Relationship of Abdominal Visceral and Subcutaneous Adipose Tissue With Lipoprotein Particle Number and Size in Type 2 Diabetes

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OBJECTIVE—Insulin resistance and type 2 diabetes are associated with an atherogenic lipoprotein profile. We examined the role of visceral and subcutaneous fat depots, independent of BMI, on the dyslipidemia associated with type 2 diabetes.

RESEARCH DESIGN AND METHODS— A total of 382 subjects with type 2 diabetes underwent abdominal computed tomography to evaluate subcutaneous (SAT) and visceral adipose tissue (VAT) distribution and had anthropometric measurements to determine BMI and waist and hip circumference. Fasting blood was obtained for lipoprotein particle number and size using nuclear magnetic resonance spectroscopy. The relationship of lipoprotein particle number and size with BMI, SAT, and VAT was examined using multivariable regression models adjusted for age, sex, diabetes therapy, duration of diabetes, smoking, statin use, and A1C levels. The relation of VAT to lipoprotein particle number and size was further evaluated after the addition of BMI, BMI plus SAT, or BMI plus homeostatis is model assessment of insulin resistance (HOMA-IR) to the model.

RESULTS—VAT was positively related to VLDL particle number ($P < 0.0001$), LDL particle number ($P < 0.01$), and VLDL size ($P < 0.0001$) and negatively related to LDL size ($P < 0.0001$) and HDL size ($P < 0.0001$). These relationships remained unchanged after addition of BMI and SAT to the model. After addition of HOMA-IR, VAT remained positively related to VLDL particle number ($P < 0.0001$) and size ($P < 0.01$) and negatively related to LDL and HDL particle size ($P < 0.0001$ for both comparisons). Neither BMI nor SAT was independently related to lipoprotein parameters.

CONCLUSIONS—In patients with type 2 diabetes, higher VAT independent of BMI was associated with higher VLDL and LDL particle number, larger VLDL particles, and smaller LDL and HDL particles. This lipoprotein pattern has been associated with increased risk for atherosclerosis and cardiovascular disease. ***Diabetes*** **57:2022–2027, 2008**

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Dyslipidemia and increased adiposity, especially of abdominal type, are common metabolic features of type 2 diabetes. The dyslipidemia associated with type 2 diabetes is characterized by changes in lipoprotein particle number and size and has been attributed to insulin resistance (1,2). Studies using nuclear magnetic resonance (NMR) spectroscopy to analyze lipoprotein subclass profile along with euglycemic-hyperinsulinemic clamps (1) or frequently sampled intravenous glucose tolerance tests (2) to assess insulin sensitivity have clearly demonstrated that all three major human lipoproteins are affected by insulin resistance. The alterations in lipoprotein particle number and size in type 2 diabetes and insulin resistance have been linked to increased risk for cardiovascular disease (CVD) in both cross-sectional (3–9) and prospective studies (10,11).

Obesity has been clearly demonstrated to be associated with insulin resistance and its metabolic consequences, including type 2 diabetes, dyslipidemia, and CVD (12–14). Recently, studies have suggested that fat tissue distribution may be more important than overall fat mass for these associations (15–17). Epidemiologic and physiologic studies have suggested that abdominal fat is more strongly associated with metabolic risk factors and CVD than total amount of body fat (15,16,18). Whether specific abdominal fat compartments—for example, visceral abdominal fat (VAT) compared with subcutaneous abdominal fat (SAT)—carry greater metabolic and cardiovascular risks remains more controversial (16,17), especially in subjects with type 2 diabetes (17). Even though many studies have pointed to a greater cardiovascular and metabolic risk associated with VAT (18–27), SAT has also been associated with insulin resistance and metabolic disorders in other studies (27–30). For this report, we examined the association between abdominal fat compartments measured by computed tomography (CT) and lipoprotein particle number and size using NMR spectroscopy in 382 subjects with type 2 diabetes who participated in the CHICAGO study (31). We further analyzed how the relationship of abdominal fat depots to lipoprotein parameters was impacted by BMI as a measure of overall adiposity or by hip circumference as an index of peripheral subcutaneous fat mass.

