Overweight Latino Children and Adolescents Have Marked Endothelial Dysfunction and Subclinical Vascular Inflammation in Association With Excess Body Fat and Insulin Resistance

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OBJECTIVE — We measured plasma markers of endothelial dysfunction, vascular inflammation, and pro-coagulation in obese Hispanic/Latino children and adolescents with normal glucose tolerance and determined their relationship to body composition and indexes of glucose and lipid metabolism.

RESEARCH DESIGN AND METHODS — A total of 38 lean or obese Hispanic children and adolescents (10–18 years of age) were selected. The overweight group ($n = 21$) had a BMI >85th percentile for their age and sex, and the lean group ($n = 17$) had a BMI between the 25th and 50th percentiles. Studies included an oral glucose tolerance test, measurements of plasma glucose and lipids, several markers of endothelial function and inflammation, and determination of body composition by dual X-ray absorptiometry.

RESULTS — The obese group had higher systolic blood pressure and plasma triglycerides and was more insulin resistant than the lean group. The obese group also had higher plasma soluble intercellular adhesion molecule (259.5 ± 60.0 vs. 223.2 ± 47.5 ng/ml, $P = 0.047$), tumor necrosis factor-α (2.57 ± 1.1 vs. 1.74 ± 0.6 pg/ml, $P = 0.008$), high-sensitivity C-reactive protein (2.0 vs. 0.13 mg/l, $P < 0.0001$), plasminogen-activated inhibitor-1 (47.0 ± 35.7 vs. 12.0 ± 5.2 ng/ml, $P < 0.0001$), tissue plasminogen activator (6.1 ± 1.9 vs. 4.1 ± 0.8 ng/ml, $P = 0.001$), and white blood cell count (6.9 vs. 5.3×10^3, $P = 0.031$) and lower levels of adiponectin (8.7 ± 3.3 vs. 12.6 ± 5.2 μg/ml, $P = 0.022$). No significant differences were observed for soluble vascular cell adhesion molecule or interleukin-6.

CONCLUSIONS — Overweight Hispanic children and adolescents with normal glucose tolerance exhibit increased plasma markers of endothelial dysfunction and subclinical inflammation in association with obesity and insulin resistance. These abnormalities may predispose them to the development of type 2 diabetes and cardiovascular disease.

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Obesity and diabetes have become worldwide health problems, both being major risk factors for the development of cardiovascular disease (1). The Latino or Hispanic population in the U.S., the largest minority group in the country, has a particularly high risk for the development of type 2 diabetes due to a strong genetic predisposition in combination with multiple social, cultural, and lifestyle factors (2). The prevalence of overweight Hispanic youth in the U.S. has approximately doubled in the last 10 years, such that 21.8% of young Hispanics are now overweight (3,4). It has been estimated that nearly 50% of Hispanic children born in or after the year 2000 will develop diabetes during the course of their lifetime (5).

Endothelial dysfunction and subclinical inflammation are key elements in the development of atherosclerotic cardiovascular disease and are closely associated with insulin resistance (6). In addition, they predict the development of type 2 diabetes (7). Therefore, a common ground may predispose individuals for the development of both type 2 diabetes and cardiovascular disease (8). In the last few years, studies in overweight or obese children and adolescents have shown consistent vascular abnormalities such as decreased peripheral vascular reactivity and arterial distensibility (9), increased intima-media thickness of the carotid artery (10), and elevated circulating levels of soluble adhesion molecules and C-reactive protein (CRP) (11,12). These studies have been conducted primarily in non-Hispanic populations. We hypothesized that overweight Hispanic children and adolescents would be insulin resistant and have increased plasma markers

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Abbreviations: AUC, area under the curve; CIR, corrected insulin response; CRP, C-reactive protein; HOMA, homeostasis model assessment; HOMA β-cell, HOMA of β-cell function; HOMA-IR, HOMA of insulin resistance; hs-CRP, high-sensitivity CRP; IL, interleukin; ISI, insulin sensitivity index; JDC, Joslin Diabetes Center; OGTT, oral glucose tolerance test; PAI-1, plasminogen activator inhibitor-1; sICAM, soluble intercellular adhesion molecule; sVCAM, soluble vascular cell adhesion molecule; TNF-α, tumor necrosis factor; tPA, tissue plasminogen activator; WBC, white blood cell count.

of endothelial dysfunction and subclinical inflammation similar to those of other populations that have been studied. To test this, we evaluated glucose and lipid parameters, insulin sensitivity, and various markers of endothelial function, coagulation, fibrinolysis, and subclinical inflammation as well as several adipocytokines in obese and in lean Hispanic children and adolescents with normal glucose tolerance.

