children discovered to have IFG on diabetes screening might justifiably be considered to be at increased risk for developing type 2 diabetes in the future, relative to children with NFG. This is an issue of clinical significance, since current clinical recommendations call for screening children at risk for type 2 diabetes with a single fasting blood draw to measure plasma glucose (8).

Therefore, the purpose of this study was to determine whether overweight Latino children (with a positive family history of type 2 diabetes) with IFG (≥100 mg/dl) have either diminished insulin sensitivity (i.e., increased insulin resistance) or decreased β-cell function compared with those with NFG.

RESEARCH DESIGN AND METHODS

— We analyzed data from the first annual visit of 207 overweight Latino children enrolled in the University of Southern California (USC) SOLAR

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Abbreviations: ADA, American Diabetes Association; AIRg, acute insulin response to glucose; DI, disposition index; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NFG, normal fasting glucose; USC, University of Southern California.

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

(Study of Latino Adolescents at Risk) Diabetes Project, a longitudinal study exploring risk factors for type 2 diabetes in a high-risk childhood cohort. We have previously reported on subsets of this cohort (7,9,10). Children (119 males and 88 females) who met the following criteria were recruited through clinics and word of mouth: *1*) age 8–13 years, *2*) BMI ≥85th percentile for age and sex (11), *3*) Latino ancestry (all four grandparents), and 4) family history of type 2 diabetes in a parent, sibling, or grandparent. Children were either of Mexican-American or Central-American heritage. Exclusion criteria included prior major illness or medications/conditions known to influence body composition, insulin action, or insulin secretion (e.g., diabetes [2], glucocorticoid therapy, hypothyroidism). Parental informed consent and child assent were obtained, and the study was approved by the institutional review board, Health Science Campus, USC.

Outpatient visit: oral glucose tolerance test

Children arrived at the USC General Clinical Research Center at ~8:00 A.M. after an overnight 12-h fast. An oral glucose tolerance test was performed as previously described (9), with subjects ingesting 1.75 g oral glucose solution/kg body wt (to maximum 75 g) at time 0. Blood was sampled for glucose and insulin at times −5 min ("fasting") and 120 min ("2 h").

Inpatient visit

Children were admitted to the General Clinical Research Center in the afternoon within approximately 2 weeks of completing the oral glucose tolerance test. Total body fat mass and total soft lean tissue mass were determined by dual-energy X-ray absorptiometry (Hologic QDR 4500W; Hologic, Bedford, MA). Children fasted overnight, with only water permitted after 8:00 P.M.

Insulin-modified frequently sampled intravenous glucose tolerance test commenced the following morning, as previously described (9). At time 0, glucose (25% dextrose, 0.3 g/kg body wt) was intravenously administered. Blood samples were collected at time points −15, −5, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min. Insulin (0.02 units/kg body wt, Humulin R [regular insulin for human injection]; Eli Lilly, Indianapolis, IN) was intravenously injected at 20 min. Plasma was analyzed for glucose and insulin, and values were entered into the MINMOD Millenium 2003 computer program (version 5.16) to determine insulin sensitivity (S_i), acute insulin response to glucose (AIRg = insulin area under the curve above basal for the first 10 min of the frequently sampled intravenous glucose tolerance test), and DI (DI = the product of $S_i \times$ AIRg, an index of pancreatic β-cell function) (12). Fasting plasma was also sent for lipid analysis.

Measures and assays

Height (by stadiometer) and weight (by clinical balance) were measured, and BMI and BMI percentiles for age and sex were determined based upon established Centers for Disease Control normative curves using EpiInfo 2004, version 3.3. Tanner stage was determined on physical exam by a pediatrician according to breast stage in girls and pubic hair stage in boys (13,14). Seated blood pressure was measured in the upper arm. Glucose was assayed by a Yellow Springs Instrument 2700 Analyzer (YSI, Yellow Springs, OH). Insulin was assayed by the specific human insulin enzyme-linked immonosorbent assay kit from Linco (St. Charles, MO; intra-assay coefficient of variation 4.7–7.0%, interassay coefficient of variation 9.1–11.4%, and cross-reaction with human proinsulin 0%). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as HOMA-IR = fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5 (15). Fasting triglycerides and HDL and total cholesterol were measured using the Vitros Chemistry DT Slides (Johnson & Johnson Clinical Diagnostics, Rochester, NY). LDL cholesterol was calculated using the Friedwald formula.

