Persistence of Pre-Diabetes in Overweight and Obese Hispanic Children

Association With Progressive Insulin Resistance, Poor β-Cell Function, and Increasing Visceral Fat

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OBJECTIVE—To examine changes in risk factors in overweight and obese Hispanic children at high risk of developing type 2 diabetes.

RESEARCH DESIGN AND METHODS—We recruited 128 overweight/obese Hispanic children with a family history of type 2 diabetes primarily from clinics in East Los Angeles. Children were evaluated annually for 4 years with an oral glucose tolerance test, applying American Diabetes Association criteria to define diabetes and pre-diabetes. Insulin sensitivity (S_i), acute insulin response (AIR) to glucose, and β-cell function (BCF) were determined from frequently sampled intravenous glucose tolerance tests, and total body fat by dual-energy X-ray absorptiometry and intra-abdominal and subcutaneous abdominal adipose tissue (IAAT and SAAT) by magnetic resonance imaging were assessed in years 1, 2, and 4.

RESULTS—No subjects developed type 2 diabetes, 40% never had pre-diabetes, 47% had intermittent pre-diabetes with no clear pattern over time, and 13% had persistent pre-diabetes. At baseline, those with persistent pre-diabetes had lower BCF and higher IAAT. In repeated measures, S_i deteriorated regardless of pre-diabetes, and there was a significant effect of pre-diabetes on AIR (42% lower in pre-diabetes; \( P = 0.01 \)) and disposition index (34% lower in pre-diabetes; \( P = 0.021 \)) and a significant interaction of pre-diabetes and time on IAAT (greater increase over time in those with pre-diabetes; \( P = 0.034 \)).

CONCLUSIONS—In this group of Hispanic children at high risk of type 2 diabetes, 1) pre-diabetes is highly variable from year to year; 2) the prevalence of persistent pre-diabetes over 3 years is 13%; and 3) children with persistent pre-diabetes have lower BCF, due to a lower AIR, and increasing visceral fat over time.

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There are more than 35 million people of Hispanic origin in the U.S. today, totaling 12.5% of the population, making them the largest and fastest growing minority group. The disproportionate burden of obesity and its related comorbidities in Hispanics, especially type 2 diabetes, is evident early in life. For example, the lifetime risk of developing diabetes is highest among Hispanics, with a lifetime risk of ~50% for children born in the year 2000 (1). Also, in 2000, 43.8% of Hispanics ages 12–19 were overweight, and 23.4% were obese; these values were approximately double that of non-Hispanic whites (2). Hispanic children are more insulin resistant than Caucasian children, independent of body fat content (3). Despite these alarming observations and substantial health risks, there is a paucity of information on the physiological and metabolic causes of the development of type 2 diabetes in this high-risk population.

Increased obesity is a major determinant of insulin resistance, but studies in adults have shown that insulin resistance alone is insufficient to cause type 2 diabetes. Rather, the progression to type 2 diabetes has been shown to be a combination of insulin resistance and the inability of β-cells to adequately compensate through an increase in insulin secretion (4–7). As proposed by Bergman et al. (8) and others (6,9), β-cell compensation can be determined by the disposition index, defined as the product of insulin secretion and insulin sensitivity (S_i). Poor β-cell function (BCF), indicated by low disposition index, is predictive of the development of type 2 diabetes in Pima Indians (9,10), in young Hispanic women who experienced gestational diabetes mellitus (GDM) (11,12), in Mexican-American adults (13), and in pre-diabetic African American adults (14).

Numerous studies in overweight and obese children and adolescents have documented the high prevalence of pre-diabetes, as indicated by either high fasting glucose or impaired glucose tolerance (15–17). In our recent reports from ongoing studies among overweight and obese Hispanic children with a family history of type 2 diabetes, we found a cross-sectional prevalence of pre-diabetes of 32% (15,18). In these prior cross-sectional studies, impaired glucose tolerance and impaired fasting glucose were associated with ~16% lower BCF, but there were no differences in insulin resistance, body composition, or fat distribution. Most prior reports examining pre-diabetes in overweight and obese children have looked at a cross-sectional sample with one-time assessment of glucose tolerance as a measure of pre-diabetes. These studies are limited by the poor test-retest reliability of the oral glucose tolerance test (OGTT) for assessing pre-diabetes and the likelihood of physiological variation and fluctuations over time in glucose tolerance status. In the current study, we aimed to extend and validate prior cross-sectional findings with a longitudinal design over 4 years in which we evaluated glucose tolerance, S_i, BCF, body fat, and visceral fat on an annual basis. Using this approach, we were able...
to classify subjects on the basis of the persistence of pre-diabetes over 4 consecutive years as never, intermittent, or persistent. This strategy enabled us to therefore identify with greater confidence those children with pre-diabetes (i.e., those with persistent pre-diabetes). Using this rigorous longitudinal design and robust definition of pre-diabetes, we aimed to extend our understanding of the natural history of the progression of type 2 diabetes risk factors in overweight and obese Hispanics by examination of the temporal patterns of changes in diabetes risk factors over time.