RESEARCH DESIGN AND METHODS

— A total of 42 subjects were screened for the study; 3 were excluded due to impaired glucose tolerance and 1 to diabetes on the oral glucose tolerance test (OGTT) (all in the overweight group). Therefore, 38 normoglycemic Hispanic children and adolescents, 10–18 years of age, were included in the study. Hispanic (Latino) ethnicity was considered if both parents and all grandparents were of Hispanic origin; 25 of the 38 children/adolescents had parents from either Dominican Republic and/or Puerto Rico and the rest from South America (6), Central America (6), and Mexico (1), consistent with the origin of Latinos in the Boston area. The obese group ($n = 21$) was comprised of participants with a BMI greater than the 85th percentile for their age and sex, whereas the lean group ($n = 17$) consisted of those with a BMI between the 25th and 50th percentile using data from the Centers for Disease Control (13). Only girls with regular menses were included, and all studies were done during the follicular phase of the menstrual cycle. Premenstrual girls were excluded. Exclusion criteria were BMI between the 50th and 85th percentile, impaired glucose tolerance, diabetes or other chronic diseases, pregnancy, current or past smoking, hypertension, anemia, endocrine disorders, severe dyslipidemia (triglycerides ≥400 mg/dl, total cholesterol ≥300 mg/dl), or peripheral vascular disease. None of the participants were engaged in a regular physical activity program or taking any medications. Recruitment for the study was coordinated by the staff of the Latino Diabetes Initiative at Joslin Diabetes Center (JDC) in Boston and advertised in several community centers in the Boston Metropolitan area. Only one subject of any given family was included in the study. The protocol was approved by the Committee on Human Studies of the JDC and the Scientific Advisory Committee of the Clinical Research Center at the Beth Israel Deaconess Medical Center. At least one parent or guardian gave written consent for the participation of the study participants in the protocol.

Protocol

The protocol included a visit in the morning, after a 12-h overnight fast, to the clinical research center at the JDC. Volunteers avoided coffee and vigorous exercise for at least 24 h before their evaluation. The visit included medical history and physical examination, an OGTT, laboratory measurements, assessment of insulin resistance, and body composition.

Medical history and physical examination. A complete medical history was obtained from one of the parents and the participant and by reviewing past medical records, if necessary. Tanner stage was estimated. Blood pressure was measured according to standard guidelines.

OGTT. The OGTT protocol was in accordance with World Health Organization recommendations. The glucose load was calculated as 1.75 g glucose/kg, with a maximum amount of 75 g. Samples for plasma glucose and insulin were collected at baseline and 30, 60, 90, and 120 min after the oral glucose load.

Laboratory measurements. A fasting blood sample was drawn to measure plasma glucose, insulin, A1C, white blood cell count (WBC), lipids, free fatty acids, urea nitrogen, creatinine, soluble vascular cell adhesion molecule (sVCAM), soluble intercellular adhesion molecule (sICAM), plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA), tumor necrosis factor-α (TNF-α), interleukin (IL)-6, high-sensitivity CRP (hs-CRP), and adiponectin. Plasma glucose, total serum cholesterol, triglycerides, blood urea nitrogen, and creatinine were measured using the Synchron CX analyzer (Beckman Systems, Oxford, CT), whereas HDL cholesterol was measured directly (Polymedco, Cortland Manor, NY). LDL cholesterol concentration was estimated by the Friedewald formula (14) or was directly measured (Polymedco) if triglycerides were >250 mg/dl, total cholesterol was >240 mg/dl, or HDL cholesterol was <35 mg/dl. The WBC was measured with the Beckman Coulter HmX (Beckman Coulter, Fullerton, CA). A1C was determined using ion-exchange, high-performance liquid chromatography.

Insulin (Immulite, two-site chemiluminescent immunometric assay; Diagnostic Products, Los Angeles, CA), free fatty acid (enzymatic colorimetric method, NEFA C kit; Waco Chemicals, Richmond, VA), and all vascular markers and adipocytokines were measured at the core laboratory of the clinical research center at the Beth Israel Deaconess Medical Center, Boston, Massachusetts. Accepted commercial kits used were sICAM and sVCAM (ELISA; R&D Systems, Minneapolis, MN), TNF-α and IL-6 (ELISA; R&D Systems), hs-CRP (solid-phase, chemiluminescent immunometric assay; Diagnostic Products), PAI-1 and tPA (ELISA; Diagnostica Stago, Parsipanny, NJ), and adiponectin (ELISA; Linco Research, St. Charles, MI).

