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Relation of Subcutaneous and Visceral Adipose Tissue to Coronary and Abdominal Aortic Calcium (From the Framingham Heart Study)

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Abstract

Body fat distribution may be differentially associated with subclinical cardiovascular disease. We sought to examine whether body mass index (BMI), waist circumference (WC), subcutaneous (SAT) and visceral (VAT) adipose tissue are associated with either prevalence of coronary (CAC) or abdominal aortic calcium (AAC) in the Framingham Heart Study. Participants (n=3130, mean age 52 years, 49% women) free of clinical cardiovascular disease from the Framingham Heart Study underwent multidetector computed tomography assessment for quantification of subcutaneous and visceral fat volume and coronary and abdominal aortic calcification. Coronary artery calcification (CAC) and abdominal aortic calcification (AAC) were examined in relation to BMI, WC, SAT, and VAT in age- sex- and multivariable-adjusted models. All measures of adiposity were associated with CAC in age-sex adjusted models (all p-values<0.008). All relations were attenuated in multivariable models (all p-value>0.14). BMI, WC, and VAT (but not SAT) were associated with abdominal aortic calcification in age- sex-adjusted models (all p-values<0.012). However, all relations were attenuated in multivariable models (all p-values>0.23). Similar findings were observed in quartile-based analyses. In conclusion, general measures of obesity and measures of central abdominal fat are related to CAC and AAC. However, these cross-sectional associations are attenuated by cardiovascular disease risk factors, possibly because they may mediate the association between adiposity measures and subclinical cardiovascular disease.

Keywords

visceral fat; subcutaneous fat; obesity; calcification; epidemiology; risk factors

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Introduction

Obesity and associated metabolic risk factors are associated with cardiovascular disease.[1] Obesity is also associated with coronary artery calcium (CAC),[2-5] a marker for atherosclerotic burden, which is positively associated with coronary heart disease and cardiovascular disease events.[6-8] Because abdominal adiposity may be more atherogenic than generalized adiposity,[9, 10] measures of central obesity, particularly visceral abdominal tissue (VAT) may be more strongly associated with CAC. Prior studies that have examined this question were conducted in small, selected samples, limiting the generalizability of their findings.[4, 11] The purpose of this analysis is to comprehensively evaluate the association between body fat depots and prevalence of coronary and abdominal aortic calcification (AAC) in a community-based sample.

Methods

Study participants were from the Framingham Heart Study Multi-detector Computed Tomography (MDCT) Study, a sub-study derived from the Framingham Heart Study Offspring and Third Generation cohorts. The study design has been described elsewhere.[12-14] From June 2002 to April 2005, 3529 participants (2111 Third Generation, 1418 Offspring participants) underwent MDCT for assessment of aortic and coronary calcium. Study inclusion was weighted towards participants who resided in the Greater New England area, and those from larger Framingham Heart Study families; additional details regarding study exclusions have been described previously.[9] Of the 3529 participants who underwent imaging, 3495 had interpretable coronary and aortic calcium measures, 3338 additionally had interpretable SAT and VAT measures, 3143 were free of clinical cardiovascular disease, 3143 attended a contemporaneous examination, and 3130 of whom had a complete covariate profile, resulting in a final sample size of 3130 participants.

The study was approved by the institutional review boards of the Boston University Medical Center and Massachusetts General Hospital. All subjects provided written informed consent. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Participants underwent eight-slice multi-detector computed tomography imaging of the chest and abdomen as previously described (LightSpeed Ultra, General Electric, Milwaukee, WI).[15] Subcutaneous and visceral adipose tissue volumes (SAT and VAT) were assessed using an Aquarius 3D Workstation (TeraRecon Inc., San Mateo, CA) via fat pixel identification (image display window width of -195 to -45 Hounsfield Units (HU); window center of -120 HU). Inter-class correlations for inter-reader comparisons were 0.992 for VAT and 0.997 for SAT.[15]

To image the heart, on average forty-eight 2.5 mm contiguous slices were obtained using a prospectively EKG triggered scanning protocol; image acquisition was initiated at 70% of the cardiac cycle (120 kVp, 400 mA, temporal resolution 330 ms) using a procedure has been previously described.[16] MDCT scans were quantified for both the presence and quantity of AAC and CAC by an experienced reader using a dedicated offline workstation (Aquarius, Terarecon, San Mateo, CA).[17] CAC or AAC (present/absent) was based on age- and sex-specific 90th percentile cutpoints derived from a healthy referent sample.[18]

