Published in final edited form as:
Obesity (Silver Spring). 2009 November ; 17(11): 2054–2059. doi:10.1038/oby.2009.60.

Visceral and Subcutaneous Adiposity and Brachial Artery Vasodilator Function

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Abstract

Endothelial dysfunction may link obesity to cardiovascular disease (CVD). We tested the hypothesis that visceral abdominal tissue (VAT) as compared with subcutaneous abdominal tissue (SAT) is more related to endothelium-dependent vasodilation. Among Framingham Offspring and Third Generation cohorts (n=3020, mean age 50 years, 47% women) We used multivariable linear regression adjusted for CVD and its risk factors to relate computed tomography-assessed VAT and SAT, body mass index (BMI) and waist circumference (WC), with brachial artery measures. In multivariable-adjusted models, BMI, WC, VAT and SAT were positively related to baseline artery diameter and baseline mean flow velocity (all $p<0.001$), but not hyperemic mean flow velocity. In multivariable-adjusted models, BMI ($p=0.002$), WC ($p=0.001$) and VAT ($p=0.01$), but not SAT ($p=0.24$) were inversely associated with FMD%. However there was little incremental increase in the proportion of variability explained by VAT ($R^2=0.266$) as compared to SAT ($R^2=0.265$), above and beyond traditional risk factors. VAT, but not SAT was associated with FMD% after adjusting for clinical covariates. Nevertheless, the differential association with VAT as compared to SAT was minimal.

Keywords

Adiposity; obesity; endothelial dysfunction; visceral fat; subcutaneous fat; flow-mediated dilation; epidemiology; computed tomography

Introduction

Brachial artery flow-mediated dilation (FMD) is a noninvasive measure of endothelial function associated with incident CVD.(1-3) Prior studies have demonstrated associations

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between obesity and abnormal FMD.(4,5) Abdominal adiposity, assessed by waist to hip ratio,(6,7) and waist circumference,(7) is more strongly associated with CVD risk and with vascular endothelial dysfunction,(6) compared to generalized adiposity measures such as body mass index (BMI). Radiographically-assessed visceral (VAT) and subcutaneous (SAT) adipose tissue volumes allow for the study of these two distinct abdominal adipose compartments. Prior data suggest that VAT may be more closely related than SAT to cardiometabolic risk factors.(8-10) such as hypertension, diabetes, and dyslipidemia, all of which are related to endothelial dysfunction.(11) Based on the stronger association between VAT and CVD risk factors, we hypothesized that compared to SAT, VAT is more closely related to endothelial dysfunction as assessed by brachial artery vasodilator function.

Materials and Methods

Details regarding study recruitment, sample exclusions, covariate assessment, CT protocols, biomarker assessment, and statistical methods can be found in the online-only Data Supplement.

Briefly, the study sample consisted of Framingham Offspring and Third Generation participants who had undergone both endothelial function as well as coronary and abdominal CT measurements (final sample size=3020). Multidetector computed tomography measurements in which visceral and subcutaneous fat were measured yielded inter-reader reproducibility measures on a randomly selected 100 participant subset yielded intra-class correlations of 0.992 and 0.997 for VAT and SAT respectively.(12) Fasting brachial artery tracings were acquired and measured by one of three experienced sonographers following rigorous standardized written protocols.(11,13) Intraobserver and interobserver correlation coefficients for baseline and deflation diameters were 0.99 in a sample of 20 studies separated by one year.

The primary exposures of interest are VAT and SAT. We provide data for BMI and WC for comparison as these are traditionally measured adiposity measures. The primary dependent variables of interest are FMD and hyperemic flow however we provide results for baseline brachial measures for context. Age-, sex-, and cohort-adjusted Pearson correlations were employed to assess relations among VAT, SAT, BMI and WC, and with the four brachial variables. Multivariable linear regression analysis was employed to assess relations between VAT, SAT, BMI and WC, individually, with the four dependent brachial measures. SAT, VAT, BMI and WC were sex-standardized within each sex to mean 0, standard deviation 1 to facilitate comparison of regression coefficients. Details regarding primary and secondary analyses are available in the Data supplement as described above.

