Adipocytokines Attenuate the Association Between Visceral Adiposity and Diabetes in Older Adults

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OBJECTIVE — To examine whether adiponectin is independently associated with diabetes and whether adiponectin and other adipocytokines account for the relationship between fat and diabetes.

RESEARCH DESIGN AND METHODS — A nested case-control study from the Health, Aging, and Body Composition (Health ABC) study. We measured four adipocytokines: adiponectin, interleukin (IL)-6, tumor necrosis factor-α, and plasminogen activator inhibitor 1 (PAI-1). Regional fat area was determined by computed tomography scan. The 519 case subjects had diabetes defined by fasting plasma glucose level ≥126 mg/dl or by use of diabetes medications. The 519 control subjects had normal glucose tolerance and were matched by sex, race, and study site. Sex-specific logistic models were adjusted for age, race, site, total adiposity, smoking, and physical activity.

RESULTS — Higher adiponectin levels were associated with lower risk of diabetes ($P < 0.001$). Visceral fat was the only adiposity measure associated with diabetes after adjusting for BMI (odds ratio 3.0 [2.1–4.3] in women and 1.3 [1.0–1.6] in men, $P < 0.001$ between-sex comparison). Adipocytokines attenuated the association between visceral fat and diabetes for both sexes but more strongly in men (women 2.3 [1.5–3.3], men 1.1 [0.9–1.4]). In men, adiponectin, IL-6, and PAI-1 remained independently associated with diabetes after adjusting for fat depots; in women, adiponectin was the only independently associated adipocytokine. Controlling for insulin, HDL, triglycerides, and blood pressure did not change these results.

CONCLUSIONS — Adiponectin is associated with lower odds of diabetes in older men and women. Whereas several adipocytokines explained the relationship between visceral adiposity and diabetes in men, only adiponectin partially mediated this association among women.

Diabetes Care 27:1375–1380, 2004

Overweight and obesity are well-established risk factors for type 2 diabetes. However, abdominal adiposity is more strongly associated with diabetes than overall obesity measured by BMI (1,2). Visceral adipose tissue (3,4), subcutaneous abdominal fat (4,5), and intermuscular fat (4,6) have all been correlated with metabolic derangements such as insulin resistance, dyslipidemia, and diabetes.

Adipose tissue has recently been discovered to secrete several novel proteins and cytokines, called adipocytokines, which may mediate insulin resistance or modulate the likelihood that obesity results in the development of type 2 diabetes. Increased levels of interleukin-6 (IL-6) (7), leptin (8), plasminogen activator inhibitor 1 (PAI-1) (9), tumor necrosis factor-α (TNF-α) (10), and decreased levels of adiponectin (11) have been associated with insulin resistance or type 2 diabetes. Most of these studies used surrogate measures of adiposity and evaluated the effect of one adipocytokine with diabetes.

We evaluated the cross-sectional association between total body fat and regional fat distribution (visceral, subcutaneous abdominal, and thigh intermuscular) with type 2 diabetes in older adults. We determined whether the relationship between fat and diabetes could be explained by independent relationships with several adipocytokines.

RESEARCH DESIGN AND METHODS

— Participants enrolled in the Health, Aging, and Body Composition (Health ABC) study were well-functioning men and women between 70 and 79 years of age who were recruited at two clinical sites, Pittsburgh, Pennsylvania, and Memphis, Tennessee. To be eligible for the study, participants had to report no difficulty in walking one-quarter mile, climbing 10 steps, or performing basic activities of daily living.

We performed a nested case-control study using stored serum specimens, physical examination measurements, radiographic test results, and questionnaire data gathered at the clinical visit between 1997 and 1998. We identified 519 men and women with diabetes (case subjects) if they were using a hypoglycemic medication or had a fasting plasma glucose level ≥126 mg/dl. We randomly selected 519 participants with normal glucose tolerance (control subjects), defined by a fasting plasma glucose level <110 mg/dl, a 2-h postchallenge glucose level <140 mg/dl, and no self-report of diabetes, who were frequency matched with case subjects by sex, race, and study site. All participants signed an informed consent that

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Received for publication 21 October 2003 and accepted in revised form 19 December 2003.