Risk factors were obtained at offspring examination cycle 7 or the first examination of the Third Generation. BMI was defined as weight (kilograms) divided by height-squared (meters). Waist circumference was measured using a tape measure at the level of the umbilicus. Fasting samples were used to measure plasma glucose, total and HDL cholesterol, and triglycerides. Diabetes was defined as follows: fasting plasma glucose ≥126 mg/dL at a Framingham Heart

Study examination or current treatment with either a hypoglycemic agent or insulin. Participants who smoked at least one cigarette/day for the past year were defined as current smokers. Physician-administered questions were used to quantify alcohol use; drinks per week were dichotomized using the following cut-points: >14 drinks/week (men) or >7 drinks/week (women). Hypertension was defined as a systolic blood pressure ≥140 mm Hg, or a diastolic blood pressure ≥90 mm Hg, or the use of anti-hypertension therapy.

All measures of adiposity were standardized to a mean of 0 and standard deviation of 1. We examined the relation between quartiles of each adiposity variable and the presence of CAC or AAC, as well as continuous measures of adiposity and the presence of CAC or AAC using generalized estimating equations to account for familial relations in our study sample. Models were age-sex and multivariable adjusted (age, sex, systolic blood pressure, hypertension treatment, total/HDL cholesterol, triglycerides, lipid treatment, diabetes).

Results

Study sample characteristics are presented in Table 1. Overall, the mean age was 52 years, nearly half the participants were women. Fifteen percent (n=457) of the individuals had CAC and 19% had AAC.

In age- sex-adjusted models, participants with BMI, WC, SAT, and VAT in the fourth quartile had a higher prevalence of CAC (all $p<0.05$; Table 2). For example, individuals in the fourth quartile of VAT had a 1.56-fold increased odds of CAC (OR 1.56, 95% CI 1.15-2.10, $p=0.004$). After multivariable adjustment, all relations were attenuated (all p-values>0.11).

When each measure of adiposity was modeled continuously (Table 3), BMI, WC, SAT, and VAT were all associated with CAC in age-sex adjusted models (all p-values<0.008). Upon multivariable adjustment, all relations were attenuated (p-value>0.14).

For AAC, we found that in an age- sex-adjusted model only those participants with BMI, WC, and VAT in the fourth quartile had a higher prevalence of AAC (all p-values<0.008; Table 4). All relations were attenuated after multivariable adjustment (all p-values<0.98).

When BMI, WC, SAT, and VAT were modeled continuously (Table 3), body mass index, waist-circumference and visceral abdominal fat were significantly associated with AAC in an age- sex-adjusted model (all p-values<0.012). After multivariable adjustment, all associations were rendered statistically non-significant (all p-values>0.14).

Discussion

We found significant associations between all measures of adiposity and CAC in age- sex-adjusted models. However, all relations were attenuated upon multivariable adjustment. Similarly for AAC, we observed associations between most measures of adiposity (excluding SAT) in age- sex-adjusted models, which were attenuated upon multivariable adjustment. These findings suggest that shared risk factors between adipose tissue and CAC explain most of our observations.

In early work, Mahoney at al found that higher BMI in childhood, and higher BMI and waist-hip-ratio in young adulthood was associated with the early presence of CAC among participants from the Muscatine Study.[3] Among 2951 black and white adults from the CARDIA study, Lee et al observed an association between waist girth and CAC in models adjusted for demographics.[5] Similar to our findings, after adjustment for traditional cardiovascular disease risk factors, the associations were no longer significant. In contrast, among 443 cardiovascular disease-free individuals without diabetes, Cassidy et al found a positive association between

WC and CAC among low-risk, but not high-risk individuals after adjusting for age, sex, hypertension, and cholesterol.[2] However, these studies did not use a direct measure of VAT, and instead relied upon waist circumference as a proxy.

Among studies that have used a direct measure of VAT, findings were similar. Allison et al examined 3028 self-referred individuals and found that VAT was associated with CAC in men, but not women.[19] These findings are in our contrast to our work, and may be due to the selected nature of the sample (ie self-referral sample), and the use of self-reported covariates, which may underestimate the true risk factor burden. In contrast, among 220 women and 190 men age 55-80 years old from the Rancho Bernardo Study, Kim et al observed no association between VAT and CAC in multivariable models.[11] However, we cannot compare these findings directly with the results of the present study, as no age- sex-adjusted model was presented in the paper.

