Visceral Adiposity and the Risk of Impaired Glucose Tolerance

A prospective study among Japanese Americans

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OBJECTIVE — Greater visceral adiposity, higher insulin resistance, and impaired insulin secretion increase the risk of type 2 diabetes. Whether visceral adiposity increases risk of impaired glucose tolerance (IGT) independent of other adipose depots, insulin resistance, and insulin secretion is not known.

RESEARCH DESIGN AND METHODS — Study subjects included 128 Japanese Americans with normal glucose tolerance at entry. Baseline variables included plasma glucose and insulin measured after an overnight fast and during a 75-g oral glucose tolerance test, fat areas by computed tomography, insulin secretion (incremental insulin response [IIR] [30 min insulin − fasting insulin]/30 min glucose), and insulin resistance index (homeostasis model assessment for insulin resistance [HOMA-IR]).

RESULTS — During the 10- to 11-year follow-up period, we confirmed 57 cases of IGT. Significant predictors of IGT included intra-abdominal fat area (IAFA) (odds ratio [OR] for a 1 SD increase 3.82, 95% CI 1.63–8.94 at a fasting plasma glucose [FPG] level of 4.5 mmol/l), HOMA-IR (2.41, 1.15–5.04), IIR (0.30, 0.13–0.69 at an FPG level of 4.5 mmol/l), the interactions of IAFA by FPG ($P = 0.003$), and IIR by FPG ($P = 0.030$) after adjusting for age, sex, FPG, and BMI. The multiple-adjusted OR of IAFA increased and that of IIR decreased as FPG level decreased because of these interactions. Even after adjustment for total fat area, total subcutaneous fat area, or abdominal subcutaneous fat area, all of these associations remained a significant predictor of IGT incidence.

CONCLUSIONS — Greater visceral adiposity increases the risk of IGT independent of insulin resistance, insulin secretion, and other adipose depots in Japanese Americans.

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A central pattern of body fat distribution is now generally considered to play an important role in the insulin resistance syndrome, which is the cluster of obesity, insulin resistance, hyperinsulinemia, dyslipidemia, glucose intolerance, and hypertension (1–5). In particular, visceral adiposity has been reported to play a key role in these diseases compared with other measurements of regional or generalized obesity (1,2). We have reported that visceral fat plays an important role in the development of type 2 diabetes independent of other measurements of total and regional adiposity (3–7).

Impaired glucose tolerance (IGT) is a strong predictor of not only type 2 diabetes (7), but also cardiovascular disease and other diabetes complications (8,9). Thus, it is important to clarify the determinants of IGT. A few epidemiological studies have reported an association between greater abdominal obesity, measured by waist circumference or the ratio of waist-to-hip circumference, and the risk of IGT (10–12). In these studies, visceral adiposity was not distinguished from subcutaneous abdominal fat, and control for other potentially confounding variables, such as insulin secretion and insulin resistance, was not performed. In the present study, we therefore prospectively examined the relationship between directly measured visceral adiposity and the risk of IGT independent of other measurements of total and regional adiposity, insulin resistance, and insulin secretion.

RESEARCH DESIGN AND METHODS

Study population

The study population consisted of third-generation (Sansei, mean age 39.5 ± 4.1 years) Japanese Americans with normal glucose tolerance (NGT) (as defined below) who were enrolled in the Japanese American Community Diabetes Study. Details about selection and recruitment of the sample population have been previously described (13). In brief, subjects were chosen from volunteers. Subjects were enrolled through a community-wide recruitment using a comprehensive mailing list and telephone directory that included nearly 95% of the Japanese-American population of King County, WA. Sansei were defined as any Japanese person born in the continental U.S. of Nisei parents or of one Nisei parent and one Sansei parent. The strategy was to study ~10% of the Sansei population 34 years

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Abbreviations: CT, computed tomography; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment for insulin resistance; IAFA, intra-abdominal fat area; IGT, impaired glucose tolerance; IIR, incremental insulin response; OGTT, oral glucose tolerance test; OR, odds ratio; NGT, normal glucose tolerance; TFA, total fat area.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

of age or older who were nondiabetic. Subjects returned for follow-up examinations 6 and 10–11 years after a baseline evaluation.

