Visceral Adiposity, Not Abdominal Subcutaneous Fat Area, Is Associated With an Increase in Future Insulin Resistance in Japanese Americans

Tomoshige Hayashi,[1,2] Edward J. Boyko,[1,3] Marguerite J. McNeely,[3] Donna L. Leonetti,[4] Steven E. Kahn,[1,3] and Wilfred Y. Fujimoto[3]

OBJECTIVE—Visceral adiposity is generally considered to play a key role in the metabolic syndrome. We sought to determine whether greater visceral adiposity directly measured by computed tomography (CT) is associated with increased future insulin resistance independent of other adipose depots.

RESEARCH DESIGN AND METHODS—We followed 306 nondiabetic Japanese Americans over 10–11 years. Baseline variables included BMI; waist circumference; and abdominal, thoracic, and thigh fat areas measured by CT. Total fat area was estimated by the sum of all of these fat areas. Visceral adiposity was measured as intra-abdominal fat area at the umbilicus level. Total subcutaneous fat area was defined as total fat area minus intra-abdominal fat area. Insulin resistance was evaluated by homeostasis model assessment for insulin resistance (HOMA-IR), fasting plasma insulin level, Matsuda index, and area under the oral glucose tolerance test curve (AUC) of insulin.

RESULTS—Both baseline intra-abdominal fat area ($P = 0.002$) and HOMA-IR ($P < 0.001$) were independently associated with increased HOMA-IR at 10–11 years in a multiple linear regression model after adjustment for abdominal subcutaneous fat area, age, sex, 2-h plasma glucose level, and incremental insulin response. Intra-abdominal fat area remained a significant predictor of increased HOMA-IR at 10–11 years even after adjustment for total subcutaneous fat area, total fat area, BMI, or waist circumference, but no other measure of CT-measured regional or total adiposity was significantly related with HOMA-IR at 10–11 years in models that contained intra-abdominal fat area. Similar results were obtained for predicting future fasting plasma insulin level, Matsuda index, and AUC of insulin.

CONCLUSIONS—Greater visceral adiposity is associated with an increase in future insulin resistance. ***Diabetes*** **57:1269–1275, 2008**

From the [1]Epidemiologic Research and Information Center, Veterans Affairs Puget Sound Health Care System; the [2]Department of Preventive Medicine and Environmental Health, Graduate School of Medicine, Osaka City University, Osaka, Japan; the [3]Department of Medicine, University of Washington, Seattle, Washington; and the [4]Department of Anthropology, University of Washington, Seattle, Washington.

Corresponding author: Edward J. Boyko, MD, MPH, Veterans Affairs Puget Sound Health Care System (S-152E), 1660 S. Columbian Way, Seattle, WA 98108. E-mail: eboyko@u.washington.edu.

Received for publication 27 September 2007 and accepted in revised form 15 February 2008.

Published ahead of print at http://diabetes.diabetesjournals.org on 25 February 2008. DOI: 10.2337/db07-1378.

AUC, area under the oral glucose tolerance test curve; CT, computed tomography; HOMA-IR, homeostasis model assessment for insulin resistance.

See accompanying commentary, p. 1153.

Although the pathogenesis of the metabolic syndrome and each of its components is complex and not fully understood, both insulin resistance and central adipose tissue appear to be important. Moreover, central obesity has been reported to correlate strongly with insulin resistance (1–7). However, excess central obesity can accumulate either intraperitoneally or subcutaneously, and this has led to a debate whether visceral or abdominal subcutaneous fat is more strongly associated with insulin resistance (1–7). Some studies have reported that excess visceral fat is more strongly associated with insulin resistance than any other adipose tissue compartment (1–5). Others have reported that excess abdominal subcutaneous fat is more strongly associated with insulin resistance than visceral fat (6,7). Because these studies were all cross-sectional, conclusions about temporal sequence and cause and effect relationships cannot be made.

Although the glucose clamp is considered to be the "gold standard" test for examining insulin resistance, practical considerations limit its use in large-scale epidemiologic research. The homeostasis model assessment for insulin resistance (HOMA-IR) was developed to serve as a surrogate measure of insulin resistance that only requires assessment of basal glucose and insulin concentrations (8), and it, along with fasting plasma insulin, has frequently been used in epidemiological studies to assess insulin sensitivity (9). Because fasting plasma insulin and HOMA-IR reflect mainly hepatic insulin resistance in the basal state, other surrogate measures have been developed to assess whole-body insulin sensitivity, such as the Matsuda index derived from the oral glucose tolerance test. This measure has been reported to be highly correlated with the rate of whole-body insulin disposal during the euglycemic insulin clamp (10).

