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Pre-diabetes in overweight youth and early atherogenic risk

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ABSTRACT

Purpose. To compare atherogenic lipoprotein particles and vascular smooth muscle biomarkers in overweight youth with pre-diabetes (PD) vs. normal glucose tolerance (NGT).

Methods. 144 adolescents (60 black, 84 white; 102 female; PD = 45, NGT = 99) aged 10–19 years underwent a fasting blood draw and 2-h OGTT. Lipoprotein particle size and subclass concentration and vascular smooth muscle biomarkers (ICAM-1, VCAM-1 and E-selectin) were compared between youth with PD and NGT.

Results. Compared with NGT, PD adolescents had smaller LDL (mean ± SE: 20.5 ± 0.1 *vs.* 21.0 ± 0.1 nm; P = 0.002) and HDL (8.62 ± 0.05 *vs.* 8.85 ± 0.04 nm; P = 0.013) size and elevated medium small (159.2 ± 10.3 *vs.* 123.8 ± 6.4 nmol/L; P = 0.037) and very small (626.3 ± 45.4 *vs.* 458.5 ± 26.4 nmol/L; P = 0.032) LDL particle concentrations, after adjustment for race and BMI. Further adjusting for fasting insulin or visceral adiposity obviated these differences between the groups except for LDL size. ICAM-1 and E-selectin did not differ in youth with PD but correlated with LDL and HDL size, and small LDL particle concentrations.

Conclusions. Overweight adolescents with PD have an atherogenic lipoprotein profile of small LDL and HDL size and increased concentrations of small LDL, moderated by insulin resistance and visceral adiposity, but independently driven by dysglycemia for LDL size. Associations between smooth muscle biomarkers and lipoproteins could be an early signal heralding the atherogenic process. It remains to be determined if correction of dysglycemia and associated lipoprotein abnormalities in obese youth could prove effective in halting this process.

Abbreviations: BMI, body mass index; CV, coefficients of variation; DEXA, dual energy X-ray absorptiometry; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment-Insulin Resistance Index; ICAM-1, intercellular adhesion molecule-1; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; NGT, normal glucose tolerance; NHANES, National Health and Nutrition Examination Survey; NMR, nuclear magnetic resonance; OGTT, oral glucose tolerance test; PD, pre-diabetes; TG, triglycerides; VAT, visceral adipose tissues; VCAM-1, vascular adhesion molecule-1; VLDL, very low-density lipoprotein.

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1. Introduction

The transition from normal glucose tolerance (NGT) to overt type 2 diabetes mellitus is characterized by an intermediate state termed pre-diabetes (PD) which is representative of individuals with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) [1,2]. Data from the National Health and Nutrition Examination Survey (NHANES) in 2005–2006 found that the overall prevalence of PD in youth in the U.S. was 16.1% but that the prevalence was 1.6- and 2.6-fold higher in overweight and obese youth, respectively, compared with normal-weight children [3].

Overweight youth with PD often present with dyslipidemia including higher total cholesterol and low-density lipoprotein (LDL) cholesterol, higher triglycerides (TG) and lower high-density lipoprotein (HDL) cholesterol [3–5]. However, traditional lipid measures only partially predict future cardiovascular disease risk [6–8] and adult studies have found adverse lipoprotein particle size and subclass concentration in individuals with PD [9,10]. In youth, only one study [11] has examined the relationship between overweight, glycemia and atherogenic lipoprotein particles in 21 obese adolescents with PD (IFG and IGT) compared with 74 normoglycemic, obese counterparts. Despite similar standard lipid profiles, those youth with PD had smaller LDL and HDL particle size, higher concentrations of small LDL and HDL particles and lower concentrations of large HDL particles, the significance of all of which disappeared except for LDL particle size, after controlling for Homeostasis Model Assessment-Insulin Resistance Index (HOMA-IR) [11]. However, the authors highlighted that their study contained a relatively small number of youth with PD, which they suggest could lead to a type II error, and was largely represented by African Americans who made up ~90% of the PD group and ~78% of the normoglycemic youth [11]. Moreover, they were unable to examine the role of visceral adiposity in mediating the relationship between glycemia and atherogenic lipoprotein particles which has been highlighted in prior studies of youth [12,13]. Finally, circulating biomarkers of vascular smooth muscle function are increased in the early stage of vascular fatty lesions and play an important role in the formation of the atherosclerotic plaque [14] alongside lipoproteins. However, there has been no examination of these vascular biomarkers in relation to glycemia and PD in youth.

Thus, the aim of the present study was: 1) to compare differences in lipoprotein particle size and concentration in a large multi-racial (black/white) cohort of overweight adolescents with PD vs. NGT; 2) to examine the role of whole body and visceral adiposity in mediating differences in lipoprotein particle size and concentration between these two groups; and 3) to investigate differences in biomarkers of vascular smooth muscle function in overweight youth with PD vs. NGT.

2. Methods

2.1. Subjects

Participants were 144 black and white overweight/obese (body mass index, BMI ≥ 85th percentile) adolescents aged 10–19 years. For some participants data on lipids or lipoprotein particle size and subclass concentration were reported before but within a different context and specific aims, as part of a grant investigating childhood insulin resistance [12,15–18]. None of these previous studies examined the role of established clinical definitions of glycemia or PD in youth on lipoprotein particle size or subclass concentration or vascular smooth muscle markers. Study participants were recruited through newspaper and bulletin board advertisements. All studies were approved by the Institutional Review Board of the University of Pittsburgh. All participants and their parents gave written informed assent and consent after a thorough explanation of the proposed study. Exclusion criteria included diagnosed diabetes and the use of medications that influence glucose and lipid metabolism or blood pressure. These medications included oral contraceptive pills, metformin, anti-psychotic drugs, fish oils and drugs for dyslipidemia and hypertension. Participants' health was assessed by medical history, physical examination and routine hematological and biochemical tests. Pubertal development was assessed by physical examination according to Tanner criteria.

2.2. Anthropometry

All participants were admitted to the Children's Hospital of Pittsburgh National Institutes of Health funded Pediatric Clinical and Translational Research Center. Body height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, using standardized equipment.

2.3. Body composition

Total body fat was assessed using dual energy X-ray absorptiometry (DEXA). Abdominal subcutaneous and visceral adipose tissues (VAT) were determined from a single axial image (10-mm thickness) of the abdomen at the level of the L4–L5 intervertebral disc using computed tomography. Both methods have been described previously [19].

2.4. Fasting blood draw and oral glucose tolerance test (OGTT)

After an overnight fast, blood samples were obtained for lipoprotein particle size and concentration and vascular smooth muscle biomarkers, followed with a 2-h OGTT (1.75 g/kg glucola, maximum 75 g) in all participants. Blood samples were obtained at −15, 0, 15, 30, 60, 90 and 120 min for determination of glucose and insulin concentrations.

2.5. Biochemical measurements

Plasma glucose was measured using a glucose analyzer (YSI, Yellow Springs, OH) and insulin concentrations were measured by radioimmunoassay [15]. Plasma lipid concentrations (total, HDL and LDL cholesterol and total and very low-density lipoprotein (VLDL)–TG) were determined using the standards of the Centers for Disease Control and Prevention as described previously [12]. For total and HDL cholesterol and total TG intra-assay coefficients of variation (CV) were 1.0%, 1.8% and 1.8% and inter-assay CV were 1.6%, 2.6% and 3.7%, respectively. LDL and VLDL were calculated using the Friedewald equation [20]. Concentrations of lipoprotein subclasses and