Abbreviations: CT, computed tomography; Health ABC, Health, Aging, and Body Composition; IL, interleukin; PAI-1, plasminogen activator inhibitor 1; TNF-α; tumor necrosis factor-α.

was approved by the Institutional Review Boards of the two clinical sites.

Fat measurements

Total fat mass was measured by whole-body dual X-ray absorptiometry scan (QDR 4500A; Hologic, Waltham, MA). Arm, leg, trunk, and total body fat were measured by dual X-ray absorptiometry, and total percent body fat was calculated. Additionally, total adiposity was estimated by BMI as body weight (in kilograms) divided by height (in meters squared). Weight was measured on a standard balance beam scale to the nearest 0.1 kg, and height was measured by a stadiometer to the nearest 0.1 cm.

We measured regional adiposity by computed tomography (CT) scans using Somatom Plus 4 (Siemens, Erlangen, Germany), Picker PQ 2000S (Marconi Medical Systems, Cleveland, OH), or a 9800 Advantage scanner (General Electric, Milwaukee, WI) with standardized protocols. Visceral fat and subcutaneous abdominal fat were measured at the L4-L5 level after participants were positioned supine. Fat areas were calculated using ILD software (RSI Systems, Boulder, CO). Visceral fat was manually distinguished from subcutaneous fat using the internal abdominal wall fascial plane. Intermuscular fat area and thigh subcutaneous fat area were measured by CT scan taken at mid-thigh level between the greater trochanter and the intercondyloid fossa. A total of 11 participants were missing total fat mass information, 42 were missing data on total percent fat, 17 were missing data on visceral fat, 24 were missing data on abdominal subcutaneous fat, 16 were missing data on thigh intermuscular fat, and 18 were missing data on thigh subcutaneous fat.

Participants underwent venipuncture at the baseline visit after an overnight fast. Serum samples were frozen at −70°C. Adiponectin and leptin levels were measured in duplicate by radioimmunoassay (Linco Research, St. Charles, MO). The intra-assay coefficient of variation was 1.78–3.59% for adiponectin and 3.7–7.5% for leptin. IL-6 and TNF-α were measured in duplicate by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). The lower limit of detection was <0.10 pg/ml for IL-6 and 0.18 pg/ml for TNF-α; coefficients of variation were 6.3 and 16%, respectively. PAI-1 was measured by a two-site enzyme-linked immunosorbent assay (Collen Laboratory) with a coefficient of variation of 3.47%. All participants had adiponectin values, but a total of 62 individuals were missing data on leptin, 47 were missing data on IL-6, 12 were missing data on PAI-1, and 61 were missing data on TNF-α. The number missing these adipocytokines did not differ by case/control status or sex.

Questionnaire variables gathered included self-identified racial group, age, and sex. Participants reported smoking history (never, former, or current smoker) and alcohol use (number of drinks per week). Physical activity was assessed using self-report of walking and exercise, assigning kilocalories per week to activities.

Seated systolic and diastolic blood pressures were measured by manual sphygmomanometer. Fasting lipoprotein levels (Vitros chemical methodology; Johnson & Johnson, Milpitas, CA) and fasting and 2-h postchallenge plasma glucose by automated glucose oxidase reaction (YSI 2300 Glucose Analyzer; YSI, Yellow Springs, OH) were also measured. Fasting serum insulin was measured by radioimmunoassay (Pharmacia, Uppsala, Sweden) in 97% of the control subjects but only 54% of the case subjects.