RESEARCH DESIGN AND METHODS

We examined longitudinal data from 128 overweight and obese Hispanic children (68 boys and 58 girls; 11.1 ± 1.8 years old at initial visit) from the University of Southern California Study Of Latinos At Risk (SOLAR) Diabetes Project. These children had an average BMI at initial visit of 28.5 (equivalent to a BMI percentile of 97.2 ± 3.3). The children were recruited from the community surrounding Los Angeles County Hospital in East Los Angeles. The majority of children (~80%) were recruited from overweight children who were referred to various pediatric clinics for evaluation, and the remainder were recruited by word-of-mouth (i.e., contacts obtained from children already in the study) and local advertising. The main inclusion criteria were a BMI ≥85th percentile for age and sex, a family history of type 2 diabetes (at least one parent or grandparent), and being of Hispanic ethnicity as defined by all four grandparents reporting to be Hispanic. Approximately 90% of the children were from Mexico with the remainder from Central America. The cohort was not therefore representative of the population at large but rather selected to represent the characteristics of a very high-risk subgroup of the population. The 128 children were selected from the larger cohort of 220 children on the basis of having completed four consecutive annual screening visits to assess diabetes risk with an OGTT. The children included in the current longitudinal analysis were comparable with others in the cohort who were not included in the analysis. The only significant difference observed was a lower fasting glucose in those included in the longitudinal analysis (92.4 ± 63 vs. 94.1 ± 6.3 mg/dl, P = 0.036). There were no significant differences for age, sex, Tanner stage, BMI (percentile and Z score), total body fat and lean mass, intra-abdominal and subcutaneous abdominal adipose tissue (IAAT and SAAT, respectively), fasting insulin, S_p, acute insulin response (AIR), and disposition index. The subsample of the 128 children had complete assessments for S_p, AIR, and disposition index by an intravenous glucose tolerance test, body composition by dual-energy X-ray absorptiometry (DEXA), and abdominal fat distribution by magnetic resonance imaging (MRI) at years 1, 2, and 4. Because of budgetary cuts, these measures were not obtained in most subjects at year 3.

The methods and study protocol have been previously outlined in detail (15). A complete medical history and physical examination was conducted by a licensed pediatric health care provider, which included Tanner staging using established 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 sex were determined based on established Centers for Disease Control normative curves using EPinfo 2000, version 1.1. A 2-h OGTT was conducted using a dose of 1.75 g glucose/kg body wt (maximum 75 g) as previously described (15). Using American Diabetes Association criteria (19), pre-diabetes was defined as the fasting glucose/kg body wt (maximum 75 g) as previously described (15). A whole-body DEXA scan was performed to determine whole-body composition using a Hologic QDR 4500W. Central fat distribution was measured by MRI at the LAC/USC Imaging Science Center using a GE 1.5 Sgna LX-Ecospeed with a GE 1.5-Tesla magnet and a single slice at the level of the umbilicus. This procedure measures IAAT and SAAT.

Statistical analysis. For the evaluation of patterns of pre-diabetes across time, prevalence (percentage of total cases) at each of the four visits was calculated. Examination of the patterns of pre-diabetes over time led to classification of participants into three groups, as follows. Group 1: never, defined by a negative test for pre-diabetes at all four visits; group 2: intermittent, defined by one or two positive tests for pre-diabetes from the four annual visits; and group 3: persistent, defined by three or four positive tests for pre-diabetes at the four annual visits.