Data collection

All evaluations were performed at the General Clinical Research Center, University of Washington. The protocol for this research was reviewed by the Human Subjects Review Committee at the University of Washington, and signed informed consent was obtained from all participants. A 75-g oral glucose tolerance test (OGTT) was used to classify all subjects as having NGT, IGT, or type 2 diabetes based on the 1997 American Diabetes Association criteria (14). Diabetes was diagnosed if subjects reported a history of diabetes and were taking oral hypoglycemic medication or insulin, if the fasting plasma glucose (FPG) level was ≥7.0 mmol/l, or if the 2-h value was ≥11.1 mmol/l. IGT was diagnosed if subjects had no history of diabetes and if the FPG level was <7.0 mmol/l with a 2-h value ≥7.7 and <11.1 mmol/l. Subjects with an FPG level <7.0 mmol/l and a 2-h OGTT value <7.7 mmol/l were included in the NGT category. IGT status at follow-up was based on the same criteria as above. We classified subjects as having IGT if they were classified with IGT at least once and not with type 2 diabetes during the 10- to 11-year follow-up period. Plasma glucose was assayed by an automated glucose oxidase method. Fasting plasma insulin was measured by radioimmunoassay as previously reported (7). Insulin sensitivity was estimated by using homeostasis model assessment for insulin resistance (HOMA-IR; (fasting glucose [measured in millimoles per liter])(fasting insulin [measured in microunits per milliliter])/22.5) (15). To assess insulin secretion, we used the incremental insulin response (IIR) ([30 min insulin − fasting insulin]/30 min glucose), which correlates well with direct measures of stimulated insulin selection (16). Family history of diabetes was deemed positive if any first-degree relative had diabetes.

BMI was calculated as the weight in kilograms divided by the height in meters squared. Single computed tomography (CT) scans were obtained of the thorax, abdominal, and right thigh to measure fat areas (measured in centimeters squared) as previously described (17). Visceral adiposity was measured as intra-abdominal fat area (IAFA) at the umbilicus level. This measurement has been reported to have a high correlation with directly ascertained total visceral fat volume by CT or magnetic resonance image (18,19). Subcutaneous fat area was also measured by CT scans of the thorax, abdomen, and right thigh. Total fat area (TFA) was calculated as the sum of IAFA, thorax and subcutaneous abdominal fat areas, and twice the right thigh subcutaneous fat area. TFA correlates highly with fat mass as measured by hydrodensitometry among Japanese Americans ($r = 0.89–0.94$; unpublished data). Total subcutaneous fat area was defined as TFA minus IAFA. Abdominal circumference was measured at the level of the umbilicus to the nearest tenth centimeter.

Statistical analysis

Only subjects without diabetes or IGT at baseline were included in this analysis. Multiple logistic regression analysis was used to estimate the odds ratio (OR) for incident IGT in relation to an increase of 1 SD in baseline variables. Presence of effect modification was tested by the insertion of first-order interaction terms into appropriate regression models. Nonlinear effects of continuous independent variables were evaluated using quadratic and log transformations.

The 95% CI was calculated for each OR. *P* values are two-tailed. Statistical analyses were performed using the SPSS version 10.0 software package.

RESULTS — Of 139 Sansei men and women with NGT followed for 10–11 years, 6 were excluded because they developed diabetes during the follow-up period and 5 were excluded because of incomplete data collection. The study population for analyses ultimately consisted of 128 men and women. During the 10- to 11-year follow-up period, we confirmed 57 cases of IGT. In univariate logistic regression analysis, IAFA and abdominal subcutaneous fat area were associated with higher IGT incidence. HOMA-IR, but not IIR and FPG, was also associated with higher IGT incidence (Table 1).

In multiple logistic regression analysis, we examined the significance of the interaction terms between IAFA, HOMA-IR, or IIR and the other variables. After each of the first order interactions between IAFA and the other variables were examined one by one in the model, including IAFA, HOMA-IR, IIR, BMI, FPG, age, and sex, the interaction of IAFA by FPG resulted in a significant improvement in fit. Furthermore, when each of the interactions between HOMA-IR or IIR and the other variables were inserted one by one into the model, including the interaction of IAFA by FPG in the above model, the interactions of IAFA and IIR by FPG resulted in a significant improvement in fit (data not shown). Therefore, we decided to include the interactions of IAFA and IIR by FPG in the model.

A number of regression models were tested to assess the effects of body fat distribution on IGT incidence. After adjustment for HOMA-IR, IIR, BMI, FPG, age, and sex, both IAFA and the interaction of IAFA by FPG were associated with risk of IGT ($P = 0.001$ and $P = 0.003$, respectively) (Table 2, model 1). In table 2, models 2–5 were identical to model 1, with the exception that a different adiposity variable was used in place of BMI. In all of these models, these associations did not change. Also, none of the other measures of regional or total adiposity emerged as significantly related to the risk of IGT (Table 2, models 2–5). As the interaction of IAFA by FPG was significant, the multiple-adjusted OR of IAFA increased as FPG level decreased (Fig. 1). In all models, HOMA-IR, IIR, and the interaction of IIR by FPG were also associated with the risk of IGT (Table 2). As the interaction of IIR by FPG was significant, the multiple-adjusted OR of IIR decreased as FPG level decreased (Fig. 1). Insertion of quadratic or log transformations of IAFA into model 1 did not improve its fit compared with the linear model (data not shown).

