Peripheral arterial disease (PAD) affects >12% of adults in the United States and is strongly associated with multiple cardiovascular disease risk factors.1,2 PAD is associated with an increased risk of cardiovascular disease and all-cause mortality,3,4 highlighting the need for a better understanding of the pathogenesis of PAD.

Although traditional cardiovascular disease risk factors such as smoking and diabetes also are strong risk factors for PAD,6 only central obesity, but not generalized obesity, has been shown to be associated with PAD.6,7 In this context, body fat distribution is an important factor in determining overall cardiometabolic risk.8,9 Ectopic fat depots, defined as fat depots in nonclassical locations,10 typically are believed to exert systemic effects on cardiometabolic risk. However, locally acting ectopic fat depots may contribute to obesity-mediated vascular disease.10,11 In particular, perivascular fat, or fat that surrounds blood vessels, is a physiological modulator of vascular tone and adipocyte hypertrophy that can lead to hypoxia, inflammation, and oxidative stress.12 Further, recent experimental work suggests that perivascular fat may provide a mechanistic link between metabolic signals and vessel wall inflammation13 and vascular smooth muscle cell proliferation.14

We have developed a reproducible protocol to quantify periaortic fat15 in order to examine whether perivascular fat may mediate diseases of the aorta. Because prior findings demonstrated an association of central but not generalized obesity with PAD, we hypothesized that persons with greater amounts of periaortic fat will have a higher prevalence of low ankle-brachial index (ABI) values and clinical PAD.
Methods

Study Sample

In 1971, the Framingham Offspring Study enrolled children and spouses of the original Framingham Heart Study cohort. Participants for the current analysis took part in the multidetector CT substudy. From the Framingham Offspring Study, 1422 participants underwent chest and abdominal multidetector CT from 2002 to 2005. Of these, 1397 were analyzed for perivascular fat, and 1295 had nonmissing ABI ≤1.4. Of these, 1205 had nonmissing covariates and were included in the analysis.

The institutional review boards of Boston University Medical Center and Massachusetts General Hospital approved the study protocol. Written informed consent was provided by all participants.

Multidetector CT Scan Protocol

Scans of the abdomen and chest were performed with 8-slice multidetector CT. In the chest cavity, a series of 2.5-mm slices were acquired from the level of the carina to the diaphragm during an inspiratory breath-hold using prospective ECG triggering (120 kVp, 320 mA). In the abdomen, 2.5-mm slices (120 kVp, 320 mA) were obtained from the upper edge of the S1 vertebrae and 125 mm superiorly.

Measurement of Periaortic Fat Volume

Image analyses were performed on a dedicated workstation.15 Using a semiautomated method, adipose tissue quantification was performed, which required manually defining the tissue borders. To calculate adipose tissue volumes, CT attenuation thresholds (window width, 195 to 45 Hounsfield units) were used. The anatomic borders to define thoracic periaortic fat were (1) anterior (indicating the area immediately surrounding the thoracic aorta), which was defined by a line drawn horizontally through the esophagus that connected to the left costovertebral joint, and (2) posterior, which was defined by the right lateral border of the vertebral body and the anterior edge of the vertebral body. These definitions resulted in a 6.75-cm column of fat (27 slices) surrounding the thoracic aorta. The Figure shows the region that was quantified. We also defined a measure consisting of abdominal periaortic fat, which consisted of tracing 5-mm rings calibrated to the vessel diameter. However, technical limitations, including the inherent relationship with the vessel diameter and the inability to visualize the retroperitoneal lining, limited the interpretation of these data, and hence, they are not included in the current analysis. Reproducibility was excellent for intra- and interreader measurements of the thoracic periaortic fat (intraclass correlation coefficient, 0.99 and 0.98, respectively).15

We quantified visceral abdominal fat (VAT) as previously described.15 Briefly, the reader manually traced the abdominal muscular wall separating the subcutaneous from the VAT depot. Semiautomatic quantification of fat volumes was facilitated with a window width of 195 to 45 Hounsfield units.