Statistical analysis

All variables that were not normally distributed (i.e., weight, BMI, BMI percentile, total body fat mass, total soft lean tissue mass, percent body fat, fasting and 2-h glucose and insulin, S_i, AIRg, DI, HDL, and triglycerides) were log transformed before performing statistical analyses. Nontransformed values are reported for ease of interpretation. ANOVA and χ^2 analyses were used to detect differences in unadjusted measures of body composition, lipids, glucose and insulin values, and insulin action/secretion variables (S_i, AIRg, and DI) between children with IFG ($n = 25$) and NFG ($n = 182$). Differences in fasting and 2-h insulin, HOMA-IR, S_i, AIRg, and DI were further compared using ANCOVA after adjusting for age, sex, total body fat mass, and total body soft lean tissue mass as covariates. S_i was also added as a covariate when AIRg was entered as the dependent variable. To determine the relationships between S_i, AIRg, and DI on fasting glucose as a continuous variable, multivariate linear regression was performed with log fasting glucose entered as the dependent variable and age, sex, total body fat mass, total body soft lean tissue mass, and either S_i, AIRg, or DI entered as covariates. All analyses were performed using SPSS version 11.0 (SPSS, Chicago, IL), with a type I error set at $P < 0.05$.

RESULTS — Table 1 compares physical and metabolic characteristics between children with IFG ($n = 25$) and NFG ($n = 182$). Overall prevalence of IFG in this cohort was 12.1%. Compared with the NFG group, the IFG group had a higher proportion of males (80 vs. 54%, $P = 0.01$) but did not differ in age, pubertal stage, or body composition. IFG had higher fasting and 2-h glucose values than NFG. Fasting insulin and HOMA-IR were significantly higher in IFG versus NFG and remained higher after adjusting for age, sex, total body fat, and soft lean tissue mass ($P < 0.01$ for each). There were no group differences in either adjusted or unadjusted 2-h insulin levels. There was a trend toward increased prevalence of IGT in IFG compared with NFG (40.0 vs. 22.5%, $P = 0.053$). There were no differences in blood pressure or fasting lipid values nor differences in unadjusted values for S_i, AIRg, and DI between NFG and IFG.

Figure 1 shows comparisons in insulin action and secretion dynamics between IFG and NFG groups after adjusting for age, sex, total body fat, and soft lean tissue mass. S_i did not differ between the two groups (IFG: 1.96 ± 0.24 vs. NFG: 2.14 ± 0.09 [$\times 10^{-4}$ min^{-1}/(μU/ml)], $P = 0.57$). AIRg was 21% lower in IFG (1,406 ± 198 μU/ml) versus NFG (1,786 ± 72 μU/ml) children, approaching statistical significance ($P = 0.08$). DI was 15% lower in IFG versus NFG children (2,224 ± 210 vs. 2,613 ± 76, $P = 0.04$). Adding Tanner stage as a covariate did not influence the results (data not shown).