CONCLUSIONS — These prospective data demonstrated that visceral adiposity was associated with the risk of incident IGT. This finding was independent of other measures of total and regional adiposity, correlates of insulin resistance (HOMA-IR) and secretion (IIR), age, and sex. This association between visceral adiposity and the risk of IGT was the most pronounced among those with lower FPG levels.

Previous research on the association between greater abdominal obesity, measured by waist circumference or the ratio of waist-to-hip circumference, and the

Table 1—*Characteristics of study subjects at baseline according to whether IGT developed after a 10- to 11-year follow-up*

		IGT status after follow-up			
	Total (n = 128)	Not IGT (n = 71)	IGT (n = 57)	Crude OR (95% CI)	P
Age (years)	39.5 ± 4.1	39.9 ± 4.1	39.1 ± 4.1	0.83 (0.58–1.19)	0.312
Female sex (%)	46.9	47.9	45.6	0.91 (0.45–1.84)	0.798
Family history of diabetes	29.7	28.2	31.6	1.18 (0.55–2.52)	0.675
Metabolic variables					
HOMA-IR	2.78 ± 1.54	2.40 ± 1.05	3.24 ± 1.89	1.94 (1.23–3.06)	0.005
IIR	57.4 ± 44.7	59.9 ± 48.6	54.4 ± 39.4	0.88 (0.61–1.26)	0.489
FPG (mmol/l)	4.83 ± 0.49	4.76 ± 0.47	4.91 ± 0.50	1.38 (0.96–1.99)	0.082
Adipose variables					
Thoracic subcutaneous fat (cm^2)	75.3 ± 52.0	67.0 ± 43.4	85.9 ± 59.9	1.50 (1.00–2.25)	0.052
Abdomen subcutaneous fat (cm^2)	139.3 ± 70.2	125.0 ± 63.5	157.0 ± 74.6	1.63 (1.11–2.39)	0.013
Intra-abdominal fat (cm^2)	50.8 ± 32.1	45.0 ± 29.6	58.1 ± 33.8	1.52 (1.06–2.19)	0.024
Left thigh subcutaneous fat (cm^2)	66.4 ± 33.2	66.5 ± 31.6	66.3 ± 35.4	0.99 (0.70–1.41)	0.975
Total subcutaneous fat (cm^2)	346.1 ± 164.5	325.0 ± 146.7	372.9 ± 182.6	1.35 (0.94–1.95)	0.109
Total fat (cm^2)	396.9 ± 178.5	370.0 ± 162.8	431.1 ± 192.7	1.43 (0.98–2.07)	0.060
BMI (kg/m^2)	23.4 ± 2.9	23.2 ± 2.7	23.7 ± 3.0	1.22 (0.85–1.73)	0.278
Waist circumference (cm)	82.7 ± 8.4	81.7 ± 1.0	84.1 ± 1.1	1.34 (0.93–1.92)	0.113

Data are means ± SD or % unless otherwise indicated. ORs for continuous variables reflect a 1-SD magnitude increase. Total subcutaneous fat and total fat areas represent sums of adipose tissue areas as determined by multiple CT slices described in the text. HOMA-IR is based on the homeostasis model: HOMA-IR = (fasting glucose [in millimoles per liter]) (fasting insulin [in microunits per liter])/22.5). The P value is for univariate logistic regression analysis.

risk of IGT have been inconclusive (10–12). Cassano et al. (10) showed among men followed in the Normative Aging Study that waist-to-hip circumference was associated with the risk of IGT after adjustment for age, BMI, and smoking habits. Dowse et al. (11) showed in a cohort study of Hindu and Muslim Indian, Creole, and Chinese Mauritians that the ratio of the waist-to-hip circumferences was associated with an increased risk of IGT among Hindu Indian, Creole, and Chinese women, but not among men, after adjustment for age, family history, BMI, and physical inactivity, whereas it was associated with an increased risk of IGT among Muslim Indian men but not women. Haffner et al. (12) in the San Antonio Heart Study showed that after adjustment for age, sex, ethnicity, fasting serum insulin level, and change in insulin–to–change in glucose ratio (30 min insulin − fasting insulin)/(30 min glucose − fasting glucose), both BMI and the ratio of the waist-to-hip circumferences no longer predicted the development of IGT. In these studies, IAFA was not measured directly, or control for confounders such as insulin secretion and insulin resistance was not performed.

