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The relationship between insulin resistance and vascular calcification in coronary arteries, and the thoracic and abdominal aorta: The Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

Objective: Insulin resistance may be related to vascular calcification as both are associated with abdominal obesity. We investigated the association of insulin resistance with abdominal aortic calcium (AAC), coronary artery calcium (CAC) and thoracic aortic calcium (TAC), and whether it differs according to different levels of subcutaneous fat area (SFA) and visceral fat area (VFA) in a cross-sectional study design.

Methods: We investigated 1632 participants without diabetes from the Multi-Ethnic Study of Atherosclerosis with valid data on homeostasis model assessment index (HOMA-IR), AAC, CAC, and TAC. Adipocytokines, SFA, and VFA were also determined.

Results: HOMA-IR was associated with the presence of CAC, but not AAC and TAC, and the association remained significant after adjusting for traditional risk factors, adipocytokines, abdominal muscle mass, SFA, and VFA (prevalence ratio = 1.04 per one interquartile range [IQR] increase, $P = 0.01$). As the strength of the association of HOMA-IR with vascular calcification may differ by abdominal fat composition, subgroup analysis was performed among participants with different tertiles of SFA and VFA. Significant interactions between HOMA-IR with SFA and VFA separately were observed for the presence of TAC, but not AAC and CAC, even after adjusting for confounding factors. The association of HOMA-IR with TAC tended to be stronger in participants with more SFA and VFA.

Conclusions: Atherosclerotic calcification, especially in the coronary arteries, is related to insulin resistance. Further studies are needed to delineate the mechanisms by which visceral obesity can lead to vascular calcification.

1. Introduction

Excess adipose tissue is a cardiovascular disease (CVD) risk factor and is one of the main driving forces for the metabolic syndrome. In addition to its role in lipid storage and mobilization, adipose tissue is an endocrine organ [1] and excess adiposity is associated with dysregulated secretion of adipocytokines including IL-6, adiponectin, resistin, and leptin [2], which may lead to insulin

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resistance [3]. Abdominal adiposity can be classified by computed tomography (CT) into two primary components, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). SAT and VAT produce and secrete different adipocytokines at different levels [4].

Previous studies show conflicting results on the association of insulin resistance associated with coronary artery calcification in asymptomatic individuals with both positive [5–8] and negative findings [9]. As adipose tissue and adipocytokines play an important role in insulin resistance, they may confound the association between insulin resistance and vascular calcification, and may explain the discrepancy of the previous reports. In addition to the coronary arteries, calcium can also deposit in arteries of other vascular beds during the chronic inflammatory process of atherosclerosis development [10–12]. As calcification in different vascular beds could be developed at similar extent and time frame in a systemic manner [13], insulin resistance may be more closely related to systemic calcification in several vascular beds than to calcification in different individual vascular beds. In this study, we investigated the association of insulin resistance with the prevalence and extent of calcified atherosclerosis in the coronary arteries, and thoracic and abdominal aorta as well as their combination, and whether this association was independent of adipocytokines, inflammation biomarkers, abdominal muscle mass, subcutaneous fat area (SFA) and visceral fat area (VFA) in a cross-sectional study design. We also investigated whether the strength of such association would differ according to levels of SFA and VFA.

2. Methods

2.1. Participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal cohort, consisting of 6814 men and women in four major ethnic groups, non-Hispanic whites, African American, Hispanic American, and Chinese Americans. All participants were between 45 and 84 years of age and free of clinically apparent CVD at baseline. Participants were examined approximately 2, 4, 6, and 8 years after the baseline clinical visit. The study was approved by the institutional review boards at all participating centers and informed written consent was obtained from all participants. Details of the study objectives, design, and protocol have been described previously [14].

