

Impaired Glucose Tolerance and Reduced β -Cell Function in Overweight Latino Children with a Positive Family History for Type 2 Diabetes

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The objective of this study was to examine relationships between impaired glucose tolerance (IGT) and body composition and insulin-related phenotypes in 150 overweight Latino children with a family history of type 2 diabetes. Glucose tolerance was assessed by an oral glucose challenge. Body composition was assessed by dual energy x-ray absorptiometry and magnetic resonance imaging. Insulin sensitivity, the acute insulin response, and the disposition index (DI), as an index of β -cell function, were determined by an iv glucose tolerance test and compared between normal glucose-tolerant and IGT children. IGT was present in 28% of children, and was similar

across obesity groups, but higher in children exposed to gestational diabetes mellitus (41% IGT). There were no significant differences in body composition, fat distribution, insulin sensitivity, or acute insulin response, but DI was significantly lower in IGT children by 16% ($P < 0.02$), and DI was inversely related to age. In conclusion, IGT is present in 28% of overweight Latino children with a family history of type 2 diabetes, is not influenced by obesity, is more prevalent in children exposed to gestational diabetes mellitus, and is related to poor β -cell function, which shows signs of deterioration with age in this population. (*J Clin Endocrinol Metab* 89: 207–212, 2004)

PREVIOUS STUDIES IN children have highlighted the concern for type 2 diabetes (1) and prediabetes, or impaired glucose tolerance (IGT) (2). This significant clinical issue is greater for overweight children and especially among certain ethnic groups, including Latinos, African-Americans, and Native Americans (3). Several factors have been hypothesized to contribute to the development of IGT and type 2 diabetes in children. Suggested factors include greater adiposity, especially visceral fat, and insulin resistance exacerbated by transient pubertal insulin resistance. Supporting these hypotheses, we have previously shown that Latino children have a lower insulin sensitivity (SI) than Caucasian children, independent of adiposity (4), and that increased total adiposity and visceral fat both contribute independently to lower SI in Latino children (5). However, no study has compared differences in body fat, fat distribution, and insulin-related phenotypes in normal glucose-tolerant (NGT) vs. IGT children.

Because IGT and type 2 diabetes have only recently emerged as significant issues in the pediatric population, there is a lack of detailed information on the factors that might contribute to these clinical problems. Based on var-

ious studies in adults (6–10), it is generally hypothesized that obesity leads to hyperinsulinemia and a state of insulin resistance, which leads to IGT and eventually type 2 diabetes. In addition, as suggested by Bergman and colleagues (11, 12) and demonstrated in both Pima Indians (8, 9) and pregnant Latino women (13), the inability to appropriately increase insulin secretion in response to insulin resistance is a critical factor leading to the development of type 2 diabetes. These findings indicate that the compensatory response to insulin resistance at the level of the β -cell plays a key role in the development of type 2 diabetes. However, there is a paucity of detailed studies that have examined the underlying factors that could contribute to prediabetes in children at risk.

To study these issues in more detail, we have established a cohort of overweight Latino children with a positive family history (FH) of type 2 diabetes for the University of Southern California (USC) SOLAR (Study of Latino Adolescents at Risk) Diabetes Project. In the present analysis, we examined demographic, body composition, and metabolic differences in children with NGT vs. IGT. We also examined if any of the measured outcomes were predictive of whether children had NGT or IGT. We originally hypothesized that children with IGT would be more overweight, have greater visceral fat, and be more insulin-resistant than children with NGT. The data show that 28% of overweight Latino children with a FH of type 2 diabetes have IGT and this is even higher (41%) in children exposed *in utero* to gestational diabetes mellitus (GDM). In contrast to our hypothesis, we did not find evidence that IGT was associated with obesity indices, but IGT was associated with poor β -cell function (BCF), which shows signs of deterioration with age in this population.