Results

Participant Characteristics

Clinical, adiposity and brachial reactivity characteristics of participants are shown in Table 1. Participants had a mean age of 50±10 years and 47% were women. Table 2 demonstrates that the four adiposity measures studied were all highly correlated (all p-values <0.0001).

VAT, SAT and Brachial Artery Vasodilator Function

Median time between CT and FMD measurements was 66 days. In age-, sex-, and cohort-adjusted as well as multivariable-adjusted models all four adiposity measures correlated with baseline brachial artery diameter and FMD%, and baseline but not hyperemic mean flow velocity (Table 3). VAT as well as SAT were related to baseline brachial artery diameter and baseline mean flow velocity in age-, sex-, and cohort and multivariable-adjusted models (Table 4). Whereas VAT as well as SAT were related to FMD% in age-, sex-, and cohort-

adjusted models, upon multivariable-adjustment, VAT, but not SAT, was associated with FMD% (p=0.01). There was little incremental increase in the proportion of variability explained by VAT (R^2=0.266) as compared to SAT (R^2=0.265) above and beyond traditional CVD risk factors (Table 4). Hyperemic mean flow velocity was borderline-associated with VAT (p=0.04), but not with SAT in age-, sex-, and cohort-adjusted. None of the adiposity measures were associated with hyperemic mean flow in multivariable-adjusted models.

Because we observed significance for individual fat depots with baseline endothelial function measures, we entered VAT together with SAT into a single multivariable model for baseline endothelial function measures. When considered jointly in a multivariable model, both VAT and SAT remained significantly related to baseline brachial artery diameter (VAT: multivariable-adjusted β=0.12±0.02, p<0.0001; SAT: multivariable-adjusted β=0.03±0.01, p=0.038) and to baseline mean flow velocity (VAT: β=0.37±0.12, p=0.002; SAT: β=0.24±0.10, p=0.02).

Secondary Analyses

Adding CRP to multivariable models did not substantively change associations between any of adiposity measures studied and brachial artery measures (Electronic Supplement Table). When the sum of VAT and SAT was considered as an independent variable (reflecting total abdominal fat), results did not materially differ from models considering VAT alone, with the exception of the finding that VAT+SAT was only associated with FMD% (p=0.056; Table 4). There was no evidence of effect modification by age (<50 or ≥50 years) or sex of relations between VAT or SAT and endothelial function (data not shown).

Stepwise regression models were constructed with covariates forced in for the purpose of assessing whether VAT remained significant in models that also considered measures of overall adiposity (BMI and WC). In models considering VAT (p=0.049) and BMI (p<0.001), both were positively related to baseline brachial artery diameter). Similarly, both VAT (p=0.003) and WC (p<0.0001) were positively related to baseline brachial artery diameter. VAT did not enter the final model for baseline mean flow velocity or FMD%, whereas BMI and WC both did.

Discussion

Principal Findings

In a large, community-based sample, VAT and SAT assessed by MDCT were associated with baseline brachial measures, and VAT alone was related to FMD%. If VAT and SAT were included in the same model, both were related to baseline brachial artery diameter and baseline mean flow velocity. None of the adiposity measures studied was related to hyperemic mean flow velocity. The addition of VAT to models for FMD containing classic CVD risk factors only minimally increased the R^2. Whereas our findings suggest that VAT, in contrast to SAT, is related to FMD% and therefore possibly to endothelium-dependent vasodilatory dysfunction, after accounting for classic risk factors VAT does not explain a large proportion of the variability in FMD%.