Stastistical analysis

Baseline characteristics of case and control subjects were compared by χ^2, Student's *t* test, or Kruskall-Wallis test as appropriate. We performed log transformation for all adipocytokine measurements to normalize their distribution. Pearson correlation coefficients between adiposity measures and adipocytokines were performed. We used multivariate logistic regression models to assess the association with each fat depot and diabetes, adjusting for age, smoking status, and physical activity. We also examined higher-order interactions between the three covariates used for matching case and control subjects: sex, race, and study site. None of these interactions were statistically significant ($P < 0.10$). Interactions between race and fat measures, race and adipocytokines, and total and regional adiposity measures were also not statistically significant. We performed sex-specific models and combined measures of total and regional adiposity, and to allow comparisons of associations, all measures of adiposity were expressed as odds units per SD. We restricted our final model and all mediation analyses to subjects who were not missing adiposity or adipocytokine measurements (375 women and 529 men). These analyses were performed using STATA software (version 6.0; Stata, College Station, TX).

We evaluated the effects of adipocytokines as potential explanatory variables in the relationship between adiposity and diabetes. We built sequential models adjusting for each adipocytokine alone and then with multiple adipocytokines together. We also examined variables associated with the metabolic syndrome as potential explanatory variables. Models including fasting insulin were limited by missing data among 46% of those with diabetes, primarily participants who were using insulin therapy.

RESULTS

— Participants with diabetes were more likely to have elevated systolic blood pressure and triglycerides and less likely to be active (Table 1). Each measure of adiposity, except thigh subcutaneous fat and total percent fat mass, was greater among women with diabetes than in the nondiabetic control subjects (Table 2). Women had higher total fat mass, abdominal subcutaneous fat, and thigh subcutaneous fat than men, regardless of diabetes status. Women with diabetes had similarly elevated abdominal visceral fat area compared with diabetic men (166 vs. 178 cm^2, $P = 0.08$), but nondiabetic women had significantly lower visceral fat area compared with nondiabetic men (110 vs. 142 cm^2, $P < 0.001$).

The cases with diabetes had higher median IL-6, leptin, PAI-1, and TNF-α than the control subjects, whereas adiponectin was significantly lower in the cases (Table 2). Among both the case and control subjects, men and women had a similar range of results for most adipocytokines. Leptin was significantly higher among women than among men, regardless of diabetes status.

As expected, total fat mass and BMI were closely correlated measures of total adiposity ($r = 0.89$, $P < 0.001$); total fat mass was also highly correlated with abdominal subcutaneous fat area ($r = 0.85$, $P < 0.001$). All other correlations between adiposity measures ranged between 0.05 and 0.79. Adipocytokines were not highly correlated; the most notable correlations were between leptin and PAI-1 ($r = 0.23$, $P < 0.001$), TNF-α

Table 1—*Characteristics of the study population

	Diabetes (case subjects)	Normal glucose metabolism (control subjects)	*P* value
n	519	519	
Age (years)	73.7 ± 2.9	73.5 ± 2.9	0.31
Female sex	221 (42.6)	221 (42.6)	
Black race	295 (56.8)	295 (56.8)	
Tobacco use			
Never	213 (41.2)	219 (42.4)	0.07
Past	253 (48.9)	226 (43.7)	
Current smoker	51 (9.9)	72 (13.9)	
Alcohol use			
None	409 (79.0)	380 (73.6)	0.12
Some (1–7 drinks/week)	79 (15.3)	95 (18.4)	
Heavy (>5/day or 8/week)	30 (5.8)	41 (7.9)	
Physical activity, kcal/week			
<500	317 (61.1)	267 (51.4)	0.007
500–1,500	112 (21.6)	142 (27.4)	
>1,500	90 (17.3)	110 (21.2)	
Systolic blood pressure (mmHg)	138.5 ± 21.8	135.6 ± 21.2	0.03
Diastolic blood pressure (mmHg)	70.2 ± 11.6	72.8 ± 11.7	<0.001
Fasting glucose (mmol/l)	8.8 ± 3.1	5.0 ± 0.4	<0.001
2-h glucose tolerance test (mmol/l)	15.4 ± 4.7	5.8 ± 1.1	<0.001
Fasting insulin (IU/ml)†‡	9.3 (6.2–14.7)	6.5 (4.7–9.6)	<0.001
Total cholesterol (mmol/l)	5.1 ± 1.1	5.2 ± 1.0	0.62
LDL cholesterol (mmol/l)	3.1 ± 0.9	3.1 ± 0.9	0.29
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.4 ± 0.5	<0.001
Triglycerides (mmol/l)†	1.5 (1.1–2.2)	1.2 (0.9–1.5)	<0.001

