Abdominal fat distribution and peripheral and hepatic insulin resistance in type 2 diabetes mellitus

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Miyazaki, Yoshinori, Leonard Glass, Curtis Triplitt, Estela Wajcberg, Lawrence J. Mandarino, and Ralph A. DeFronzo. Abdominal fat distribution and peripheral and hepatic insulin resistance in type 2 diabetes mellitus. Am J Physiol Endocrinol Metab 283: E1135–E1143, 2002.—We examined the relationship between peripheral/hepatic insulin sensitivity and abdominal superficial/deep subcutaneous fat (SSF/DSF) and intra-abdominal visceral fat (VF) in patients with type 2 diabetes mellitus (T2DM). Sixty-two T2DM patients (36 males and 26 females, age 55 ± 3 yr, body mass index = 30 ± 1 kg/m2) underwent a two-step euglycemic insulin clamp (40 and 160 mU·m−2·min−1) with [3-3H]glucose. SSF, DSF, and VF areas were quantitated with magnetic resonance imaging at the L4–5 level. Basal endogenous glucose production (EGP), hepatic insulin resistance (basal EGP × FPI), and total glucose disposal (TGD) during the first and second insulin clamp steps were similar in male and female subjects. VF (159 ± 9 vs. 143 ± 9 cm2) and DSF (199 ± 14 vs. 200 ± 15 cm2) were not different in male and female subjects. SSF (104 ± 8 vs. 223 ± 15 cm2) was greater (P < 0.0001) in female vs. male subjects despite similar body mass index (31 ± 1 vs. 30 ± 1 kg/m2) and total body fat mass (31 ± 2 vs. 33 ± 2 kg). In male T2DM, TGD during the first insulin clamp step (1st TGD) correlated inversely with VF (r = −0.45, P < 0.01), DSF (r = −0.46, P < 0.01), and SSF (r = −0.39, P < 0.05). In males, VF (r = 0.37, P < 0.05), DSF (r = 0.49, P < 0.01), and SSF (r = 0.33, P < 0.05) were correlated positively with hepatic insulin resistance. In females, the first TGD (r = −0.45, P < 0.05) and hepatic insulin resistance (r = 0.49, P < 0.05) correlated with VF but not with DSF, SSF, or total subcutaneous fat area. We conclude that visceral adiposity is associated with both peripheral and hepatic insulin resistance, independent of gender, in T2DM. In male but not female T2DM, deep subcutaneous adipose tissue also is associated with peripheral and hepatic insulin resistance.

visceral fat; deep and superficial subcutaneous fat

REDUCED INSULIN-MEDIATED GLUCOSE disposal in muscle and impaired suppression of hepatic glucose production by insulin are common metabolic features of both obesity and type 2 diabetes mellitus (13). A close association between obesity and type 2 diabetes mellitus also is well established (16, 25). Many studies have documented that intra-abdominal visceral fat (VF) is closely associated with insulin resistance in obese nondiabetic and type 2 diabetes mellitus subjects (3, 5–11, 22, 23). However, several studies have demonstrated that subcutaneous fat (SF), not VF, is the best predictor of insulin resistance in obese individuals (1, 2, 21, 23). The factors responsible for these inconsistent results have yet to be elucidated. Two potential explanations that might account for these discordant reports are failure to account for 1) differences in gender and 2) differences in metabolism between superficial and deep subcutaneous fat (DSF) depots (27). To the best of our knowledge, all previous studies have examined the association between insulin resistance and fat topography in men alone, in women alone, or in a combined analysis of men plus women. Most studies involving only female subjects have reported that visceral, but not subcutaneous, fat is associated with insulin resistance (3, 8–10, 33). In contrast, most studies employing male subjects have reported that SF or both VS and SF are correlated with insulin resistance (1, 2, 6, 23).