RESEARCH DESIGN AND METHODS

Subjects for the current analysis were Caucasian and African-American participants in the CHICAGO trial, a prospective study of the effects of pioglitazone compared with glimepiride on carotid intima-media thickness in subjects with type 2 diabetes recruited from 28 clinical sites in Chicago (31). The details of the study have been previously reported (31,32). Data included

in this report were obtained before randomization to treatment groups. All subjects were asymptomatic for coronary artery disease at baseline. The study was approved by central and local institutional review board committees, and all participants provided written informed consent. All subjects underwent measurements of height, weight, and waist and hip circumference by a trained nurse at the baseline visit. Waist circumference was measured at the smallest circumference between the ribs and iliac crest, and hip circumference was measured at maximum circumference between the iliac crest and crotch to the nearest 0.1 cm. BMI was calculated as weight in kilograms divided by the square of height in meters.

Subjects underwent an abdominal CT scan for determination of VAT and SAT. Abdominal adipose tissue content and distribution were quantified by CT scan at the level of L4-L5 vertebra when subjects were in supine position with both arms stretched above the head (33–35). A single 6-mm slice was taken during suspended respiration after a normal expiration. Total abdominal adipose tissue (TAT) area was measured by delineating the body surface with a receiver operator instrument (ROI) and then computing the adipose tissue volume using an attenuation range of −190 to −30 HU (33–35). VAT area was quantified by delineating the abdominal cavity at the internal aspect of the abdominal wall and the posterior aspect of the vertebral body with an ROI (33–35). SAT was calculated by subtracting VAT from TAT area. To obtain VAT and SAT volumes, the area for each fat component was multiplied by the slice thickness. Fasting blood samples were obtained at the baseline visit for measurement of lipids, A1C, and lipoprotein profile (31,32). Lipoproteins were analyzed using NMR technology by LipoScience (Raleigh, NC) (1).

Statistical methods. Homeostatis model assessment insulin resistance (HOMA-IR) was calculated according to the following formula: [fasting glucose (mmol/l) × fasting insulin (U/ml)]/22.5. Log transformation of the data was performed when necessary to achieve homogeneity of variance. Pearson correlation coefficients were used after adjustment for age and sex to assess the relationship between each subclass lipoprotein particle number and size and BMI, waist circumference, A1C, SAT, and VAT. Each subclass lipoprotein particle number and size was further examined in relation to BMI, SAT, and VAT areas using a general linear model with sex, statin use, and diabetes therapy as fixed variables and age, duration of diabetes, years of smoking, and A1C levels as continuous variables. The multivariable analyses were repeated with the addition of BMI to the models when assessing the relation of VAT or SAT to lipoprotein number and size or with the addition of both VAT and SAT to the model when assessing the relation of BMI to lipoprotein parameters. To evaluate the impact of insulin resistance on these relationships, HOMA-IR was further added to the models. The associations between VAT and lipoprotein particle number and size were further examined by multivariable models after addition of SAT or of hip circumference to models that included BMI. Similar analyses were performed to evaluate the association of SAT to lipoprotein parameters before and after adjustment for BMI or for BMI and VAT. Analyses were performed for the entire group and then separately for statin-treated and untreated subjects. The relation of A1C to BMI, VAT, and SAT was examined using a general linear model with sex, statin use, and diabetes therapy as fixed variables and age, duration of diabetes, and years of smoking as continuous variables. Additional models were performed after the addition of BMI and BMI plus VAT and SAT. General linear modeling was also used to examine the relation of non-HDL cholesterol to BMI, VAT, and SAT areas with sex, statin use, and diabetes therapy as fixed variables and age, duration of diabetes, years of smoking, and A1C levels as continuous variables. Analyses were performed using the 11.0 PC package of SPSS statistical software (SPSS, Chicago, IL). A $P < 0.01$ was considered significant to adjust for evaluation of multiple lipoprotein parameters (VLDL, LDL, and HDL particle number and size) for their relation to VAT (which was our primary analysis) and other adiposity measures (as secondary analyses).

RESULTS

The baseline characteristics of study subjects are presented in Table 1. The mean age was 61 years. Thirty-eight percent of subjects were women, 55% were on statin therapy, and 65% were current or former smokers. Subjects were on the following diabetes therapies at the time of participation in the study: 15% of subjects were not taking any medications for diabetes, 15% were taking sulfonylureas alone, 29% were taking metformin alone, 31% were taking a combination of metformin and sulfonlyureas, and 10% were on insulin therapy. The average BMI was 32.5 kg/m^2, the mean duration of type 2 diabetes was 92 months, and the mean A1C was 7.4%. Mean HDL cholesterol was 1.2 nmol/l, LDL cholesterol 2.8 nmol/l, and triglyceride 1.8 nmol/l. In age- and sex-adjusted correlations, VAT was positively associated with VLDL particle number, LDL particle number, and VLDL size and negatively associated with LDL size and HDL size (Table 2). BMI and SAT were not associated with particle size or number for any lipoprotein species (Table 2). Waist circumference was negatively associated with LDL and HDL size. A1C was positively associated with VLDL and LDL particle number and negatively associated with LDL size (Table 2).

