Fasting and 2-Hour Plasma Glucose and Insulin

Relationship with risk factors for cardiovascular disease in overweight nondiabetic children

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OBJECTIVE — To determine whether elevated fasting or 2-h plasma glucose and/or insulin better reflects the presence of cardiovascular disease (CVD) risk markers in an overweight pediatric population with normal glucose tolerance.

RESEARCH DESIGN AND METHODS — A total of 151 overweight youths (8–17 years old) were evaluated with oral glucose tolerance tests and measurement of CVD risk factors. The study population was categorized according to quartiles of fasting and 2-h glucose and insulin levels. ANCOVA, adjusted for age, sex, race, Tanner stage, and percent body fat (measured by dual-energy X-ray absorptiometry), was used to compare metabolic variables between the quartiles of glucose and insulin groups.

RESULTS — Increasing quartiles of fasting and 2-h insulin were associated with increasing CVD risk factors. Glucose quartiles on the other hand, either fasting or at 2 h, were not.

CONCLUSIONS — These data suggest that hyperinsulinemia may be the earliest and/or primary metabolic alteration in childhood associated with risk markers for CVD. Prospective studies are needed.

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The prevalence of childhood overweight is increasing relentlessly (1–2). An increase in the rates of prediabetes and type 2 diabetes seems to follow the upward trend of obesity (3). Longitudinal studies in adults demonstrate that cardiovascular disease (CVD) changes are established before a diagnosis of diabetes is made and correlate better with 2-h glucose levels (4–5). Guidelines on diabetes and CVD from the European Society of Cardiology and the European Association for the Study of Diabetes have summarized that 2-h glucose provides better information about risk for CVD than fasting glucose and predicts increased cardiovascular risk in subjects with normal fasting glucose levels (6).

Meta-analyses of prospective data from 11 populations have shown that hyperinsulinemia, defined by the highest quartile cutoff for fasting insulin, was associated with cardiovascular mortality independently of other risk factors (7). A review of 19 Western prospective studies showed that the odds ratio (OR) for coronary heart disease for raised fasting insulin as well as nonfasting insulin were more modest than previously suspected (OR 1.12 [95% CI 0.98–1.28] and 1.35 [1.14–1.60], respectively) (8).

No studies have evaluated whether a fasting or 2-h glucose and/or insulin value reflects better the presence of CVD risk factors in overweight children with normal glucose tolerance. The purpose of this investigation was to assess the relationship between glucose and insulin quartiles and CVD risk factors in an overweight pediatric population.

RESEARCH DESIGN AND METHODS

Overweight (BMI ≥85th percentile for age and sex) but otherwise healthy youth, 71 African American and 80 Caucasian (aged 8–17 years), underwent assessment of glucose tolerance at the Pediatric Clinical and Translational Research Center at Children's Hospital of Pittsburgh. Exclusion criteria and source of recruitment have been previously described (9). The investigation was approved by the Institutional Review Board of the University of Pittsburgh. Parental informed consent and child assent were obtained. All participants underwent an examination with height and weight measurements and BMI calculation. Body composition was measured by dual-energy X-ray absorptiometry (DEXA; Lunar, Madison, WI).

Biochemical measurements

Plasma glucose, insulin, lipid profile, adiponectin, leptin, and the nontraditional CVD risk markers intracellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin were measured as described previously (9–11). Proinsulin, fibrinogen, and high-sensitivity C-reactive protein (hs-CRP) were measured at the Esoterix Endocrinology Laboratory (Calabasas Hills, CA). For hs-CRP, values >10 mg/l were excluded because they may be a sign of occult infection or other systemic inflammatory process (10 of 151 participants) (12).