Data are *n* (%) or means ± SD. *Case subjects are defined by fasting glucose ≥7.0 mmol/l or use of a diabetes medication; control subjects had fasting glucose <6.1 mmol/l and 2-h postchallenge glucose <7.8 mmol/l and were matched to cases by sex, race, and study site; †median (25–75%); ‡missing data on 238 (45.6%) case subjects and 15 (2.9%) control subjects.

and PAI-1 ($r = 0.22$, $P < 0.001$), and TNF-α and IL-6 ($r = 0.21$, $P < 0.001$).

We evaluated the relationships between each fat depot and diabetes separately for men and women, adjusting for race, site, age, smoking, and physical activity. With the exception of thigh subcutaneous fat, increasing levels of each fat depot were associated with increased

Table 2—*Distribution of fat measures and adipocytokines for women and men in the Health ABC study*

	Women			Men		
	Diabetes (case subjects)	No diabetes (control subjects)	*P* value	Diabetes (case subjects)	No diabetes (control subjects)	*P* value
n	221	221		298	298	
BMI (kg/m^2)	30.8 ± 5.7	27.5 ± 5.8	<0.001	28.5 ± 4.1	26.7 ± 3.9	<0.001
Waist circumference (cm)	105.5 ± 13.2	97.3 ± 14.1	<0.001	104.3 ± 12.5	98.9 ± 11.9	<0.001
Total fat mass (kg)	32.2 ± 9.6	28.3 ± 9.8	<0.001	25.1 ± 7.5	22.4 ± 7.1	<0.001
Total percent fat mass (%)	40.2 ± 5.6	39.1 ± 6.4	0.08	28.8 ± 5.1	27.5 ± 5.3	0.003
Abdominal subcutaneous fat area (cm^2)	387.1 ± 128.4	345.2 ± 137.7	0.001	248.9 ± 93.1	224.5 ± 92.4	0.001
Abdominal visceral fat area (cm^2)	165.9 ± 66.5	109.8 ± 47.8	<0.001	177.7 ± 80.7	141.7 ± 69.1	<0.001
Thigh intermuscular fat area (cm^2)	13.3 ± 6.8	10.7 ± 6.7	<0.001	12.1 ± 8.9	9.5 ± 6.1	<0.001
Thigh subcutaneous fat area (cm^2)	112.4 ± 53.0	111.1 ± 50.0	0.79	47.1 ± 20.5	48.9 ± 21.3	0.30
Adipocytokines*						
Adiponectin (μg/ml)	7 (5–11)	11 (7–15)	<0.001	6 (4–8)	8 (5–12)	<0.001
Leptin (ng/ml)	20.4 (11.8–29.6)	17.0 (10.4–27.2)	0.03	7.5 (4.6–12.3)	5.5 (3.3–9.4)	<0.001
IL-6 (pg/ml)	2.3 (1.6–3.6)	1.6 (1.1–2.4)	<0.001	2.2 (1.6–3.2)	1.7 (1.3–2.5)	<0.001
PAI-1 (ng/ml)	33 (18–53)	20 (12–35)	<0.001	26 (16–45.7)	17 (10–28)	<0.001
TNF-α (pg/ml)	3.4 (2.6–4.5)	2.7 (2.1–3.9)	<0.001	3.6 (2.7–4.7)	3.1 (2.4–3.8)	<0.001

Data are *n* (%) or means ± SD. *Median (25–75%).