The results from multivariable regression models are

TABLE 1
Baseline characteristics of study participants

Subjects with type 2 diabetes (n)	382
Age (years)	61 ± 8
BMI (kg/m^2)	32.5 ± 5.1
Waist (cm)	108 ± 13
Hip (cm)	113 ± 12
Sex (%)	
Men	62
Women	38
Statin use (%)	
On statin	55
No statin	45
Smoking (%)	
Current	16
Former	49
Never	35
Duration of type 2 diabetes (months)	92 ± 86
Diabetes therapy (%)	
None	15
Sulfonylurea	15
Metformin	29
Sulfonylurea and metformin	31
Insulin	10
A1C (%)	7.4 ± 0.9
Total cholesterol (nmol/l)	4.7 ± 0.9
LDL cholesterol (nmol/l)	2.8 ± 0.8
HDL cholesterol (nmol/l)	1.2 ± 0.3
Triglyceride (nmol/l)	1.9 ± 1.3
VLDL number (nmol/l)	70.12 ± 49.91
LDL number (nmol/l)	1,440.56 ± 422.33
HDL number (nmol/l)	31.89 ± 6.44
VLDL size (nm)	52.83 ± 10.18
LDL size (nm)	20.52 ± 0.78
HDL size (nm)	8.61 ± 0.38
VAT (cm^3)	132.0 ± 56.8
SAT (cm^3)	196.3 ± 80.2

Data for continuous variables are presented as means ± SD.

TABLE 2
Age- and sex-adjusted Pearson correlation coefficients between log-transformed lipoprotein particle size and number and BMI, waist circumference, VAT, SAT, and A1C

Variable	BMI	Waist	VAT	SAT	A1C
Particle no.					
VLDL	0.11	0.13	0.34*	0.04	0.14†
LDL	0.04	0.08	0.15*	0.002	0.13†
HDL	−0.10	−0.06	−0.04	0.04	−0.05
Size					
VLDL	0.05	0.02	0.25*	−0.06	0.05
LDL	0.07	−0.16*	−0.34*	0.005	−0.17*
HDL	−0.08	−0.16*	−0.30*	−0.02	−0.06

*$P \leq 0.001$; †$P \leq 0.01$.

shown in Table 3. After adjustment for age, sex, diabetes therapy, duration of diabetes, statin use, A1C, and smoking years, VAT was positively associated with VLDL and LDL particle number and VLDL particle size and negatively associated with LDL and HDL size. These associations remained significant after adjustment for BMI. Addition of SAT with BMI to the model did not change the strength of the associations (data not shown). SAT was not associated with lipoprotein particle size or number before or after adjustment for BMI (Table 3) or after adjustment for BMI and VAT (data not shown). BMI was borderline associated with VLDL and HDL particle number, and the borderline association with HDL particle number persisted after adjustment for SAT and VAT (Table 3). Addition of HOMA-IR did not change the associations between VAT and VLDL particle number or size or VAT and LDL or HDL size (Table 4).

It has been suggested that lower-body subcutaneous fat may have beneficial effects on insulin sensitivity and cardiometabolic risk. We therefore added hip circumference, as an index of lower-body subcutaneous fat mass, to the multivariable model for the relationship of VAT to lipoprotein particle number and size. After addition of hip circumference to the multivariable model, we noted a 4–10% increase in regression coefficient for the models examining the relation between VAT and each lipoprotein particle number and size (data not shown).

Because of the potent effect of statins on lipoprotein metabolism, we assessed the relationship between VAT and lipoprotein parameters in statin users and nonusers separately (Table 5). The association between VAT and LDL particle number was only present among statin nonusers, but VAT was strongly and significantly related to VLDL particle number and size and LDL and HDL particle size among statin users (Table 5).