**Results**

Annual OGTTs were completed over 4 consecutive years on 128 children. The prevalence of IGT at each of the annual visits ranged from 20.3 to 22.7%, and the pattern of IGT and IFG over the 4 years is shown in Table 1. Table 1 shows that 66 children tested negative for IGT at all four annual visits and at the other extreme, only six children tested positive at each annual visit. Similarly, 90 children tested negative for IFG at all four annual visits, and only one tested positive for IFG at each annual visit. Between these two extremes there was tremendous variability in the individual patterns of change in glucose status over the 4 years. This variation precluded the ability to ascertain with any confidence segments of the cohort that progressed from normal to pre-diabetes or reversed from pre-diabetes over the 4 years. By defining pre-diabetes as the presence of either IFG or IGT, we characterized the group as a function of the persistence of pre-diabetes over 4 years. Fifty-one children (40%) never had pre-diabetes at any visit, 61 children (47%) had intermittent pre-diabetes, and 16 children (13%) had persistent pre-diabetes over 4 years. The unadjusted baseline characteristics of these three groups are shown in Table 2. Although those with persistent pre-diabetes tended to be female and further along in maturation, these differences were not significant in a χ² analysis. Those with persistent pre-diabetes had significantly higher fasting and 2-h glucose, greater visceral fat, and poorer BCF at baseline (Table 2).
Using repeated-measures ANOVA, we examined the patterns of changes in key variables over time adjusting for appropriate covariates (Table 3). Over the 3 years, body weight increased by ~20 kg, but the rate of increase in body weight was similar in the three subgroups that differed by pre-diabetes status (data not shown). BMI Z score and BMI percentile were stable over time in the group as a whole and in all subgroups. Also, the rate of maturation (change in Tanner stage) was similar in all subgroups (data not shown). Fat mass significantly increased over the 3 years, but fat mass and the change in fat mass over time were not significantly influenced by pre-diabetes status. After adjusting for fat mass, SAAT did not significantly change over time, but there was a trend for the interaction of time and IGT status ($P = 0.07$) with greater change observed in the groups with intermittent and persistent pre-diabetes. Changes in IAAT over time were significantly associated with pre-diabetes status ($P = 0.034$ for the interaction of time and pre-diabetes status). As shown in Table 3, IAAT significantly increased in those with persistent pre-diabetes and was relatively stable in the other two groups. These effects remained significant even after including SAAT as an additional covariate in the model.

Changes in metabolic parameters relating to type 2 diabetes (fasting and 2-h glucose, fasting insulin, $S_i$, AIR, and disposition index) are also shown in Table 3. Fasting and 2-h glucose were significantly higher in those with persistent pre-diabetes but did not change over time in any of the subgroups. Fasting insulin was not significantly influenced by persistence of pre-diabetes and did not significantly change over time. $S_i$ declined in all groups, regardless of IGT status with a similar degree of decline in all groups (Table 3). The AIR to glucose was significantly lower in the group with persistent pre-diabetes ($P = 0.01$ for overall effect of pre-diabetes status; Table 3). As also shown in Table 3, disposition index was significantly lower in those with persistent pre-diabetes ($P = 0.021$), although the changes over time were not significantly influenced by persistent pre-diabetes status.

**DISCUSSION**

In the current study, we report findings from a cohort of 128 overweight and obese Hispanic children at high risk of developing type 2 diabetes evaluated annually for 4 years. Our main findings are threefold. First, diagnosis of pre-diabetes over time is highly variable from year to year, making it very difficult to identify systematic patterns of change over time. The prevalence of persistent pre-diabetes was 13%, lower than in prior cross-sectional reports (15) but still alarmingly high. Second, we showed that in the cohort as a whole, there was progressive deterioration of $S_i$, but those subjects with persistent pre-diabetes had a lower BCF, explained by a lower than expected AIR for the given degree of insulin resistance. Third, we found that those children with persistent pre-diabetes had an increasing visceral relative to subcutaneous abdominal fat accumulation over time.

We are only aware of one other longitudinal study of glucose tolerance status in children (20). In this study, 117 obese adolescents (84 with normal glucose tolerance and 33 with IGT) completed a follow-up OGTT 2 years later. Fifteen subjects reverted to normal glucose tolerance, 10 had persistent IGT, and 8 subjects with IGT at baseline (7 African Americans, 1 Caucasian, and 0 Hispanics) developed type 2 diabetes. Severe obesity, IGT, and African American ancestry predicted the development of type 2 diabetes (fasting glucose, insulin, and C-peptide were not predictive). Outcomes were limited to parameters derived from the OGTT and height and weight. These findings, compared with our experience of no progression to type 2 diabetes in our Hispanic cohort, suggest the possibility of an ethnic disparity in the natural history of the development of pediatric type 2 diabetes, although analysis of ethnic differences is limited by the underrepresentation of Hispanics from the prior study (only four of the subjects with IGT at baseline were Hispanic) and may be additionally confounded by a much higher degree of adiposity at baseline (per BMI criteria) in the prior study compared with our cohort.
As we have shown previously (15,21), the overweight and obese Hispanic children of this cohort are extremely insulin resistant. We have also previously shown that the two factors are strongly associated. Although the overall effect of time on BCF was not significantly different according to pre-diabetes status, although there was a hint of a greater decline in those with pre-diabetes from years 2 to 4 (1.7 ± 0.1 to 1.3 ± 0.1 × 10^{-4} min^{-1} · μU^{-1} · ml^{-1}). Where the groups did differ was in the compensation to the progressive insulin resistance. Those individuals with persistent pre-diabetes showed a lower than expected AIR, corresponding to a lower BCF (Table 3).