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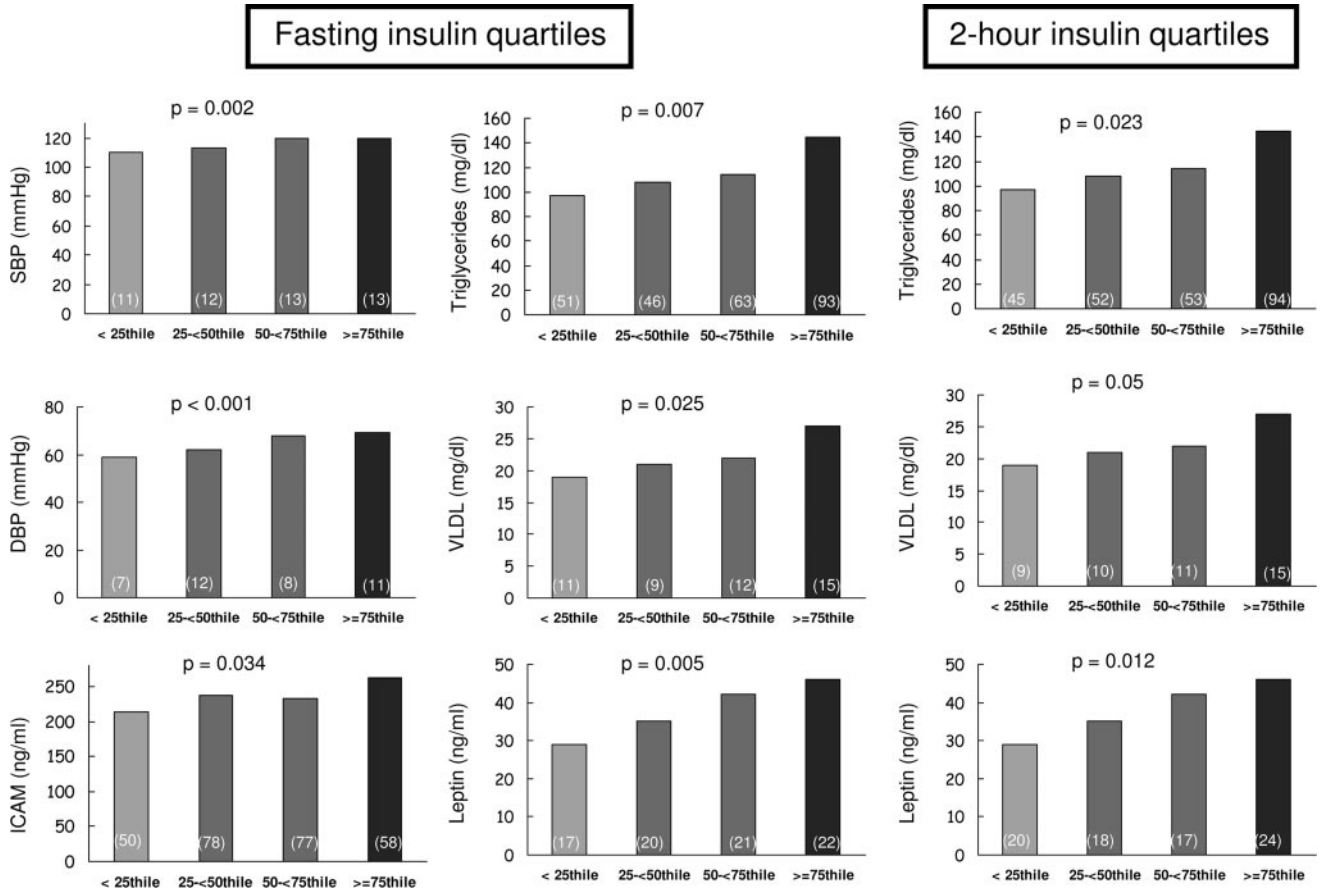

Figure 1—*CVD risk markers according to fasting and 2-h insulin quartiles. DBP, diastolic blood pressure; ICAM, intracellular adhesion molecule-1; SBP, systolic blood pressure.*

Statistical analysis

Data are presented as means ± SD for normally distributed continuous variables, median (interquartile range) for non-normal continuous variables, and *n* (%) for categorical variables. Independent Student *t* tests were used to compare normally distributed continuous subject characteristics, and Pearson χ^2 test was used to compare proportions. The study population was categorized according to quartiles of fasting and 2-h glucose and insulin levels to assess differences between the quartiles in CVD risk factors. ANCOVA, adjusted for age, sex, race, Tanner stage (prepubertal and pubertal), and percent body fat (measured by DEXA), was used to compare metabolic variables between the quartiles of glucose and insulin groups. Statistical analyses were performed using SPSS 15.0 (SPSS, Chicago, IL). All statistical tests were two-tailed, and *P* values of ≤0.05 were considered to be statistically significant.