The data in Table 2 show that glycohemoglobin level was significantly associated with VLDL and LDL particle number and LDL size. After adjustment for age, sex, baseline diabetes therapy, duration of diabetes, smoking years, and statin use, A1C level remained positively associated with VLDL particle number and LDL particle number and negatively associated with LDL particle size. These significant associations remained intact after addition of BMI or after addition of BMI, VAT, and SAT to the model (data not shown). In multivariable models, neither BMI nor SAT was a significant predictor of non-HDL cholesterol (not shown). VAT had a borderline significant association with non-HDL cholesterol; $P = 0.02$, $r^2 = 0.15$, 0.03 (0.02–0.04) mmol/l increase for each 10 cm^3 increase in VAT.

DISCUSSION

In this population of middle- and older-aged men and women with type 2 diabetes, higher VAT was strongly associated with changes in lipoprotein particle number and size (1,2). These associations were independent of overall adiposity as measured by BMI and were independent of SAT content. The associations persisted after adjustment for HOMA-IR as a measure of insulin resis-

TABLE 3
Multivariable-adjusted linear regression models for relation of SAT, VAT, or BMI to lipoprotein particle number and size

	Multivariable model*			Multivariable model with SAT or VAT adjusted for BMI or with BMI adjusted for both SAT and VAT		
	r^2	Change in lipoprotein size or number†	*P* value	r^2	Change in lipoprotein size or number†	*P* value
VLDL particle no. (nmol/l)						
SAT	0.10	1.14 (−1.29 to 1.68)	0.50	0.12	−1.09 (−1.67 to 1.40)	0.7
VAT	0.20	4.25 (2.74–6.69)	<0.0001	0.20	4.58 (2.75–7.64)	<0.0001
BMI	0.10	0.47 (0.13–1.66)	0.02	0.20	−0.11 (−0.65 to 0.51)	0.9
LDL particle no. (nmol/l)						
SAT	0.12	1.02 (−1.29 to 1.68)	0.50	0.12	−1.09 (−1.67 to 1.40)	0.7
VAT	0.14	1.29 (1.08–1.53)	0.004	0.14	1.29 (1.06–1.58)	0.01
BMI	0.12	0.13 (−0.12 to 0.21)	0.3	0.15	0.11 (−0.18 to 0.22)	0.7
HDL particle no. nmol/l						
SAT	0.15	1.00 (−1.10 to 1.10)	0.9	0.17	1.07 (−1.04 to 1.19)	0.3
VAT	0.14	−1.06 (−1.20 to 1.061)	0.3	0.15	1.02 (−1.13 to 1.17)	0.8
BMI	0.15	−0.15 (−0.20 to −0.11)	0.02	0.17	−0.17 (−0.27 to −0.11)	0.02
VLDL size (nm)						
SAT	0.14	−1.05 (−1.15 to 1.04)	0.30	0.14	−1.08 (−1.19 to 1.03)	0.2
VAT	0.17	1.24 (1.11–1.38)	<0.0001	0.17	1.32 (1.16–1.49)	<0.0001
BMI	0.13	−0.11 (−0.13 to 0.14)	0.7	0.18	−0.12 (−0.18 to 0.13)	0.4
LDL size (nm)						
SAT	0.21	1.01 (−1.01 to 1.02)	0.8	0.22	1.01 (−1.01 to 1.03)	0.3
VAT	0.29	−1.06 (−1.08 to −1.04)	<0.0001	0.29	−1.07 (−1.10 to −1.05)	<0.0001
BMI	0.22	−0.10 (−0.11 to 0.10)	0.31	0.31	0.10 (−0.11 to 0.11)	0.6
HDL size (nm)						
SAT	0.19	1.00 (−1.02 to 1.02)	0.9	0.21	1.01 (−1.01 to 1.04)	0.3
VAT	0.26	−1.07 (−1.10 to −1.05)	<0.0001	0.26	−1.08 (−1.11 to −1.05)	<0.0001
BMI	0.19	−0.11 (−0.11 to 0.10)	0.1	0.31	−0.10 (−0.11 to 0.11)	0.6

*Multivariable model is adjusted for age, sex, diabetes therapy at baseline, duration of diabetes, years of smoking, statin use, and A1C. †Change in variable for every 10 cm^3 increase in VAT or SAT or every 1 kg/m^2 increase in BMI.