In the Context of Current Literature

Both BMI and WC are associated with biomarkers of endothelial dysfunction in prior studies.(4,5,11,14) Our study extends these findings by evaluating separate abdominal adiposity compartments, VAT and SAT, with endothelial function in a large cohort unselected for adiposity-related characteristics. Our result that VAT, as opposed to SAT, was inversely related to FMD% was similar to a small study (n=61) of ultrasound assessed

VAT and SAT.(15) In the PIVUS study of elderly (age 70 years; n=287) Swedish individuals, neither VAT nor SAT as measured by magnetic resonance imaging was related to brachial artery FMD%, but VAT was related to decreased resistance artery vasodilation by invasive forearm plethysmography. Variation in sample size and age of participants between our study and the Swedish investigation may account for differing results.(16)

Whereas BMI and WC were inversely related to FMD% in the present study, in a cohort study of 2109 healthy Finnish young adults (aged 24-39 years), BMI was positively related to FMD% after adjusting for several CVD risk factors.(17) The reasons underlying the opposite FMD%-BMI association observed in the prior study may reflect the Finnish study's lower mean age and BMI levels as compared to our study sample.

Mechanisms Possibly Underlying Relations between VAT and SAT with Brachial Reactivity

Our finding that much of the association between SAT and FMD% was accounted for by classic CVD risk factors is not surprising given that SAT has demonstrated relations with hypertension, dyslipidemia,(18,19) and insulin resistance.(19-22) VAT is more closely associated with adverse cardiometabolic risk factor profiles.(10,18,19,23,24) This may explain why we found that VAT, but not SAT, remained significantly related to FMD% even upon adjusting for several of these factors within our multivariable models. Furthermore, gene expression studies reflect differential(25) and possibly more atherogenic gene expression profiles(26) in VAT as compared to SAT. Thus, it is possible that novel risk factors may underlie the association between VAT and FMD%. Indeed, VAT has been demonstrated to be a unique pathogenic depot that produces a variety of bioactive substances involved in multiple pathways including inflammatory (e.g. interleukin-6,(27)), adipokine (adiponectin(28)), vascular growth factor (VEGF(27), hemostatic (PAI-1(27)) and renin-angiotensin-aldosterone system (angiotensinogen(29)). Derangements in these pathways have been linked to endothelial dysfunction,(30-35) and therefore may underlie the demonstrated association between VAT and endothelium-dependent vasodilation

VAT may also be related to endothelium-dependent vasodilation via its relative proximity to key vessels such as arterioles.(36) Secretion of adipokines from perivascular fat may underlie the association between obesity and endothelial dysfunction. (36) Overproduction of free-fatty acid-induced reactive-oxygen species is another possible mechanism underlying the association between VAT and endothelial dysfunction. Indeed, investigators recently demonstrated concomitant increases in vascular reactive-oxygen species (ROS) levels and NADPH oxidase activity in the aorta of obese fa/fa Zucker diabetic fatty (ZDF) rats (i.e. rat model of visceral-type obesity) as compared with wild-type rats.(37)

VAT Versus Anthropometric Adiposity Measurements

Our results do not suggest that the VAT-FMD% association is either stronger or more significant than that of BMI or WC with FMD% or WC and FMD. It is possible that the anatomic site at which VAT is considered could have unique associations with endothelial function measures that may be weakened when considering total abdominal VAT as we have done. VAT measurements at different spinal levels vary regards to association with the metabolic syndrome.(38) Because WC is measured at a single anatomic level as compared to VAT measured volumetrically in our study, its association with FMD% may be stronger. Nonetheless, neither BMI nor WC can differentially examine SAT as compared to VAT, the primary aim of our study.