Controversy has arisen from cross-sectional studies as to whether abdominal obesity, IAFA, or subcutaneous abdominal fat area is more closely related to insulin resistance (5,20–22). Some studies have reported that visceral fat is the major determinant of insulin resistance (5,20), but others have suggested that subcutaneous abdominal fat is more important (21,22). Cross-sectional research is also unable to examine the temporal sequence of the development of insulin resistance in relation to visceral fat. Prospective studies may be better suited to address this issue. Thus, in a prospective analysis, we have reported that greater IAFA measured by CT was associated with an increased risk of type 2 diabetes and that this effect was independent of other measurements, such as total and regional adiposity, insulin secretion, and insulin resistance (7). Furthermore, subcutaneous fat area was not associated with the risk of type 2 diabetes (7). In the present study, greater subcutaneous fat was associated with an increased risk of IGT in univariate analysis but not in multiple variable-adjusted analysis including IAFA, whereas greater IAFA was associated with an increased risk of IGT in all models (Table 2). To our knowledge, this is the first prospective study to evaluate the relation of directly measured visceral adiposity to the risk of IGT incidence.

In the present study, both insulin resistance (HOMA-IR) and insulin secretion (IIR) were associated with a risk for IGT, as previously demonstrated (12). The interaction of IIR by FPG was significant, which demonstrated that higher insulin secretion was associated with a decreased risk of IGT only among those with lower FPG levels. Therefore, for Japanese Americans, enhanced insulin secretion may compensate for insulin resistance early on during the transition from NGT to IGT.

Although in the present study we did not identify why visceral fat increases the risk of IGT, a plausible mechanism may be at least in part due to insulin resistance resulting from the liberation of free fatty acids from visceral fat (23). Visceral fat has been reported to have higher rates of lipolysis than subcutaneous fat by catecholamines and less suppression by insulin (23). This may in turn result in increased delivery of free fatty acid to the liver via the portal vein. One consequence of this could be stimulation of hepatic glucose production by fatty acids (23). In addition, fatty acids have been shown to interfere with hepatic insulin removal (23), which may further accentuate insulin resistance. Against this hypothesis for the role of visceral fat in the development of insulin resistance and subsequent IGT is the recent demonstration that postprandial free fatty acid increase was primarily due to nonsplanchnic fat depots (23). In the present study, adjustment for insulin resistance (HOMA-IR) did not remove a significant association between

Table 2—*Multivariate models of IGT incidence in relation to baseline values of insulin resistance, insulin secretion, and intra-abdominal fat area*

Model	Variables in the model	OR (95% CI)	*P*
1	Intra-abdominal fat area	See Figure 1	0.001
	BMI	0.72 (0.41–1.26)	0.252
	HOMA-IR	2.41 (1.15–5.04)	0.019
	IIR	See Figure 1	0.019
	FPG	—	0.482
	Age	0.82 (0.55–1.23)	0.339
	Female sex	2.07 (0.78–5.46)	0.143
	Intra-abdominal fat × FPG	See Figure 1	0.003
	IIR × FPG	See Figure 1	0.030
2	Same variables as model 1, except total fat area is substituted for BMI		
	Intra-abdominal fat area	See Figure 1	0.003
	Total fat area	0.96 (0.50–1.85)	0.899
	Intra-abdominal fat × FPG	See Figure 1	0.005
3	Same variables as model 1, except total subcutaneous fat area is substituted for BMI		
	Intra-abdominal fat area	See Figure 1	0.003
	Total subcutaneous fat area	0.96 (0.52–1.76)	0.899
	Intra-abdominal fat × FPG	See Figure 1	0.005
4	Same variables as model 1, except abdominal subcutaneous fat area is substituted for BMI		
	Intra-abdominal fat area	See Figure 1	0.005
	Abdominal subcutaneous fat area	1.23 (0.69–2.17)	0.484
	Intra-abdominal fat × FPG	See Figure 1	0.006
5	Same variables as model 1, except waist circumference is substituted for BMI		
	Intra-abdominal fat area	See Figure 1	0.001
	Waist circumference	0.87 (0.46–1.64)	0.665
	Intra-abdominal fat × FPG	See Figure 1	0.001

ORs for continuous variables reflect a 1-SD magnitude increase. In all models, HOMA IR, IIR, and the interaction of IIR by FPG were also associated with the risk of IGT.

