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Visceral and Subcutaneous Adipose Tissue Volumes Are Cross-Sectionally Related to Markers of Inflammation and Oxidative Stress

The Framingham Heart Study

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Background—Excess adiposity is associated with greater systemic inflammation. Whether visceral adiposity is more proinflammatory than subcutaneous abdominal adiposity is unclear.

Methods and Results—We examined the relations of abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), assessed by multidetector computerized tomography, to circulating inflammatory and oxidative stress biomarkers in 1250 Framingham Heart Study participants (52% women; age 60±9 years). Biomarkers were examined in relation to increments of SAT and VAT after adjustment for age, sex, smoking, physical activity, menopause, hormone replacement therapy, alcohol, and aspirin use; additional models included body mass index and waist circumference. SAT and VAT were positively and similarly (with respect to strength of association) related to C-reactive protein, fibrinogen, intercellular adhesion molecule-1, interleukin-6, P-selectin, and tumor necrosis factor receptor-2 (multivariable model R^2 0.06 to 0.28 [SAT] and 0.07 to 0.29 [VAT]). However, compared with SAT, VAT was more highly associated with urinary isoprostanes and monocyte chemoattractant protein-1 (SAT versus VAT comparison: isoprostanes, R^2 0.07 versus 0.10, $P=0.002$; monocyte chemoattractant protein-1, R^2 0.07 versus 0.08, $P=0.04$). When body mass index and waist circumference were added to the models, VAT remained significantly associated with only C-reactive protein ($P=0.0003$ for women; $P=0.006$ for men), interleukin-6 ($P=0.01$), isoprostanes ($P=0.0002$), and monocyte chemoattractant protein-1 ($P=0.008$); SAT only remained associated with fibrinogen ($P=0.01$).

Conclusions—The present cross-sectional data support an association between both SAT and VAT with inflammation and oxidative stress. The data suggest that the contribution of visceral fat to inflammation may not be completely accounted for by clinical measures of obesity (body mass index and waist circumference). **(*Circulation*. 2007;116:1234-1241.)**

Key Words: obesity ■ abdominal visceral fat ■ inflammation ■ computed tomography ■ epidemiology

Obesity is a state of chronic low-grade inflammation characterized by elevated concentrations of circulating inflammatory markers.[1–10] Prospective studies have shown that C-reactive protein (CRP) and interleukin (IL)-6 are associated with increased risk for diabetes mellitus[11–13] and cardiovascular disease.[14] Therefore, inflammation may be a critical link between obesity and obesity-associated disorders such as insulin resistance,[15] diabetes mellitus,[16,17] hypertension,[18,19] and dyslipidemia.[20,21]

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We investigated the associations of distinct abdominal fat compartments (subcutaneous [SAT] and visceral [VAT] adipose tissues), as measured by a volumetric multidetector

Received April 19, 2007; accepted July 18, 2007.

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Guest Editor for this article was Donna K. Arnett, PhD.

The online-only Data Supplement, consisting of expanded Methods and tables, is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.710509/DC1.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.107.710509**

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computed tomography (CT) method, with a panel of systemic inflammatory markers. On the basis of the prior literature,[5,8] we hypothesized that the association of VAT with systemic inflammatory markers would be stronger than that for SAT. We also sought to assess whether CT-based measurements of SAT and VAT explained additional interindividual variability in biomarker concentrations above that accounted for by the simple clinical anthropometric measures of obesity, body mass index (BMI), and waist circumference (WC).

Methods

Participants for this study were selected from the Framingham Offspring Multi-Detector CT Study, a substudy of the Framingham Offspring Study designed for assessment of coronary artery and aortic calcium. Details regarding study recruitment, sample exclusions, covariate assessment, CT protocols, biomarker assessment, and statistical methods can be found in the online-only Data Supplement. The study was approved by the Boston University Medical Center and Massachusetts General Hospital institutional review boards. All participants 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.