Because of potential confounding effects due to subjects with IGT, we repeated the above analyses in subgroups after excluding all subjects with IGT from both the NFG and IFG groups. The IFG subgroup (i.e., fasting glucose ≥100, 2-h glucose <140, $n = 15$) showed signifi-

Table 1—*Body composition and metabolic parameters in children with NFG versus IFG*

	NFG	IFG	*P* value
n	182	25	
Age	11.1 ± 1.7	11.5 ± 1.6	0.19
Sex (male/female)	99/83	20/5	**0.01**
Tanner stage			
1	77	9	0.97
2	50	8	
3	15	2	
4	24	4	
5	16	2	
Height (cm)	148.9 ± 11.7	150.3 ± 9.9	0.57
Weight (kg)	64.7 ± 20.1	63.5 ± 15.7	0.98
BMI (kg/m^2)	28.5 ± 5.5	27.8 ± 4.7	0.58
BMI percentile	97.3 ± 2.9	96.8 ± 3.3	0.42
Total body fat mass (kg)	25.4 ± 10.4	23.8 ± 8.5	0.60
Total soft lean tissue mass (kg)	37.0 ± 10.3	37.3 ± 9.3	0.76
Percent body fat (%)	38.3 ± 6.1	37.1 ± 7.2	0.60
Fasting glucose (mg/dl)	89.7 ± 4.6	104.6 ± 4.9	**<0.001**
2-h glucose (mg/dl)	125.7 ± 17.5	133.2 ± 18.4	**0.046**
Fasting insulin (μU/ml)	15.7 ± 9.6	20.2 ± 12.7	**0.042**
2-h insulin (μU/ml)	157.1 ± 138.8	146.9 ± 93.0	0.895
HOMA-IR	3.50 ± 2.18	5.20 ± 3.23	**0.002**
IGT	41 (22.5)	10 (40.0)	0.053
Systolic blood pressure (mmHg)	109.7 ± 9.7	111.0 ± 10.9	0.59
Diastolic blood pressure (mmHg)	63.1 ± 5.5	64.0 ± 6.9	0.51
Total cholesterol (mg/dl)	153.8 ± 26.0	148.2 ± 29.7	0.33
LDL cholesterol (mg/dl)	94.6 ± 21.2	88.6 ± 22.1	0.19
HDL cholesterol (mg/dl)	37.1 ± 8.9	37.8 ± 6.3	0.52
Triglycerides (mg/dl)	110.4 ± 57.8	109.2 ± 70.1	0.78
S_i [$\times 10^{-4}$ min^1/(μU/ml)]	2.13 ± 1.49	2.04 ± 1.16	0.97
AIRg (μU/ml)	1,782 ± 1,255	1,433 ± 1,288	0.29
DI	2,603 ± 1135	2,294 ± 1,180	0.13

Data are means ± SD or *n* (%), unless otherwise indicated. Unadjusted differences between IFG and NFG for continuous variables were determined by ANOVA using log-transformed values for nonnormally distributed variables (nontransformed values displayed for ease of interpretation). Differences between IFG and NFG for categorical variables (sex, Tanner stage) were determined by χ^2. *P* values <0.05 are shown in bold.

cantly lower (36%) AIRg (1,187 ± 242 vs. 1,841 ± 77, $P = 0.02$) and DI (2027 ± 255 vs. 2,721 ± 81, $P = 0.02$) than the NFG subgroup (i.e., fasting glucose <100, 2-h glucose <140, $n = 141$), while S_i was not significantly different between the subgroups (IFG: 1.80 ± 0.32 vs. NFG: 2.15 ± 0.10, $P = 0.58$). As with the complete sample, there were no significant differences in body composition or Tanner stage between subgroups (data not shown), while the IFG subgroup again had a higher percentage of males (87 vs. 56%, $P = 0.02$). Fasting glucose remained higher in the IFG subgroup (104.3 ± 3.9 vs. 89.6 ± 4.5 mg/dl, $P < 0.001$), while 2-h glucose was not significantly different (121.1 ± 7.4 vs. 118.5 ± 11.8 mg/dl) compared with the NFG subgroup. While fasting insulin (IFG: 18.7 ± 10.6 and NFG: 16.0 ± 9.8 μU/ml) and 2-h insulin (IFG: 110.5 ± 58.5 and NFG: 135.2 ± 116.2 μU/ml) were not significantly different between subgroups, HOMA-IR was higher in the IFG subgroup (4.82 ± 2.8 vs. 3.6 ± 2.2, $P = 0.02$).

