Relation of Abdominal Fat Depots to Systemic Markers of Inflammation in Type 2 Diabetes

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OBJECTIVE — Both visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) have been linked to systemic inflammation in nondiabetic cohorts. We examined the relationships between VAT and SAT and systemic inflammatory markers in a large well-characterized cohort of subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Three hundred eighty-two subjects with type 2 diabetes in the CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) study cohort underwent abdominal computed tomography to determine SAT and VAT distribution. Fasting blood was obtained for measurement of inflammatory markers. The relationships between inflammatory markers and BMI, SAT, and VAT were examined using regression models adjusted for age, sex, diabetes treatment, duration of diabetes, smoking, statin use, and A1C.

RESULTS — VAT was positively related to CRP, monocyte chemoattractant protein (MCP), intracellular adhesion molecule (ICAM)-1, and plasminogen activator inhibitor type 1 (PAI-1) antigen before adjustment for BMI. After adjustment for BMI, the relationship to CRP was lost but positive associations with MCP ($P < 0.01$), PAI-1 ($P < 0.0001$), ICAM-1 ($P < 0.01$), and vascular cell adhesion molecule ($P = 0.01$) were evident. BMI was positively related to CRP ($P < 0.0001$) and IL-6 ($P < 0.01$) even after adjustment for VAT and SAT. SAT was not related to any inflammatory marker after adjustment for BMI.

CONCLUSIONS — In this large group of subjects with type 2 diabetes, BMI was most strongly associated with CRP and IL-6 levels. SAT was not associated with markers of systemic inflammation. The size of the VAT depot provided information additional to that provided by BMI regarding inflammatory markers that are strongly related to vascular wall remodeling and coagulation. Our findings suggest that adipose tissue distribution remains an important determinant of systemic inflammation in type 2 diabetes.

Obesity, especially of the abdominal type, is associated with a proinflammatory state. The association between obesity and inflammation was first reported by Hotamisligil et al. (1), who demonstrated expression of tumor necrosis factor-α (TNF-α) in adipose tissue, an increase in its expression in obesity, and its ability to induce insulin resistance. Since this report, adipose tissue has been recognized as an important source of a number of hormones and cytokines, including TNF-α, interleukin (IL)-6, and monocyte chemoattractant protein (MCP)-1 (2). While adipokines such as leptin and adiponectin are exclusively produced by adipocytes, inflammatory cytokines can be produced by both adipocytes and adipose tissue macrophages (ATMs) (2). Obesity is associated with an increase in ATM infiltration (3) and activation (4). Epidemiological studies have demonstrated an increase in plasma levels of inflammatory markers such as C-reactive protein (CRP), IL-6, and TNF-α in obesity and a strong association with these levels and risk for type 2 diabetes and cardiovascular disease (2,5). Weight loss in humans has been associated with a reduction in ATM infiltration and levels of systemic inflammatory markers (6). There is also evidence that adipose tissue isolated from specific fat depots, such as visceral fat, may express higher levels of inflammatory markers such as IL-6 (7), MCP-1 (8), and plasminogen activator inhibitor type 1 (PAI-1) (9).

For this report, we examined the association between abdominal fat compartments measured by computed tomography (CT) and markers of systemic inflammation in 382 subjects with type 2 diabetes who participated in the Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) study (10). To our knowledge, this is the largest cohort in which the relationship between adipose tissue distribution (using abdominal CT) and inflammation in subjects with type 2 diabetes has been examined. A recent study of mostly non-Hispanic whites with low prevalence of diabetes and cardiovascular disease showed that both visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) are associated with inflammatory markers, though the association for VAT was stronger (11). In this analysis, we determined whether adipose tissue distribution and specific adipose tissue depots remain important determinants of systemic inflammation in type 2 diabetes.

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

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pioglitazone compared with glimepiride on carotid intima-media thickness in subjects with type 2 diabetes (10). The details of the study have been previously reported (10). Data included in this report were obtained before randomization to treatment groups. 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.