Results

Table 1 shows the study participants' clinical, multidetector CT, and biomarker characteristics. The mean age of the 1250 individuals (52% women) was 60±9 years. Mean SAT was 3023±1329 cm^3, and mean VAT was 2126±1112 cm^3.

Correlations With SAT and VAT

SAT and VAT were positively and similarly correlated with most circulating inflammatory biomarkers (Table 2). CD40 ligand, lipoprotein-associated phospholipase A2 (Lp-PLA2), osteoprotegerin, and tumor necrosis factor (TNF)-α were not correlated with either SAT or VAT. BMI and WC were correlated with the same biomarkers as SAT and VAT and were additionally correlated with TNF-α.

Multivariable-Adjusted Regressions With SAT and VAT

In multivariable models, CRP, fibrinogen, intercellular adhesion molecule-1 (ICAM-1), IL-6, isoprostanes, monocyte chemoattractant-1 (MCP-1), P-selectin, and TNF receptor-2 remained associated with both SAT and VAT; myeloperoxidase was significantly associated with SAT and had a borderline association with VAT (Table 3). With the exception of CRP (sex interaction $P=0.02$ for SAT and $P<0.0001$ for VAT), there was no evidence of significant effect modification by sex on the association of SAT or VAT with other biomarkers. In women, for a 1-SD increase in SAT, estimated CRP was 1.7 mg/L higher on average, whereas for a 1-SD increase in VAT, CRP was 1.8 mg/L higher. In contrast, the association in men was less strong: For a 1-SD increase in SAT and VAT, estimated CRP was 0.6 and 0.7 mg/L higher, respectively. For most markers, the estimated increase in concentrations per 1 SD of SAT was comparable to and not statistically significantly different from that of VAT (Table 3), with 2 exceptions. For isoprostanes, the magnitude of the estimated association with VAT was almost double that of SAT (Table 3; $P=0.002$ for difference in effect between SAT versus VAT). Although less striking, we also observed differences in the magnitude of the SAT versus VAT association with MCP-1 (Table 3; $P=0.04$ for SAT versus VAT comparison).

TABLE 1. Clinical Characteristics of Participants (n=1250)

Characteristic	
Age, y	60±9
Women, %	52
BMI, kg/m^2	28.3±5.1
Waist circumference, cm	100±14
Smoking, current:former:never, %	10:52:38
Aspirin ≥3 times/wk, %	31
Alcohol intake, ≥14 drinks/wk (men) or ≥7 drinks/wk (women), %	16
Postmenopausal, % (women)	83
Hormone replacement therapy, % (women)	36
Physical activity index	38±6
Hypertension treatment, %	30
Total cholesterol/HDL ratio	4.1±1.3
Triglycerides, mg/dL	138±96
Diabetes mellitus, %	10
Prevalent cardiovascular disease, %	12
CT fat measures	
SAT, cm^3	
Sex-pooled	3023±1329
Women	3320±1424
Men	2699±1133
VAT, cm^3	
Sex-pooled	2126±1112
Women	1645±870
Men	2652±1110
Biomarkers	
CRP, mg/L	
Women	2.5 (1.1 to 6.0)
Men	1.7 (0.9 to 3.7)
CD40 ligand, plasma, ng/mL	1.3 (0.6 to 4.1)
Fibrinogen, mg/dL	368 (326 to 414)
ICAM-1, ng/mL	239 (210 to 274)
IL-6, pg/mL	2.6 (1.7 to 4.1)
Isoprostanes, pg/mL	1137 (541 to 1986)
Lp-PLA2 activity, $nmol \cdot mL^{-1} \cdot min^{-1}$	142 (120 to 166)
Lp-PLA2 mass, ng/mL	283 (231 to 355)
MCP-1, pg/mL	306 (248 to 380)
Myeloperoxidase, ng/mL	40.4 (28.3 to 60.9)
Osteoprotegerin, pmol/L	5.2 (4.3 to 6.1)
P-selectin, ng/mL	36 (28 to 45)
TNF-α, pg/mL	1.2 (0.9 to 1.6)
TNF receptor-2, pg/mL	1955 (1671 to 2336)

Values are mean±SD, percent, or median (25th to 75th percentile). HDL indicates high-density lipoprotein; ICAM, intercellular adhesion molecule; Lp-PLA2, lipoprotein-associated phospholipase A2; MCP, monocyte chemoattractant-1; and TNF, tumor necrosis factor.