Abbreviations: AIR, Acute insulin response; BCF, β -cell function; BMI, body mass index; CDC, Centers for Disease Control and Prevention; DEXA, dual energy x-ray absorptiometry; DI, disposition index; FH, family history; GCRC, General Clinical Research Center; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance/tolerant; MRI, magnetic resonance imaging; NGT, normal glucose tolerance/tolerant; SI, insulin sensitivity; SOLAR, Study of Latino Adolescents at Risk.

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Subjects and Methods

A total of 150 children (85 boys, 65 girls) were recruited to the SOLAR Project through clinics, health fairs, newspaper announcements, and word of mouth. The children were required to meet the following inclusion criteria: 1) age, 8–13 yr; 2) body mass index (BMI), greater than or equal to the 85th percentile for age and gender based on the standards of the Centers for Disease Control and Prevention (CDC) (14), and an initial telephone prescreening; 3) Latino ancestry (all four grandparents Latino by self-report); and 4) FH of type 2 diabetes in at least one parent, sibling, or grandparent. Children were of Mexican-American (71%), Central American (16%), or mixed Mexican-Central American (13%) heritage. Children were excluded if they had prior major illness, including type 1 or type 2 diabetes, took medications, or had a condition known to influence body composition, insulin action, or insulin secretion (e.g. glucocorticoid therapy, hypothyroidism). The Institutional Review Board, Health Science Campus, at the USC approved the SOLAR study. Informed consent and assent were obtained from all parents and children, respectively.

Protocol design

Outpatient screening visit. Children arrived at the USC General Clinical Research Center (GCRC) at approximately 0800 h after an overnight fast. Weight and height were measured, followed by a physical examination (including Tanner staging based on breast stage in girls and pubic hair stage in boys). A medical history was conducted, including parental interview detailing FH of diabetes and GDM and the child's birth weight. After these procedures, an oral glucose tolerance test was conducted. Children who met the following screening criteria were invited back for further testing during an inpatient GCRC visit: 1) BMI greater than or equal to the 85th percentile for age and gender based on the CDC standards (14) based on height and weight measures at the GCRC; and 2) absence of type 1 or type 2 diabetes using the guidelines of the American Diabetes Association (3). Note that for the purposes of this study we used the CDC definitions for weight status in children (*i.e.* at risk of overweight is a BMI age/gender percentile between the 85th and 94th percentile, and overweight is a BMI age/gender percentile \geq 95th percentile). All but eight children met the BMI criteria, and none of the 150 children screened positive for diabetes.

Inpatient visit. Of the 150 children completing the outpatient visit, 122 returned to the GCRC within 15 ± 10 (sd) d. Children were admitted to the GCRC in the early afternoon and then completed tests for body composition using dual energy x-ray absorptiometry (DEXA) and abdominal fat by magnetic resonance imaging (MRI). The children were served dinner and an evening snack, with only water permitted after 2000 h. The next morning, SI and the acute insulin response (AIR) to iv glucose were determined from an iv glucose tolerance test.

Detailed methodologies

An oral glucose tolerance test was conducted using a dose of 1.75 g glucose/kg body weight (to a maximum of 75 g). Blood was sampled and assayed for glucose and insulin at $-5'$ (fasting) and $120'$ (2-h) relative to glucose ingestion.

Height (by a wall-mounted stadiometer) and weight (by a balance beam medical scale) were recorded at each visit to the nearest 0.1 cm and 0.1 kg, respectively, and the average of the two measurements was used for analysis. BMI and BMI percentiles for age and gender were determined based on established CDC normative curves using EpiInfo 2000, Version 1.1 (CDC, Atlanta, GA). Waist circumferences and skinfolds (axilla, chest, subscapular, superiliac, abdomen, triceps, calf, and thigh) were measured using the procedures of Lohman *et al.* (15). A whole-body DEXA scan was performed to determine whole body composition using a Hologic QDR 4500W (Hologic, Bedford, MA). Central fat distribution was measured by MRI at the Los Angeles County/University of Southern California (LAC/USC) Imaging Science Center using a 1.5 Signa LX-Ecospeed 1.5 Tesla magnet (General Electric) and a single slice at the level of the umbilicus.