Subjects underwent an abdominal CT scan for determination of VAT, SAT, and total abdominal adipose tissue (TAT). Abdominal adipose tissue content and distribution were quantified by CT scan at the level of L4–L5 vertebrae while the subjects were in supine position with both arms stretched above the head. A single 6-mm slice was taken during suspended respiration after a normal expiration. TAT was measured by delineating the body surface with a receiver operator instrument and then by computing the adipose tissue volume using an attenuation range of −190 to −30 HU. 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 the receiver operator instrument. SAT area was calculated by subtracting VAT from TAT volume. To obtain VAT, SAT, and TAT 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 inflammatory markers and A1C. Inflammatory markers were measured using kits according to the manufacturer's instructions: plasma CRP (Roche Diagnostics, Indianapolis, IN), intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 (R&D Systems, Minneapolis, MN), matrix metalloproteinase (MMP)9 (R&D Systems), and PAI-1 (Trinity Biotech USA, St. Louis, MO). Fibrinogen was measured by direct coagulation analysis (Dade Behring Marburg, Marburg, Germany), human insulin by ELISA (Linco, St. Charles, MO), and A1C by high-performance liquid chromatography (Bio-Rad, Hercules, CA). IL-6 was measured by ELISA (Quantikine HS; R&D Systems).

Statistical methods

Log transformation of the data was performed when it was necessary to achieve homogeneity of variance. Sex differences in inflammatory biomarkers, VAT, SAT, TAT, and BMI were compared by ANCOVA adjusted for age, BMI, baseline diabetes treatment, duration of diabetes, years of smoking, statin use, and A1C.

Age- and sex-adjusted Pearson correlation coefficients were used to assess the relationship between BMI, waist circumference, A1C, SAT, VAT, TAT, and each inflammatory marker. We also performed multivariable regression models adjusted for age, sex, baseline diabetes treatment, duration of diabetes, years of smoking, statin use, and A1C to evaluate the relationship between each inflammatory marker and SAT, VAT, and BMI. SAT, VAT, and BMI were first standardized to mean 0 and SD 1. We calculated regression coefficients quantifying the estimated change in log-transformed biomarker per SD increase in SAT, VAT, or BMI separately and then transformed back to estimate the percent change in each biomarker. The multivariable analyses were repeated with addition of BMI to the models when assessing the relationship between VAT or SAT and inflammatory markers or with the addition of both VAT and SAT to the model when assessing the relationship between BMI and inflammatory markers. The associations between VAT and inflammatory markers 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 associations between SAT and inflammatory markers before and after adjustment for BMI or for BMI and VAT. To further examine the role of smoking, we repeated all of the above analyses by placing smoking as a categorical variable instead of years of smoking as follows: current smokers ($n = 58$), ex-smokers ($n = 186$), and nonsmokers ($n = 127$). To evaluate whether the associations between abdominal fat depots and inflammatory markers were related to the degree of obesity, we repeated the above analyses in two groups based on a median split of BMI. Analyses were performed using the 11.0 PC package of SPSS statistical software (SPSS, Chicago, IL). $P \leq 0.01$ was considered significant in order to adjust for evaluation of multiple inflamma-

Table 1—Baseline characteristics of study participants

Age (years)	61 ± 8
BMI (kg/m^2)	32.5 ± 5.1
Waist circumference (cm)	108 ± 13
Hip circumference (cm)	113 ± 12
Duration of type 2 diabetes (months)	92 ± 86
A1C (%)	7.4 ± 0.9
Smoking	
Current	16
Former	49
Never	35
Diabetes therapy	
None	15
Sulfonylurea	15
Metformin	29
Sulfonylurea and metformin	31
Insulin	10
Statin use	
Statin	55
No statin	45
Sex	
Men	62
Women	38

Data are means ± SD or %. Study participants are subjects with type 2 diabetes ($n = 382$).

tory markers for their relationship to VAT (which was our primary analysis).

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 therapy at the time of participation in the study: 15% were not taking any medications for diabetes, 15% were taking sulfonylureas, 29% were taking metformin, 31% were taking a combination of metformin and sulfonylureas, and 10% were on insulin therapy. The average ± SD BMI was 32.5 ± 5.1 kg/m^2, the mean duration of type 2 diabetes was 92 ± 86 months, and the mean A1C was 7.4 ± 0.9%. The median (interquartile range) CRP level was 2.7 mg/l (1.4–5.5), ICAM-1 was 241 ng/ml (196–294), MCP was 61 pg/ml (43–61), VCAM-1 was 670 mg/dl (537–816), fibrinogen was 322 mg/dl (249–391), MMP9 was 439 ng/ml (305–613), PAI-1 was 29 ng/ml (20–43), and IL-6 was 2.49 pg/ml (1.8–3.8) (data not shown).