IAFA and the risk of IGT. Furthermore, this association was independent of total body fat and regional fat depots. Therefore, visceral adiposity may have effects on IGT incidence through mechanisms unrelated to insulin resistance. Furthermore, the interaction of IAFA by FPG was significant, which demonstrated that greater visceral fat was associated with an increased risk of IGT only among those with lower FPG levels and that some of the effect of visceral fat may be in part mediated by insulin resistance (HOMA-IR) or unknown variables that might affect both visceral fat and the risk of IGT among those with higher FPG levels. The role of body fat depots in the pathogenesis of insulin resistance and IGT requires further investigation.

The overall incidence of IGT was 44.5%. This seemingly high rate might not be unexpected in the third-generation of our study because we previously reported that in the second-generation of Japanese Americans IGT incidence was 54% for women and 37% for men over the 5-year follow-up interval (24).

There are several potential limitations to our study. 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 ($r = 0.89–0.94$). Visceral fat volume was also estimated with a single CT scan at the L4–L5 level. This measurement has been reported to have a high correlation with directly ascertained total visceral fat volume (18,19). The surrogate measures were also used to estimate insulin resistance (HOMA-IR) and secretion (IIR). 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 (25). Therefore, it is likely that the significant associations between the risk of IGT and IAFA, insulin resistance, and insulin secretion are underestimated. Since we studied a single ethnic group, our results may not be representative of the general population but may apply to native Japanese and possibly other Asian Americans. Although, the ethnic homogeneity of this cohort provides high assurance that potential confounding of the study findings by ethnic admixture is unlikely. We could not detect the association between BMI, waist circumference, and the risk of IGT, even in the univariate analysis. Our subjects in this study were nonobese by BMI or waist circumference, but Asians have been reported to have a higher percentage of fat at the same BMI

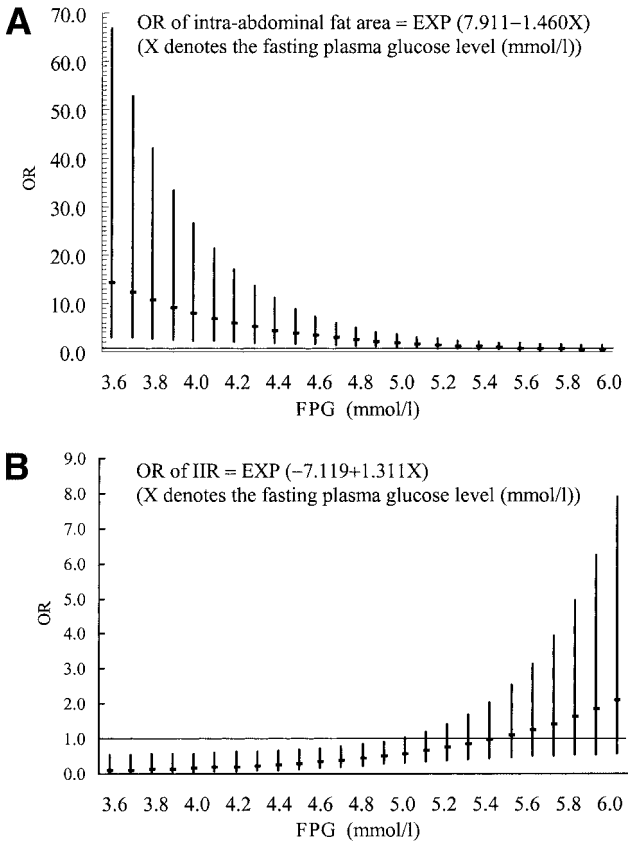

Figure 1—*Multiple-adjusted ORs and 95% CI for a 1-SD increase in intra-abdominal fat* (A) *and IIR* (B) *area based on model 1 in Table 2. Vertical lines, 95% CI for each FPG level; horizontal bars, ORs; X, the FPG level (in millimoles per liter); EXP, exponential. Models 2–5 in Table 2 gave almost the same results (data not shown).*

level than Caucasians (26). The lack of association between BMI and IGT risk in our sample may be due to the relatively narrow range of observed BMI in combination with the relatively poor predictive power of overall adiposity in contrast to IAFA in predicting the occurrence of this outcome.

In conclusion, the present results provide evidence that visceral fat is a significant prospective risk factor for IGT among Japanese Americans. This association is independent of insulin resistance and secretion, which suggests that the effect of visceral fat on diabetes risk may be mediated by mechanisms not reflected by HOMA-IR and IIR. The mechanism by which visceral fat is associated with the risk for IGT remains to be determined. To confirm these findings, further research on these associations is needed.

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