A frequently sampled iv glucose tolerance test was performed with a glucose dose at time zero (25% dextrose, 0.3 g/kg body weight) and sampling at 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min. Insulin [0.02

U/kg body weight, Humulin R (regular insulin for human injection), Eli Lilly and Company, Indianapolis, IN) was injected iv at 20 min. Values for glucose and insulin were entered into the MINMOD MILLENIUM 2002 computer program (Version 5.16, Richard N. Bergman) for determination of SI, the AIR to glucose, and glucose effectiveness (16). The disposition index (DI; product of SI and the acute response to glucose) was used as an index of the compensatory adaptation to insulin resistance, a reflection of BCF.

Blood samples during the oral glucose tolerance test were centrifuged, and plasma was placed on ice and analyzed within 1 h at the LAC/USC Medical Center Core Laboratory with a Dimension Clinical Chemistry system using the Hexokinase method (Dade Behring, Deerfield, IL). Blood samples from the iv glucose tolerance test were centrifuged, and plasma was stored on ice before storage at -80 C. Aliquots were assayed in duplicate for glucose using the glucose oxidase method and a Yellow Springs Instrument 2700 Analyzer (YSI Inc., Yellow Springs, OH). Insulin was assayed in duplicate using an ELISA kit from Linco (St. Charles, MO).

Statistical analysis

Children with NGT *vs.* IGT were compared using ANOVA or general linear models when covariates were included. The proportion of children with IGT by gender, Tanner stage, obesity status, and maternal GDM status was compared with the overall group proportion using χ^2 tests for significance. Logistic binomial regression was used to identify the significant predictors of children with NGT *vs.* IGT. Forward stepwise linear regression analysis was used to identify significant predictors of 2-h glucose values from the oral glucose tolerance test and the DI from the iv glucose tolerance test. All analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, IL), with a type I error set at $P < 0.05$.

Results

The descriptive comparisons of children who were NGT *vs.* IGT are shown in Table 1. Of the 150 children completing the oral glucose tolerance test, 42 (28%) had IGT, and none had impaired fasting glucose. The proportion of children with IGT was similar between boys (29%) and girls (26%). There was no significant difference in age or Tanner stage between NGT and IGT children (the girls in the study were of similar age to the boys but had a more advanced Tanner stage, with a mean Tanner stage of 2.8 in girls and 2.0 in boys). The proportion of children at Tanner stage 4 with IGT tended to be higher (50%) than at other Tanner stages (Table 1), but because of limited numbers of children at higher Tanner stages, this difference did not reach statistical significance ($P = 0.2$ by Pearson χ^2 test). There was no significant difference in height, weight, BMI, or BMI percentile in NGT *vs.* IGT children (Table 1). Moreover, as shown in Table 1, the proportion of children with IGT was not significantly different in those children categorized as normal weight (BMI $<$ 85th percentile), at risk of overweight (85th–94th percentile), overweight (95th–98th percentile), or obese (\geq 99th percentile). Among those children whose mothers reported GDM when the mother was pregnant with that child, the proportion of children with IGT was significantly higher compared with those who reported no GDM (41% *vs.* 23%; $P = 0.035$ by Pearson χ^2 test). The proportion of children with IGT was not significantly influenced by degree of FH of type 2 diabetes and was similar in those children with neither parent but at least one grandparent with a positive FH (28% IGT) *vs.* other groups (Table 1). There was no significant difference in birth weight in NGT *vs.* IGT children. Fasting glucose and insulin were similar, but 2-h glucose and 2-h insulin were significantly higher in IGT children (Table 1).