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TABLE 2. Pearson Correlation Coefficients Between Log-Transformed Biomarkers and SAT, VAT, BMI, and WC (Age- and Sex-Adjusted)

Marker	No.	SAT	VAT	BMI	WC
CRP*					
Women	646	0.45†	0.47†	0.52†	0.51†
Men	596	0.30†	0.33†	0.38†	0.37†
CD40 ligand, plasma	1241	−0.02	−0.05	−0.04	−0.04
Fibrinogen	1243	0.27†	0.22†	0.29†	0.27†
ICAM-1	1241	0.12†	0.12†	0.16†	0.16†
IL-6	1241	0.23†	0.23†	0.27†	0.25†
Isoprostanes	1010	0.13†	0.22†	0.18†	0.20†
Lp-PLA2 activity	1240	−0.02	0.02	0.01	0.01
Lp-PLA2 mass	1240	−0.04	−0.02	−0.04	−0.04
MCP-1	1226	0.07‡	0.13†	0.09‡	0.11†
Myeloperoxidase	1208	0.10†	0.06§	0.10†	0.10†
Osteoprotegerin	1240	0.01	0.03	0.04	0.06§
P-selectin	1243	0.09‡	0.12†	0.11†	0.14†
TNF-α	920	0.05	0.06	0.09‡	0.09‡
TNF receptor-2	1214	0.17†	0.12†	0.21†	0.19†

*CRP is a sex-specific correlation.
†$P<0.001$, ‡$P<0.01$, §$P<0.05$.

Multivariable-Adjusted Regressions With Both SAT and VAT in Models

If SAT and VAT were included in the same multivariable-adjusted model, both SAT and VAT remained significant correlates of CRP, fibrinogen, and IL-6. Only VAT remained significantly associated with isoprostanes, MCP-1, and P-selectin, whereas only SAT remained significantly associated with ICAM-1, myeloperoxidase, and TNF receptor-2 (data not shown).

Addition of SAT and VAT to Multivariable Models That Included BMI and WC

To assess whether CT-based measures of abdominal fat compartments added to the amount of marker variability explained by models that already included BMI and WC, we added SAT and VAT separately to models that included BMI and WC (Table 3). In models that also adjusted for BMI and WC, SAT remained associated with fibrinogen only ($P=0.01$), whereas VAT remained significantly associated with CRP, IL-6, isoprostanes, and MCP-1. In women, after adjustment for BMI and WC, the additional estimated increase in CRP was 0.57 mg/L per 1 SD of VAT, whereas in men, the estimate was only half this magnitude.

Secondary Analyses

We hypothesized that some previously described correlates of inflammatory markers, including systolic and diastolic blood pressure, lipid treatment, total cholesterol/HDL ratio, triglycerides, diabetes mellitus, and cardiovascular disease, might serve as intermediate mechanisms linking SAT, VAT, and inflammation. If these covariates were added to the models, results were not altered materially (data not shown). Similarly, the exclusion of participants with cardiovascular disease (n=151), diabetes mellitus (n=129), or CRP concentrations >10 mg/L (n=94) did not substantively alter the present findings (data not shown). Overall, we found evidence for a statistically significant but small degree of effect modification of age on the association between SAT and fibrinogen and between VAT and CRP. Additionally, we detected an effect modification of smoking on the association between SAT and 3 markers (CRP, IL-6, and isoprostanes). Current smoking essentially eliminated the association between SAT and both IL-6 and isoprostanes. Interactions with obesity were not significant for any marker (Data Supplement, Table I).