The purpose of this study was to determine whether greater visceral adiposity directly measured by computed tomography (CT) was associated independent of other adipose depots, with a future increase in insulin resistance as assessed by multiple measures, including HOMA-IR, fasting plasma insulin, the Matsuda index, and the insulin area under the oral glucose tolerance test curve (AUC) (10).

RESEARCH DESIGN AND METHODS

The study population consisted of second- and third-generation (mean age 50.3 years) Japanese Americans enrolled in the Japanese American Community Diabetes Study who did not have type 2 diabetes at entry or during the 10- to 11-year follow-up. Details about selection and recruitment have been described previously (11,12). Subjects were chosen from volunteers through

community-wide recruitment and were representative of Japanese-American residents of King County, WA, in age distribution, residential distribution, and parental immigration pattern. A comprehensive mailing list and telephone directory that included almost 95% of the Japanese-American population of King County, WA, was used. All participants were of 100% Japanese ancestry. Subjects returned for follow-up examinations 5–6 and 10–11 years after a baseline evaluation.

For the current analysis, eligible subjects had a fasting plasma glucose <7.0 mmol/l and 2-h plasma glucose after a 75-g oral glucose tolerance test <11.1 mmol/l. These subjects were not taking oral hypoglycemic medications or insulin at baseline or at the 5- to 6-year and 10- to 11-year examinations. We excluded 238 of the 658 subjects in the original cohort because they did not meet the above criteria. We excluded an additional 93 people because of death, loss to follow-up, or withdrawal from the study. Another 21 individuals who completed follow-up but had missing covariate information were also excluded. The analytic cohort consisted of 306 people. The follow-up rate in the present study was 78% (327 of 420) at the 10- to 11-year examination.

Data collection. All evaluations were performed at the General Clinical Research Center, University of Washington. The protocol for this research was approved by the Human Subjects Review Committee at the University of Washington, and signed informed consent was obtained from all participants. All subjects were classified as having normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes based on a 75-g oral glucose tolerance test after a 10-h fast interpreted using the American Diabetes Association 1997 criteria with plasma collected at 0 min and at 30, 60, and 120 min after the glucose load (13). Plasma glucose was assayed by an automated glucose oxidase method. Fasting plasma insulin was measured by radioimmunoassay as reported previously (14). The proportion of insulin measured that was proinsulin was in the range of 10–15%. Insulin sensitivity was estimated by using fasting plasma insulin, HOMA-IR calculated as [fasting glucose (mmol/l) × fasting insulin (μU/ml)]/22.5, and Matsuda index as {10,000/square root of [fasting glucose (mg/dl) × fasting insulin (μU/ml) × [mean glucose (mg/dl) × mean insulin (mg/dl) during oral glucose tolerance test]}, and AUC for insulin (8,10). A modified Matsuda score was calculated because of the absence of the 90-min post–glucose load value in our study. AUC for insulin was calculated using the trapezoidal rule. Increasing values of the insulin resistance measures indicate greater resistance, except for the Matsuda index, where the opposite is true. To assess insulin release, we used the incremental insulin response [(30 min insulin − fasting insulin)/30 min glucose], which correlates well with direct measures of stimulated insulin secretion (15).

BMI was calculated as the weight in kilograms divided by the square of height in meters. Single CT scans were obtained of the thorax, abdomen, and right thigh to measure fat areas (cm^2) as described previously (16). In addition to subcutaneous fat at each of these sites, visceral adiposity was measured as intra-abdominal fat area at the umbilicus level. This latter measurement was reported to have a high correlation with directly ascertained total visceral fat volume by CT or magnetic resonance imaging (17,18). Total fat area was calculated as the sum of intra-abdominal fat area, subcutaneous thorax and subcutaneous abdominal fat areas, and twice the right thigh subcutaneous fat area. In research that we have previously conducted, total fat area correlates highly with fat mass, as measured by hydrodensitometry among Japanese Americans (r = 0.89–0.94) (19). Total subcutaneous fat area was defined as total fat area minus intra-abdominal fat area. Waist circumference was measured at the level of the umbilicus to the nearest tenth centimeter.

Statistical analysis. Pearson correlation coefficients were calculated for comparisons between HOMA-IR, fasting plasma insulin level, Matsuda index, or AUC of insulin at 10–11 years follow-up and measures of body fat or metabolic characteristics at baseline. Multiple linear regression analysis was used to model a future insulin resistance measure as a function of other variables, while adjusting for the baseline value of the same insulin resistance measure. To assess whether the correlation between baseline measures of regional or total adiposity and future insulin resistance measures varied significantly by sex, first-order interactions between these variables and sex were inserted into a regression model that contained the interaction term and both covariates as main effects. Analysis of residuals was performed to examine model fit and adherence to regression assumptions. The dependent variables in regression models were log-transformed to satisfy the assumption of normality of residuals and to stabilize variance of residuals. Multicollinearity was assessed using the variance inflation factor (20). A variance inflation factor >10 is regarded as indicating serious multicollinearity, and values >4.0 may be a cause for concern (20). All P values are two-tailed. Statistical analyses were performed using Stata SE, version 10.0 (Stata, College Station, TX).