TABLE 1. Descriptive statistics in NGT vs. IGT children

	NGT	IGT
Total no. (n = 150)	108	42 (28%)
Gender		
Boys (n = 85)	60	25 (29%)
Girls (n = 65)	48	17 (26%)
Age (yr)	11.0 ± 1.7	11.2 ± 1.7
Weight (kg)	63.0 ± 19.9	64.3 ± 22.0
Height (cm)	148.7 ± 11.5	149.1 ± 11.6
BMI (kg/m ²)	27.9 ± 5.5	28.3 ± 7.6
BMI percentile	96.1 ± 7.4	94.2 ± 12.5
No. of cases at		
<85th percentile ^a	5	3 (38%)
≥85th and ≤95th percentile	17	7 (29%)
≥95th and ≤99th percentile	47	16 (25%)
>99th percentile	39	16 (29%)
Tanner stage	2.2 ± 1.3	2.3 ± 1.4
Number of cases		
Tanner 1	38	16 (30%)
Tanner 2	38	12 (24%)
Tanner 3	11	2 (15%)
Tanner 4	9	9 (50%)
Tanner 5	11	3 (21%)
GDM		
No GDM	85	25 (23%)
GDM	23	16 (41%)
FH^b		
0 Parents	51	20 (28%)
Mother	30	14 (32%)
Father	16	4 (20%)
Mother + father	5	2 (29%)
Birth weight (kg)	3.7 ± 0.95	3.6 ± 0.7
Fasting glucose (mg/dl)	92.2 ± 9.6	94.3 ± 8.5
2-h glucose (mg/dl)	118.6 ± 11.8	149.1 ± 10.1
Fasting insulin (μU/ml)	16.1 ± 9.4	16.6 ± 11.1
2-h insulin (μU/ml)	119.1 ± 92.9	213.6 ± 149.2

There is one case where Tanner stage was not ascertained; three missing values for fasting and 2-h insulin and birth weight were not ascertained in six subjects. Variables in **bold** are significantly different between NGT and IGT at $P < 0.05$.

^a Results from eight children with a BMI percentile <85th percentile are included because the oral glucose tolerance test screening was conducted and the children were later excluded from other measures because they did not meet the inclusion criteria.

^b FH of type 2 diabetes where all children had at least one grandparent diagnosed with type 2 diabetes.

Table 2 summarizes the body composition, fat distribution, and SI data in NGT vs. IGT children. There were no significant differences in any skinfold measure, waist circumference, body composition data by DEXA, or abdominal fat distribution by MRI, SI, and the AIR in these two groups. Visceral fat was similar in the two groups after adjusting for sc abdominal fat, age, gender, and Tanner stage (adjusted least square mean ± SE = 47.0 ± 1.6 vs. 48.7 ± 2.7 cm²; $P = 0.5$). The similar relationship between visceral fat and sc abdominal fat in the two groups is shown in Fig. 1 and demonstrates equivalence of abdominal fat partitioning across the two groups.

When SI was adjusted for age, gender, Tanner stage, total fat, visceral fat, and sc abdominal fat, there was still no significant difference between NGT and IGT children [adjusted least square mean ± SE = 2.1 ± 0.1 vs. 1.8 ± 0.18 × 10⁻⁴ min⁻¹/(μU/ml); $P = 0.2$]. The similar relationships between SI and total fat in the two groups are shown in Fig. 2 (with

TABLE 2. Body fat and SI data in NGT and IGT children

	NGT (n = 87)	IGT (n = 35; 29%)
Waist (cm)	86.6 ± 12.5	85.9 ± 13.1
Abdominal (mm)	26.7 ± 9.1	26.2 ± 8.3
Chest (mm)	10.9 ± 5.2	11.3 ± 5.2
Calf skinfold (mm)	14.7 ± 5.3	14.3 ± 5.0
Triceps skinfold (mm)	14.5 ± 6.6	14.7 ± 5.3
Total fat (kg)	23.6 ± 9.6	22.6 ± 9.6
Trunk fat (kg)	11.5 ± 5.2	11.1 ± 5.2
Total lean (kg)	35.9 ± 10.3	36.3 ± 10.0
Total bone (kg)	1.7 ± 2.0	1.5 ± 0.4
% Total fat	37.9 ± 0.07	36.3 ± 0.01
IAAT (cm ²)	47.4 ± 18.5	46.2 ± 22.1
SAAT (cm ²)	316.5 ± 136.5	295.7 ± 132.4
IAAT:SAAT	0.18 ± 0.18	0.17 ± 0.06
SI [×10 ⁻⁴ min ⁻¹ /(μU/ml)]	2.1 ± 1.3	2.0 ± 1.1
AIR (μU/ml)	1793 ± 1241	1646 ± 1492
DI × 10⁻⁴ min⁻¹	2654 ± 926	2233 ± 1052 (P = 0.02)
Sg (percentage/min)	10 ± 0.6	9 ± 0.6