RESULTS — Of the 151 subjects, 71 were African American (59% female, 41% male; mean age 12.3 ± 2 years; Tanner stage 22.9% prepubertal, 77.1% pubertal; mean BMI 32.1 ± 5.8 kg/m^2; BMI percentile 98.2 ± 2.0; percent body fat 43.2 ± 7.5%) and 80 were Caucasian (54% female, 46% male; mean age 13.1 ± 2.6 years; Tanner stage 21.9% prepubertal, 78.8% pubertal; mean BMI 33.0 ± 6.8 kg/m^2; BMI percentile 98.4.2 ± 1.6; percent body fat 43.8 ± 6.1%).

There were no significant associations between quartiles of glucose levels, either fasting (mean glucose 77 ± 4, 85 ± 1, 90 ± 1, and 94 ± 2 mg/dl, respectively, in the lowest, 2nd, 3rd, and highest quartiles) or at 2 h (mean glucose 94 ± 7, 108 ± 3, 118 ± 3, and 129 ± 4 mg/dl, respectively, in the lowest, 2nd, 3rd, and highest quartiles), with any of the CVD risk factors (*P* for trend >0.05) after adjusting for age, sex, race, Tanner stage, and percent body fat.

The median (interquartile range) values for fasting insulin levels was 13.7 (12.0–15.3), 21.0 (18.4–22.0), 28.7 (26.2–30.7), and 43.8 (37.8–53.7) μIU/ml for quartiles 1, 2, 3, and 4, respectively. For 2-h insulin levels the values were 48.1 (30.7–52.9), 76.4 (69.1–84.2), 125.4 (107.0–155.4), and 222.8 (202.0–300.0) μIU/ml for quartiles 1, 2, 3, and 4, respectively.

Quartiles of insulin, fasting and at 2 h, were associated with heightened CVD risk factors. Figure 1 indicates CVD risk factors that showed a statistically significant trend. Systolic and diastolic blood pressure, triglycerides, VLDL cholesterol, intracellular adhesion molecule-1, and leptin increased significantly with increasing fasting insulin; triglycerides, VLDL-cholesterol, and leptin increased with increasing 2-h insulin. HDL cholesterol decreased with increasing quartiles of fasting insulin (44 ± 12, 42 ± 9, 40 ± 7, 39 ± 9 mg/dl for quartiles <25, 25–<50, 50–<75 and ≥75, respectively; *P* for trend = 0.04)

CONCLUSIONS — Our findings in overweight nondiabetic children demonstrate that *1*) an increase in insulin quartiles, fasting and at 2 h, was associated with higher levels of a number of CVD

risk factors; and 2) glucose quartiles were not associated with increased risk factors for CVD.

With childhood obesity reaching epidemic proportions, there is a need to determine the best marker for early identification of CVD morbidity in this population. In our study, quartiles of glucose, both fasting and at 2 h, were not associated with heightened risk factors for CVD. These children had glucose levels that were within normal range. It is arguable that, in children, glucose levels may need to be in the impaired fasting glucose or impaired glucose tolerance range in order to begin to observe a relationship with CVD risk factors.

Insulin levels have also been described to play a significant role with regard to risk for CVD. In our study, increases in insulin quartiles, fasting and at 2 h, were associated with increase in a number of CVD risk factors. It has been postulated that diabetes and CVD may share an underlying cause, a theory known as the "common soil" hypothesis (13–14). Insulin resistance has been proposed as central to both progression to type 2 diabetes and CVD. Our data, although cross-sectional, suggest that hyperinsulinemia may well be the first and earlier abnormality that presents in children at risk. We could speculate that this may lead to an increase in CVD risk factors and, with time, to glucose dysregulation. Prospective studies are needed, and interventions should be initiated early in life in overweight at-risk youths.

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