Strengths and Limitations

Strengths of our current investigation include a large community-based sample, unselected for adiposity-related traits or CVD, with routine ascertainment of covariates and

sophisticated adiposity and brachial measures. Using volumetric MDCT fat measures in addition to BMI and WC allowed us to study the separate effects of subcutaneous and visceral fat compartments. Our sample is geographically, ethnically, and racially relatively homogenous, which may limit generalizability to other samples. The average time between endothelial function measurements and MDCT measurements was generally greater for Offspring participants than Third Generation participants, which could produce misclassification bias towards the null value to a greater extent for Offspring than for Third Generation participants. However, the primary goal of our study was to compare the relations between measures of endothelial function and SAT and VAT, which were measured at the same time. It was not practical to administer nitroglycerin to our community based volunteers; thus, we do not have a measure of non–endothelium-dependent vasodilation. Although we cannot exclude the possibility that alterations in vascular smooth muscle function influenced our results. We did not measure deep subcutaneous fat, and therefore we cannot comment on its relative associations with endothelial function measures. We did not assess the effects of weight loss in different fat compartments on endothelial function. Although our VAT and SAT measures were performed additionally on computed tomography scans for vascular calcium assessment, the measurement of VAT or SAT in future investigations would need to balance potential risks posed by ionizing radiation. VAT and SAT also can be measured by ultrasound and magnetic resonance imaging, which offer the advantage of no radiation exposure. However, in our study, VAT and SAT measurements were made secondarily off of computed tomography scans originally performed for the quantification of abdominal aortic calcification.

Whether VAT directly contributes to impaired endothelial function cannot be determined with our cross-sectional, observational study design. Whereas it is important to note that VAT explained only a minimal amount of the variability in FMD, there are several possible interpretations. Given the minimal change in R^2, we acknowledge that the FMD-VAT association may be due to residual confounding. However, it is also plausible that in creating our multivariable model we over-adjusted, by potentially including covariates that serve as intermediate mechanisms. For instance, VAT may longitudinally contribute to the development of increasing blood pressure, unfavorable lipid profiles, impaired glucose handling and CVD, which in turn contribute to impaired endothelial function. The large sample size permits us to discern cross-sectional associations of very modest magnitude that are likely of biological significance; even though the clinical significance of the associations could be questioned. We did not account for multiple testing. Our findings need to be replicated.

Conclusions

Both VAT and SAT were related to baseline brachial artery diameter and baseline mean flow velocity upon adjustment for clinical covariates. VAT, but not SAT was associated with FMD% after adjusting for clinical covariates. However, the differential association with VAT as compared to SAT was minimal. The longitudinal relations between various fat compartments and measures of endothelial function merits further study.

Acknowledgments

This work was supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (N01-HC-25195; RO1 HL70100; 1ROI HL60040). Dr. Vasan is supported in part by 2K24HL04334 (NHLBI/NIH)

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Table 1
Clinical, Brachial and Adiposity Characteristics (n=3020)

Clinical Characteristics	
Age, years	50±10
Women, %	47
Offspring participants, %	38
Triglycerides, mmol/L (mg/dL)	1.15±1.04 (128±92)
Total/HDL cholesterol	4.0±1.4
Systolic blood pressure, mm Hg	122±16
Diastolic blood pressure, mm Hg	76±9
Heart rate, beats/min	63±10
Hypertension treatment, %	19
Fasting glucose, mmol/L, (mg/dL)	5.49±1.17 (99±21)
Lipid treatment, %	14
Aspirin use, %	17
Diabetes, %	6
Current smoking, %	13
Menopausal, % (of women)	23
Moderate/heavy alcohol use,* %	16
Prevalent CVD, %	6
Adiposity Measures	
VAT, cm^3	1810±1036
SAT, cm^3	2864±1366
BMI, kg/m^2	27.7±5.2
Waist circumference, cm	97±14
Women	93±15
Men	101±12
Brachial Measures	
Baseline brachial artery diameter, mm	4.27±0.86
Flow-mediated dilation, %	4.35±3.49
Baseline mean flow velocity, cm/s	7.58±4.39
Hyperemic mean flow velocity, cm/s	57.4±19.8