ABI and PAD Assessment

At examination 8 (2005 to 2008), ankle and brachial blood pressures were routinely measured on all participants. Participants rested for a minimum of 5 minutes in the supine position on the examining table before blood pressure measurement. Blood pressure cuffs were applied to bare ankles with the midpoint of the bladder over the posterior tibial artery approximately 3 cm above the medial malleolus. Systolic blood pressure was obtained using a 9.6-MHz Doppler pen probe and an ultrasonic Doppler flow detector. For each limb, the cuff was inflated rapidly to the maximal inflation level and deflated at a rate of 2 mm Hg per second until the systolic blood pressure became audible. Measurements were obtained in the following order: right arm, right ankle, left ankle, left arm. All limb blood pressures were repeated in reverse order. Measurement was obtained from the dorsalis pedis artery only if the posterior tibial pulse could not be located by palpation or with the Doppler pen probe.

The ABI was calculated for each leg as the ratio of the average systolic blood pressure in the ankle divided by the average systolic blood pressure in the arm. The higher arm mean was used to calculate the ABI for each leg. The lower of the ABIs from the 2 legs was used for analysis.

As part of routine Framingham Heart Study research examinations, a physician-administered medical history interview was conducted that included queries about lower-extremity revascularization. Medical records were obtained to verify self-report of all revascularization procedures. The physician also used a standardized questionnaire to query the participant about symptoms of intermittent claudication (IC).2 IC was defined as exertional discomfort in the calf that appeared sooner with uphill or more rapid walking pace and was relieved with rest. An end point review panel of 3 senior investigators made the final determination of the presence of IC. The mean time between CT scan acquisition and ABI measurement was 2.5 years.

Risk Factor Assessment

Cardiometabolic risk factors also were quantified during the examination 8. Body mass index (BMI) was defined as the weight (kg) divided by height (m²). Waist circumference (WC) was ascertained at the umbilicus. Fasting morning blood samples were collected for blood glucose and lipids. Diabetes was defined as a fasting plasma glucose of at least 126 mg/dL or hypoglycemic treatment. Current-smokers were defined as participants who smoked at least 1 cigarette per day in the year prior to their eighth examination. The definition of hypertension used was systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or antihypertensive therapy.

Circulating fasting plasma levels of resistin and adiponectin were quantified by ELISA. Intraassay coefficients of variation were 9.0% for resistin and 5.8% for adiponectin.

Statistical Analysis

Thoracic periaortic fat and VAT volumes were normally distributed. ABI was dichotomized at ≤0.9; participants with a history of
Table 1. Study Sample Characteristics Among Participants (n=1205)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.9±8.9</td>
</tr>
<tr>
<td>Women</td>
<td>647 (53.7)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.4±5.3</td>
</tr>
<tr>
<td>WC, cm</td>
<td>99.1±13.5</td>
</tr>
<tr>
<td>Triglycerides, mg/dL*</td>
<td>102 (73–144)</td>
</tr>
<tr>
<td>Total/HDL cholesterol, mg/dL</td>
<td>3.52±1.05</td>
</tr>
<tr>
<td>Lipid treatment</td>
<td>518 (42.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>688 (57.1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>97 (8.1)</td>
</tr>
<tr>
<td>Current-smoker</td>
<td>106 (8.8)</td>
</tr>
<tr>
<td>Former-smoker</td>
<td>647 (53.7)</td>
</tr>
<tr>
<td>Adiponectin, µg/mL†</td>
<td>9.9±6.0</td>
</tr>
<tr>
<td>Resistin, ng/mL†</td>
<td>14.6±8.2</td>
</tr>
<tr>
<td>Thoracic periaortic fat, cm³</td>
<td>16.3±9.1</td>
</tr>
<tr>
<td>VAT, cm³</td>
<td>2089.9±1099.9</td>
</tr>
<tr>
<td>ABI ≤0.9</td>
<td>45 (3.8)</td>
</tr>
<tr>
<td>IC</td>
<td>35 (2.9)</td>
</tr>
<tr>
<td>Lower-extremity revascularization‡</td>
<td>7 (0.6)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or no. (%), unless otherwise indicated. HDL indicates high-density lipoprotein.