IAAT, Intraabdominal adipose tissue; SAAT, sc abdominal adipose tissue by MRI; Sg, glucose effectiveness by the Bergman minimal model. All variables are not significantly different between NGT and IGT children except the DI, which is in **boldface** type.

similar findings when plotted vs. visceral fat; data not shown). These subtle differences in SI and the AIR resulted in a 16% significantly lower DI in IGT children ($P = 0.02$; Table 2). The different hyperbolic relationships and the lower DI in children with NGT are shown in Fig. 3.

Stepwise regression analysis was conducted to examine the effect of the following variables on 2-h glucose: DI, age, gender, Tanner stage, waist circumference, BMI percentile, total fat mass, total lean tissue mass, maternal GDM, fasting glucose, and fasting insulin. The one and only significant variable selected in the model was the DI, and this only explained 4% of the variance in 2-h glucose. None of the aforementioned variables were significant when the ratio of 2-h to fasting glucose was used as the dependent variable. In addition, in binomial logistic regression analysis, DI was the only variable significantly related to NGT vs. IGT status.

Stepwise regression analysis was conducted to examine the effect of the following variables on the DI: age, gender, Tanner, waist circumference, BMI percentile, total fat mass, total lean tissue mass, maternal GDM, fasting glucose, and fasting insulin. The one and only significant variable selected in the model was age, which was inversely correlated with the DI ($r = -0.37$; $P < 0.001$).

Discussion

In this paper, we present a detailed comparison of metabolic and physiological differences in children with NGT vs. IGT. These results suggest that: 1) 28% of overweight Latino children with a positive FH of type 2 diabetes already have IGT; 2) in this overweight sample of children, IGT does not appear to be influenced by degree of overweight; 3) IGT may be more prevalent in children exposed to GDM and in children in later stages of puberty; 4) NGT and IGT children are very similar with respect to body composition, visceral adiposity, SI, and AIR; 5) based on a significantly lower DI, children with IGT show evidence of poor BCF; and 6) BCF is already showing signs of deterioration with age in this

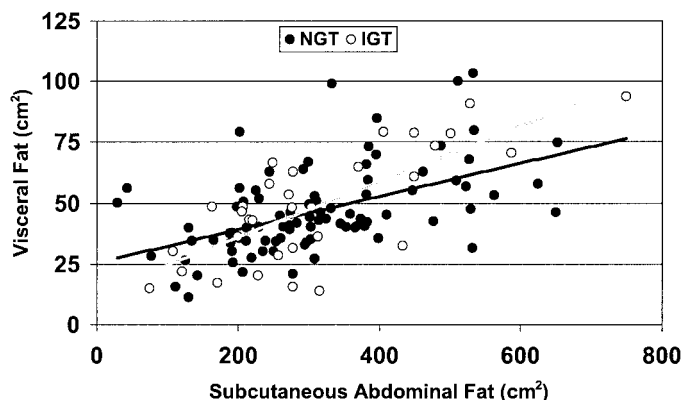


FIG. 1. Visceral fat *vs.* sc abdominal fat in NGT *vs.* IGT children. Visceral fat plotted as a function of sc abdominal fat in children with NGT (solid circles, black line; $R^2 = 0.55$; slope = 0.11 ± 0.02 ; intercept = 13.5 ± 6.4 cm²) and IGT (open circles, gray line; $R^2 = 0.26$; slope = 0.07 ± 0.01 ; intercept = 25.7 ± 4.1 cm²). Regression lines are not significantly different for slope or intercept. Visceral and sc abdominal fat measured by MRI (IGT defined by 2-h glucose ≥ 140 mg/dl after an oral glucose tolerance test).