For continuous variables, values are mean±SD; categorical variables, percentages

* >14 drinks per week men; >7 drinks per week women

Table 2

Age- Sex- and Cohort-Adjusted Pearson Correlations among Adiposity Measures

	VAT (cm^3)		SAT (cm^3)		BMI (kg/m^2)	
	Correlation coefficient	***P***	**Correlation coefficient**	***P***	**Correlation coefficient**	***P***
SAT (cm^3)	0.62	<0.0001	-		-	
BMI (kg/m^2)	0.70	<0.0001	0.85	<0.0001	-	
Waist (cm)	0.72	<0.0001	0.87	<0.0001	0.91	<0.0001

Table 3

Age- and Sex- and Cohort- adjusted Pearson Correlations between Adiposity and Vasodilator Function Measures

	Brachial artery diameter (mm)		Flow-mediated dilation (%)		Baseline mean flow velocity (cm/s)		Hyperemic mean flow velocity (cm/s)	
	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*
VAT (cm^3)	0.26	<0.0001	-0.07	<0.0001	0.23	<0.001	-0.04	0.059
SAT (cm^3)	0.19	<0.0001	-0.06	0.001	0.18	<0.001	0.01	0.61
BMI (kg/m^2)	0.31	<0.0001	-0.09	<0.0001	0.24	<0.001	-0.03	0.15
Waist (cm)	0.28	<0.0001	-0.10	<0.0001	0.23	<0.0001	-0.02	0.35

Obesity (Silver Spring). Author manuscript; available in PMC 2011 May 3.

Table 4

Multivariable-adjusted Regression Models for Association between Adiposity and FMD Vasodilator Function

	Model Adjustment	Brachial artery diameter			Flow-mediated dilation			Baseline mean flow velocity			Hyperemic mean flow velocity		
		β (SE)	*P*	R^2	β (SE)	*P*	R^2	β (SE)	*P*	R^2	β (SE)	*P*	R^2
Clinical Covariates*	**Age- sex- cohort-**	-	-	0.550	-	-	0.221	-	-	0.018	-	-	0.157
	Multivariable	-	-	0.567	-	-	0.264	-	-	0.154	-	-	0.193
VAT† (cm^3)	**Age- sex- cohort-**	0.16 (0.01)	**<0.001**	0.579	-0.27 (0.06)	**<0.001**	0.226	1.11 (0.09)	**<0.001**	0.070	-0.81 (0.39)	**0.04**	0.158
	Multivariable	0.14 (0.01)	**<0.001**	0.584	-0.19 (0.07)	**0.01**	0.266	0.54 (0.10)	**<0.001**	0.163	-0.52 (0.44)	0.24	0.193
SAT† (cm^3)	**Age- sex- cohort-**	0.11 (0.01)	**<0.001**	0.566	-0.18 (0.06)	**0.002**	0.224	0.80 (0.08)	**<0.001**	0.051	0.18 (0.35)	0.60	0.157
	Multivariable	0.09 (0.01)	**<0.001**	0.576	-0.07 (0.06)	0.24	0.265	0.42 (0.08)	**<0.001**	0.162	0.52 (0.37)	0.15	0.193
BMI (kg/m^2)	**Age- sex- cohort-**	0.18 (0.01)	**<0.001**	0.594	-0.29 (0.06)	**<0.001**	0.228	1.07 (0.08)	**<0.001**	0.076	-0.48 (0.35)	0.17	0.158
	Multivariable	0.17 (0.01)	**<0.001**	0.598	-0.19 (0.06)	**0.002**	0.267	0.67 (0.09)	**<0.001**	0.172	-0.09 (0.39)	0.81	0.193
Waist (cm)	**Age- sex- cohort-**	0.17 (0.01)	**<0.001**	0.587	-0.31 (0.06)	**<0.001**	0.228	1.05 (0.08)	**<0.001**	0.072	-0.27 (0.36)	0.45	0.157
	Multivariable	0.16 (0.01)	**<0.001**	0.592	-0.22 (0.06)	**0.001**	0.267	0.59 (0.09)	**<0.001**	0.168	0.10 (0.40)	0.80	0.193
VAT+SAT‡ (cm^3)	**Multivariable**	0.12 (0.01)	**<0.001**	0.582	-0.12 (0.06)	0.056	0.265	0.52 (0.09)	**<0.001**	0.164	0.22 (0.40)	0.57	0.193

