Persistence of the Metabolic Syndrome Over 3 Annual Visits in Overweight Hispanic Children: Association with Progressive Risk for Type 2 Diabetes

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Objective To examine an association between persistent metabolic syndrome (MetS) and the risk for type 2 diabetes in overweight Hispanic children.

Study design A total of 73 subjects (mean age, 11.0 ± 1.7 years) from a longitudinal study were classified as Never (negative for MetS at all 3 annual visits), Intermittent (positive for MetS at 1 or 2 visits), or Persistent (positive for MetS at all 3 visits). Measures included dual-energy x-ray absorptiometry, magnetic resonance imaging, the 2-hour oral glucose tolerance test, and the frequently sampled intravenous glucose tolerance test.

Results The Persistent group had a faster rate of fat mass gain than the Never group (20% vs 15% gain of baseline value; $P < .05$ for time*group interaction [time = visit]). Independent of body composition, the Persistent group increased by 70% in insulin incremental area under the curve, whereas the other groups decreased ($P < .05$ for time*group interaction). Despite no time*group interactions for insulin sensitivity, acute insulin response, or disposition index, the Persistent group maintained 43% lower insulin sensitivity ($P < .01$) and by visit 2 had a 25% lower disposition index ($P < .05$) compared with the Never group.

Conclusions Patients with persistent MetS had accelerated fat gain, increased insulin response to oral glucose, and decreased sensitivity and beta cell function, indicators of progressively greater risk for type 2 diabetes *(J Pediatr 2009;155:535-41)*.

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Obesity and Hispanic ethnicity are 2 independent risk factors for the development of type 2 diabetes in youth. Even in childhood, there is a linear relationship between increased body fat and decreased insulin sensitivity.[1-4] Futhermore, independent of body composition, Hispanic children are more insulin-resistant than Caucasian children.[5] National Health and Nutrition Examination Survey III data show that the metabolic syndrome (MetS), a cluster of risk factors for diabetes and cardiovascular disease,[6] is more common in Hispanic adolescents than in Caucasians or African American adolescents.[7]

MetS was found in 30% of the Study of Latino Adolescents at Risk for Diabetes (SOLAR) cohort of overweight Hispanic youth.[8] This cross-sectional analysis demonstrated that insulin sensitivity was inversely associated with the number of features of MetS, and that those with MetS (exhibiting 3 or more features) had 62% lower insulin sensitivity than those with no features of MetS, independent of sex, age, sexual maturation, and body composition. This relationship has not yet been evaluated over time, however.

The overall objective of the present study was to examine whether the persistence of MetS is associated with changes in risk factors for type 2 diabetes in childhood in overweight Hispanic youth. The first aim was to identify how many children in the cohort consistently had MetS at 3 annual measurements. The second aim was to determine if those with persistent MetS had differences in insulin and glucose indices over time, independent of adiposity.

AIR	Acute insulin response to glucose	IAAT	Intra-abdominal adipose tissue
ANCOVA	Analysis of covariance	IAUC	Incremental area under the curve
ANOVA	Analysis of variance		
AUC	Area under the curve	MetS	Metabolic syndrome
BMI	Body mass index	MRI	Magnetic resonance imaging
DEXA	Dual-energy x-ray absorptiometry	OGGT	Oral glucose tolerance test
		SAAT	Subcutaneous abdominal adipose tissue
DI	Disposition index		
FSIVGTT	Frequently sampled intravenous glucose tolerance test	SI	Insulin sensitivity
		SOLAR	Study of Latino Adolescents at Risk for Diabetes
HDL	High-density lipoprotein		

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Methods

The study participants were a subset of the University of Southern California SOLAR project, a longitudinal cohort study that tracks the incidence of type 2 diabetes. Study inclusion criteria were (1) Hispanic origin, defined by all 4 grandparents being Hispanic, as determined by parental self-report; (2) family history of type 2 diabetes in at least 1 grandparent, parent, or sibling; (3) age 8 to 13 years; (4) body mass index (BMI) of at least the 85th percentile for age;[9] and (5) absence of diabetes, as confirmed by an oral glucose tolerance test (OGTT).[10] Subjects (n = 73) were selected because they had complete data for the MetS parameters for each of the first 3 annual study visits. The mean age of the subjects was 11.0 ± 1.7 years at baseline. This sample (n = 73) did not differ at baseline from the rest of the larger initial cohort (n = 182) in key characteristics, including age, sex, Tanner stage, BMI, body composition, fasting glucose, 2-hour glucose, and insulin sensitivity ($P > .05$ as assessed using independent t-tests and χ^2 tests.) None of the subjects was diabetic. The University of Southern California's Institutional Review Board approved the study design. Written informed consent was obtained from parents, and assent was obtained from subjects.