Recent evidence suggests that there may be significant metabolic differences between deep and superficial subcutaneous adipose tissue depots (27, 31). Within the subcutaneous adipose tissue, there is a superficial fascial plane that separates the SF into a superficial layer with compact fascial septa (Camper’s fascia) and a deep layer with more loosely organized fascial septa (Scarpa’s fascia). The superficial fat layer is comprised of small tightly packed lobules, whereas the deeper layer is made up of larger, irregularly distributed lobules. Recently, Kelley et al. (31) reported that the DSF, but not the superficial subcutaneous fat (SSF), is strongly associated with peripheral insulin resistance and features of the insulin resistance syndrome in nondiabetic individuals. However, these investigators employed a combined analysis of male plus female subjects, and they did not study diabetic subjects.

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In the present study, we have examined the relationship between intra-abdominal VF/SSF/DSF and peripheral tissue (muscle)/hepatic sensitivity to insulin by use of a two-step euglycemic hyperinsulinemic (40 and 160 mU·m⁻²·min⁻¹) clamp performed with [³⁵S]glucose in male and female type 2 diabetes mellitus patients. To the best of our knowledge, this is the first study to examine the relationship between peripheral/hepatic sensitivity to insulin and superficial and deep subcutaneous, as well as visceral, fat topography in a large number of type 2 diabetic subjects. It also is the first study to report data on fat topography and insulin sensitivity separately in male and female subjects.

**METHODS**

**Subjects.** Sixty-two patients with type 2 diabetes mellitus (males/females = 36/26) were recruited from the outpatient clinic of the Texas Diabetes Institute. Entry criteria included an age of 30–70 yr, body mass index (BMI) <37 kg/m², and a fasting plasma glucose concentration (FPG) between 140 and 260 mg/dl. The patient characteristics of the 36 males and 26 females are shown in Table 1. All patients were in good general health without evidence of cardiac, hepatic, renal, or other chronic diseases as determined by medical history, physical examination, and screening blood tests. In all subjects, body weight was stable (within ±2 lb) for at least 3 mo before study. Twenty-five subjects were taking a stable dose (for at least 6 mo) of sulfonylurea drugs, and 37 subjects were treated with diet alone. Patients who previously had received insulin, metformin, or a thiazolidinedione were excluded. For 3 days before study, subjects were instructed to ingest a weight-maintaining diet containing 200 kcal/kg FFM.

**Study design.** Within a 5- to 7-day interval, all subjects received 1) measurement of fat-free mass (FFM) and fat mass (FM) using an intravenous bolus of [³¹H₂O; 2) quantitation of total subcutaneous, superficial subcutaneous, deep subcutaneous, and intra-abdominal VF content at lumbar (L) levels 4–5 (L₄₅); 3) a euglycemic insulin clamp study in combination with [³⁵S]glucose to examine hepatic and peripheral tissue sensitivity to insulin. Fasting plasma lipids [total cholesterol, HDL, low-density lipoprotein (LDL), cholesterol, triglycerides, FPG, and hemoglobin (Hb) A₁C] were measured on the day of the insulin clamp. All subjects gave their written voluntary, informed consent before participation. The protocol was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio.

**FFM and FM**

At 8:00 AM (time 0), subjects received a 100-µCi intravenous bolus of [³¹H₂O, and plasma tritiated water radioactivity was determined at 90, 105, and 120 min for calculation of FFM and FM, as described previously (8). **Abdominal fat distribution.** Intra-abdominal VF and SF depots were measured by MRI by use of imaging procedures that have been published previously (32). Briefly, images were acquired on a 1.9-T Elscint Prestige MRI system using a spin lattice longitudinal relaxation time-weighted spin echo pulse sequence with a repetition time of 500 ms and an echo time of <20 ms. A sagittal localizing image was used to center transverse sections on the line through the space between L₁ and L₅. Ten 5.0-mm-thick sections were acquired with a gap of 1.0 mm to prevent signal crossover from adjacent sections. The field of view ranged from 30 to 50 cm, depending on body size. Phase encoding was in the anteroposterior direction to minimize the effects of motion-induced phase artifacts that might otherwise be distributed laterally through a large portion of the abdomen. The field of view was adjusted for body size to ensure 2-mm pixel spacing. Signal averaging (4 signals averaged) was used to reduce the effect of motion-related artifacts. Additionally, respiratory gating was used to combat motion-induced artifacts and to reduce the blurring of fat boundaries in the anterior region of the abdomen. Images were processed using Alice software (Perceptive Systems, Boulder, CO) to determine abdominal subcutaneous and intra-abdominal VF areas. The SF was analyzed by selecting the outer and inner margins of subcutaneous adipose tissue as regions of interest from the cross-sectional images and counting the number of pixels between the outer and inner margins of subcutaneous adipose tissue. The abdominal SF was subdivided into intra-abdominal and DSF areas by identifying the fascial line that demarcates these two fat depots (Fig. 1 and Ref. 30).