Men had a higher amount of VAT than women ($P < 0.0001$), whereas women had a higher amount of SAT than men ($P < 0.0001$) (Table 2). BMI and

Table 2—Sex differences in inflammatory markers, BMI, VAT, SAT, and TAT in type 2 diabetes

	Men	Women	$P*$
CRP (mg/l)	2.3 (1.3–4.3)	3.6 (1.6–9.7)	<0.0001
ICAM-1 (ng/ml)	243 (202–294)	234 (179–301)	0.7
MCP (pg/ml)	62 (44–89)	60 (43–87)	0.8
VCAM-1 (mg/dl)	682 (545–834)	656 (525–807)	0.07
Fibrinogen (mg/dl)	306 (245–375)	357 (276–421)	<0.0001
MMP9 (ng/ml)	451 (318–658)	392 (298–559)	0.4
PAI-1 (ng/ml)	28 (20–43)	30 (21–44)	0.1
IL-6 (pg/ml)	2.4 (1.8–3.6)	2.5 (1.8–4.1)	0.9
BMI (kg/m^2)	31.8 (28.4–35.2)	32.7 (28.6–38.4)	0.2
VAT (cm^3)	137 (105–180)	103 (80–131)	<0.0001
SAT (cm^3)	175 (128–220)	220 (165–276)	<0.0001
TAT (cm^3)	311 (245–395)	328 (249–397)	0.9

Data are medians (interquartile range 25th–75th percentiles). *ANCOVA for comparison between sexes adjusted for age, BMI, diabetes therapy, duration of diabetes, years of smoking, statin use, and A1C.

TAT were similar between men and women. CRP and fibrinogen levels were higher in women than men ($P < 0.0001$) (Table 2).

In age- and sex-adjusted correlations (Table 3), VAT was positively associated with CRP, ICAM-1, MCP, MMP9, and PAI-1. BMI was positively associated with CRP, fibrinogen, PAI-1, and IL-6, whereas SAT was positively associated only with CRP (Table 3). TAT was positively associated with CRP, ICAM-1, and PAI-1. Waist circumference was positively associated with CRP, ICAM-1, MMP9, PAI-1, and IL-6 (Table 3). A1C was not associated with any of the inflammatory markers (Table 3).

The results from multivariable regression models adjusted for age, sex, diabetes treatment, duration of diabetes, A1C, and smoking years are shown in Table 4. The percent change in each inflammatory marker per SD of adiposity measurement is given for significant associations. We also adjusted for statin use, as these drugs have been shown to influence the levels of

circulating inflammatory markers (12). After these adjustments, VAT remained positively associated with CRP, ICAM-1, MCP, and PAI-1 (Table 4). After addition of BMI to the model, the association of VAT with CRP was no longer evident; however, VAT remained associated with ICAM-1, MCP, and PAI-1, and a positive association was observed between VAT and VCAM-1 (Table 4). BMI was strongly and positively associated with CRP and IL-6, and the associations persisted after adjustment for VAT and SAT (Table 4). The relationship between CRP and BMI was stronger in women ($R^2 = 0.32$; $P = 0.001$) than men ($R^2 = 0.17$; $P = 0.02$) even after adjustment for VAT and SAT (data not shown). BMI was also positively associated with fibrinogen and MMP9; however, the significant association was lost after adjustment for VAT and SAT (Table 4). SAT was associated with CRP and IL-6 but not after adjustment for BMI (Table 4). Adjustment for smoking as a categorical variable rather than years of smoking did not alter any of these associ-

ations. Tests for heterogeneity (Caucasian vs. African American) were not significant for any of the associations shown in Table 4.

Even though SAT was not associated with any of the inflammatory markers, we tested whether it altered the association of VAT with these markers. We added SAT to the multivariable model analyzing the relationship between VAT and the inflammatory markers, and this addition did not modify the association between VAT and any of the inflammatory markers (data not shown). It has also been suggested that lower-body SAT may mitigate the adverse influence of VAT on cardiometabolic risk. We therefore added hip circumference, as an index of lower-body subcutaneous fat mass, to the multivariable model for the relationship between VAT and inflammatory markers. The addition of hip circumference to the multivariable model also did not significantly alter the association between VAT and any of the inflammatory markers (data not shown).

As noted above, our results differ from those reported in a large cohort of predominantly nondiabetic and less obese subjects (11). In order to gain insight into whether this difference is related to the presence of diabetes or to more pronounced obesity in our cohort, the associations between adipose tissue depots and inflammatory markers were examined separately in two groups based on a median split of BMI at 31.1 kg/m^2. No independent associations between SAT and any of the inflammatory markers were observed in either BMI category. The positive relationships between VAT and PAI-1, MCP, ICAM-1, and VCAM-1 were present in both BMI groups and were stronger in the lower median split of BMI (data not shown).