TABLE 4
Multivariable-adjusted linear regression model for relation of VAT to lipoprotein particle number and size before and after adjustment for HOMA-IR

	Multivariable model plus BMI*			Multivariable model plus BMI and HOMA-IR*		
	r^2	Change in lipoprotein size or number†	P value	r^2	Change in lipoprotein size or number†	P value
Particle no. (nmol/l)						
VLDL	0.2	4.56 (2.51–8.28)	<0.0001	0.23	3.94 (2.31–6.75)	<0.0001
LDL	0.14	1.29 (1.06–1.58)	0.01	0.14	1.23 (−1.00 to 1.53)	0.06
Size (nm)						
VLDL	0.17	1.32 (1.16–1.49)	<0.0001	0.21	1.23 (1.08–1.40)	0.002
LDL	0.29	−1.07 (−1.10 to −1.05)	<0.0001	0.31	−1.06 (−1.09 to −1.04)	<0.0001
HDL	0.26	−1.08 (−1.11 to −1.05)	<0.0001	0.29	−1.07 (−1.10 to −1.04)	<0.0001

*Multivariable model is adjusted for age, sex, diabetes therapy, duration of diabetes, years of smoking, statin use, and A1C. †Increase in variable for every 10 cm^3 increase in VAT.

tance for all of the lipoprotein parameters except for LDL particle number. The associations were strongest in subjects who were not on statin therapy but remained significant for VLDL particle number and size and LDL and HDL size in subjects who were treated with statins. We did not observe associations between SAT and lipoprotein particle number or size. We observed a borderline negative association between BMI and HDL particle number, as higher BMI was associated with a decrease in HDL particle number. Our data suggest that in type 2 diabetes, adverse changes in lipoprotein particle number and size are most strongly related to accumulation of visceral fat rather than overall adiposity.

TABLE 5
Multivariable-adjusted linear regression models for relation of VAT to lipoprotein particle number or size after adjustment for BMI for the overall group and separately for statin users and nonusers

	Model r^2*	Change in lipoprotein size or number†	P value
VLDL particle no. (nmol/l)			
Overall	0.20	4.58 (2.75–7.64)	<0.0001
Statin	0.18	3.72 (1.86–7.46)	<0.0001
No statin	0.25	5.87 (2.70–12.7)	<0.0001
LDL particle no. (nmol/l)			
Overall	0.14	1.29 (1.06–1.58)	0.01
Statin	0.09	1.12 (−1.16 to 1.47)	0.38
No statin	0.18	1.49 (1.09–2.04)	0.01
VLDL size (nm)			
Overall	0.17	1.32 (1.16–1.49)	<0.0001
Statin	0.20	1.42 (1.19–1.69)	<0.0001
No statin	0.15	1.22 (1.02–1.48)	0.03
LDL size (nm)			
Overall	0.29	−1.07 (−1.10 to −1.05)	<0.0001
Statin	0.27	−1.06 (−1.10 to −1.03)	<0.0001
No statin	0.29	−1.08 (−1.12 to −1.04)	<0.0001
HDL size (nm)			
Overall	0.26	−1.08 (−1.11 to −1.05)	<0.0001
Statin	0.25	−1.06 (−1.10 to −1.02)	<0.0001
No statin	0.29	−1.10 (−1.15 to −1.06)	<0.0001

*Multivariable model for the overall group is adjusted for age, sex, diabetes therapy at baseline, duration of diabetes, years of smoking, statin use, and A1C. Multivariable model for statin and no statin groups is adjusted for age, sex, diabetes therapy at baseline, duration of diabetes, years of smoking, and A1C. †Increase in variable for every 10 cm^3 increase in VAT.

Whereas the harmful impact of central fat on insulin sensitivity and metabolic disorders is well accepted (15), the individual contribution of VAT and SAT to metabolic risk remains uncertain (15–17). Visceral fat is considered to have greater lipolytic activity compared with subcutaneous fat and has favored access to the liver through the portal vein. Thus, it has been proposed that the high free fatty acid (FFA) flux from visceral fat may reduce hepatic insulin sensitivity, favor hepatic fat accumulation, and thereby promote an atherogenic lipid profile (36). However, a number of studies have suggested that SAT may have as strong or even stronger deleterious impact on insulin sensitivity and metabolic risk than VAT (28–30,37). SAT comprises a larger fat depot than visceral fat (38) and contributes ~75% of the total FFA to the peripheral circulation (39,40). Other studies have suggested a less important role for SAT compared with VAT (20,27,41). In a recent report, surgical removal of SAT in obese subjects did not result in metabolic improvements or beneficial changes in cardiovascular risk factors (42). In our study, SAT was not associated with the changes in lipoprotein particle size or number typically observed with insulin resistance. Unlike most previous studies, however, our study focused exclusively on subjects with type 2 diabetes, a large proportion of whom were obese (20,27–29). The relationship between central fat depots and metabolic risk could be modified in diabetes either by the more severe degree of insulin resistance in type 2 diabetic compared with obese nondiabetic subjects or by the failure of insulin secretion to compensate for the metabolic derangements produced by insulin resistance (43,44). Increasing evidence indicates that adipose tissue, especially VAT, is the source of a number of hormones (45), cytokines, and inflammatory factors (46) that can impact substrate flux and lipid metabolism in distant tissues. It is possible that this secretory pattern is altered by the presence of type 2 diabetes (47). Recently, an association between small LDL particles and plasminogen activator inhibitor-1 in subjects with type 2 diabetes has been shown to be related to VAT (48).

