Journal of Clinical Lipidology (2016) ■, ■–■

Journal of Clinical Lipidology

Original Article

Sex differences in the associations of visceral adiposity, homeostatic model assessment of insulin resistance, and body mass index with lipoprotein subclass analysis in obese adolescents

Jacquelyn A. Hatch-Stein, MD*, Andrea Kelly, MD, MSCE, Samuel S. Gidding, MD, Babette S. Zemel, PhD, Sheela N. Magge, MD, MSCE

Division of Endocrinology and Diabetes, The Children's Hospital of Philadelphia, Philadelphia, PA, USA (Drs Hatch-Stein, Kelly and Magge); Nemours Cardiac Center, A. I. DuPont Hospital for Children, Wilmington, DE, USA (Dr Gidding); Division of Gastroenterology, Hepatology, and Nutrition, The Children's Hospital of Philadelphia, Philadelphia, PA, USA (Dr Zemel); and Division of Endocrinology and Diabetes, Center for Translational Science, Children's National Health System, Washington, DC, USA (Dr Magge)

KEYWORDS:
Lipoprotein subclasses;
Visceral fat;
Obesity;
Pediatric;
Sex differences

BACKGROUND: The relationship of lipoprotein particle subclasses to visceral adipose tissue area (VAT-area) in obese children has not been examined previously.

OBJECTIVES: The study aims were to compare the relationships of VAT-area, homeostatic model assessment of insulin resistance (HOMA-IR), and body mass index (BMI) with lipids and lipoprotein subclasses in obese adolescents and to determine whether these relationships vary by sex.

METHODS: This cross-sectional study of obese adolescents (BMI ≥ 95th percentile), aged 12 to 18 years, measured VAT-area by dual-energy X-ray absorptiometry, BMI, fasting lipids, lipoprotein subclasses, and HOMA-IR. Linear regression models evaluated the associations of VAT-area, HOMA-IR, and BMI with lipid cardiometabolic risk factors. Sex-stratified analyses further explored these associations.

RESULTS: Included were 127 adolescents (age = 14.4 ± 1.5 years; 53.5% female; 88.2% African-American), mean BMI = 34.0 ± 5.1 kg/m^2. VAT-area was negatively associated with low-density lipoprotein particle (LDL-P) size ($\beta = -0.28$, $P = .0001$), high-density lipoprotein particle (HDL-P) size ($\beta = -0.33$, $P < .0001$), and large HDL-P concentration ($\beta = -0.29$, $P < .0001$) and positively associated with small LDL-P concentration ($\beta = 0.23$, $P = .0005$) and small HDL-P concentration ($\beta = 0.25$, $P = .05$). When VAT-area, HOMA-IR, and BMI associations were compared, VAT-area had the strongest associations with most of the lipoprotein subclasses. After sex stratification, the associations of VAT-area with HDL cholesterol, LDL-P size, and large LDL-P concentration were significant only for females (all $P < .05$).

CONCLUSIONS: In a cohort of largely African-American obese adolescents, VAT-area was associated with a more atherogenic lipoprotein subclass profile. When compared with HOMA-IR and BMI, VAT-area had the strongest associations with most lipoprotein subclasses. The relationships between VAT-area and certain lipoprotein subclasses are significantly different in males vs females.

* Corresponding author. Division of Endocrinology and Diabetes, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, 11 NW, Philadelphia, PA 19104-4399, USA.

E-mail address: hatchsteinj@email.chop.edu

Submitted October 20, 2015. Accepted for publication February 10, 2016.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2016.02.002

Introduction

Specific depots of adipose tissue, rather than total body fat mass, may be more strongly associated with dyslipidemia, metabolic dysregulation, future diabetes, and cardiovascular disease.[1–3] Recent studies in adults have found a significant association between visceral adipose tissue area (VAT-area) and standard cardiometabolic risk (CMR) factors, even after adjustment for age, body mass index (BMI), and waist circumference.[4,5] Racial, ethnic, and sex differences in VAT-area are apparent, with men and Caucasians having higher VAT-area than women and African-Americans, respectively.[3,5,6]