At either visit 2 or 3 (from 2002 to 2005), all the MESA participants underwent CT scans of the chest for coronary artery calcium (CAC) and thoracic aortic calcium (TAC), whereas a random subsample of 1974 participants underwent abdominal CT scanning for an ancillary study to determine the presence and extent of calcified atherosclerosis in the abdominal aorta. These CT scans were later interrogated for abdominal body composition [15–17] and these participants also had circulating levels of adipocytokines measured from stored blood samples. Among these 1974 participants, 1910 participants have valid data in all the markers of subclinical calcified atherosclerosis, i.e. CAC, TAC, and abdominal aortic calcium (AAC); 1635 of them did not have prevalent diabetes (defined as fasting glucose <7.0 mmol/l and not taking glucose-lowering medications). After excluding 3 participants with missing data on insulin resistance, a total of 1632 participants were included in this analysis.

2.2. Vascular calcification and body fat composition

The calcium measurements (i.e. CAC and TAC) were derived from CT scans as described previously [16–21]. Briefly, all the MESA participants underwent CT scans of the chest for CAC and TAC using either an electron-beam CT scanner at 3 field centers or a multidetector row helical CT scanner at the other 3 field centers. Participants were scanned twice consecutively at the same visit at one of the field centers, and these scans were read independently at a centralized reading center using a standard protocol. The average of the results of the two scans was used to provide a more accurate estimate of the amount of calcium present. For all calcium measurements, calcification was identified as a plaque of $\geq$1 mm^2 with a density of $\geq$130 Hounsfield units (HU) and quantified using the previously described Agatston scoring method [22].

Using the abdominal CT scans obtained for determining the presence and extent of calcified atherosclerosis in the abdominal aorta (AAC), body composition of the abdomen was assessed using Medical Imaging Processing Analysis and Visualization (MIPAV) software version 4.1.2, that produced areas of subcutaneous and visceral fat, measured in square centimeters [19]. For each participant, a transverse cross section slice at the L4/L5 vertebral junction was analyzed. Fat tissue was identified as having a density between −190 and −30 HU. Lean muscle mass was identified as a density between 0 and 100 HU.

2.3. Laboratory assessment

At visits 2 and 3, venous blood was collected after a 12-h fast, then shipped to the MESA central laboratory for the measurement of total cholesterol, high-density lipoprotein (HDL) cholesterol and glucose levels. Dyslipidemia was defined as a total cholesterol to HDL cholesterol ratio >5.0 or the use of any lipid-lowering medication. Fasting blood was also used for the measurement of insulin levels and the inflammation markers C-reactive protein (CRP), fibrinogen and IL-6 as described previously [15,17]. Circulating levels of adiponectin, leptin, TNF-α, and resistin were measured in stored fasting blood samples from visits 2 and 3 using Bio-Rad Luminex flow cytometry (Millepore, Billerica, MA) [15].

2.4. Other variables of interest

Information on age, ethnicity, education, smoking, alcohol use, total gross family income, family history of CVD, physical activity, and medication use for hypertension, hypercholesterolemia and diabetes were obtained using standardized questionnaires from either visit 2 or 3, which was contemporaneous with the measurement of body composition and adipocytokines. However, data on education and family history of CVD were obtained from the baseline visit and visit 2 respectively. Participants wore light clothing and no shoes when measuring height and weight. Body mass index (BMI) was measured as the weight in kilograms divided by height in meters squared. A standard flexible tape measure was used to measure hip and waist circumferences. Resting blood pressure (BP) was measured three times in a seated position and the average of the last two BP readings was used in the analysis. Hypertension was defined as BP $\geq$ 140/90 mm Hg. Participants who had previous diagnosis of hypertension and took anti-hypertensive medications were defined as hypertensive. Physical activity was measured as the total number of hours of moderate and vigorous activities per week, multiplied by metabolic equivalent (MET) level as described elsewhere [18].

2.5. Statistical analysis

Data analysis was performed using SPSS (version 21, IBM, Armonk, NY, USA) or STATA (version 12.1, StataCorp, College Station, TX, USA). Data were presented as mean (SD) or percentage. For variables with a skewed distribution, data were presented as median (interquartile range [IQR]). Insulin resistance was estimated using the homeostasis model assessment index (HOMA-IR),