To assess the possibility that decreased AIRg may only be most apparent in those children who are most insulin resistant, we performed the same analyses (ANCOVA with covariates age, sex, total fat mass, and total soft lean tissue mass) only in subjects with S_i below the full study group median of 1.73 [$\times 10^{-4}$ min^1/(μU/ml)]. In this particularly insulin-resistant subpopulation, we again found no significant difference in S_i (0.97 ± 0.12 vs. 1.09 ± 0.04 [$\times 10^{-4}$ min^1/(μU/ml)], $P = 0.34$), but AIRg was 32% lower (1,778 ± 326 vs. 2,603 ± 101 μU/ml, $P < 0.001$) and DI was 41% lower (1,498 ± 289 vs. 2,538 ± 90, $P < 0.001$) in IFG ($n = 10$) versus NFG ($n = 94$).

Table 2 demonstrates the results of multivariate linear regression to assess predictors of fasting glucose as a continuous variable rather than as the categorical variable of IFG versus NFG. Age, total body fat mass, and total body soft lean tissue mass were not significant determinants of fasting glucose in any of the regression models. Sex was significant in all models, with males tending to have higher fasting blood glucose than females. Tanner stage did not effect the regression results and was not a significant predictor of fasting glucose (data not shown). S_i was not a significant determinant of fasting glucose (model 2), whereas AIRg (model 3, negative effect) and DI (model 4, negative effect) were significant determinants, accounting for 4.3 and 4.5% of the variance in fasting glucose, respectively.

CONCLUSIONS

The primary objective of this study was to determine whether overweight Latino children with IFG have either diminished S_i or decreased β-cell function compared with those with NFG. We found that children with IFG, while having the same degree of insulin resistance, had diminished β-cell function relative to their NFG counterparts. Furthermore, β-cell secretion (AIRg) and function (DI) were inversely and linearly related with fasting glucose. To our knowledge, this is the first description of the underlying pathophysiology of IFG in children.

In at-risk adult populations, increased insulin resistance and decreased insulin secretion constitute independent risk factors for type 2 diabetes (16,17). While the incidence of type 2 diabetes in children has risen dramatically over the last decade (18), particularly in minority youth (19), the underlying pathophysiology leading to diabetes in youth has yet to be clearly demonstrated. We have previously shown that 28% of overweight Latino adolescents with a family history of type 2 diabetes have IGT. In addition, compared with their normal glucose tolerant counterparts, those with IGT had similar degrees of insulin resistance but impaired insulin secretion relative to the degree of their insulin resistance (7). Others have also shown altered relationships between insulin action and secretion in children with IGT (20), which presumably represents an intermediate state between normal glucose homeostasis and diabetes (2).

Our current data indicate that, similar to IGT, IFG in this insulin-resistant child-