To further investigate the relation between increasing VAT relative to SAT with inflammation and oxidative stress, we compared concentrations of CRP and isoprostanes divided on the basis of sex-specific SAT and VAT tertiles (Figure). CRP was associated with increasing SAT and VAT tertiles in both women and men. For isoprostanes, most of the relations with VAT appeared to be driven by those with the highest tertile of SAT.

In a secondary analysis, we also examined the significance of BMI and WC in multivariable-adjusted models with SAT or VAT in relation to the biomarkers (reflecting the models presented in Table 3). When we considered $P<0.01$ as indicating significance, for SAT, BMI was significant in the following models: CRP (women and men), fibrinogen, and IL-6, whereas WC was significant for osteoprotegerin and P-selectin (Data Supplement, Table II). For VAT, BMI was significant for CRP (women only), fibrinogen, and IL-6, whereas WC was not significant in any of the models.

Discussion

Principal Findings

In the present large, community-based sample, CT-based measures of abdominal adiposity were significantly associ-

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TABLE 3. Multivariable-Adjusted Linear Regression Models of Relation of SAT or VAT to Biomarkers: R^2 and Effect Size of SAT or VAT, Before and After Adjustment for BMI and WC

	Multivariable Model‡ Plus SAT or VAT			Multivariable Model‡ Plus BMI/WC Plus SAT or VAT		
	Model R^2	Increase in Marker§ per 1 SD of SAT or VAT	P*	Model R^2	Increase in Marker§ per 1 SD of SAT or VAT	P†
CRP, mg/L						
Women						
SAT	0.28	1.7 (1.4, 2.0)	<0.0001	0.34	0.11 (−0.21, 0.49)	0.51
VAT	0.29	1.8 (1.4, 2.1)	<0.0001	0.36	0.57 (0.25, 0.92)	0.0003
Men						
SAT	0.18	0.6 (0.4, 0.8)	<0.0001	0.23	0.02 (−0.18, 0.25)	0.84
VAT	0.19	0.7 (0.5, 0.9)	<0.0001	0.24	0.26 (0.1, 0.5)	0.006
CD40 ligand, ng/mL						
SAT	0.03	−0.05 (−0.13, 0.05)	0.33	0.03	0.03 (−0.12, 0.21)	0.69
VAT	0.03	−0.08 (−0.17, 0.02)	0.12	0.03	−0.05 (−0.18, 0.09)	0.44
Fibrinogen, mg/dL						
SAT	0.19	19 (15, 23)	<0.0001	0.20	8.0 (1.7, 14.3)	0.01
VAT	0.16	17 (13, 21)	<0.0001	0.20	3.4 (−2.0, 8.9)	0.22
ICAM-1, ng/mL						
SAT	0.11	7.4 (4.4, 10.5)	<0.0001	0.12	−1.3 (−6.4, 3.8)	0.61
VAT	0.11	7.3 (4.0, 10.7)	<0.0001	0.12	0.17 (−4.23, 4.67)	0.94
IL-6, pg/mL						
SAT	0.12	0.5 (0.3, 0.6)	<0.0001	0.14	0.12 (−0.05, 0.30)	0.17
VAT	0.12	0.5 (0.4, 0.6)	<0.0001	0.14	0.20 (0.05, 0.36)	0.01
Isoprostanes, pg/mL						
SAT‖	0.07	160 (83, 243)	<0.0001	0.09	−78 (−182, 37)	0.18
VAT	0.10	313 (218, 414)	<0.0001	0.10	223 (103, 355)	0.0002
Lp-PLA2 activity, nmol · mL^{-1} · min^{-1}						
SAT	0.22	0.4 (−1.4, 2.3)	0.65	0.23	−2.5 (−5.5, 0.6)	0.11
VAT	0.23	1.9 (−0.2, 4.0)	0.07	0.23	1.3 (−1.5, 4.2)	0.36
Lp-PLA2 mass, ng/mL						
SAT	0.04	−1.2 (−6.3, 4.1)	0.66	0.04	−1.1 (−9.8, 7.9)	0.81
VAT	0.04	0.1 (−5.7, 6.0)	0.97	0.04	1.6 (−6.3, 9.7)	0.70
MCP-1, pg/mL						
SAT‖	0.07	7.8 (1.7, 14.0)	0.01	0.07	−3.4 (−13.5, 7.1)	0.53
VAT	0.08	15.0 (8.2, 22.0)	<0.0001	0.08	12.5 (3.3, 21.9)	0.008
Myeloperoxidase, ng/mL						
SAT	0.05	2.6 (1.2, 4.0)	0.0002	0.05	1.6 (−0.7, 4.1)	0.20
VAT	0.04	1.5 (0.0, 3.0)	0.05	0.05	−0.7 (−2.6, 1.3)	0.50
Osteoprotegerin, pmol/L						
SAT	0.20	0.02 (−0.06, 0.10)	0.62	0.21	−0.13 (−0.26, 0.01)	0.06
VAT	0.20	0.05 (−0.04, 0.14)	0.25	0.20	−0.01 (−0.13, 0.11)	0.82
P-selectin, ng/mL						
SAT	0.06	1.3 (0.5, 2.0)	0.001	0.07	−0.6 (−1.8, 0.7)	0.37
VAT	0.07	1.9 (1.0, 2.7)	<0.0001	0.07	0.9 (−0.2, 2.1)	0.11
TNF-α, pg/mL						
SAT	0.04	0.03 (0.00, 0.07)	0.08	0.04	−0.03 (−0.10, 0.03)	0.31
VAT	0.04	0.04 (0.00, 0.08)	0.06	0.04	0.00 (−0.06, 0.05)	0.92
TNF receptor-2, pg/mL						
SAT	0.16	97 (66, 128)	<0.0001	0.17	12.9 (−37.7, 64.7)	0.62
VAT	0.14	74 (40, 108)	<0.0001	0.17	−18.4 (−61.4, 25.6)	0.41