Although the overall effect of time on BCF was not significant in the repeated-measures ANOVA, post hoc analysis suggested reductions over time regardless of pre-diabetes status. By visit 4, the mean value of the disposition index was significantly lower than at visits 1 and 2 (2.405 ± 147; 2.368 ± 173, and 1972 ± 134 × 10^{-4} min^{-1} at visits 1, 2, and 4, respectively; visit 4 was significantly different from visits 1 and 2; P < 0.05). This reduction in disposition index is equivalent to ∼136 disposition index units per year or a 6% decline in BCF per year. This deterioration in BCF compares with a ∼10% per-year decline in Hispanic women with prior GDM (23).

One of our major findings was a greater accumulation of visceral adipose tissue over time, specifically in those children with persistent pre-diabetes (Table 3). From the current study, it is very difficult to determine whether persistent pre-diabetes caused the greater accumulation of visceral adipose tissue or vice versa, but nevertheless, we have shown that the two factors are strongly associated. This finding suggests a possible hypothesis that persistent hyperglycemia may lead to greater visceral fat accumulation. In the current study, we were limited in our assessment of visceral fat to a single-slice MRI. Further studies...
are needed to examine whether this association is linked also to fat spillover into other organs, such as muscle and liver. Fat deposition in the liver is associated with insulin resistance and hyperinsulinemia in nonobese normal subjects (24–26) and in obese subjects with type 2 diabetes (26,27), and this seems to be independent of total body adiposity. The time course and temporal patterns of these effects are not clearly established, such that it is unknown whether insulin resistance causes greater fat spillover or vice versa (28). An alternative hypothesis explaining the observed relationship between visceral adipose tissue and pre-diabetes pattern might be that increased visceral fat leads to increased release of free fatty acids into the portal circulation. This could potentiate both insulin resistance and the gradual loss of BCF, consistent with the portal theory of insulin resistance and lipotoxicity as a proposed cause of β-cell failure (29). Future work should examine whether persistent pre-diabetes and/or insulin resistance is associated with liver fat accumulation and/or loss of BCF due to lipotoxicity.

The variability in evaluation of IFG and IGT from year to year could be either physiological fluctuations over time or measurement error. There is not much data on day-to-day variation in fasting and 2-h glucose data during an OGTT in children. We have conducted test-retest reliability in 23 overweight and obese Latino children (mean age 13.6 ± 1.6 years). The average time between repeated tests was 41.4 ± 20.7 days (>90% retested within 2 months). For fasting glucose, the test-retest correlation was moderate (r = 0.52), and the within-subject coefficient of variation (CV) was 4.7%. For 2-h glucose, the test-retest correlation was similar (r = 0.52), but the within-subject CV was much higher (16.2%). This poor reliability adds strength to the justification of basing diagnosis of pre-diabetes on more than one oral glucose challenge test whether for research or clinical purposes.

Two major limitations of this study should be pointed out. The first issue relates to the specific population in this study (overweight Latino children and youth with a family history of type 2 diabetes) and therefore limits generalizability of our findings to other groups. The second issue is that the outcome of the current study was pre-diabetes, not type 2 diabetes. The pattern of change in risk factors over time may be different for type 2 diabetes compared with pre-diabetes.

In conclusion, this detailed longitudinal cohort study has shown that in overweight and obese Hispanic adolescents with a family history of type 2 diabetes, the pattern of pre-diabetes over time is highly variable from year to year, but the prevalence of persistent pre-diabetes is estimated to be 13%. Furthermore, we have shown that persistent pre-diabetes is associated with compromised BCF, a lower than expected AIR in response to progressive insulin resistance, and a greater accumulation of visceral fat over time. Thus, persistence of pre-diabetes, rather than the finding of pre-diabetes at any single time point, in addition to longitudinal accumulation of visceral adipose tissue, may be more specific markers of future diabetes risk.

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