CONCLUSIONS — We found that adipose tissue distribution is an important determinant of systemic inflammation in a large, multiethnic population of well-characterized subjects with type 2 diabetes. To our knowledge, this is the largest cohort of subjects with type 2 diabetes who have undergone determination of abdominal fat distribution by imaging for analysis of its relationship to systemic inflammation. VAT was positively associated with a number of inflammatory markers even after adjustment for BMI. BMI, independent of VAT and SAT, was the primary determinant of CRP and IL-6. After adjustment for BMI, SAT was not

Table 3—Age- and sex-adjusted Pearson correlation coefficients between log-transformed inflammatory markers and BMI, waist circumference, TAT, VAT, SAT, and A1C

	BMI	Waist	TAT	VAT	SAT	A1C
CRP	0.34*	0.26*	0.28*	0.18*	0.17*	0.003
ICAM-1	0.12	0.16*	0.17†	0.21*	0.08	−0.02
MCP	0.05	−0.03	0.06	0.16*	−0.01	0.003
VCAM-1	−0.04	0.05	0.02	0.10	−0.04	0.02
Fibrinogen	0.16*	0.13	0.12	0.07	0.08	−0.04
MMP9	0.13	0.18*	0.13	0.17*	−0.04	−0.03
PAI-1	0.14†	0.18*	0.18†	0.29*	0.05	−0.04
IL-6	0.21*	0.19*	0.12	0.07	0.04	0.07

*$P \leq 0.001$; †$P \leq 0.01$.

Table 4—*Multivariable-adjusted linear regression models for relation of SAT, VAT, or BMI to inflammatory markers*

	Multivariable model*			Multivariable model with SAT or VAT adjusted for BMI or with BMI adjusted for both SAT and VAT		
	R^2	P	Log difference ± SE per SD (% change†)	R^2	P	Log difference ± SE per SD (% change†)
CRP (mg/l)						
SAT	0.23	<0.0001	0.148 ± 0.026 (41†)	0.26	0.07	0.063 ± 0.034
VAT	0.16	0.003	0.088 ± 0.029 (22†)	0.24	0.9	0.003 ± 0.031
BMI	0.24	<0.0001	0.159 ± 0.023 (44†)	0.26	0.001	0.132 ± 0.039 (36†)
ICAM-1 (ng/ml)						
SAT	0.09	0.05	0.025 ± 0.013	0.09	0.7	0.007 ± 0.017
VAT	0.09	0.001	0.046 ± 0.013 (11†)	0.09	0.008	0.040 ± 0.015 (10†)
BMI	0.06	0.03	0.025 ± 0.011	0.10	0.5	0.014 ± 0.019
MCP (pg/ml)						
SAT	0.10	0.9	−0.001 ± 0.016	0.10	0.7	−0.008 ± 0.022
VAT	0.13	0.001	0.057 ± 0.017 (14†)	0.11	0.001	0.061 ± 0.019 (15†)
BMI	0.09	0.2	0.017 ± 0.014	0.12	0.6	−0.013 ± 0.024
VCAM-1 (mg/ml)						
SAT	0.07	0.5	−0.007 ± 0.01	0.07	0.8	−0.003 ± 0.013
VAT	0.07	0.3	0.010 ± 0.011	0.09	0.01	0.027 ± 0.011 (6†)
BMI	0.07	0.3	−0.009 ± 0.009	0.09	0.1	−0.021 ± 0.015
Fibrinogen (mg/dl)						
SAT	0.14	0.02	0.018 ± 0.008	0.15	0.5	0.008 ± 0.011
VAT	0.12	0.2	0.011 ± 0.009	0.13	0.8	−0.001 ± 0.01
BMI	0.13	0.003	0.022 ± 0.007 (5†)	0.15	0.2	0.017 ± 0.012
MMP9 (ng/ml)						
SAT	0.14	0.1	0.021 ± 0.013	0.15	0.9	−0.002 ± 0.018
VAT	0.14	0.03	0.033 ± 0.015	0.15	0.2	0.020 ± 0.017
BMI	0.14	0.01	0.031 ± 0.012 (7†)	0.17	0.2	0.027 ± 0.020
PAI-1 (ng/ml)						
SAT	0.12	0.3	0.015 ± 0.016	0.14	0.4	−0.019 ± 0.021
VAT	0.18	<0.0001	0.074 ± 0.017 (19†)	0.17	<0.0001	0.055 ± 0.017 (14†)
BMI	0.13	0.02	0.033 ± 0.014	0.17	0.3	0.023 ± 0.024
IL-6 (pg/ml)						
SAT	0.16	0.001	0.058 ± 0.017 (14†)	0.17	0.3	0.021 ± 0.022
VAT	0.10	0.07	0.025 ± 0.016	0.14	0.8	−0.006 ± 0.02
BMI	0.15	<0.0001	0.069 ± 0.015 (17†)	0.17	0.01	0.062 ± 0.025 (15†)