TABLE 1
Characteristics of study subjects at baseline

n	306
Age (years)	48 (39–62)
Female sex (%)	48
Metabolic variables	
Fasting plasma insulin (pmol/l)	66 (54–84)
Fasting plasma glucose (mmol/l)	5.00 (4.72–5.33)
Proportions of subjects with NGT and NFG, IFG only, IGT, and type 2 diabetes	
NGT and NFG (%)	70.9
IFG only (%)	2.0
IGT (%)	27.1
HOMA-IR	2.50 (1.86–3.32)
AUC insulin ($\times 10^3$ pmol/l × min)	46.2 (34.9–67.1)
Matsuda index	11.0 (8.2–14.8)
2-h plasma glucose (mmol/l)	6.83 (5.88–7.88)
Incremental insulin response	40.3 (28.3–61.2)
Adipose variables	
Intra-abdominal fat area (cm^2)	66.7 (34.4–97.8)
Abdomen subcutaneous fat area (cm^2)	138.3 (101.0–192.2)
Total subcutaneous fat area (cm^2)	348.3 (268.3–460.2)
Total fat area (cm^2)	423.1 (324.4–543.1)
Waist circumference (cm)	84.6 (79.3–90.1)
BMI (kg/m^2)	23.4 (21.5–25.7)

Data are medians (interquartile range) or %. Impaired glucose tolerance (IGT): fasting plasma glucose (FPG) level <7.0 mmol/l and 2-h glucose ≥7.7 and <11.1 mmol/l. Impaired fasting glucose (IFG) only: FPG level ≥6.1 mmol/l and <7.0 mmol/l and 2-h glucose <7.7 mmol/l. Normal glucose tolerance (NGT) and normal fasting glucose (NFG) only: FPG level <6.1 mmol/l and 2-h glucose <7.7 mmol/l. AUC denotes area under the curve during the oral glucose tolerance test.

RESULTS

Baseline characteristics of the study subjects are shown in Table 1. Study subjects on average were not obese, with a median BMI of 23.4 kg/m^2, but 32.4% met the obesity criterion of the Japan Society for the Study of Obesity (BMI ≥25.0 kg/m^2), while only 4.2% met the non-Asian criterion (BMI >30 kg/m^2) (21).

Correlation coefficients between HOMA-IR or fasting plasma insulin level, Matsuda index, or AUC for insulin at 10–11 years follow-up and measures of body fat or metabolic characteristics at baseline are shown in Table 2. All measures of regional or total adiposity at baseline were significantly correlated with future HOMA-IR, fasting plasma insulin level, Matsuda index, or AUC of insulin at 10–11 years follow-up in the expected direction (negative for Matsuda index and positive otherwise).

A number of regression models were tested to assess the associations between body fat distribution and future HOMA-IR (Table 3). Intra-abdominal fat area at baseline was associated with an increased future HOMA-IR after adjusting for age, sex, HOMA-IR, incremental insulin response, 2-h plasma glucose, and abdominal subcutaneous fat area at baseline (model 1 of Table 3). Models 2–5 of Table 3 were identical to model 1, with the exception that a different adiposity variable was substituted for abdominal subcutaneous fat area. The association between baseline intra-abdominal fat area and future HOMA-IR persisted (models 2–5 of Table 3). None of the other measures of regional or total adiposity emerged as significantly related to increased future HOMA-IR (models 1–5 of Table 3). Baseline HOMA-IR was also associated with

TABLE 2
Correlation coefficients between insulin resistance measures at the 10- to 11-year follow-up and measures of body fat or metabolic characteristics at baseline