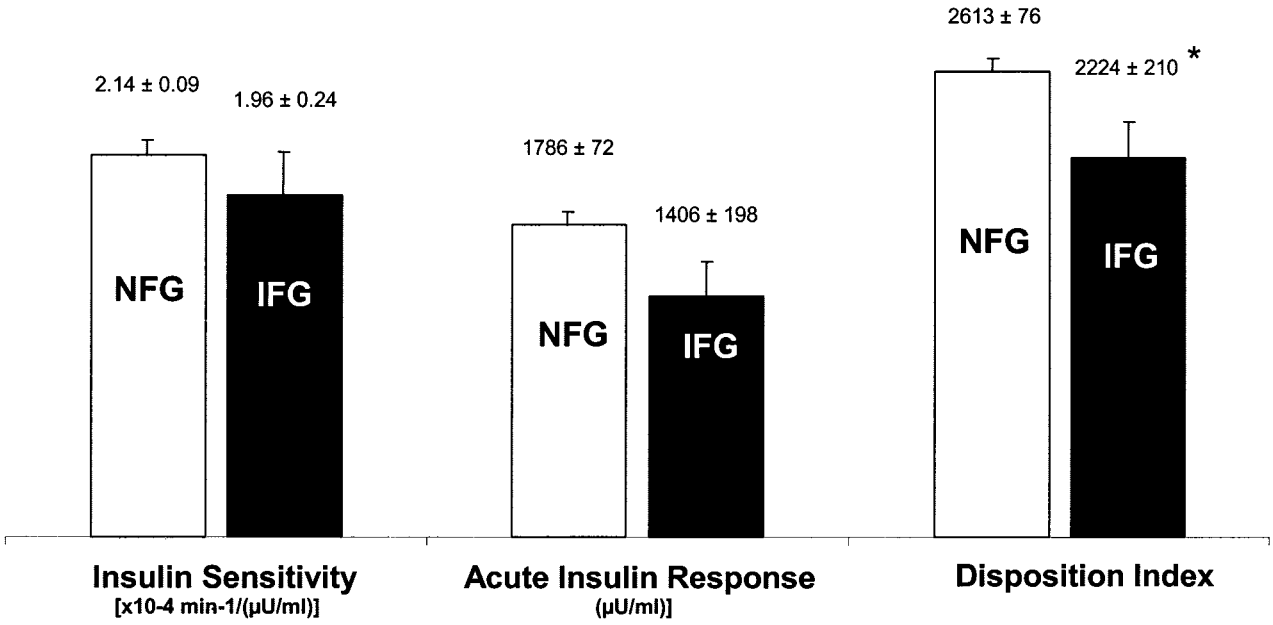

Figure 1—*Data are represented as estimated marginal means ± SE, analyzed by ANCOVA, adjusting for age, sex, total body fat mass, and total body lean tissue mass.**P *values for NFG vs. IFG:* S_i*:* P = *0.57; AIR:* P = *0.08; DI:* P = *0.04.*

hood cohort is characterized by diminished insulin secretion relative to the degree of insulin resistance. Notably, the IFG group was not more insulin resistant than the NFG group, at least as determined by frequently sampled intravenous glucose tolerance test, which measures total body S_i (21). This finding is unlikely to be due to the relatively small number of subjects in this study, as power analyses indicate we would need to study >2,000 children (278 with IFG) for the degree of S_i difference between IFG and NFG to reach statistical significance. The elevated fasting insulin and HOMA-IR in the IFG children have also been described in adults with IFG (3,4) and may suggest relatively higher hepatic insulin resistance in IFG versus NFG. Supporting this concept, Weyer, Bogardus, and Pratley (3) used the euglycemic-hyperinsulinemic clamp with tritiated glucose tracer to show that Pima Indian adults with IFG, when compared with either IGT or normoglycemic subjects, have greater hepatic glucose production that is not suppressible by supraphysiologic levels of insulin. Thus, while total body S_i may not be different, these data suggest that children with IFG may have relatively higher hepatic insulin resistance than their NFG counterparts.

Our data suggest that insulin secretion, as measured by AIRg, was lower in the IFG group (P = 0.08). Differences likely did not quite reach statistical significance due to the confounding presence of children with IGT in both the IFG and NFG groups, since excluding these IGT children demonstrated significantly lower AIRg in IFG versus NFG children. In addition, significant reduction in AIRg was most apparent in those children who were most insulin resistant. The occurrence of lower insulin secretion in IFG children with greater insulin resistance supports the concept that chronic insulin resistance may increase β-cell secretory demands, resulting ultimately in β-cell failure and altered glucose homeostasis in susceptible individuals (22). While it thus appears likely that insulin resistance may be the initial feature leading eventually to β-cell dysfunction and hyperglycemia, longitudinal studies will be necessary to prove this sequence of events in children.