R^2=percentage of variance in the dependent variable that is explained by the independent variable(s).

*P for SAT or VAT; †P for SAT or VAT in models with BMI/WC.

‡Adjusted for sex, age, smoking, aspirin, alcohol intake, menopausal-status and hormone replacement therapy (women only), and physical activity index.

§Average expected increase in biomarker concentration from the median biomarker concentration (95% CI).

‖Comparison of model R^2 for SAT vs VAT for each biomarker was only significant for isoprostanes (P=0.002) and MCP-1 (P=0.04).

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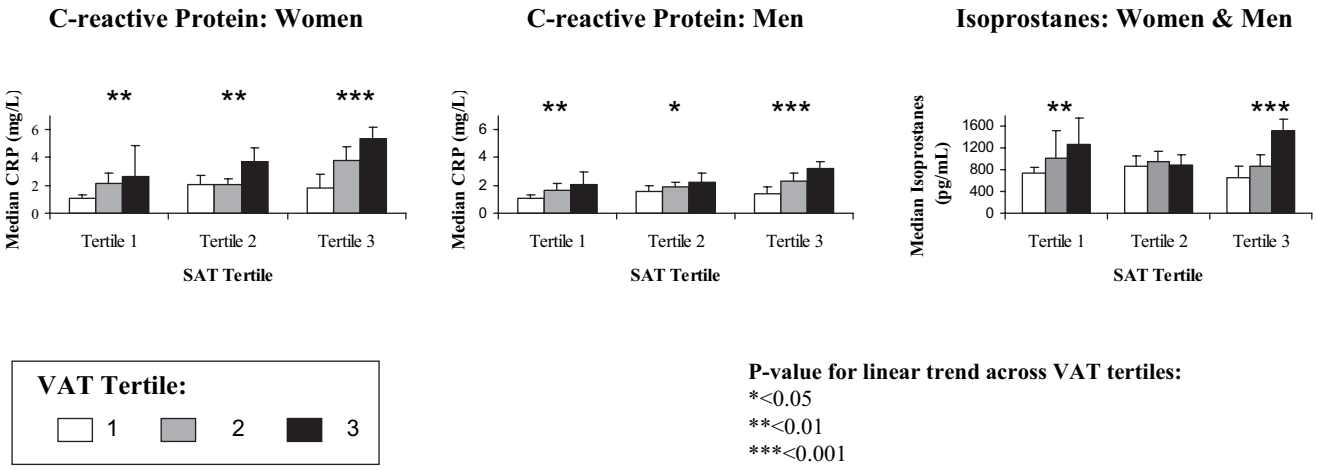