*Median with 25th to 75th percentiles.
†in a subsample of 975 participants.
‡Seven participants with lower-extremity revascularization were part of the 66 participants with IC or low ABI; 3 also had prevalent IC, 1 had an ABI ≤0.9, 1 had both IC and abnormal ABI, and 2 had neither.

Results

Study Sample Characteristics

The mean age of the study sample was 65.8 years, and 53.7% were women (Table 1). Overall, 45 participants had an ABI ≤0.9, 35 had a history of IC, and 66 had either a low ABI or IC. Thoracic periaortic fat was strongly associated with VAT (r=0.74; P<0.001).

Association Between Periaortic Fat and Combined Low ABI and IC

In minimally adjusted models per SD increase in periaortic fat, the odds ratio (OR) for low ABI or IC was 1.79 (95% CI, 1.40 to 2.30; P<0.001) (Table 2). Further adjustment for clinical covariates modestly affected the OR (1.52; P=0.004). Similarly, additional adjustment for BMI or VAT did not materially affect the results (BMI-adjusted OR, 1.69; VAT-adjusted OR, 1.67). In contrast, VAT was associated with low ABI or IC in minimally adjusted models (OR, 1.44; 95% CI, 1.12 to 1.87; P=0.005), but these findings were attenuated after adjustment for standard covariates (OR, 1.23; P=0.16).

We also examined the associations between BMI and WC with low ABI or IC (Table 2). BMI was not associated with the combined end point in minimally adjusted models (OR, 1.19; P=0.18), whereas WC was modestly associated with low ABI or IC in age- and sex-adjusted models (OR, 1.37; P=0.02), which was attenuated on adjustment for VAT (OR, 1.14; P=0.49).

Association Between Periaortic Fat and Low ABI or IC

Results for low ABI or IC as separate outcomes were similar to the combined outcome models (Table 3).

Secondary Analysis

In secondary analyses of a subset of participants (n=975), we also adjusted our primary model of VAT as a correlate for...
low ABI or IC for adiponectin and resistin. The results were not materially different (OR, 1.73; \( P=0.01 \)).

**Discussion**

**Principal Findings**
In our community-based sample of participants from the Framingham Heart Study, we demonstrated that periaortic fat is associated with low ABI and IC. We did not observe a similar association with BMI, WC, or VAT. Our findings suggest a potential role for periaortic fat in the pathogenesis of PAD.

**In the Context of Current Literature**
The association between BMI and PAD has been inconsistent.\(^{18,19}\) Some studies demonstrate a linear association between BMI and ABI level,\(^{20}\) whereas others showed no association\(^{5}\) or an association with the highest BMI in participants within the lowest ABI category\(^{21}\) or in those with a high ABI (\(>1.3\)).\(^{18}\) Central obesity, but not BMI, has previously been associated with PAD in a cohort of elderly men.\(^{6}\) Similarly, in a study of elderly participants from the Osteoporotic Fractures in Men study, waist-to-hip ratio, but not BMI, was associated with low ABI.\(^{7}\) In the German cohort of the Reduction of Atherothrombosis for Continued Health registry, 50% of patients with PAD had abdominal obesity.\(^{22}\) Obesity previously has been associated with the severity of PAD.\(^{23}\) Obese patients report more calf pain than the general population, and obese patients who undergo surgical treatment for obesity have a lower risk of developing calf pain.\(^{24}\) Taken together, the literature suggests that body composition, particularly for persons with increased central fat, may indicate increased risk for PAD. The present study extends these findings by identifying an association between periaortic fat and PAD.