Table 3—*Multivariate models for diabetes with and without variables associated with the metabolic syndrome

Variable	Women	Men
Model 1		
Visceral fat (per SD cm^2)	2.26 (1.56–3.29)	1.10 (0.86–1.41)
BMI (per SD kg/m^2)	1.00 (0.77–1.29)	1.33 (0.97–1.82)
Adiponectin (μg/ml)	0.54 (0.35–0.82)	0.64 (0.46–0.87)
IL-6 (pg/ml)	1.36 (0.92–2.00)	1.64 (1.15–2.34)
PAI-1 (ng/ml)	1.13 (0.80–1.59)	1.73 (1.30–2.32)
TNF-α (pg/ml)	1.38 (0.77–2.47)	2.09 (1.22–3.59)
Model 2 (after adjustment for HDL, triglycerides, and systolic and diastolic blood pressure)		
Visceral fat (per SD cm^2)	2.32 (1.57–3.43)	1.08 (0.83–1.39)
BMI (per SD kg/m^2)	0.99 (0.76–1.29)	1.38 (0.99–1.91)
Adiponectin (μg/ml)	0.61 (0.38–0.98)	0.62 (0.43–0.87)
IL-6 (pg/ml)	1.31 (0.88–1.95)	1.65 (1.14–2.38)
PAI-1 (ng/ml)	1.12 (0.79–1.60)	1.59 (1.17–2.18)
TNF-α (pg/ml)	1.32 (0.70–2.50)	1.67 (0.92–3.04)

Data are OR (95% CI). *Both models are adjusted for race, study site, age, smoking, and physical activity; all adipocytokine measures have been log transformed.

odds of diabetes for both sexes. Only the effect of visceral adiposity with diabetes differed significantly by sex (odds ratio [OR] 3.5 in women versus 1.7 men, $P < 0.001$ for interaction between sexes). Therefore, we evaluated the effect of adipocytokines on the association between visceral fat and diabetes separately for men and women.

We combined a measure of total adiposity and all significant measures of regional adiposity in models that were adjusted for race, site, age, smoking, and physical activity. In both men and women, visceral fat was the only regional adiposity measure significantly associated with diabetes. BMI was the total adiposity measure that was best associated with diabetes. In men, BMI was independently associated with diabetes (OR 1.48 per SD, 95% CI 1.10–1.99; $P = 0.009$) after controlling for visceral fat mass (1.31, 1.04–1.65; $P = 0.02$). However, among women the association between BMI and diabetes was completely attenuated by visceral adiposity (BMI: OR 1.03 per SD, 95% CI 0.80–1.32, $P = 0.83$; visceral fat: OR 3.01 per SD, 95% CI 2.10–4.31, $P < 0.001$).

We evaluated the unadjusted association between each adipocytokine and visceral adiposity separately for each sex. In women, visceral adiposity was significantly associated with each adipocytokine ($r = 0.27$–0.33, $P < 0.001$ for each). Similarly, most adipocytokines were correlated with visceral fat in men, but IL-6 was not significantly correlated ($r = 0.06$, $P = 0.20$).

We evaluated the independent relationship with each adipocytokine and diabetes using these adjusted models of visceral adiposity. Leptin was the only adipocytokine that was not independently associated with diabetes in both men and women. In women, only adiponectin remained significantly associated with diabetes (OR 0.54 per SD, 95% CI 0.35–0.82; $P = 0.004$) even after adjustment for three additional adipocytokines (IL-6, PAI-1, and TNF-α) (Table 3). The subsequent addition of variables associated with the metabolic syndrome (HDL, triglycerides, and systolic and diastolic blood pressure) slightly attenuated the relationship of adiponectin with diabetes (0.61, 0.38–0.98; $P = 0.04$). In men, three adipocytokines (adiponectin [0.62, 0.43–0.87; $P = 0.006$], IL-6 [1.65, 1.14–2.38; $P = 0.008$], and PAI-1 [1.59, 1.17–2.18; $P = 0.003$]) remained independently associated with diabetes even after adjustment for lipids and blood pressure. In exploratory analyses, insulin was not independently associated with diabetes in either men or women and did not alter the association of visceral fat with diabetes.

Figure 1 shows the effect of sequential adjustment for four adipocytokines and the variables associated with the metabolic syndrome on the association between visceral fat and diabetes for men and women. In women, adjustment for all adipocytokines, lipids, and blood pressure decreased the association of visceral fat and diabetes by approximately one-quarter (OR 3.0–2.3). However, visceral fat remained strongly associated with increased odds of diabetes in women (OR 2.32 per SD, 95% CI 1.57–3.43). In contrast, for men, just the addition of adiponectin or PAI-1 alone completely attenuated the relationship between visceral fat and diabetes.