Sex-specific tertiles of VAT by sex-specific SAT tertiles for CRP; age-adjusted *P* value for linear trend is presented for women (left) and men (middle). Right, Sex-specific tertiles of VAT by SAT tertiles for urinary isoprostanes for women and men combined; age- and sex-adjusted *P* value for linear trend is presented. Error bar represents upper 95% CI of the mean marker, and mean marker levels were back-transformed; the CRP data and the *P* values for trend are age-adjusted, and isoprostane data are age- and sex-adjusted.

ated with several systemic biomarkers of inflammation and oxidative stress in women and men. Whereas most markers were similarly associated with SAT and VAT, isoprostanes and MCP-1 were more strongly associated with VAT than with SAT. When both SAT and VAT were considered in the same model, CRP, fibrinogen, and IL-6 remained correlated with both adipose tissue depots, whereas other markers were associated only with SAT or VAT. In addition, the association between VAT and CRP, IL-6, isoprostanes, and MCP-1 concentrations remained significant after we accounted for clinical measures of overall and central adiposity, which suggests that VAT may be a critical correlate of inflammation that is not completely accounted for by BMI and WC. We also observed that abdominal adiposity was more strongly associated with CRP in women than in men. Finally, we did not find an association between either SAT or VAT with circulating concentrations of CD40 ligand, Lp-PLA2 activity or mass, osteoprotegerin, or TNF-α.

In the Context of the Current Literature

The present finding that CRP was positively and similarly correlated with both SAT and VAT agrees with previous findings in small cross-sectional studies.[5,7,9] Lemieux et al[7] reported positive correlations between SAT and VAT with CRP concentrations (r=0.28 for SAT and r=0.33 for VAT) in 159 healthy middle-aged white men. Similar strong relations were reported in a sample of 112 white postmenopausal women.[22] We observed a significant sex interaction for CRP, because both SAT and VAT were more strongly associated with CRP in women than in men. Whereas 2 recent cross-sectional studies suggested stronger associations between clinical measures of adiposity and markers of inflammation in white women than in men,[23,24] we extended these findings of sex differences to relations of CT-based measurements of abdominal fat distribution and inflammation. Additionally, we found that VAT remained associated with CRP after adjustment for BMI and WC in both men and women. Therefore, whereas both SAT and VAT are correlates of CRP concentrations, the present data suggest that VAT may be a critical correlate that is not completely accounted for by routine clinical measurements.

It has been proposed that a mechanistic link between adiposity and CRP may be explained by IL-6 and TNF-α.[1,25,26] Both cytokines are produced in adipose tissue,[27,28] are upregulated in obese states,[23,29] and induce hepatic production of CRP.[30,31] Some cross-sectional studies demonstrate stronger associations of IL-6 and TNF-α with abdominal girth[23,24,32] or visceral fat area[8] than with BMI, yet correlations between circulating concentrations of IL-6 or TNF-α and radiographic measures of fat distribution have not been well studied. We found that SAT and VAT were similarly related to IL-6 and that this relation persisted for VAT alone after adjustment for BMI and WC. TNF-α, however, was not associated with either SAT or VAT. Although it has been shown that adipose tissue from obese individuals expresses 2.5-fold more TNF-α mRNA than is expressed in lean control subjects,[33] tissue RNA expression is not always reflected in circulating concentrations of the protein.[34] Whereas ≈30% of circulating IL-6 originates in adipose tissue, systemic release of TNF-α is much more variable and is believed to function primarily in a paracrine fashion.[10] However, we did find strong correlations with circulating concentrations of the soluble receptor TNF receptor-2 and both SAT and VAT in the present study, consistent with relations between TNF receptor-2 and obesity.[35–37]