Our regression analyses showing that AIRg (but not S_i) is a significant contributor to the variability in fasting glucose provide further evidence that reduction in AIRg is primarily responsible for the decrease in DI in IFG children with insulin resistance. Sex was also a significant contributor to the variability of fasting glucose, as males tended to have higher fasting glucose than females, as others have also reported (23). This must be due to some factor other than insulin action/

Table 2—*Determinants of fasting glucose with log fasting plasma glucose as the dependent variable*

	Standardized β coefficient	*P* value
Model 1: R^2 = 0.073		0.004
Sex	−0.24	0.001
Model 2: R^2 = 0.073		0.009
Sex	−0.24	0.001
S_i	−0.02	0.810
Model 3: R^2 = 0.116		<0.001
Sex	−0.26	<0.001
AIRg	−0.23	0.002
Model 4: R^2 = 0.118		<0.001
Sex	−0.30	<0.001
DI	−0.24	0.002

Analysis by multivariate linear regression. All models included covariates of age, total body fat mass, and total soft lean tissue mass (not shown, *P* values not significant in all models).

secretion dynamics, as males in our study also had higher DI than females (2,840 ± 113 vs. 2,195 ± 138, $P = 0.002$). Thus, the lower DI seen in IFG versus NFG children cannot be explained by the higher proportion of boys in the IFG group, as this sex difference would tend to raise the mean DI in the IFG group, reducing the difference in DI from the NFG group.

The ADA defines pre-diabetes as either IFG or IGT (2). Like us, others have found discordance between IFG and IGT status (i.e., many children with IFG have normal 2-h glucose tolerance, while others with IGT have NFG [24]). Additionally, the prevalence of IFG (1.8–13.3%) (24–27) appears to be lower than the prevalence of IGT (14–36%) (7,20,26, 28). The relative merits of screening for diabetes in high-risk youth with a fasting glucose versus an oral glucose tolerance test remains to be determined by prospective longitudinal studies demonstrating the sensitivity, specificity, and relative predictive value of IFG versus IGT for the eventual development of type 2 diabetes.

Our linear regression data neither support nor refute the validity of the 100-mg/dl cut point to define IFG, as the effect of β-cell function on determining fasting glucose appears to be a linear process. Indeed, in separate ANCOVA analyses in our current study population, we consistently found that DI was significantly lower in the IFG than the NFG group, whether we defined IFG as 105, 100, 95, or 90, while S_i was always the same in the two groups (data not shown). We conclude that fasting glycemia in insulin-resistant children is determined to a significant degree by the ability of the β-cell to respond to the insulin-resistant state, and this is a linear relationship without a clear "threshold" response level. Validation of the 100-mg/dl cut point for IFG will require documentation of increased risk of progression to type 2 diabetes in such children. Despite this limitation, our present investigation demonstrates that IFG, as currently defined, identifies children with impaired β-cell function that is of a similar degree to children we previously described with IGT (7). Based on current knowledge, we thus support the current ADA definition of pre-diabetes, for both IFG and IGT, to designate overweight Latino children and adolescents at potentially increased risk of type 2 diabetes.

While our current and previous findings (7) suggest that both categories of pre-diabetes are associated with an underlying defect in insulin secretion in the face of insulin resistance, it is important to note that we studied an ethnically homogenous group of Latino children, all of whom were overweight and had a family history of type 2 diabetes. One must therefore be cautious in generalizing our results, and future studies will be important to determine the consistency of our findings of diminished β-cell function in IFG in other pediatric populations of differing ethnicity and body composition.

In conclusion, overweight, insulin-resistant Latino children (with positive family history for type 2 diabetes) with IFG demonstrate impaired β-cell function compared with children with NFG, as evidenced by reduced insulin secretion relative to their degree of insulin resistance. This impairment in β-cell function in IFG subjects appears comparable with that previously described in IGT children (7). As such, both categories of pre-diabetes, IFG and IGT, may identify children likely to be at similar degrees of risk for progression to type 2 diabetes. The actual risk of progression to type 2 diabetes in such children remains to be determined by prospective longitudinal studies.

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