CONCLUSIONS — In our cohort of well-functioning older adults, visceral adiposity was the fat measure most closely associated with presence of diabetes in both men and women. Increasing levels of visceral fat were associated with approximately threefold increased risk of diabetes in women and a modest 30% increased risk in men. Adiponectin level was associated with decreased odds of diabetes in both men and women. Adiponectin partially explained the association between visceral adiposity and diabetes; addition of adiponectin or PAI-1 alone completely explained the association between visceral adiposity and diabetes in men. In contrast, among women, whereas adiponectin and other adipocytokines partially mediated this association, visceral fat remained associated with a twofold increased risk of diabetes.

Abdominal or central fat distribution was first formally recognized to be related to diabetes in 1947 by Vague (12). Vague's anthropometric observations have been confirmed by numerous epidemiologic studies (13,14). Detailed studies of abdominal fat compartments with CT or magnetic resonance imaging suggest that the visceral fat depot component of central fat may be more closely associated with adverse metabolic outcomes (15,16). Our study confirmed the strong association between visceral fat and diabetes in older adults but found a stronger association with visceral fat and diabetes among women than men, which has not been reported in prior studies. This may be due to a significantly lower visceral fat area in nondiabetic women compared with nondiabetic men and a similar visceral fat area for both diabetic men and women. Other explanations may be that visceral fat has a stronger impact on adverse metabolic complications in women than in men or that men with higher levels of visceral adiposity have already died be-

