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Associations of hyperglycemia and insulin resistance with biomarkers of endothelial dysfunction in Hispanic/Latino youths: Results from the Hispanic Community Children's Health Study/Study of Latino Youth (SOL Youth)

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ABSTRACT

Aims: We hypothesized that Hispanic/Latino youth at high risk for diabetes would have elevated biomarkers of endothelial dysfunction.
Methods: Among 1316 children 8–16 years old from the Study of Latino Youth (SOL Youth), we used Poisson regression to obtain prevalence ratios (PRs) and 95% CIs for the cross-sectional association of quartiles of fasting glucose, HbA1c, and insulin resistance with E-selectin and plasminogen activator inhibitor-1 (PAI-1) levels above the median (≥48.1 and ≥2.02 ng/mL, respectively).
Results: Levels of E-selectin and PAI-1 were higher in children who were obese or had higher levels of hs-CRP ($p < 0.05$). Insulin resistance was independently associated with higher levels of PAI-1 (adjusted PR and 95% CI for the highest versus lowest quartile (Q4 vs Q1): 2.25 [1.64, 3.09]). We found stronger evidence of associations of insulin resistance with higher levels of PAI-1 among boys as compared with girls (p-interaction = 0.10).
Conclusions: Insulin resistance was associated with endothelial dysfunction, as measured by higher levels of PAI-1, in Hispanic/Latino youth. These biomarkers may be useful in risk stratification and prediction of diabetes and cardiovascular disease in high-risk youth.

1. Introduction

Endothelial dysfunction is characterized by impaired vasoregulation, abnormal angiogenesis (either increased or decreased), impaired permeability of the endothelium, and increased inflammation.[1] There is a complex interplay of endothelial function with inflammation, hyperglycemia, and diabetes. In the setting of diabetes, hyperglycemia may contribute to endothelial dysfunction through the development of advanced glycation endproducts.[1] However, there may be a bidirectional relation between endothelial dysfunction and hyperglycemia. The endothelium may help regulate insulin secretion by directing lipid transport into beta cells, maintaining blood flow, and promoting cytokine activity, and may therefore contribute to the development of diabetes.[1,2] This suggests the hypothesis that among children and adolescents at high risk of future diabetes, an association may be detected between endothelial function and markers of hyperglycemia and insulin resistance.

Several biomarkers may be used as noninvasive measures of endothelial dysfunction. E-selectin is a cellular adhesion molecule that is produced in response to inflammation (signaled by interleukin [IL]-1 and tumor necrosis factor [TNF]-alpha).[3,4] Plasminogen activator inhibitor-1 (PAI-1) inhibits the degradation of blood clots,[4] and is a biomarker of coagulation. Inflammation may lead to endothelial dysfunction and a procoagulant state, both of which may contribute to the development of insulin resistance and atherosclerosis.[3,4] In adults, higher levels of these biomarkers have been associated with hyperglycemia, insulin resistance, and diabetes.[3,5–12]

Since endothelial dysfunction may contribute to the long-term development of atherosclerosis and cardiovascular disease (CVD) in

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people with diabetes, a better understanding of the relationship between endothelial biomarkers and future diabetes risk could facilitate primary prevention of diabetes and CVD. Few studies have investigated the correlates of biomarkers of endothelial dysfunction in youth.[13] This may be especially relevant in those of Hispanic/Latino background, who by virtue of their race/ethnic background are identified as a high-risk group, relative to youths from other backgrounds, that should be considered for testing for childhood onset type 2 diabetes.[14] Those studies that have been conducted in youth have reported positive, negative, and null associations of biomarkers of endothelial dysfunction in relation to hyperglycemia and insulin resistance, and have therefore been inconclusive as a whole.[13,15–17]

In a population based, multi-center sample of Hispanic/Latino children 8 to 16 years of age, we aimed to characterize the associations of hyperglycemia and insulin resistance with biomarkers of endothelial dysfunction. We hypothesized that biomarkers reflecting hyperglycemia and insulin resistance would be positively associated with endothelial dysfunction. The large sample size also allowed us to examine whether these patterns were consistent across demographic subgroups defined by age, sex and body mass index.

2. Subjects, materials and methods

2.1. Study population

The Hispanic Community Children's Health Study/Study of Latino (SOL) Youth recruited 1466 boys and girls from four field centers: Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California. The design of the SOL Youth Study has been described previously.[18] Participants were eligible for the study if they had a parent/legal guardian in the parent study (the Hispanic Community Health Study/Study of Latinos [HCHS/SOL][19]) and were living ≥5 days per week and 9 months per year with the parent/legal guardian; were 8–16 years of age by the time of the baseline examination; and were free of any known physical or cognitive condition that could interfere with completing the examination.

