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Research paper

# The association among peri-aortic root adipose tissue, metabolic derangements and burden of atherosclerosis in asymptomatic population

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ABSTRACT

*Aim:* To describe the relationship between a novel measurement of peri-arotic root fat and ultrasound measures of carotid artery remodeling.
*Materials and methods:* We studied 1492 consecutive subjects (mean age: 51.04 ± 8.97 years, 27% females) who underwent an annual cardiovascular risk survey in Taiwan. Peri-aortic root fat (PARF) was assessed by cardiac CT using three-dimensional (3D) volume assessment. Carotid artery morphology and remodeling were assessed by ultrasound. We explored the relationships between PARF volumes, cardiometabolic risk profiles and carotid morphology and remodeling.
*Results:* Mean PARF volume in current study was 20.8 ± 10.6 ml. PARF was positively correlated with measures of general adiposity, systemic inflammation, and several traditional cardiometabolic risk profiles (all $p < 0.001$) and successfully predicted metabolic syndrome (MetS) (AUROC: 0.75, 95%, confidence interval: 0.72–0.77). Higher PARF was independently associated with increased carotid artery intima-media thickness (IMT) (β-coef.: 0.08) and diameter (β-coef.: 0.08, both $p < 0.05$) after accounting for age, sex, BMI and other cardiovascular risk factors. The addition of PARF beyond metabolic syndrome components significantly provided incremental prediction value for abnormal IMT (ΔAUROC: 0.053, $p = 0.0021$).
*Conclusion:* Peri-aortic root fat is associated with carotid IMT, even after adjustment for cardiometabolic risks, age and coronary atherosclerosis. Further research studies are warranted to identify the mediators

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of downstream pathophysiologic effects on carotid arteries by PARF and understand the mechanisms related to this correlation.


## 1. Introduction

High-resolution B mode ultrasound provides a convenient, non-invasive way to evaluate carotid artery morphology and remodeling, and has substantially improved our understanding of the pathophysiology of arterial vascular disease.[1] Furthermore, atherosclerotic burden, when defined by intima-media thickness (IMT) or presence of focal plaque, effectively risk-stratifies patients for both cerebrovascular and coronary artery disease.[2–4] Additionally, a large body of literature has linked obesity to cardiometabolic risk.[4] Although, the risk associated with obesity depends not only on the total body fat burden but also on its distribution. In particular, specific areas of regional visceral fat are associated with higher risk.[5,6]

Excessive visceral adiposity contributes to a prothrombotic and pro-inflammatory state that is characterized by a cluster of metabolic abnormalities that constitutes the "metabolic syndrome", including impaired glucose tolerance, hypertension, and unfavorable lipid profiles.[7–9] Pericardial fat (PCF), the visceral adipose tissue confined to peri-cardiac space surrounding coronary arteries, is particularly associated with coronary artery disease risk and coronary calcifications[10,11], which is due in part to paracrine and vasocrine effects of inflammatory cytokines produced in PCF. On one hand, greater PCF was associated with increased carotid artery stiffness in the Multi-Ethnic Study of Atherosclerosis,[12] though greater PCF was not independently related to IMT in their same cohort.[13] On the other hand, accumulation of other regional perivascular fat depots, such as thoracic peri-aortic fat, is associated with larger aortic dimensions, calcification and further related to microvascular dysfunction and large artery stiffness after adjustment for anthropometric measures.[14] Possible mechanisms include the infiltrations of perivascular fat by macrophages, inflammatory cytokines diffuse through arterial wall and directly released into the circulation with downstream effect.[15,16] However, these measures are typically quantified at downstream location and distal to the origins of head and neck arteries[17,18]

Based on these, we speculated that visceral adipose tissue surrounding the aorta at a more proximal or upstream site may have significant downstream biological effects on carotid arteries. We therefore developed a novel and reproducible method to quantify adipose tissue surrounding the aortic root, and related this measure of peri-aortic root fat (PARF) to markers of cardiometabolic risk and structural carotid artery disease in an asymptomatic cohort.

## 2. Method

### 2.1. Study population

The study was approved by the Institutional Review Board of Mackay Memorial Hospital, Taipei, Taiwan. From 2005 to 2009, 2485 subjects underwent a cardiovascular health survey in a tertiary medical center in Taipei, Taiwan that included a non-contrast multi-detector computed tomography scan of the chest for coronary calcium scoring. A subset of 1524 participants also had a carotid artery ultrasound scan and were eligible for inclusion in the present study. All participants completed a detailed physical examination and questionnaire for baseline characteristics, medical history, and lifestyle risk factors such as smoking, alcohol use, and physical activity. Presence of cardiovascular disease was defined as history of myocardial infarction, coronary arterial disease, peripheral arterial disease, or stroke. History of hypertension was defined as either systolic blood pressure higher than 140 mmHg, diastolic pressure higher than 90 mmHg or previously diagnosed hypertension on treatment.

A Hitachi 7170 Automatic Analyzer (Hitachi Corp. Hitachinaka Ibaraki, Japan) was used to measure fasting and post-prandial glucose level (hexokinase method), total cholesterol, triglyceride and uric acid (UA). Lipid profiles including low- (LDL) and high-density (HDL) lipoprotein cholesterol (homogenous enzymatic colorimetric assay), blood urea nitrogen, and creatinine-derived eGFR level (kinetic colorimetric assay) were obtained by a Hitachi 7170 Automatic Analyzer (Hitachi Corp. Hitachinaka Ibaraki, Japan). High-sensitivity CRP (hs-CRP) levels were determined using a highly sensitive, latex particle-enhanced immunoassay Elecsys 2010 (Roche, Mannheim, Germany).

### 2.2. Baseline anthropometrics and metabolic syndrome

Anthropometric measures collected were height, weight, body mass index (BMI), waist and hip circumference. Standardized blood pressures were measured at rest by medical staff blinded to the other test results. Total body fat mass was measured by bioelectrical impedance using a Tanita-305 foot-to-foot body-fat analyzer (Tanita Corp., Tokyo, Japan). The definition of metabolic syndrome used a waist circumference cut-off of $\geq$90 cm and 80 cm for Taiwanese men and women,[19] respectively. Additional criteria were: systolic blood pressure $\geq$130 mmHg or diastolic blood pressure $\geq$85 mmHg, triglyceride level $\geq$150 mg/dL, fasting blood sugar level $\geq$100 mg/dL, and HDL $\leq$40 and 50 mg/dL in men and women, respectively. Total "metabolic score" was defined as the cumulative number of individual criteria out of 5. Subjects with 3 or more criteria were categorized as having metabolic syndrome.

### 2.3. Coronary calcium score (CCS) measurement

Multi-detector CT (MDCT) of the heart was performed using a 16-slice scanner (Sensation 16, Siemens Medical Solutions, Forchheim, Germany) with 16 $\times$ 0.75 mm collimation, rotation time 420 ms and tube voltage of 120 kV. In one breath-hold, images were acquired from above the level of tracheal bifurcation to below the base of the heart using prospective ECG triggering with the centre of the acquisition at 70% of the R–R interval. From the raw data, the images were reconstructed with standard kernel in 3 mm thick axial, non-overlapping slices and 25 cm field of view. All image analyses were performed on a dedicated workstation (Aquarius 3D Workstation, TeraRecon, San Mateo, CA, USA). A coronary calcified lesion was defined as an area with a density >130 HU and covering at least 6 pixels. The Agatston method was used to determine the coronary calcium score (CCS) by multiplying each lesion area by a weighted CT attenuation score in the lesion.

### 2.4. Peri-aortic root fat

Peri-aortic root fat (PARF) quantified from CT using a dedicated