Assessment of insulin resistance. We evaluated the glucose and insulin area under the curve (AUC) with the trapezoidal method $1/2\ \Sigma(t_{i+1} - t_i)\ (y_i + y_{i+1})$ (15). Common insulin sensitivity indexes were used: homeostasis model assessment (HOMA) of insulin resistance (16) (HOMA-IR) (fasting insulin × fasting glucose/22.5), HOMA of β-cell function (HOMA β-cell) (% = 20 × insulin/[glucose − 3.5]), insulin sensitivity index (ISI: 22.5/(fasting insulin × [fasting glucose/18.01]), and the 1/fasting insulin index. We used insulin secretion indexes as the corrected insulin response (CIA) {100 × 30 min insulin/[30 min glucose × (30 min glucose − 70 mg/dl)]} and the insulin-to-glucose ratio [(30 min insulin − fasting insulin)/(30 min glucose − fasting glucose)] (16).

Body composition. Total body and trunk fat were estimated through dual-energy X-ray absortiometry with a Hologic QDR 4500 densitometer machine (Hologic, Bedford, MA).

Statistical analysis. The sample size was calculated to achieve 80% statistical power at a two-sided significance level of 0.05 for a *t* test in order to identify a difference in the plasma markers of endothelial function of at least 15% between the groups, based on previous data on obese children and adolescents (11,12,17). A conservative expected difference between the groups of 50 ng/ml for sICAM and 105 ng/ml for sVCAM, with expected SDs of 10 and 21 ng/ml, respectively, would require at least 13 subjects in each of the study groups. Statistical analysis was performed using SPSS for Windows, version 11 (SPSS, Chicago, IL). For all comparative data, an α-error of 0.05 and a β-error of 0.2 were considered. The Kolmogorov-Smirnov test was used to assess the normality assumption of continuous distribution. The results are presented as means ± SD, median, 25th-75th percen-

Table 1—*Demographic and clinical characteristics in both study groups*

	Lean	Overweight	*P*
n	17	21	
Age (years)	14.18 ± 2.3	13.33 ± 2.7	0.314
Female sex (%)	9 (52.9)	10 (47.6)	0.746
Birth weight (kg) (*n*)	3.34 ± 0.63 (12)	3.82 ± 0.92 (16)	0.123
Tanner stage (1/2/3/4/5)	0/3/3/4/7	2/5/2/7/5	0.487
BMI (kg/m^2)	19 ± 2.3	32 ± 6	<0.0001
Percentile BMI*	34.8 ± 15.4	97.1 ± 3.5	<0.0001
Weight (kg)	51.9 ± 12.9	79.9 ± 19	<0.0001
Waist-to-hip ratio	0.79 ± 0.08	0.88 ± 0.11	0.003
Total fat (%)	24 ± 6	42 ± 9	<0.0001
Trunk fat (%)	19 ± 5	42 ± 9	<0.0001
Systolic blood pressure (mmHg)	101.5 ± 7	116.6 ± 12	<0.0001
Diastolic blood pressure (mmHg)	68.6 ± 5.6	70.9 ± 5.9	0.245
A1C (%)	5.2 ± 0.33	5.4 ± 0.44	0.190
Total cholesterol (mg/dl)	142.06 ± 23.1	149.76 ± 23.6	0.318
HDL (mg/dl)	42.0 ± 10.9	37.52 ± 7.5	0.162
LDL (mg/dl)	89.24 ± 15.9	93.50 ± 20.8	0.484
Triglycerides (mg/dl)	58.82 ± 34.9	108.29 ± 61.2	0.004
Free fatty acids (mEq/l)	0.57 ± 0.19	0.56 ± 0.23	0.972

Data are means ± SD and *n* (%). Comparisons were performed with *t* test for continuous variables and with χ^2 for dichotomous variables. *Percentiles based on data from the Centers for Disease Control.

tile intervals (interquartile range), and percentages, as applicable. For continuous variables, two-sided *t* test was used for the comparison of differences between groups. All nonparametrically distributed variables were log transformed before applying this parametric analysis. All categorical variables were analyzed using the χ^2 test or Fisher's exact test when applicable. Pearson correlations were performed to evaluate the association of normally distributed variables and Spearman's ρ correlations when variables exhibited a non-normal distribution. Partial Pearson correlations among study variables were further performed when adjusting for sex and age. Stepwise linear regression models were constructed for the identification of variables associated with the plasma levels of markers of inflammation, endothelial activation, coagulation/fibrinolysis, adipose tissue–related protein, white blood cell count, and indexes of insulin sensitivity and β-cell function.