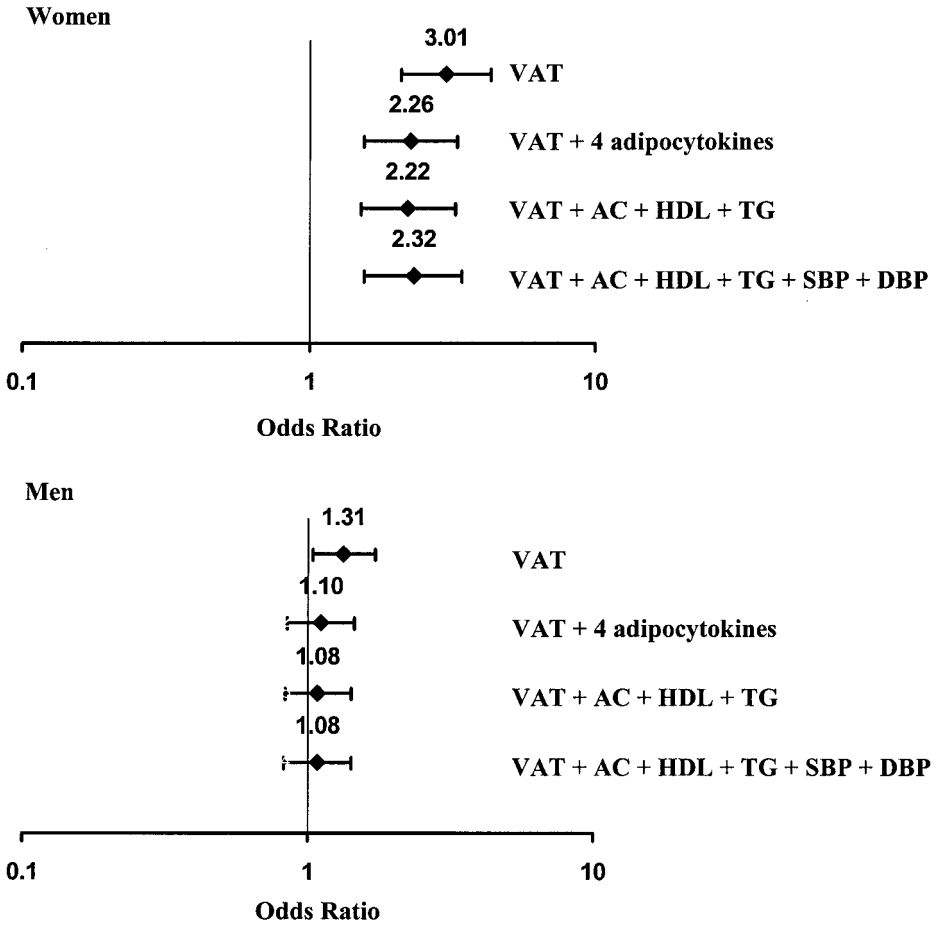

Figure 1—*Adjusted ORs and 95% CIs for the association between visceral fat [per SD cm^2] and diabetes with serial adjustment for explanatory variables for each sex separately. Each model is adjusted for race, site, age, smoking, physical activity, and BMI. The numbers represent the OR estimate for each model. AC, adipocytokines (adiponectin, IL-6, PAI-1, and TNF-α); DBP, diastolic blood pressure; SBP, systolic blood pressure; TG, triglycerides; VAT, visceral adipose tissue.*

cause of its complications or were otherwise ineligible for participation in the Health ABC study.

The discovery of leptin in 1994 revolutionized the view of adipose tissue as a secretory organ (17). Since then, adipose tissue has been recognized to produce several other cytokines and proteins including, among others, adiponectin, IL-6, PAI-1, and TNF-α (18). Visceral fat secretes relatively higher amounts of PAI-1 (19) and TNF-α (20) than subcutaneous fat, whereas correlations for adiponectin and IL-6 with abdominal fat depots are inconsistent. In a prior cross-sectional study from the Health ABC study, participants with diabetes and impaired glucose regulation (either impaired fasting glucose or impaired glucose tolerance) had increased odds of elevated C-reactive protein, IL-6, and TNF-α in separate models after controlling for visceral fat, total adiposity, and other confounding factors (21).

We are aware of two prior studies that have evaluated the effect of more than one adipocytokine simultaneously with differing results. In the EPIC-Potsdam Study, investigators found that a combined elevation of IL-1β and IL-6 independently increased the risk of type 2 diabetes (22), and in an analysis of Pima Indians, researchers found that no adipocytokine predicted diabetes (23). Because the adipocytokines we evaluated were only modestly correlated with each other, it is possible that these proteins act in distinct pathways that link visceral adiposity to type 2 diabetes. We found that in men, adiponectin, IL-6, and PAI-1 were independently associated with type 2 diabetes, even after adjustment for dyslipidemia, blood pressure, and fasting insulin. The associations in women were quite different. Adiponectin was the only adipocytokine found to be independently associated with diabetes and remained significantly associated after adjustment for lipids and blood pressure. This sexual dimorphism for the adipocytokines is unclear. Because most of the association between visceral fat and diabetes in women remained unexplained in our study, it is possible that there are other novel factors that may differentially influence diabetes risk between sexes.

We studied a large and well-defined population of men and women with and without diabetes in our study as well as state-of-the-art radiographic measures of regional fat distribution and total fat mass. However, the Health ABC study enrolled only white and black, older, well-functioning adults and, therefore, these results may not generalize to younger adults or those of other ethnic minority groups. Moreover, because this study was cross-sectional in design, we are unable to determine whether visceral adiposity or the associated adipocytokines caused diabetes. We examined many associations in this study, which increases the risk that some of the associations we observed are chance findings. Therefore, our results need confirmation in other studies.

Visceral adiposity was the fat depot most closely associated with diabetes for both older men and women, although the

relationship was much stronger among women. Our findings suggest that several adipocytokines may act by independent mechanisms to explain the risk of visceral adiposity with diabetes. Other fat-derived proteins, lifestyle, or genetic factors may mediate the greater risk of visceral adiposity and diabetes in women.

Acknowledgments— This study was supported by National Institutes of Health Grants 5-K12-AR47659 and P30-AG15272 (to A.M.K.). The Health ABC study was funded by National Institute on Aging contracts N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106.

We thank Dr. Eric Vittinghoff for his statistical expertise and help with testing the mediation analyses.

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