The role of adipose tissue distribution in insulin sensitivity and metabolic risk extends beyond abdominal fat. Increases in hepatic and skeletal muscle fat have also been associated with insulin resistance (30,49). Furthermore, lower body fat has been shown to at least partially

counteract the influence of abdominal fat and protect against insulin resistance (50). Peripheral body fat, mainly stored in subcutaneous thigh and gluteal regions, has lower lipolytic activity compared with central fat and may serve as a metabolic sink by taking up excess circulating FFA and even preventing ectopic fat accumulation (51). Recent data indicate that waist and hip circumference have opposite associations with coronary artery disease; the risk for developing coronary artery disease increased with waist circumference, but the risk was lowered by increasing hip circumference (52). A recent study has shown that subjects with type 2 diabetes had less leg fat mass and greater liver and trunk fat mass compared with similarly obese subjects without type 2 diabetes (30). Interestingly, in our study adjustment for hip circumference in multivariable analyses tended to strengthen the associations between VAT and atherogenic lipoprotein particle number and size parameters, suggesting that higher fat content in the gluteal-femoral area could mitigate the negative impact of visceral fat on lipoprotein metabolism. However, overall changes were small, and we did not perform imaging studies to quantify lower body fat depots.

Studies using NMR technology to analyze subclass lipoprotein profile have demonstrated that progressive insulin resistance is associated with an increase in VLDL size and large VLDL particle concentration, a decrease in LDL size reflecting marked increase in small LDL particles and a reduction in large LDL, an overall increase in the number of LDL particles, and a decrease in HDL size as a result of reduction of large HDL particles and a modest increase in small HDL (1). These alterations in lipoprotein particle number and size are considered to be atherogenic and to predispose to CVD (3–11). In this study, we demonstrate that these unfavorable changes in lipoprotein profile were related to increasing VAT independent of overall adiposity or of SAT, suggesting that VAT has serious negative consequences on lipoprotein metabolism leading to increased risk for CVD in subjects with type 2 diabetes. Statin therapy abolished the relation between VAT and LDL particle number but was not able to abolish the relationship between VAT and VLDL particle number or between VAT and VLDL, LDL, and HDL particle size. These data could indicate that statin therapy only partially addresses lipoprotein-related CVD risk in subjects with type 2 diabetes. Residual excess CVD risk in subjects with diabetes who have been treated with statins has been observed (53) and may be addressed by therapies that impact residual lipoprotein abnormalities. Our data also emphasize that the adverse effects of VAT on lipoprotein parameters are not completely reversed by statin therapy, underlining the importance of interventions that produce weight loss, particularly in the visceral fat depot.

Strengths of our study include inclusion of a large sample of well-characterized subjects with type 2 diabetes, the use of NMR technology for determination of subclass lipoprotein profile, and the use of CT scanning to quantitate VAT and SAT. We were also able to adjust for a number of potential confounders, including smoking history, sex, and statin use. With respect to limitations, our study does not permit firm conclusions regarding causality. In addition, we do not have measures of overall truncal, hepatic, or lower-extremity fat that could have provided additional information on the association between body fat distribution and lipoprotein particle number and size. Our study included only diabetic subjects, and relationships may be different in those without diabetes. In addition, our subjects had BMIs that clustered in the obese range, as is typical for type 2 diabetes. The influence of adipose tissue distribution on lipoprotein parameters could be different in those with lower BMI.

In summary, increasing VAT independent of BMI and SAT was associated with an atherogenic lipoprotein profile in subjects with type 2 diabetes. In contrast, in our study we were unable to show an association between SAT or BMI and lipoprotein parameters. The data suggest that the atherogenic lipoprotein profile associated with type 2 diabetes is related to VAT accumulation. Prospective studies will be needed to provide more information regarding the causal nature of these associations.

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