RESULTS

Demographic and general metabolic characteristics

Table 1 shows the demographic and clinical characteristics of the study participants. Both lean and obese groups were comparable regarding age, sex distribution, birth weight, and Tanner stage. By study design, the obese group had a higher BMI. Many anthropometric, hemodynamic, and metabolic variables were significantly different between the two study groups. Nineteen of the 21 subjects in the obese group and 10 of the 17 in the lean group (59%) had either a parent or a grandparent with type 2 diabetes.

Measurements of glucose homeostasis and insulin sensitivity

Whereas there was no significant difference in plasma glucose values between the two groups at baseline and during the OGTT, insulin concentrations were significantly different at all time points (Fig. 1). In the lean and obese groups, respectively, fasting glucose was 89 ± 4 and 91 ± 6 mg/dl ($P = 0.334$), fasting insulin was 10.5 ± 4.9 and 27.6 ± 17.2 μUI/ml ($P < 0.0001$), glucose AUC was 14488.8 ± 1,600 and 14687.7 ± 1,814 mg · min^{-1} · dl^{-1} ($P = 0.736$); insulin AUC was 9116.8 ± 4,680 and 15625.6 ± 7,296 μUI · min^{-1} · ml^{-1} ($P = 0.002$), CIR was 1.29 ± 0.96 and 1.78 ± 1.05 ($P = 0.145$), insulin-to-glucose ratio was 2.41 ± 2.26 and 3.26 ± 2.56 ($P = 0.293$), 1/fasting insulin (insulin sensitivity) was 0.12 ± 0.06 and 0.05 ± 0.03 ($P \leq 0.0001$), ISI was 0.22 ± 0.12 and 0.53 ± 0.26 ($P \leq 0.0001$), HOMA-IR was 2.30 ± 1.1 and 6.23 ± 3.9 ($P \leq 0.0001$), and HOMA β-cell was 147.4 ± 80.2 and 369.2 ± 283.7 ($P \leq 0.0001$).

Markers of endothelial function and subclinical inflammation

The obese group had increased levels of several plasma markers associated with endothelial dysfunction, subclinical inflammation, and altered thrombosis/fibrinolysis (sICAM, TNF-α, PAI-1, tPA, and hs-CRP). In addition, WBC was higher and adiponectin levels were lower in the obese than in the lean group (Fig. 2). The groups did not differ in plasma concentrations of sVCAM and IL-6 (Fig. 2).

Family history of type 2 diabetes

No statistically significant differences in any of the evaluated variables in the study were identified when comparing individuals with and without family history of type 2 diabetes within the lean group. Data not shown.

Correlations among the various metabolic and vascular variables were observed. Both BMI and trunk fat were positively associated with hs-CRP ($r = 0.69$, $P < 0.0001$, and $r = 0.70$, $P < 0.0001$, respectively), PAI-1 ($r = 0.70$, $P < 0.0001$, and $r = 0.65$, $P < 0.0001$,

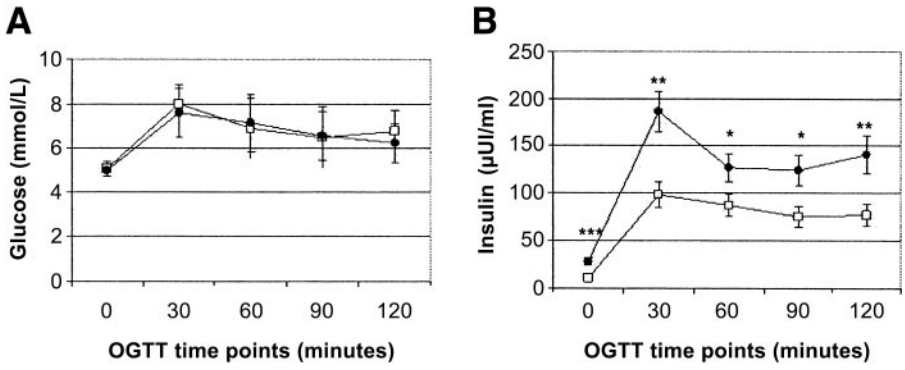

Figure 1—*Plasma glucose levels* (A) *and insulin concentrations* (B) *during the OGTT in the lean* (□) *and obese* (●) *groups.* *P < *0.05*, **P < *0.01*, ***P < *0.0001*.