	10-year HOMA-IR	10-year fasting plasma insulin level	10-year Matsuda index	10-year AUC insulin
Age	−0.009 (0.869)	−0.067 (0.239)	−0.113 (0.048)	0.091(0.113)
Metabolic variables at baseline				
Fasting plasma insulin	0.501 (<0.001)	0.507 (<0.001)	−0.414 (<0.001)	0.426 (<0.001)
Fasting plasma glucose	0.287 (<0.001)	0.197 (<0.001)	−0.333 (<0.001)	0.233 (<0.001)
HOMA-IR	0.529 (<0.001)	0.517 (<0.001)	−0.440 (<0.001)	0.445 (<0.001)
AUC insulin ($\times 10^3$ pmol/l $\times$ min)	0.347 (<0.001)	0.349 (<0.001)	−0.340 (<0.001)	0.398 (<0.001)
Matsuda index	−0.393 (<0.001)	−0.384 (<0.001)	0.512 (<0.001)	−0.418 (<0.001)
2-h plasma glucose	0.022 (0.700)	0.003 (0.962)	−0.097 (0.090)	−0.005 (0.925)
Incremental insulin response	0.163 (0.004)	0.193 (0.001)	−0.234 (<0.001)	0.427 (<0.001)
Adipose variables at baseline				
Intra-abdominal fat area	0.344 (<0.001)	0.315 (<0.001)	−0.398 (<0.001)	0.287 (<0.001)
Abdomen subcutaneous fat area	0.298 (<0.001)	0.283 (<0.001)	−0.295 (<0.001)	0.199 (<0.001)
Total subcutaneous fat area	0.256 (<0.001)	0.252 (<0.001)	−0.252 (<0.001)	0.166 (0.004)
Total fat area	0.310 (<0.001)	0.299 (<0.001)	−0.319 (<0.001)	0.215 (<0.001)
Waist circumference	0.378 (<0.001)	0.332 (<0.001)	−0.366 (<0.001)	0.246 (<0.001)
BMI	0.374 (<0.001)	0.341 (<0.001)	−0.316 (<0.001)	0.195 (0.001)

Data are correlation coefficients (*P* for the correlation coefficients).

increased future HOMA-IR (models 1–5 of Table 3). Age, incremental insulin response, sex, and 2-h plasma glucose were not significant (Table 3). Similar results were obtained for the models predicting future fasting plasma insulin level, Matsuda index, or AUC of insulin (Tables 3 and 4). We also examined the first-order interaction terms between sex and the measures of regional or total adiposity, in the prediction of HOMA-IR, fasting plasma insulin, Matsuda index, or AUC of insulin in all models of Tables 3 and 4. None of the interactions between sex and the measures of regional or total adiposity was significant, thereby indicating that the associations between adiposity and future insulin resistance measure did not vary by sex. No evidence of multicollinearity (variance inflation factor of ≥4) was seen in any model in Tables 3 and 4.

DISCUSSION

These prospective data demonstrated that baseline visceral adiposity was related to future fasting plasma insulin level, HOMA-IR, Matsuda index, and AUC of insulin. These findings were independent of baseline fasting plasma insulin level, HOMA-IR, Matsuda index, or AUC of insulin (depending on the model) and age, sex, 2-h plasma glucose level, incremental insulin response, and other measures of total and regional adiposity, such as BMI, total subcutaneous fat area, abdominal subcutaneous fat area, or waist circumference. No other CT measurement of regional or total adiposity was related to future fasting plasma insulin level, HOMA-IR, Matsuda index, or AUC of insulin in models that contained intra-abdominal fat area.

Controversy has arisen from previous cross-sectional studies as to whether intra-abdominal fat area or abdominal subcutaneous fat area is more closely related to insulin resistance (1–7). Several cross-sectional studies have reported that intra-abdominal fat area is the major determinant of insulin resistance (1–4). However, two other studies have suggested that abdominal subcutaneous fat area is a more important determinant of insulin resistance than intra-abdominal fat area (6,7). Incomplete control for confounding or biased study population selection may explain the inconclusive association. Furthermore, it is not possible to draw conclusions about the temporal sequence of these associations because of the cross-sectional nature of these data. Wagenknecht et al. (5) showed in 1,457 men and women in the Insulin Resistance Atherosclerosis Study Family Study that intra-abdominal fat area, abdominal subcutaneous fat area, and their interaction were inversely associated with insulin sensitivity calculated by the minimal model analysis adjusted for age, BMI, sex, and ethnicity. Their results were also based on cross-sectional data. To our knowledge, ours is the first prospective study to evaluate the relationship of directly measured visceral adiposity to future fasting plasma insulin level, HOMA-IR, Matsuda index, or AUC of insulin.

We previously reported in the same population the effect of baseline fasting plasma insulin and baseline intra-abdominal fat area on intra-abdominal fat area measured after 5 and 10–11 years follow-up (22,23). Both baseline higher fasting plasma insulin level and greater intra-abdominal fat area were positively and independently correlated with intra-abdominal fat area at 5 and 10–11 years (23). In the present study, we demonstrated in the same population that both baseline greater intra-abdominal fat area and higher fasting plasma insulin level were positively and independently correlated with longitudinal increases in insulin resistance. Taken together, our previously published and current results suggest that the development of intra-abdominal fat area accumulation and insulin resistance go hand-in-hand. A positive feedback loop might serve as a model for this association. It is not possible from the research that we have previously performed or described in this article to determine which phenomenon comes first. A study of these phenomena in young adults or children may be informative in this regard.