Fewer published reports exist looking at the relation between adiposity, in particular central obesity, and AAC. Among 168 men, AAC severity as measured on lateral radiographs was correlated with truncal fat mass (an indirect measure of VAT) quantified by dual energy Xray absorptiometry,[20] but similar effects in post-menopausal women were not observed.[21] Among 148 patients with peripheral artery disease, Golledge et al found a 6-fold increase in the odds of AAC in the upper as compared to the lower tertile of the VAT compartment (measured as the transverse diameter of the abdominal cavity) in models adjusted for age, sex, hypertension, diabetes, smoking, and cholesterol.[22] While intriguing, these findings are limited with the small sample size with all with peripheral arterial disease with a likely distribution of AAC far exceeding that of a population-based sample, very wide confidence limits, and an indirect measure of VAT.

These findings highlight the strong association between measures of adiposity and subclinical disease, as well as the mediation of these associations by cardiovascular disease risk factors that are likely in the causal pathway from adiposity to subclinical disease.

The large sample size, the community-based setting, the volumetric assessment of visceral and subcutaneous fat with CT are strengths of our investigation. Limitations include the cross-sectional design of the study, so that causality cannot be inferred. Further, the Framingham Offspring Study is comprised of primarily white participants, limiting the generalizability of our findings to other ethnic groups. Lastly, we did not assess progression of arterial calcification; it is possible that measures of adiposity may be associated with progression of CAC or AAC.

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Table 1

Study Sample Characteristics; data represent means (standard deviation) or n (percents)

Variable	N=3130
Age (years)	52 (11)
Women	1528 (49%)
Systolic Blood Pressure (mm Hg)	122±18
Hypertension Treatment	528 (17%)
Smoking	397 (13%)
Total/HDLCholesterol	3.9±1.4
Triglycerides*(median (25th, 75th)	102 (71, 154)
Total Cholesterol (mg/dl)	197 (35)
HDL Cholesterol (mg/dl)	54 (17)
LDL Cholesterol (mg/dl)	118 (31)
Lipid Treatment	372 (12%)
Diabetes	156 (5%)
Body Mass Index (kg/m^2)	27.7±5.9
Waist Circumference (inch)	38.1±5.6
Subcutaneous Abdominal Fat (cm^3)	2827±1396
Visceral Abdominal Fat (cm^3)	1772±1004
%Coronary Artery Calcium >90%	457 (15%)
%Abdominal Aortic Calcium >90%	601 (19%)

To convert from mg/dl to mmol/L, divid by 38.67 for total cholesterol, HDL, and LDL; and by 88.57 for triglycerides.

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Table 2

Association between different measures of Adiposity and Coronary Artery Calcium. Data represents odds ratio for each quartile* of coronary artery calcium with 95% confidence intervals.

	Quartile 2**	p-value	Quartile 3**	p-value	Quartile 4**	p-value
Body Mass Index						
Age- sex-adjusted	1.29 (0.95-1.76)	0.11	1.29 (0.95-1.75)	0.10	1.93 (1.44-2.59)	<.0001
Multivariable-adjusted***	1.12 (0.82-1.54)	0.48	0.99 (0.72-1.37)	0.97	1.30 (0.94-1.79)	0.11
Waist Circumference						
Age- sex-adjusted	1.19 (0.89-1651)	0.24	1.32 (0.97-1.79)	0.08	1.80 (1.34-2.41)	<.0001
Multivariable-adjusted***	1.05 (0.77-1.43)	0.77	1.01(0.73-1.39)	0.96	1.18 (0.85-1.64)	0.32
Subcutaneous Abdominal Fat						
Age- sex-adjusted	0.91 (0.68-1.23)	0.55	1.03 (0.77-1.36)	0.85	1.33 (1.00-1.78)	0.05
Multivariable-adjusted***	0.80 (0.59-1.08)	0.15	0.82 (0.61-1.10)	0.19	0.97 (0.72-1.31)	0.85
Visceral Abdominal Fat						
Age- sex-adjusted	0.93 (0.69-1.26)	0.65	1.12 (0.83-1.52)	0.46	1.56 (1.15-2.10)	0.004
Multivariable-adjusted***	0.75 (0.55-1.02)	0.07	0.77 (0.55-1.06)	0.10	0.87 (0.61-1.23)	0.43

*Quartile cut-points for women are: BMI: 22.8, 25.7, 30.1 kg/m^2; for Waist are: 31.8, 35.5, 39.8 inches; for SAT are: 2033, 2857, 4084 cm^3; for VAT are: 681, 1167, 1804 cm^3. In men: BMI are: 25.3, 27.8, 30.5 kg/m^2; for Waist are:35.3, 39.0, 42 inches ; for SAT are: 1796, 2398, 3196 cm^3; for VAT 1457, 2093, 2794 cm^3.