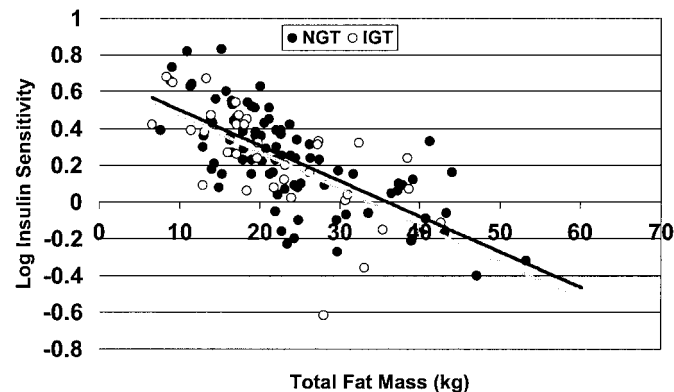


FIG. 2. SI *vs.* total body fat in NGT *vs.* IGT children. Log SI [$\times 10^{-4}$ min⁻¹/(μ U/ml)] plotted as a function of total fat mass in children with NGT (solid circles, black line; $R^2 = 0.49$; slope = -0.19 ± 0.02 ; intercept = 0.69 ± 0.05) and IGT (open circles, gray line; $R^2 = 0.45$; slope = -0.19 ± 0.02 ; intercept = 0.67 ± 0.09). Regression lines are not significantly different for slope or intercept. SI measured by iv glucose tolerance test; total fat mass measured by DEXA.

population. We discuss these findings as well as their clinical implications in the paragraphs that follow.

Only a few prior studies have examined IGT in overweight children. In a study from 1968, Paulsen *et al.* (17) conducted oral glucose tolerance tests in 66 obese children (4–16 yr). Because Paulsen *et al.* published the raw data, we were able to apply the same cut-point as the current study (2-h glucose ≥ 140 mg/dl), and showed that 24% of the obese children with a positive FH of diabetes had IGT, similar to what we currently report. In a smaller study from 1980, 5 of 15 very overweight children had impaired 2-h glucose (18). Similarly, Sinha *et al.* (2) found IGT in 23% of a sample of 167 children and adolescents, all of whom had a BMI greater than the 95th percentile for age and gender. Collectively, these three prior studies (2, 17, 18), together with the current study, show a consistent finding of IGT in 20–30% of overweight children. Interestingly, the more recent studies show similar

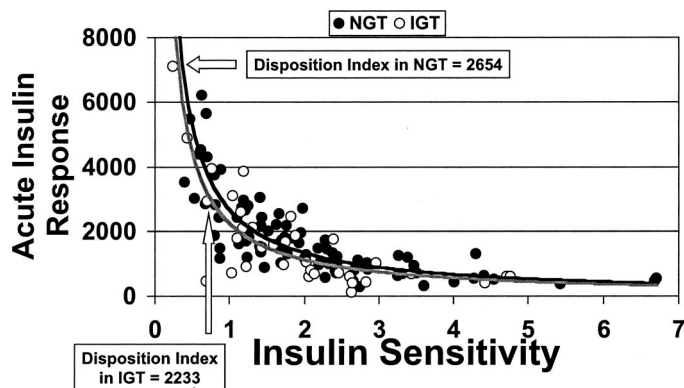


FIG. 3. Hyperbolic relationships between AIR to glucose and SI in NGT and IGT children. AIR to glucose (μ U/ml) plotted as a function of SI [$\times 10^{-4}$ min⁻¹/(μ U/ml)] in children with NGT (solid circles, black line) and IGT (open circles, gray line). The hyperbola for the IGT group represents a DI significantly lower than for the NGT group. AIR to glucose and SI measured by iv glucose tolerance test.

rates to the older studies from 1968 and 1980, suggesting that IGT among overweight children is not a new phenomenon.