In addition to adipocytes, inflammatory cells such as monocytes and macrophages are components of adipose tissue and accumulate in obese states.[38] Macrophages secrete MCP-1, and in human adipose tissue, MCP-1 mRNA concentrations are correlated with measures of adiposity, with higher expression in VAT than in SAT.[39,40] Furthermore, circulating concentrations of MCP-1 are elevated in obesity and fall with exercise and loss of visceral fat.[41] Adding to the current literature, we found that MCP-1 was more strongly associated with VAT than with SAT and that VAT may contribute to MCP-1 variability beyond the contributions of BMI and WC.

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Oxidative stress, as reflected by isoprostanes (a metabolite of lipid peroxidation that serves as a time-integrated marker of oxidative stress)[42] and myeloperoxidase (an oxidative enzyme produced by macrophages), has been positively associated with obesity in a few studies that assessed central obesity via waist-hip ratio or estimated visceral fat with bioelectric impedance.[43–46] In the present study, myeloperoxidase was correlated with both SAT and VAT. A prior small study has shown a decrease in both myeloperoxidase and isoprostanes with a diet and exercise intervention in obese men,[46] but we believe the present finding of myeloperoxidase in relation to SAT and VAT is novel. Furthermore, the results of the present study are among the first to show a direct correlation of urinary isoprostane concentrations and SAT or VAT, with stronger correlations observed for VAT than for SAT. We also show that isoprostanes remained associated with VAT after adjustment for BMI and WC. The present data support the hypothesis that visceral adiposity is a unique correlate of oxidative stress.

Although a few small studies have reported high concentrations of soluble ICAM-1[47–49] and P-selectin[50] in the plasma of obese individuals, the relation of these adhesion molecules to fat distribution has not been well studied. ICAM-1 has been demonstrated to be associated with BMI and waist-hip ratio.[49] We found that SAT and VAT were similarly associated with circulating concentrations of ICAM-1 and with P-selectin. Neither of these relations remained significant after adjustment for BMI and WC. Therefore, it does not appear that the relation between either ICAM-1 or P-selectin and visceral adiposity is independent of clinically assessed anthropometry.

In the present study, we did not find an association between either SAT or VAT and circulating concentrations of CD40 ligand, Lp-PLA2 activity or mass, osteoprotegerin, or TNF-α. Although we used a precise measure of abdominal fat masses, our measures of inflammatory markers are limited to those present in the peripheral circulation. It is possible that some markers may be metabolized by the liver and may show a different association if they are measured in the portal circulation.[26] Fontana et al[26] recently demonstrated that IL-6 concentrations are 50% higher in portal vein samples than in those from the radial artery in obese women. However, it is notable that we found clear associations between SAT and VAT and circulating concentrations of many markers but no association between others. The present investigation of SAT was limited to SAT in the abdominal area, and thus, we cannot comment on associations between inflammatory markers and SAT in other regions.

Strengths and Limitations

Strengths of the present study include the large community-based sample, with participants not selected for adiposity-related traits. Routine assessment of clinical characteristics was performed, which allowed for adjustment for various potential confounders. We investigated a broad panel of circulating markers of systemic inflammation that represent various steps along the inflammatory pathway. We formally compared the strengths of association of SAT versus VAT with the individual biomarkers, and our models accounted for the explanatory contribution of BMI and WC.