**Potential Mechanisms**
Experiments in rat aorta demonstrate that periaortic adipose tissue releases growth factors that stimulate smooth muscle cell proliferation that is enhanced in aged rats and rats fed a high-fat diet.\(^{14}\) These findings suggest that perivascular adipose tissue may promote vascular disease through dysfunction of smooth muscle cells. Adipocytes secrete numerous other factors, including proinflammatory cytokines and adipokines, that also may promote development of vascular disease.\(^{13}\) Recent in vitro work demonstrated that under basal conditions, human perivascular adipocytes show evidence of a proinflammatory state and reduced adipocyte differentiation. Thus, perivascular adipocytes may contribute to adventitial inflammation and, in turn, the development of atherosclerosis. Greenstein et al\(^{12}\) isolated perivascular adipose tissue from small arteries taken from gluteal fat biopsy samples and demonstrated that the adipocytes secrete adiponectin, a physiological modulator of vascular tone. On further examination of perivascular fat from obese subjects, the investigators noted a loss of this vasodilatory effect due to adipocyte hypertrophy, leading to inflammation and oxidative stress. In the obese Zucker rat, hind limb blood flow was reduced with concomitant stiffer vessels, and this was independent of muscle mass and physical activity,\(^{25}\) providing a potential mechanism for which obesity can lead to PAD. The pathophysiologic mechanisms by which local adipose tissue influences development of vascular disease remain to be determined and represent an exciting area of active research.

**Clinical and Research Implications**
These findings highlight the potential toxic role of periaortic fat on the peripheral vasculature and suggest a potential mechanism whereby obesity might lead to the development of PAD. Further research is necessary to uncover the specific mechanisms of disease. Whether reduction of periaortic fat can lead to reduced PAD or PAD progression requires further examination.

**Strengths and Limitations**
The strength of the present analysis was the detailed characterization of ectopic fat depots, which allowed us to examine the associations between thoracic periaortic fat and VAT with low ABI and IC. Important covariates were routinely collected, limiting any potential for recall bias. Some limitations warrant mention. First, the participants were white, limiting generalizability to other races/ethnicities. Second, our measure of abdominal periaortic fat is not reliable, limiting our ability to directly quantify this fat depot in the abdomen. We used thoracic periaortic fat as a proxy measure of perivascular fat through the entire arterial tree because we were unable to quantify perifemoral artery fat. Further research is necessary to better understand the distribution of periaortic fat through the vascular territory. Ectopic fat depots are hypothesized to primarily have systemic effects, such as VAT,\(^{8}\) or local effects, such as pericardial fat or periaortic fat. The results from the present study suggest that only periaortic fat and not BMI, WC, or VAT are associated with PAD, rendering a systemic effect of periaortic fat unlikely. However, this study is cross-sectional; therefore, causation cannot be inferred. Smoking was defined as cigarette smoking within the past 12 months; thus, some degree of misclassification may occur among participants who stopped smoking within this time interval.

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**Disclosures**
Dr Massaro currently has research grants from GlaxoSmithKline and Sanofi-Aventis, and has consulting agreements with Eli Lilly and Interleukin Genetics. The other authors report no conflicts.

**References**


**CLINICAL PERSPECTIVE**

Central obesity is associated with peripheral arterial disease, suggesting that ectopic fat depots may be associated with localized diseases of the aorta and lower-extremity arteries. We hypothesized that persons with greater amounts of periaortic fat are more likely to have clinical peripheral arterial disease and a low ankle-brachial index. We found that periaortic fat is associated with peripheral arterial disease and low ABI, whereas no association with body mass index, waist circumference, or visceral abdominal fat was observed. Periaortic fat is associated with low ABI and intermittent claudication.
Periaortic Fat Deposition Is Associated With Peripheral Arterial Disease: The Framingham Heart Study
Caroline S. Fox, Joseph M. Massaro, Christopher L. Schlett, Sam J. Lehman, James B. Meigs, Christopher J. O'Donnell, Udo Hoffmann and Joanne M. Murabito

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