The specific effect of FH on the likelihood of having IGT is difficult to determine from these studies because there has been no systematic comparison in the literature and previous studies have not always specified aspects of FH. In the current sample, all children had at least one grandparent with type 2 diabetes, but we did not detect any significant difference in the proportion of children with IGT as a function of the degree of FH. The prevalence of IGT was 28% in children with neither parent having type 2 diabetes and in children with at least one parent with type 2 diabetes. Although the prevalence of IGT was different in those children who had a mother with type 2 diabetes (32%) *vs.* those with a father with type 2 diabetes (20%), this did not reach statistical significance. Further studies in larger numbers are needed to more systematically examine the influence of FH of type 2 diabetes on risk factors in offspring. Similarly, there has been no previous study of ethnic differences. In the study of Sinha *et al.* (2), the proportion of children with IGT was similar across ethnic groups (the sample consisted of 58% white, 23% black, and 19% Latino children). Nevertheless, because of the small numbers, there is still a need to perform a more systematic comparison of metabolic differences in NGT *vs.* IGT children across the spectrum of ethnicities.

In the current study, we observed a similar proportion of children with IGT across groups subdivided by degree of overweight. In addition, there was no significant difference in total body fat or abdominal fat distribution in children with NGT *vs.* IGT. This was an unexpected finding and is in contrast to Sinha *et al.* (2), who observed a higher BMI in severely overweight adolescents with IGT. However, our finding is consistent with the earlier study of Paulsen *et al.* (17) who also showed that the extent of IGT was independent of the duration or degree of obesity.

The absence of any obvious effects or differences in adiposity in NGT *vs.* IGT children suggests that obesity itself may not be the critical factor. An alternative explanation could be that an increase in fat mass or in specific fat depots like visceral fat or intramyocellular lipid may create the right

physiological conditions (*i.e.* greater insulin resistance and greater insulin demand) that will challenge BCF. Ultimately, it would be the ability of β -cells to compensate to the degree of insulin resistance that will contribute to a failure in glucose regulation. Alternatively, the remarkable similarities between children with NGT and IGT suggests that other intrinsic or genetic factors, which are present in a proportion of the population, contribute to IGT and/or poor BCF.

Longitudinal studies in the present cohort are needed to verify which critical factors, including obesity-related factors, predict the conversion from NGT to IGT and from the latter to type 2 diabetes. A previous 25-yr longitudinal study of 181 normoglycemic individuals with no FH and 150 normoglycemic individuals with a positive FH provides interesting results (19). This study showed that in those with no FH, the incidence of new cases of type 2 diabetes was 1.8 per 1000 person-years, similar to other population studies, and that degree of obesity had only a small effect on risk of developing type 2 diabetes (19). However, degree of obesity did have a large effect on the development of type 2 diabetes in the group with a positive FH (16.7 *vs.* 8.8 per 1000 person-years). Therefore, although type 2 diabetes is predominantly seen in obese individuals, nonobese individuals with a positive FH are still at higher risk, possibly due to the presence of as yet unidentified intrinsic factors that may determine the ability of β -cells to compensate to insulin resistance. Thus, further studies are needed in nonobese individuals with a positive FH of type 2 diabetes.

Because maternal GDM was not an exclusion factor in this study, we were able to compare subgroups of children who were either exposed or not exposed to this condition. The children exposed to GDM were almost twice as likely to have IGT. This difference was not influenced by degree of overweight; in other words, among children exposed to GDM, the proportion of children with IGT was not affected by degree of overweight. GDM has long been known to contribute to greater obesity and IGT in offspring, probably due to exposure to high insulin secretion *in utero* (20, 21). With the current results, we extend this observation to offspring of Latino women with GDM and apparent IGT during early maturation.

Several longitudinal studies have shown that insulin resistance is present well before the eventual development of hyperglycemia (22–24). It is also now generally accepted that insulin resistance alone is insufficient to cause the development of type 2 diabetes, but rather, it may do so in combination with the presence of poor BCF (12). This phenomenon has been shown in previous longitudinal studies in Pima Indians (8). Furthermore, in Mexican-American women with previous GDM, improvements in SI achieved through 30 months of treatment with troglitazone significantly reduced the incidence of type 2 diabetes. This effect was associated with conservation of pancreatic BCF and reduced secretory demands (13). Collectively, these findings led Kahn (25) to recently conclude that “it is now becoming apparent that the relentless decline in BCF commences well before the clinical diagnosis of diabetes.” Therefore, for prevention and treatment efforts to be effective, there is a need to understand genetic and metabolic factors relating to progressive β -cell dysfunction.