VAT-area has also been associated with various lipoprotein subclasses, which provide additional risk information beyond the standard lipid panel. In obese adults, VAT-area is associated with smaller low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particle size, larger very low–density lipoprotein (VLDL) particle size, and increased LDL and VLDL particle number, as well as decreased insulin sensitivity—all characteristics of an atherogenic phenotype.[7,8] Although women typically have an overall lower-risk subclass profile, including larger LDL and HDL particles,[9,10] no significant differences by sex or race have been reported in the relationship between VAT-area and lipoprotein subclasses.[7]

As with adults, African-American children have less VAT-area compared with Caucasians and Hispanics,[11] but sex differences have yet to be established.[11,12] Early findings suggest that VAT-area may be associated with greater CMR in females vs males,[13] but the sex-specific relationship of VAT-area with lipoprotein subclasses has not been examined. The association of more standard measures of CMR, such as BMI or homeostatic model assessment of insulin resistance (HOMA-IR), with lipoprotein subclasses has received limited attention in children.[14,15] The primary aims of this study were to compare the independent relationships of VAT-area, HOMA-IR, and BMI with standard lipid measures and lipoprotein subclasses in obese adolescents and to examine the sex-specific relationships of VAT-area, HOMA-IR, and BMI with lipids and lipoprotein subclass particles.

Methods

Sample

We performed secondary analyses of cross-sectional data derived from 2 study cohorts, one consisted of baseline data from a cholecalciferol supplementation study in obese pubertal African-American adolescents; the other included obese adolescents from a study of CMR factors in pubertal adolescents. Subjects, aged 12 to 18 years, were included in the present study if they were obese (BMI $\geq$ 95th percentile for age and sex) and had a whole-body dual-energy X-ray absorptiometry (DXA) scan. Exclusion criteria for these studies included genetic syndromes or conditions known to affect glucose tolerance and/or insulin resistance (such as cystic fibrosis, Prader–Willi syndrome, and congenital lipodystrophies) and treatment with medications known to affect lipid profiles or high-dose inhaled steroids (>1000 mcg/d). Original data were collected from 10/2007 to 6/2012. Both protocols were approved by the Children's Hospital of Philadelphia Institutional Review Board, and consent/assent was obtained from parents and participants, respectively.

Anthropometric measures

Anthropometry was performed in The Children's Hospital of Philadelphia Clinical and Translational Research Center Nutrition Core Laboratory by trained research anthropometrists. Weight was measured on an electronic scale (Scale-Tronix), calibrated daily, with the participant in a light gown without shoes. Height was measured using a wall-mounted Harpenden Stadiometer (Holtain). Measurements were repeated 3 times, and average values were used. BMI z-scores were calculated using the Centers for Disease Control 2000 growth charts.[16] Pubertal staging (determined by breast stage for girls and testicular volume for boys) was performed by a pediatric endocrinologist.[17,18] Pubertal staging data were missing in 3 subjects.

Body composition

Whole-body DXA scans were acquired to measure body composition using a Hologic (Bedford, MA) Discovery system and analyzed using the Enhanced Whole Body version 13.5 software to provide a measure of visceral adiposity (VAT-area). Standard positioning techniques were used. Adolescents weighing greater than 300 pounds could not undergo DXA because of the weight limit of the scanner.

Laboratory measurements

After subjects fasted for 12 hours, a blood sample was obtained for measurement of lipids (triglycerides [TGs], total cholesterol, and high-density lipoprotein cholesterol [HDL-C]), lipoprotein subclass analysis, glucose, and insulin. Lipid analyses were performed on a Hitachi 912 using Roche reagents. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation (LDL-C = total cholesterol − HDL-C − [TG/5]) for TG < 400 mg/dL. Lipoprotein subclass analysis was measured by LipoScience, Inc (Raleigh, NC), using nuclear magnetic resonance spectroscopy. Insulin was measured by enzyme-linked immunosorbent assay, using a kit from ALPCO Diagnostics (Salem, NH). HOMA-IR was calculated using the equation (fasting insulin [uIU/mL] × fasting glycemia [mmol/L])/22.5.

Statistical analysis

Baseline descriptive measures were compared between males and females using *t*-tests for normal or normalized