*Multivariable model is adjusted for age, sex, diabetes therapy, duration of diabetes, years of smoking, statin use, and A1C. †Percent change in inflammatory markers for every 1-SD increase in VAT, SAT, or BMI.

associated with any inflammatory markers. Interestingly, adjusting for SAT (index of central SAT) or hip circumference (index of peripheral SAT) did not reduce the importance of VAT for predicting systemic inflammatory markers. Our findings suggest that both BMI and VAT are correlates of systemic inflammation in obese subjects with type 2 diabetes. Furthermore, VAT provides information additional to BMI for a number of systemic inflammatory markers that are strongly associated with vascular remodeling and coagulation (13–18).

An increase in inflammatory markers has been associated with increased risk for metabolic abnormalities and cardiovascular disease (2,5,19). Expansion of adipose tissue explains these associations,

as it promotes a systemic inflammatory response. Inflammatory molecules such as TNF-α, IL-6, serum amyloid A, and MCP-1 are produced in significant quantity by ATMs and adipocytes (2,5,19). Recently, it has been shown that obesity is associated with increased ATM infiltration (up to 40%) and a change in ATM polarization to a more proinflammatory state (3,4). Both SAT and VAT are known to secrete inflammatory cytokines in vitro and have been implicated in metabolic disorders (7–9). Subcutaneous abdominal fat is divided into superficial and deep layers by a fascial plane, and recent evidence suggests that there maybe metabolic differences between the two components (20). For example, deep but not superficial subcutaneous abdominal

tissue has been associated with peripheral insulin resistance and features of metabolic syndrome (20). We were not able to separate these compartments in the current study.

A recent study from the Framingham cohort has shown that both VAT and SAT are associated with CRP and a number of other inflammatory markers, independent of BMI; however, the associations were stronger for VAT (11). Subjects in the CHICAGO cohort were more obese compared with the Framingham cohort, and all had type 2 diabetes, whereas the prevalence of type 2 diabetes in the Framingham cohort was 10% (11). Therefore, while our data affirm the importance of adipose tissue distribution on inflammatory markers in obese subjects even af-

ter the onset of diabetes, they also suggest that relationships between specific adipose tissue depots and inflammatory markers may be modified by the onset of diabetes. Similar to previous studies, we observed sex differences in CRP and fibrinogen levels with higher levels in women (21). We also found a stronger association between CRP and BMI, independent of VAT and SAT, in women.

In multivariable fully adjusted models, an increase in VAT was strongly associated with an increase in PAI-1 levels independent of BMI. A higher PAI-1 plasma level has been linked to a higher risk of coronary heart disease in subjects with type 2 diabetes (15). Both animal and human studies suggest that PAI-1 expression is higher in VAT than SAT (9,22). Our data support the strong association between VAT and PAI-1 levels, independent of BMI, in type 2 diabetes. MCP-1 is a potent chemotactic factor for monocytes (23) and has been associated with cardiovascular disease and diabetes (16). In the Framingham cohort, MCP-1 was more strongly associated with VAT than with SAT (11). Our findings are similar to the Framingham cohort, as we also observed a strong correlation between VAT and MCP-1 that was independent of BMI. ICAM-1 and VCAM-1 are members of the cellular adhesion molecule family that have been implicated in inflammatory and atherosclerotic processes (13). Elevated levels of both have been reported in obesity (24). In the Framingham cohort, both SAT and VAT were associated with ICAM-1 but neither of these relations persisted after adjustment for BMI (11). In contrast, in our study, VAT was associated with ICAM-1 before and after adjustment for BMI. In contrast to findings in predominantly nondiabetic populations, we found no independent relationships among BMI, VAT or SAT, and fibrinogen or MMP9 in fully adjusted models (11,25).

Although prospective studies will be necessary to determine the causal nature of these associations, our results suggest that in obese subjects with type 2 diabetes, both BMI and VAT are important drivers of systemic inflammation. While BMI is strongly associated with CRP and IL-6 levels, VAT is the primary determinant of ICAM, VCAM, MCP-1, and PAI-1. ICAM and VCAM are found in the vessel wall where their level of expression is related to atherosclerotic plaque remodeling (13,17,18). MCP-1 and PAI-1 are significant markers of cardiovascular dis-

ease risk (14–16). Our findings indicate that adipose tissue distribution remains an important determinant of systemic inflammation in type 2 diabetes. They underscore the importance of managing excess adiposity, including that in the visceral fat depot, for optimally managing cardiovascular risk in subjects with type 2 diabetes.

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