In the present study, we did not assess mechanisms to explain the association between visceral fat and future fasting plasma insulin level, HOMA-IR, Matsuda index, or AUC of insulin. A plausible mechanism may be at least in part due to the portal theory (24). Visceral fat has been suggested to have greater lipolytic potential than subcutaneous fat (24,25). This may in turn result in increased delivery of free fatty acid to the liver via the portal vein, which may produce hepatic insulin resistance by stimulat-

TABLE 3
Multiple linear regression analysis of HOMA-IR and fasting plasma insulin levels at the 10- to 11-year follow-up

	Dependent variables							
	Log_e (10-year HOMA-IR)				Log_e (10-year fasting plasma insulin level)			
Independent variables from baseline in the model	β	β′	*P*	Model R^2	β	β′	*P*	Model R^2
Model 1								
Intra-abdominal fat area	0.00272	0.237	0.002		0.00277	0.258	0.001	
Abdomen subcutaneous fat area	0.00052	0.076	0.256		0.00034	0.052	0.441	
HOMA-IR	0.12450	0.378	<0.001		—	—	—	
Fasting plasma insulin	—	—	—	0.289	0.00455	0.357	<0.001	0.284
Incremental insulin response	0.00017	0.014	0.799		0.00033	0.028	0.614	
2-h plasma glucose	−0.03071	−0.095	0.072		−0.02639	−0.087	0.104	
Age	−0.00261	−0.061	0.281		−0.00407	−0.101	0.083	
Female sex	−0.08949	−0.089	0.158		−0.04686	−0.050	0.439	
Model 2: Same variables as model 1, except total subcutaneous fat area is substituted for abdomen subcutaneous fat area*								
Intra-abdominal fat area	0.00284	0.248	0.001		0.00287	0.267	<0.001	
Total subcutaneous fat area	0.00018	0.062	0.389	0.288		0.00011	0.039	0.265
HOMA-IR	0.12567	0.381	<0.001		—	—	—	
Fasting plasma insulin	—	—	—		0.00460	0.361	<0.001	
Model 3: Same variables as model 1, except total fat area is substituted for abdomen subcutaneous fat area*								
Intra-abdominal fat area	0.00266	0.232	0.006		0.00276	0.257	0.003	
Total fat area	0.00018	0.069	0.389	0.288	0.00011	0.043	0.593	0.265
HOMA-IR	0.12567	0.381	<0.001		—	—	—	
Fasting plasma insulin	—	—	—		0.00460	0.361	<0.001	
Model 4: Same variables as model 1, except BMI is substituted for abdomen subcutaneous fat area*								
Intra-abdominal fat area	0.00245	0.214	0.006		0.00254	0.236	0.003	
Body mass index	0.01753	0.107	0.128	0.292	0.01260	0.082	0.248	0.267
HOMA IR	0.12273	0.372	<0.001		—	—	—	
Fasting plasma insulin	—	—	—		0.00449	0.352	<0.001	
Model 5: Same variables as model 1, except waist circumference is substituted for abdomen subcutaneous fat area*								
Intra-abdominal fat area	0.00242	0.211	0.009		0.00253	0.235	0.004	
Waist circumference	0.00636	0.104	0.159	0.291	0.00454	0.079	0.291	0.267
HOMA-IR	0.12302	0.373	<0.001		—	—	—	
Fasting plasma insulin	—	—	—		0.00449	0.352	<0.001	

Log_e denotes natural logarithm. β and β′ denotes regression coefficient and standardized regression coefficient, respectively. *Incremental insulin response, 2-h plasma glucose, age, and female sex were not significant in any model.

TABLE 4
Multiple linear regression analysis of the Matsuda index and AUC of insulin levels at the 10- to 11-year follow-up