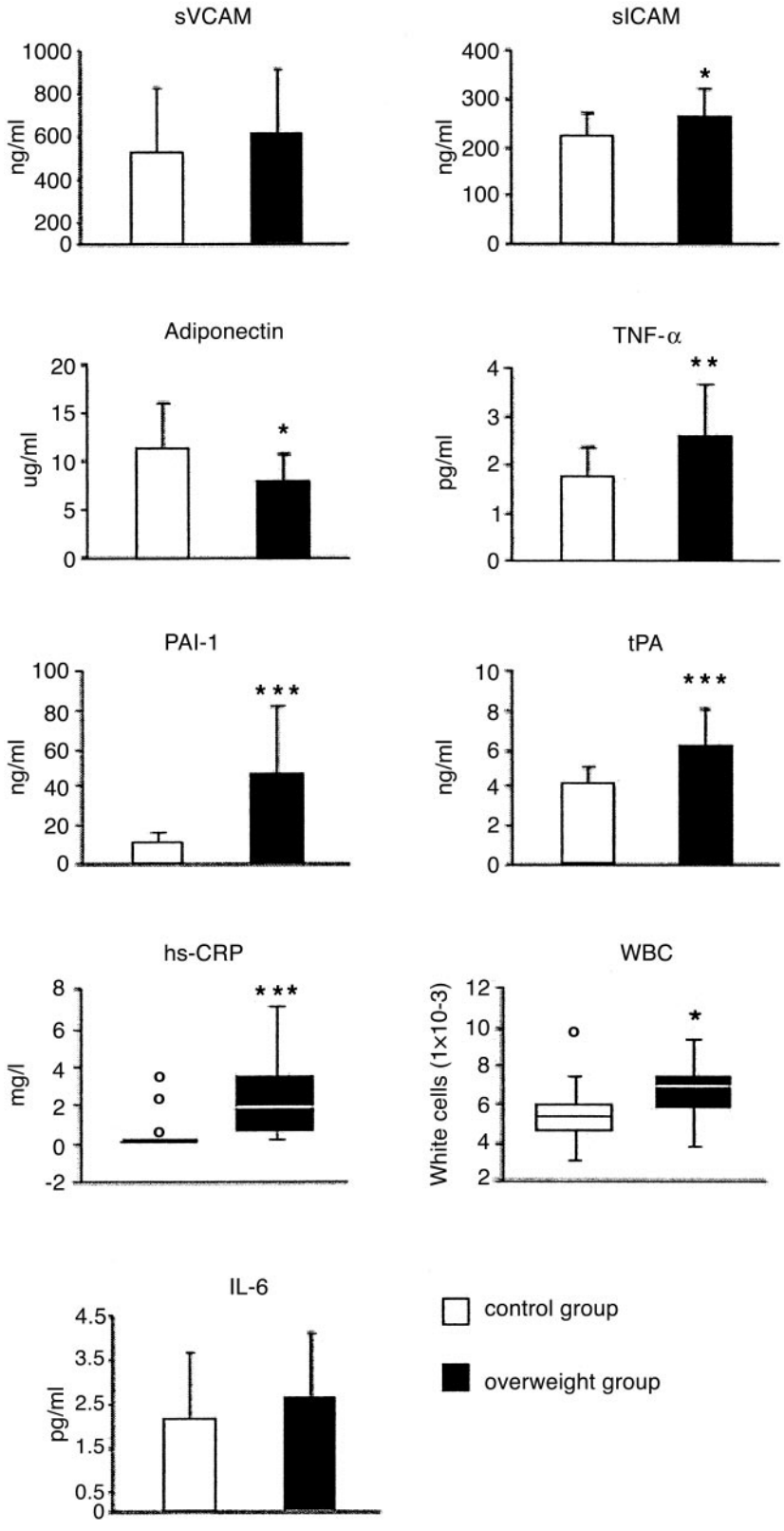

Figure 2—*Markers of endothelial activation, coagulation and fibrinolysis, vascular inflammation, and adipocytokines between the control group (□) and the overweight group (■). The variables with a normal distribution are shown with bars and SDs, whereas those with abnormal distribution are shown in a box plot format.* *P < *0.05,* **P < *0.01,* ***P < *0.0001.* ○, *outlier valves.*