*Clinical covariates alone (without fat measures). Multivariable models adjusted for age, sex, cohort, smoking, systolic and diastolic blood pressure, hypertension treatment, heart rate, total/HDL cholesterol, triglycerides, lipid treatment, aspirin, alcohol intake, diabetes, glucose, menopause, hormone replacement therapy, and prevalent CVD.

†To facilitate comparisons within each vascular measure, VAT, SAT, BMI, Waist, and VAT+SAT are sex-standardized to mean=0, standard deviation=1.

‡Sum of VAT and SAT.

Obesity (Silver Spring). Author manuscript; available in PMC 2011 May 3.

Table 5

Partial R2 for multivariable models with covariates alone and with VAT or SAT

	Brachial artery diameter			Flow-mediated dilation			Baseline mean flow velocity			Hyperemic mean flow velocity		
		+ VAT	+ SAT		+ VAT	+ SAT		+ VAT	+SAT		+ VAT	+ SAT
Age	0.004	0.002	0.004	0.002	0.002	0.002	0.005	0.006	0.004	0.015	0.014	0.015
Sex	0.231	0.242	0.236	0.048	0.050	0.049	0.0002	0.0006	0.0004	0.032	0.032	0.031
Smoking	0.0002	0.0003	0.0002	0.001	0.001	0.001	0.021	0.020	0.021	0.002	0.002	0.002
SBP	0.0009	0.0004	0.0006	0.017	0.016	0.017	0.003	0.002	0.003	0.019	0.019	0.020
DBP	0.0005	0.0001	0.0001	0.0001	0.0002	0.0002	0.0008	0.0004	0.0003	0.004	0.005	0.004
HTN treatment	0.002	0.0009	0.002	0.000003	0.00002	1.052E-7	0.00008	0.00001	0.000006	0.0006	0.0005	0.0007
Heart rate	2.07 E-7	0.0003	0.00008	0.005	0.00002	0.005	0.043	0.038	0.039	0.002	0.002	0.002
Total/HDL-c	0.002	0.0002	0.0009	0.0002	0.0005	0.0003	0.005	0.002	0.003	0.00003	0.0001	0.000007
Triglycerides	0.000008	0.00004	4.25E-8	0.0005	0.0004	0.0005	0.000007	9.02E-8	0.00002	0.000003	0.000001	0.000001
Lipid treatment	0.000009	0.0001	8.56E-7	0.0003	0.0005	0.0003	0.0009	0.0005	0.0008	0.0004	0.0005	0.0004
Aspirin	0.0002	0.0002	0.0002	0.00002	0.00001	0.00002	0.00009	0.00008	0.0001	0.0003	0.0003	0.0003
Alcohol	0.0003	0.0002	0.0004	0.000009	0.000003	0.00001	0.00005	0.00003	0.0001	0.00005	0.00005	0.00004
Diabetes	0.000009	0.000009	0.000009	0.0005	0.0005	0.0005	0.001	0.002	0.001	0.000006	0.000007	0.000006
Glucose	0.0009	0.0002	0.0005	0.000007	0.000006	0.000001	0.0008	0.0003	0.0005	0.000002	0.00001	6.68E-7
Menopause	0.00007	0.00009	0.00003	0.007	0.007	0.007	0.002	0.002	0.002	0.005	0.005	0.005
HRT	0.001	0.001	0.001	0.0006	0.0006	0.0006	0.003	0.003	0.003	0.006	0.006	0.005
CVD	0.00004	0.0002	0.00003	0.00003	0.00004	0.00002	0.001	0.001	0.0009	0.001	0.001	0.001

*Models also adjusted for cohort.