The current study excluded participants who were missing E-selectin or PAI-1 ($n = 80$); missing glucose, HbA1c, or HOMA-IR (additional $n = 10$); fasting <8 h or had unknown fasting status (additional $n = 5$); had incomplete data for key covariates (additional $n = 53$); or reported use of diabetes medications (additional $n = 1$). There were no participants who self-reported a diagnosis of diabetes. There were 326 participants missing physical activity and 66 missing pubertal stage, so we imputed these values (see description in the Statistical Analysis section). We additionally excluded one participant with extremely high values of fasting glucose (246 mg/dL), HbA1c (9.8%), and HOMA-IR (22.8), because inclusion of this individual substantially influenced the results.

SOL Youth was approved by the institutional review board at each field center. Written informed consent and assent were obtained from all parents/legal guardians and children, respectively.

2.2. Laboratory measurements

All blood specimens were drawn in the morning under fasting conditions, processed and separated on site and stored at −70 °C. The University of Minnesota's Advanced Research and Diagnostic Laboratory performed all laboratory assays. E-selectin and PAI-1 were measured from serum and plasma, respectively, using a sandwich enzyme immunoassay (R&D Systems, Minneapolis, MN) with the Beckman Coulter Biomek NXp (Beckman Coulter, Inc., Fullerton, CA). Fasting glucose was measured from plasma using a hexokinase enzymatic method on the Roche/Modular P Chemistry Analyzer and the Roche COBAS 6000 Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN). HbA1c was measured from whole blood using high performance liquid chromatography (HPLC) using a Tosoh G8 Automated HPLC Analyzer (Tosoh Bioscience, Inc., South San Francisco, CA) and was standardized to the Diabetes Control and Complications Trial assay. Insulin was measured from plasma using a sandwich immunoassay method on the Roche COBAS 6000 Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN). Lipids were measured from serum using the Roche/Modular P Chemistry Analyzer and the Roche COBAS 6000 Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN). HDL-c was measured using a direct precipitation method (Roche Diagnostics, Indianapolis, IN). Triglycerides and cholesterol were measured using an enzymatic method (Roche Diagnostics, Indianapolis, IN). LDL-c was calculated using the Friedewald equation.[20] High-sensitivity C-reactive protein (hs-CRP) was measured from serum using an immunoturbidimetric method on the Roche COBAS 6000 Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN). Laboratory inter-assay coefficients of variation were 6.2% to 11.6% for biomarkers of endothelial dysfunction; 1.3% to 3.1% for fasting glucose, HbA1c, and insulin; 1.3% to 5.2% for lipids; and 6.7% for hs-CRP.

2.3. Self-reported and measured covariates

Age, sex, Hispanic/Latino background, and pubertal stage were self-reported by the participant. Pubertal stage was determined using the Pubertal Development Scale self-assessment tool. We classified participants as either pubertal (reported menarche for girls or at least started getting facial hair for boys) or pre-pubertal (girls not having reached menarche or boys reporting no facial hair growth). The participant's parent or legal guardian reported annual household income and level of educational attainment. Height was measured to the nearest cm using a wall stadiometer (SECA 222, Germany). The mean of three height measurements was used for analysis. Weight was measured using a digital scale to the nearest.1 kg (Tanita Body Composition Analyzer, TBF 300, Japan). Standardized programs from the Centers for Disease Control were used to calculate age- and sex-specific body mass index (BMI) percentiles from the measured heights and weights.[21] Blood pressure was measured after 5 minutes of sitting rest using an OMRON HEM-907XL sphygmomanometer (Omron Healthcare Co. Ltd., Kyoto, Japan). The means of the second and third measurements were used for analysis. National Heart, Lung, and Blood Institute blood pressure level tables were used to calculate age-, sex-, and height-specific diastolic and systolic blood pressure percentiles.[22] Waist circumference was measured three times and the mean of all three measurements was used for analysis. Participants wore accelerometers (Actical model 198-0200-03; Respironics Co. Inc., Bend, OR) for 7 days to measure physical activity. Participants were considered adherent if they wore the accelerometer and had valid data for ≥8 h per day for at least 3 days.

2.4. Statistical analyses

We categorized biomarkers of hyperglycemia and insulin resistance into quartiles (fasting glucose quartiles were Q1: <88, Q2: 88 to <92, Q3: 92 to <96, and Q4: ≥96 mg/dL; HbA1c quartiles were Q1: <5.1, Q2: 5.1 to <5.3, Q3: 5.3 to <5.4, and Q4: ≥5.4%; and HOMA-IR quartiles were Q1: <1.9, Q2: 1.9 to <2.8, Q3: 2.8 to <4.4, and Q4: ≥4.4). For the purposes of assessing study population characteristics, hyperglycemia was defined in two ways: either as fasting glucose ≥100 mg/dL or HbA1c ≥5.7%.[23] Only one participant met the criteria for diabetes, based on fasting glucose ≥126 mg/dL. None had HbA1c ≥6.5%. We calculated HOMA-IR as [glucose (in mg/dL) * [insulin (in pmol/L)]/6]/405.[24] Again, for the purposes of assessing sociodemographic and clinical characteristics by level of insulin resistance, insulin resistance was defined as HOMA-IR ≥2.6, since HOMA-IR levels above this threshold have recently been shown to be associated with higher cardiometabolic risk in adolescents.[25] We used the median

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