Limitations include the use of cross-sectional data, which thereby precludes an inference of a causal relation between SAT, VAT, and systemic inflammation. The results of the present study may not be generalizable to other ethnic or age groups given that our sample was primarily white and middle-aged to elderly. Additionally, risk factors and anthropometric data were not obtained contemporaneously with the CT data; this could potentially have caused us to underestimate the magnitude of the association between the markers and the adipose tissue compartments; however, this should not affect the relative association between SAT versus VAT and the marker concentrations, which was the primary focus of the present study. Furthermore, we measured systemic and not portal concentrations of biomarkers; therefore, biomarkers that may have been upregulated locally or substantially metabolized by the liver may not have been detected accurately in the present study. We note that we did not examine site-specific (lumbar level) associations between VAT and biomarkers and that the magnitude of these associations may differ between partial volumes at specific sites and total abdominal VAT volume.[51] Finally, we acknowledge that the present study may have both false-negative and false-positive findings and will need to be replicated in additional samples. Although larger than prior reports, we had a modest sample size, which limited our ability to detect small associations. Conversely, to examine markers at several stages in the inflammatory/oxidative cascade, we examined multiple systemic biomarkers and acknowledge that some of the findings may represent false-positives secondary to multiple testing.

Implications

The present findings underscore the positive association of both SAT and VAT with circulating markers of inflammation. Prior literature has emphasized the important relations of visceral adiposity with inflammation and related cardiometabolic risk, whereas we show that both SAT and VAT appear to be associated with chronic inflammation. Therefore, SAT may have multiple metabolic and endocrinologic properties that have previously been ascribed only to VAT; this warrants investigation in further studies. To lend a clinical perspective to the present findings, we use a conversion factor of 0.9255[52] to convert adipose tissue volume to mass. In women, SAT mass of 1.3 kg and VAT mass of 0.8 kg represents 1 SD; this small increase in adipose tissue mass corresponds to an increase in CRP concentration of 1.7 mg/L for each SD of SAT and 1.8 mg/L for VAT. In men, 1.0 kg of SAT and VAT corresponds to 1 SD, and the corresponding CRP concentrations are 0.6 mg/L higher for each 1-kg increase of SAT and 0.7 mg/L for each additional kilogram of VAT. Thus, a small increase in abdominal adipose tissue relative to overall body weight is associated with significantly elevated CRP concentrations, and this relation is most marked in women.

Conclusions

We have investigated the relation of CT-based measures of abdominal fat compartments and a diverse panel of systemic biomarkers that reflect inflammation and oxidative stress. Both SAT and VAT were similarly associated with elevated

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concentrations of multiple inflammatory biomarkers. After adjustment for clinical measures of adiposity, only VAT remained associated with multiple markers, whereas SAT only remained associated with fibrinogen. The present cross-sectional data suggest a role for both abdominal SAT and VAT in inflammation and oxidative stress.

Sources of Funding

This work was supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study (N01-HC-25195 and RO1-HL076784, RO1-HL064753, and R01-AG028321 [Dr Benjamin]). Dr Meigs is supported in part by an American Diabetes Association career development award. Dr Vasan is supported in part by 2K24HL04334 (National Institutes of Health/National Heart, Lung, and Blood Institute).

Disclosures

None.

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CLINICAL PERSPECTIVE

Excess adiposity is associated with greater systemic inflammation. Whether visceral adiposity is more proinflammatory than subcutaneous abdominal adiposity is unclear. We examined the relations of abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), assessed by multidetector computerized tomography, to circulating inflammatory and oxidative stress biomarkers in 1250 Framingham Heart Study participants. SAT and VAT were positively and similarly (with respect to strength of association) related to C-reactive protein, fibrinogen, intercellular adhesion molecule-1, interleukin-6, P-selectin, and tumor necrosis factor receptor-2. However, compared with SAT, VAT was more highly associated with urinary isoprostanes and monocyte chemoattractant protein-1. When body mass index and waist circumference were added to the models, VAT remained significantly associated with only C-reactive protein, interleukin-6, isoprostanes, and monocyte chemoattractant protein-1; SAT only remained associated with fibrinogen. The present cross-sectional data support an association between both SAT and VAT with inflammation and oxidative stress. The data suggest that the contribution of visceral fat to inflammation may not be completely accounted for by clinical measures of obesity.

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