**Referent group is quartile 1 of each fat measure

***Includes adjustment for age, sex, systolic blood pressure, hypertension treatment, total/HDL cholesterol, triglycerides, lipid treatment, diabetes

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Table 3

Association between different measures of Adiposity and Coronary Artery Calcium and Abdominal Aortic Calcium. Data represents odds ratio and 95% confidence intervals of being coronary artery calcium or abdominal aortic calcium above 90% relative to per standard deviation change of fat measurements. All adiposity measurements are standardized to a mean of 0 and standard deviation of 1.

	Coronary Artery Calcium		Abdominal Aortic Calcium	
	OR per SD of fat	**p-value**	**OR per SD of fat**	**p-value**
Body Mass Index				
Age- sex-adjusted	1.21(1.05 – 1.39)	0.008	1.16(1.03 – 1.30)	0.012
Multivariable-adjusted*	1.08 (0.98 – 1.19)	0.14	1.01 (0.91 – 1.11)	0.92
Waist Circumference				
Age- sex-adjusted	1.26(1.14 – 1.39)	<.0001	1.24(1.13 – 1.36)	<.0001
Multivariable-adjusted*	1.08(0.96 – 1.22)	0.18	1.03(0.92 – 1.16)	0.56
Subcutaneous Abdominal Fat				
Age- sex-adjusted	1.18(1.06 – 1.31)	0.002	1.09(0.99 – 1.19)	0.07
Multivariable-adjusted*	1.06(0.95 – 1.19)	0.31	0.96(0.86 – 1.07)	0.42
Visceral Abdominal Fat				
Age- sex-adjusted	1.23(1.11 – 1.37)	<.0001	1.34(1.21 – 1.48)	<.0001
Multivariable-adjusted*	1.01(0.99 – 1.14)	0.92	1.07(0.96 – 1.21)	0.23

*Includes adjustment for age, sex, systolic blood pressure, hypertension treatment, total/HDL cholesterol, triglycerides, lipid treatment, diabetes

Table 4

Association between different measures of Adiposity and Abdominal Aortic Calcium. Data represents odds ratio per quartile* of abdominal aortic calcium with 95% confidence intervals.

	Quartile 2**	**p-value**	**Quartile 3****	**p-value**	**Quartile 4****	**p-value**
Body Mass Index						
Age- sex–adjusted	1.15 (0.88-1.50)	0.31	1.13 (0.87-1.48)	0.36	1.70 (1.30-2.21)	<0.0001
Multivariable-adjusted***	0.99 (0.74-1.31)	0.93	0.86 (0.63-1.16)	0.31	1.09 (0.80-1.49)	0.58
Waist Circumference						
Age- sex–adjusted	1.09 (0.84-1.43)	0.51	1.46 (1.11-1.93)	0.007	1.69 (1.29-2.23)	0.0002
Multivariable- adjusted***	0.95 (0.71-1.27)	0.73	1.10 (0.81-1.48)	0.55	1.05 (0.77-1.44)	0.77
Subcutaneous Abdominal Fat						
Age- sex–adjusted	0.93 (0.71-1.22)	0.60	1.15 (0.89-1.50)	0.29	1.09 (0.83-1.42)	0.55
Multivariable-adjusted***	0.82 (0.62-1.09)	0.18	0.94 (0.70-1.27)	0.70	0.75 (0.55-1. 01)	0.07
Visceral Abdominal Fat						
Age- sex–adjusted	1.02 (0.77-1.35)	0.89	1.31 (1.00-1.73)	0.43	2.00 (1.52-2.64)	<.0001
Multivariable-adjusted***	0.81 (0.60-1.09)	0.16	0.89 (0.66-1.21)	0.22	1.08 (0.78-1.50)	0.63

* For quartile cut-points for BMI, Waist, SAT, and VAT see the legend to Table 2

** Referent group is quartile 1 of each fat measure

*** Includes adjustment for age, sex, systolic blood pressure, hypertension treatment, total/HDL cholesterol, triglycerides, lipid treatment, diabetes