	Dependent variables							
	Log_e (10-year Matsuda index)				Log_e (10-year AUC insulin)			
Independent variables from baseline in the model	β	β′	*P*	Model R^2	β	β′	*P*	Model R^2
Model 1								
Intra-abdominal fat area	−0.00204	−0.193	0.009		0.00272	0.252	0.001	
Abdomen subcutaneous fat area	−0.00052	−0.082	0.195		−0.00033	−0.051	0.447	
Matsuda index	0.03409	0.412	<0.001		—	—	—	
AUC insulin	—	—	—	0.331	0.00316	0.244	<0.001	0.253
Incremental insulin response	−0.00097	−0.082	0.133		0.00289	0.240	<0.001	
2-h plasma glucose	0.02870	0.095	0.073		−0.01288	−0.042	0.440	
Age	−0.00009	−0.002	0.968		0.00127	0.031	0.580	
Female sex	0.11160	0.121	0.050		−0.05903	−0.063	0.333	
Model 2: Same variables as model 1, except total subcutaneous fat area is substituted for abdomen subcutaneous fat area*								
Intra-abdominal fat area	−0.00220	−0.208	0.005		0.00290	0.269	<0.001	
Total subcutaneous fat area	−0.00016	−0.061	0.372		−0.00024	−0.088	0.226	
Matsuda index	0.03439	0.415	<0.001	0.329	—	—	—	0.255
AUC insulin	—	—	—		0.00329	0.254	<0.001	
Incremental insulin response	−0.00096	−0.082	0.137		0.00287	0.239	<0.001	
Model 3: Same variables as model 1, except total fat area is substituted for abdomen subcutaneous fat area*								
Intra-abdominal fat area	−0.00203	−0.192	0.021		0.00314	0.292	0.001	
Total fat area	−0.00016	−0.067	0.372		−0.00024	−0.098	0.226	
Matsuda index	0.03439	0.415	<0.001	0.329	—	—	—	0.255
AUC insulin	—	—	—		0.00329	0.254	<0.001	
Incremental insulin response	−0.00096	−0.082	0.137		0.00287	0.239	<0.001	
Model 4: Same variables as model 1, except BMI is substituted for abdomen subcutaneous fat area*								
Intra-abdominal fat area	−0.00197	−0.186	0.017		0.00308	0.286	<0.001	
BMI	−0.01211	−0.080	0.223	0.331	−0.01469	−0.096	0.171	
Matsuda index	0.03470	0.419	<0.001		—	—	—	0.256
AUC insulin	—	—	—		0.00317	0.244	<0.001	
Incremental insulin response	−0.00099	−0.084	0.125		0.00287	0.239	<0.001	
Model 5: Same variables as model 1, except waist circumference is substituted for abdomen subcutaneous fat area*								
Intra-abdominal fat area	−0.00190	−0.180	0.024		0.00290	0.269	0.001	
Waist circumference	−0.00491	−0.087	0.21		−0.00386	−0.067	0.362	
Matsuda index	0.03423	0.413	<0.001	0.331	—	—	—	0.254
AUC insulin	—	—	—		0.00316	0.244	<0.001	
Incremental insulin response	−0.00100	−0.085	0.122		0.00288	0.239	<0.001	

Log_e denotes natural logarithm. β and β′ denotes regression coefficient and standardized regression coefficient, respectively. *2-h plasma glucose, age, and female sex were not significant in any model.

ing gluconeogenesis and interfering with hepatic insulin removal (26). Although this theory has scientific appeal, few studies on the effect of lipolysis of visceral fat on the delivery of free fatty acid to the liver are available, and the contribution of lipolysis of visceral fat to extrahepatic availability of free fatty acids may be small (27). Adipocyte-derived proteins may also play a key role in the pathogenesis of peripheral insulin resistance (28). For instance, levels of the insulin-sensitizing adipocyte-derived protein adiponectin are reported to be positively related with insulin sensitivity (29). Interestingly, visceral fat has been reported to have a more important role in producing this peptide than subcutaneous fat, and increased visceral fat is frequently associated with lower adiponectin levels (29–31). Therefore, adipocyte-derived circulating factors may be involved in part in the pathogenesis of insulin resistance associated with visceral adiposity.

There are potential limitations to our study. First, surrogate measures were used to estimate insulin resistance (HOMA-IR) and release (incremental insulin response). Any error that occurred as a result of these indirect measures, however, is likely to be random, as opposed to systematic, thereby biasing study results toward null values (32). Therefore, significant differences probably reflect underestimates of the true effect, although no differences might be explained by this random misclassification bias or absence of a true effect. Second, we used the sum of the areas of a limited number of CT scans to estimate total body fat mass. However, our group has found that this measurement correlates highly with fat mass as measured by hydrodensitometry among Japanese Americans (19). Visceral fat volume was also estimated with a single CT scan at the umbilicus (L4–L5) level. This measurement has been reported to have a high correlation with directly ascertained total visceral fat volume (17,18). Third, it is not clear whether our findings might apply to other ethnic groups. Asians and Asian Americans have been reported to have a lower prevalence of obesity by BMI compared with Caucasians and have a higher percentage of body fat at the same BMI level as Caucasians (33,34). Whether such differences also exist with regard to relationships between adiposity and future fasting plasma insulin level, HOMA-IR, Matsuda index, or AUC of insulin by ethnicity is not known. Fourth, fasting plasma insulin and HOMA-IR reflect mainly hepatic insulin resistance in the basal state. Because insulin resistance in the peripheral tissues is a major component of insulin sensitivity, as measured by the hyperinsulinemic-euglycemic clamp, we also used the Matsuda index as a surrogate marker of insulin sensitivity because it is reported to better reflect insulin-mediated peripheral glucose uptake (9,35). But whether these findings apply to insulin resistance measured using the clamp or other methods is not clear from these data. Lastly, we used plasma glucose and insulin values at 0, 30, 60, and 120 min during the oral glucose tolerance test to calculate the Matsuda index and AUC of insulin and did not use the 90-min value because it was not measured at this time point. This omission may have resulted in a Matsuda index that is less strongly correlated with the gold standard measurement of insulin resistance.