The previous study by Sinha *et al.* (2) suggested that BCF was still preserved in children with IGT, but they used cruder methods based on fasting and postchallenge insulin and C-peptide. However, in the present study, we used the DI as a more detailed measure of BCF and found evidence of reduced BCF in children with IGT. A lower DI associated with IGT has also been shown in obese adolescents with polycystic ovarian syndrome (26). Therefore, we can extend the BCF theory to Latino children, and we would hypothesize that it will be children with lowest DI (possibly regardless of glucose tolerance state) that may eventually develop type 2 diabetes.

Because of the likely importance of a low DI in predicting future development of type 2 diabetes, we performed a subanalysis comparing children with the lowest and highest tertile for this variable. In particular, we hypothesized that increased visceral fat might be associated with poor BCF. However, absolute visceral fat was not significantly different across tertiles of the DI (46.9 ± 21.7 , 47.0 ± 17.9 , and 47.3 ± 17.9 cm² from lowest to highest tertile). Furthermore, after adjusting for age, gender, Tanner stage, and total body fat, visceral fat remained similar across the tertiles of DI. In similar models, sc abdominal fat and total body fat were not significantly different across tertiles of the DI. There were no significant differences in children with a low *vs.* a high DI for any of the variables we examined except for age (11.8 ± 1.5 in children with the lower DI *vs.* 10.3 ± 1.5 in children with the higher value). In the group as a whole, the DI was significantly and inversely associated with age ($r = -0.37$; $P < 0.001$), suggesting that BCF is already showing signs of deterioration in this population. The inverse relationship with age remained significant after controlling for Tanner stage (partial $r = -0.19$; $P = 0.03$) and, in this population, it may be occurring in addition to the previously described reduction in DI that occurs as children progress from prepubertal to midpubertal (27).

Other factors have been hypothesized to contribute to poor BCF. These factors may include, but are not limited to, hyperglycemia and high levels of free fatty acids, amyloid deposition in islets, resistin, or other adipose-derived cytokines (12, 25). Further studies are warranted to investigate whether these factors are involved with the deterioration of BCF during growth and development.

The findings from this study have raised a number of important clinical implications. Both the current study and the prior study of Sinha *et al.* (2) show that an oral glucose tolerance test, and not fasting glucose, is necessary for detecting children with IGT. Despite a 28% prevalence of IGT and some children with extreme insulin resistance, all of the children in the current study had a normal fasting glucose of less than 110 mg/dl. On average, fasting glucose was only minimally elevated in IGT children (2 mg/dl higher in children with IGT and requiring a sample size of 230 per group to detect as significantly different; assume $\alpha = 0.05$ and $\beta = 0.8$). In addition, assessment of SI was not adequate in detecting children with IGT, and the small difference in SI, even after adjusting for confounding variables, would have required 138 children per group to be detected as significant. Screening for IGT would therefore currently require an oral glucose tolerance test. In addition, this observation raises the

need for the development of other markers or tests that could be more broadly applicable outside of a clinical setting.

In conclusion, this study suggests that almost one in three overweight Latino children with a positive FH of type 2 diabetes already have IGT, and the likelihood of having this condition does not seem to be associated with degree of overweight. The metabolic and physiological similarities between NGT and IGT children suggest additional factors that may contribute to glucose intolerance and poor BCF, as suggested from the lower DI in children with IGT. Finally, in this high-risk population, BCF is already showing signs of deterioration with age. Screening for BCF may be more important than screening for glucose tolerance status. Further longitudinal studies in this cohort will be required to identify the metabolic precursors and natural history for the development of type 2 diabetes during adolescence, but there is a clear need for early intervention and prevention interventions.

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