respectively), and tPA ($r = 0.54$, $P < 0.001$, and $r = 0.50$, $P < 0.01$, respectively). Triglycerides were inversely associated with adiponectin ($r = 0.46$, $P < 0.01$), while insulin AUC during the OGTT was associated with hs-CRP ($r = 0.44$, $P < 0.01$), PAI-1 ($r = 0.58$, $P < 0.0001$), and tPA ($r = 0.59$, $P < 0.0001$). HOMA-IR and HOMA β-cell were associated with hs-CRP ($r = 0.58$, $P < 0.0001$, and $r = 0.63$, $P < 0.0001$, respectively) and tPA ($r = 0.71$, $P < 0.0001$, and $r = 0.72$, $P < 0.0001$, respectively). On the other hand, a negative association was observed between the 1/fasting insulin ratio and ISI with hs-CRP ($r = -0.59$, $P < 0.0001$, and $r = -0.58$, $P < 0.0001$, respectively), PAI-1 ($r = -0.50$, $P < 0.01$, and $r = -0.49$, $P < 0.01$, respectively), and tPA ($r = -0.54$, $P < 0.001$, and $r = -0.53$, $P < 0.001$, respectively).

The age- and sex-adjusted Pearson correlations showed a significant positive association between tPA and sICAM ($r = 0.43$, $P < 0.01$) and PAI-1 ($r = 0.68$, $P < 0.001$) and a negative association with adiponectin ($r = -0.43$, $P < 0.05$). The age- and sex-adjusted Spearman correlations showed positive associations between WBC and IL-6 ($r = 0.46$, $P < 0.05$) and hs-CRP ($r = 0.58$, $P < 0.01$), as well as hs-CRP and PAI-1 ($r = 0.59$, $P < 0.01$), tPA ($r = 0.54$, $P < 0.01$), and IL-6 ($r = 0.53$, $P < 0.05$) and a negative association between hs-CRP and adiponectin ($r = -0.43$, $P < 0.05$).

Multivariate analysis

We performed stepwise linear regression including all endothelial dysfunction and inflammatory markers that were different between groups as the dependent variable. sICAM was associated with glucose at 120 min after the oral glucose load and with TNF-α ($r = 0.64$, $P = 0.01$), whereas TNF-α was associated with sICAM ($r = 0.46$, $P = 0.01$). hs-CRP was associated with IL-6, tPA, insulin-to-glucose ratio, and CIR ($r = 0.78$, $P = 0.009$). Adiponectin was associated with triglycerides and tPA ($r = 0.61$, $P = 0.024$), PAI-1 with BMI ($r = 0.68$, $P < 0.0001$), and tPA with fasting insulin, PAI-1, and HOMA-IR ($r = 0.82$, $P = 0.037$).

CONCLUSIONS — Our results demonstrate that overweight, nondiabetic Hispanic children and adolescents have evidence of endothelial dysfunction, subclinical inflammation, and altered thrombosis/fibrinolysis in association with

insulin resistance and increased total and truncal body fat.

Our results are consistent with those reported in obese Caucasian children, in whom increased levels of sICAM, sVCAM, soluble E-selectin, and soluble P-selectin have been reported (11,17). An elevation of circulating soluble adhesion molecules represents an early stage in atherosclerosis (18). These molecules are produced by injured endothelial cells, leading to the rolling, activation, and firm adhesion of circulating leukocytes to the endothelium (18). Elevated sICAM levels (and not sVCAM) also predict the development of type 2 diabetes in adults (7). Our data therefore demonstrate the presence of endothelial activation in this group of overweight children and adolescents that may reflect an increased risk for both type 2 diabetes and cardiovascular disease.