Details of the longitudinal study design have been published previously.[8,11,12] In brief, the design involves a set of yearly clinical assessments consisting of an outpatient visit during which an OGTT is conducted and an overnight inpatient visit during which a frequently sampled intravenous glucose tolerance test (FSIVGTT) is conducted.

Each child fasted overnight and came to the General Clinical Research Center at 8:00 a.m.. With the child wearing a hospital gown, height and weight were recorded in triplicate to the nearest 0.1 cm and 0.1 kg, respectively. BMI and BMI percentile for age were calculated using the EpiInfo 2000 software, version 1.1 (Atlanta, Georgia), based on established Centers for Disease Control and Prevention normative curves.[9] Sitting blood pressure was measured in triplicate.[13] Tanner stage was coded to assess sexual maturation based on breast stage in girls and pubic hair in boys during a history and physical examination conducted by a licensed pediatric care provider.[14] For the OGTT, the child was given 1.75 g of oral glucose solution per kg of body weight (to a maximum of 75.0 g). Blood was collected and assayed for glucose and insulin at 5 minutes before and 15, 30, 45, 60, and 120 minutes after glucose ingestion. Impaired glucose tolerance was defined as a 2-hour postchallenge plasma glucose value of ≥ 140 and < 200 mg/dL.[10] Two-hour insulin and glucose area under the curve (AUC) and incremental area under the curve (IAUC) values were calculated from the OGTT data (in mg/min/dL for glucose and μU/min/mL for insulin). Glucose and insulin AUC were calculated as the sum of the area of each time segment by insulin or glucose concentration, and the IAUC was calculated as the sum of the same area adjusted for the starting point.

Next, the child was admitted to the General Clinical Research Center for the inpatient visit in the afternoon and fasted from 8:00 p.m. until testing the following morning, which began at 7:30 a.m. Sitting blood pressure was again measured in triplicate, and the values from the 2 visits were averaged. A flexible intravenous catheter was placed in each arm, and the FSIVGTT was conducted. At time 0, the child was given a 0.3-g/kg dose of glucose (25% dextrose), and samples were drawn at 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 minutes after ingestion. At 20 minutes, a 0.02-U kg dose of Humulin R insulin (regular insulin for human subjects; Eli Lilly, Indianapolis, Indiana) was injected. To determine insulin sensitivity (SI) and the acute insulin response to glucose (AIR), values for glucose and insulin were entered into the MINMOD Millenium 2002 program, version 5.16 (from Richard N. Bergman) (MINMOD Inc, Pasadena, California). The disposition index (DI), an index of the compensatory adaptation to insulin resistance, was calculated as the product of SI and AIR and used to approximate beta cell function. Fasting blood samples also were evaluated for triglycerides and for total and high-density lipoprotein (HDL) cholesterol using Vitros chemistry DT slides (Johnson and Johnson Clinical Diagnostics, Rochester, New York).

After the FSIVGTT, body composition was measured by a whole-body dual-energy x-ray absorptiometry (DEXA) scan performed by a certified radiology technologist using a Hologic QDR 4500 W scanner (Hologic, Bedford, Massachusetts) A urine pregnancy test was given to all female subjects before the DEXA. In addition, waist circumference, measured at the umbilicus, was recorded to the nearest 0.1 cm. Central fat distribution was measured by magnetic resonance imaging (MRI) at the LAC/USC Imaging Science Center using a GE 1.5 Signa LX-Ecospeed with a 1.5-Tesla magnet (GE Healthcare, Piscataway, New Jersey), with a single slice at the level of the umbilicus. This procedure measured intra-abdominal adipose tissue (IAAT) and subcutaneous abdominal adipose tissue (SAAT).

No standard definition of MetS has been agreed on for children/adolescents.[15,16] For this analysis, MetS was categorized using a definition that we proposed previously[8] that applies pediatric cutoffs to the Adult Treatment Panel III definition.[17] MetS was defined as the presence of 3 or more of the following features: abdominal obesity (waist circumference ≥ 90th percentile for age, sex, and Hispanic ethnicity from National Health and Nutrition Examination Survey III data),[18] hypertriglyceridemia (triglycerides ≥ 90th percentile for age and sex),[19] low HDL cholesterol (HDL cholesterol ≤ 10th percentile for age and sex),[19] elevated blood pressure (systolic or diastolic blood pressure >90th percentile adjusted for height, age, and sex),[13] and impaired glucose tolerance, as described above.

Subjects were classified into 3 groups: Never (negative for MetS at all 3 annual visits), Intermittent (positive for MetS at 1 or 2 annual visits), and Persistent (positive for MetS at all 3 annual visits). Baseline characteristics of the 3 groups were compared using the χ^2 test and analysis of variance (ANOVA) with Bonferroni correction. All subjects had complete data for the 5 features of MetS at all 3 time points; however, a subject was still included who had missing data for MRI,