In conclusion, the present study provides evidence that visceral fat is an important predictor of future fasting plasma insulin level, HOMA-IR, Matsuda index, and AUC of insulin among Japanese Americans. This association is independent of other measures of total or regional adiposity. In particular, abdominal subcutaneous fat area and total subcutaneous fat area were not independently associated with future fasting plasma insulin level, HOMA-IR, Matsuda index, and AUC of insulin in multiple-adjusted models, which suggests that among all fat deposits, visceral fat has the most important role in predicting future insulin resistance. Our results suggest that a reduction in the size of the visceral fat depot may be effective in preventing future elevations of fasting plasma insulin level, HOMA-IR, Matsuda index, and AUC for insulin.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health Grants DK-31170, HL-49293, and DK-02654; by facilities and services provided by the Diabetes and Endocrinology Research Center (DK-17047), Clinical Nutrition Research Unit (DK-35816), and the General Clinical Research Center (RR-00037) at the University of Washington; and by the Medical Research Service and Cooperative Studies Program of the Department of Veterans Affairs. T.H. was supported in part by a research grant from the Japanese Ministry of Education, Science, Sports, and Culture (17390177). S.E.K. is the recipient of an American Diabetes Association Distinguished Clinical Scientist Award.

We gratefully acknowledge the skilled assistance of staff members, especially Jane Shofer. We are grateful to the King County Japanese-American Community for support and cooperation.

REFERENCES

1. Cnop M, Landchild MJ, Vidal J, Havel PJ, Knowles NG, Carr DR, Wang F, Hull RL, Boyko EJ, Retzlaff BM, Walden CE, Knopp RH, Kahn SE: The concurrent accumulation of intra-abdominal and subcutaneous fat explains the association between insulin resistance and plasma leptin concentrations: distinct metabolic effects of two fat compartments. *Diabetes* 51:1005–1015, 2002
2. Albu JB, Murphy L, Frager DH, Johnson JA, Pi-Sunyer FX: Visceral fat and race-dependent health risks in obese nondiabetic premenopausal women. *Diabetes* 46:456–462, 1997
3. Ross R, Freeman J, Hudson R, Janssen I: Abdominal obesity, muscle composition, and insulin resistance in premenopausal women. *J Clin Endocrinol Metab* 87:5044–5051, 2002
4. Rendell M, Hulthen UL, Tornquist C, Groop L, Mattiasson I: Relationship between abdominal fat compartments and glucose and lipid metabolism in early postmenopausal women. *J Clin Endocrinol Meta* 86:744–749, 2001
5. Wagenknecht LE, Langefeld CD, Scherzinger AL, Norris JM, Haffner SM, Saad MF, Bergman RN: Insulin sensitivity, insulin secretion, and abdominal fat: the Insulin Resistance Atherosclerosis Study (IRAS) Family Study. *Diabetes* 52:2490–2496, 2003
6. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM: Relationships of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest* 96:88–98, 1995
7. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE: Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes* 46:1579–1585, 1997
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
9. Wallace TM, Levy JC, Matthews DR: Use and abuse of HOMA modeling. *Diabetes Care* 27:1487–1495, 2004
10. Matsuda M, DeFronzo RA: Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 22:1462–1470, 1999
11. Fujimoto WY, Leonetti DL, Kinyoun JL, Shuman WP, Stolov WC, Wahl PW: Prevalence of complications among second-generation Japanese-American men with diabetes, impaired glucose tolerance, or normal glucose tolerance. *Diabetes* 36:730–739, 1987
12. Fujimoto WY, Bergstrom RW, Leonetti DL, Newell-Morris LL, Shuman WP, Wahl PW: Metabolic and adipose risk factors for NIDDM and coronary disease in third-generation Japanese-American men and women with impaired glucose tolerance. *Diabetologia* 37:524–532, 1994

13. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
14. Boyko EJ, Fujimoto WY, Leonetti DL, Newell-Morris L: Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. *Diabetes Care* 23:465–471, 2000
15. Wareham NJ, Phillips DI, Byrne CD, Hales CN: The 30 minute insulin incremental response in an oral glucose tolerance test as a measure of insulin secretion. *Diabet Med* 12:931, 1995
16. Shuman WP, Morris LL, Leonetti DL, Wahl PW, Moceri WM, Moss AA, Fujimoto WY: Abnormal body fat distribution detected by computed tomography in diabetic men. *Invest Radiol* 21:483–487, 1986
17. Schoen RE, Thaete FL, Sankey SS, Weissfeld JL, Kuller LH: Sagittal diameter in comparison with single slice CT as a predictor of total visceral adipose tissue volume. *Int J Obes Relat Metab Disord* 22:338–342, 1998
18. Han TS, Kelly IE, Walsh K, Greene RM, Lean ME: Relationship between volumes and areas from single transverse scans of intra-abdominal fat measured by magnetic resonance imaging. *Int J Obes Relat Metab Disord* 21:1161–1166, 1997
19. McNeely MJ, Shofer JB, Schwartz RS, Leonetti DL, Boyko EJ, Newell-Morris L, Kahn SE, Fujimoto WY: Use of computed tomography regional fat areas to estimate adiposity: correlation with hydrodensitometry, bioelectrical impedence, skinfold thickness, and body mass index. *Obes Res* 7 (Suppl. 1):47S, 1999
20. Glantz SA, Slinker BK: *Primer of Applied Regression and Analysis of Variance.* New York, McGraw-Hill, 1990, p. 181–238
21. Examination Committee of Criteria for 'Obesity Disease' in Japan, Japan Society for the Study of Obesity: New criteria for 'obesity disease' in Japan. *Circ J* 66:987–992, 2002
22. Boyko EJ, Leonetti DL, Bergstrom RW, Newell-Morris L, Fujimoto WY: Low insulin secretion and high fasting insulin and C-peptide levels predict increased visceral adiposity: 5-year follow-up among initially nondiabetic Japanese-American men. *Diabetes* 45:1010–1015, 1996
23. Tong J, Fujimoto WY, Kahn SE, Weigle DS, McNeely MJ, Leonetti DL, Shofer JB, Boyko EJ: Insulin, C-peptide, and leptin concentrations predict increased visceral adiposity at 5- and 10-year follow-ups in nondiabetic Japanese Americans. *Diabetes* 54:985–990, 2005
24. Frayn KN: Visceral fat and insulin resistance: causative or correlative? *Br J Nutr* 83:S71–S77, 2000
25. Micheli H, Carlson LA, Hallberg D: Comparison of lipolysis in human subcutaneous and omental adipose tissue with regard to effects of noradrenaline, theophylline, prostaglandin E1 and age. *Acta Chir Scand* 135:663–670, 1969
26. Bergman RN: New concepts in extracellular signaling for insulin action: the single gateway hypothesis. *Recent Prog Horm Res* 52:359–385, 1997
27. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD: Splanchnic lipolysis in human obesity. *J Clin Invest* 113:1582–1588, 2004
28. Wajchenberg BL: Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocr Rev* 21:697–738, 2000
29. Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, Retzlaff BM, Knopp RH, Brunzell JD, Kahn SE: Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia* 46:459–469, 2003
30. Alessi MC, Peiretti F, Morange P, Henry M, Nalbone G, Juhan-Vague I: Production of plasminogen activator inhibitor 1 by human adipose tissue: possible link between visceral fat accumulation and vascular disease. *Diabetes* 46:860–867, 1997
31. Motoshima H, Wu X, Sinha MK, Hardy VE, Rosato EL, Barbot DJ, Rosato FE, Goldstein BJ: Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. *J Clin Endocrinol Metab* 87:5662–5667, 2002
32. Rothman KJ, Greenland S: Introduction to regression models. In *Modern Epidemiology.* Philadelphia, Lippincott-Raven, 1998, p. 127–399
33. McNeely MJ, Boyko EJ: Type 2 diabetes prevalence in Asian Americans: results of a national health survey. *Diabetes Care* 27:66–69, 2004
34. Wang J, Thornton JC, Russell M, Burastero S, Heymsfield S, Pierson RN Jr: Asians have lower body mass index but higher percent body fat than do whites: comparisons of anthropometric measurements. *Am J Clin Nutr* 60:23–28, 1994
35. Abdul-Ghani MA, Matsuda M, Balas B, DeFronzo RA: Muscle and liver insulin resistance indexes derived from the oral glucose tolerance test. *Diabetes Care* 30:89–94, 2007