Vascular inflammation is a key element in the development of cardiovascular disease (18). In our study, overweight Hispanic children and adolescents had higher levels of hs-CRP, TNF-α, and white blood cells than their lean counterparts. Hs-CRP is an inflammatory marker closely associated with the release of multiple cytokines from adipose tissue, particularly visceral fat (19). It has been closely associated with obesity and the metabolic syndrome in children (20) and was found to be an important factor of the correlation between adiposity and arterial distention in adolescents (21). In our study, hs-CRP was significantly associated with BMI, trunk fat, insulin AUC, and HOMA measures and had a significant inverse relationship with adiponectin levels. Elevated hs-CRP is consistent with a proinflammatory state. Interestingly, it has also been found to predict the development of CVD and type 2 diabetes (22,23). IL-6 is a cytokine derived from adipose tissue and is increased in obesity, a finding recently reported in a group of severely obese children and adolescents in Austria (24). We did not find a significant difference in IL-6 values between lean and obese subjects in our study. It is unclear whether this is merely the result of a wider variation in the observed values in our study population, the sample size, or possible ethnicity-related differences in the production and secretion of this cytokine.

Although within the normal range, WBC was higher in the overweight group, as it has been found in obesity and the metabolic syndrome (25), consistent with a proinflammatory state.

The adipose tissue of obese individuals usually expresses increased amounts of proinflammatory proteins such as TNF-α (26). An increased number of macrophages in adipose tissue is positively associated with fat cell size (27). These macrophages release several proinflammatory cytokines, such as TNF-α, IL-6, and IL-1 (28,29). Other proinflammatory proteins secreted in the adipose tissue include inducible NO synthase, transforming growth factor-β1, CRP, sICAM, and monocyte chemoattractant protein-1 (MCP-1), as well as some procoagulant proteins, such as PAI-1, tissue factor, and factor VII (30). Increases in many of these proteins in our study participants are consistent with an underlying low-grade inflammatory state in this young population.

Elevated plasma levels of tPA and PAI-1 are now recognized as an integral feature of the insulin resistance syndrome (31). Dysfunctional endothelial cells secrete higher amounts of tPA, which largely circulate in tPA/PAI-1 complexes (30). Obesity may increase tPA levels through increased synthesis of TNF-α in humans (32). The findings of elevated tPA and PAI-1 levels in our study population are consistent with a procoagulant state usually associated with the underlying proinflammatory changes discussed above. Hispanic adults with impaired glucose tolerance and diabetes have increased levels of PAI-1, which are associated with BMI, fasting insulin, and proinsulin and are negatively associated with the ISI (33). This strong association between PAI-1 levels and obesity and insulin resistance has also been identified in children and adolescents (34,35). Accordingly, our data show that both PAI-1 and t-PA levels are strongly associated with BMI and truncal fat in Hispanic youth as well as with hs-CRP. In addition, tPA was positively associated with various indexes of insulin resistance in our study population, supporting the close link between these metabolic and vascular abnormalities.

Lower levels of adiponectin were found in the overweight compared with the lean subjects. Adiponectin is a cytokine with beneficial vascular and metabolic actions usually reduced in obese states (36). Adiponectin levels seem to be regulated by IL-6, and especially by TNF-α, which inhibits its gene expression (36,37,38). In our study, adiponectin levels were negatively associated with tryglicerides and hs-CRP, consistent with the relationship between adiponectin and metabolic and vascular inflammatory changes associated with obesity and insulin resistance. These associations have also been demonstrated in non-Hispanic obese children and adolescents (39,40). More importantly, hypoadiponectinemia has been identified as an independent risk factor for the metabolic syndrome in obese children and adolescents (41).

Whereas family history of type 2 diabetes is very common among Hispanics, we found no statistically significant differences in any of the evaluated variables in the study when comparing those with and without a family history among subjects in the lean group, suggesting that the presence of obesity and insulin resistance are the main factors associated with endothelial dysfunction in our study population.

Although the cross-sectional nature of our study does not allow us to establish a cause-effect relationship, a clear proinflammatory and procoagulant state exists in these young individuals in a close association with obesity and insulin resistance. At this point, the prognostic significance of the observed abnormalities identified in this group of Hispanic children and adolescents is not known, but the existent proinflammatory state suggests that early detrimental changes have already occurred. In adults, multiple vascular abnormalities have been identified in subjects at risk for type 2 diabetes (29). In some of these groups, such as those with impaired glucose tolerance, we have been successful in delaying or preventing the appearance of type 2 diabetes and perhaps cardiovascular disease (42).

In conclusion, we have found that overweight Hispanic children and adolescents have elevated markers of endothelial dysfunction and vascular inflammation closely related to excess body fat and increased insulin resistance. This proinflammatory and procoagulant state in these youngsters may increase their risk of developing type 2 diabetes and cardiovascular disease, further emphasizing the need for obesity prevention strategies.

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