**Table 1. Clinical and metabolic characteristics and abdominal fat distribution in male and female subjects**

<table>
<thead>
<tr>
<th>Race (MA/C/AA)</th>
<th>Male (n = 36)</th>
<th>Female (n = 26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>55 ± 2</td>
<td>54 ± 2</td>
<td>0.17</td>
</tr>
<tr>
<td>FPG, mg/dl</td>
<td>199 ± 7</td>
<td>176 ± 9</td>
<td>0.03</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>31 ± 2</td>
<td>32 ± 2</td>
<td>0.008</td>
</tr>
<tr>
<td>FM, kg</td>
<td>15 ± 1</td>
<td>17 ± 2</td>
<td>0.04</td>
</tr>
<tr>
<td>HbA₁C, %</td>
<td>9.0 ± 0.2</td>
<td>8.1 ± 0.3</td>
<td>0.01</td>
</tr>
<tr>
<td>FFA, μEq/l</td>
<td>589 ± 22</td>
<td>774 ± 41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>bEGP, mg·kg⁻¹·FMM⁻¹·min⁻¹</td>
<td>4.3 ± 0.1</td>
<td>4.3 ± 0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>1st EGP, mg·kg⁻¹·FMM⁻¹·min⁻¹</td>
<td>12.2 ± 4</td>
<td>12.4 ± 4</td>
<td>0.99</td>
</tr>
<tr>
<td>1st TGD, mg·kg⁻¹·FMM⁻¹·min⁻¹</td>
<td>3.5 ± 0.2</td>
<td>3.6 ± 0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>2nd TGD, mg·kg⁻¹·FMM⁻¹·min⁻¹</td>
<td>7.7 ± 0.5</td>
<td>8.0 ± 0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>VF, cm²</td>
<td>159 ± 9</td>
<td>143 ± 29</td>
<td>0.002</td>
</tr>
<tr>
<td>SF, cm²</td>
<td>303 ± 21</td>
<td>423 ± 24</td>
<td>0.0004</td>
</tr>
<tr>
<td>SSF, cm²</td>
<td>199 ± 14</td>
<td>200 ± 15</td>
<td>0.8</td>
</tr>
<tr>
<td>Total Chol, mg/dl</td>
<td>174 ± 14</td>
<td>172 ± 7</td>
<td>0.4</td>
</tr>
<tr>
<td>HDL Chol, mg/dl</td>
<td>32 ± 1</td>
<td>40 ± 2</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL Chol, mg/dl</td>
<td>106 ± 5</td>
<td>104 ± 5</td>
<td>0.5</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>174 ± 14</td>
<td>142 ± 13</td>
<td>0.8</td>
</tr>
</tbody>
</table>

MA, Mexican American; C, Caucasian; AA, African American; SU, sulfonylureas; BMI, body mass index; FFM, fat-free mass; FM, fat mass; FPG, fasting plasma glucose concentration; FPI, fasting plasma insulin concentration; HbA₁C, hemoglobin A₁C; FFA, fasting plasma free fatty acid concentration; bEGP, basal endogenous glucose production rate; 1st EGP, endogenous glucose production rate during 1st insulin clamp step; 1st TGD, total glucose disposal rate during 1st insulin clamp step; 2nd TGD, total glucose disposal rate during 2nd insulin clamp step; bEGP × FPI, hepatic insulin resistance index; VF, intra-abdominal visceral fat area at L₄–₅; SF, total subcutaneous fat area at L₄–₅; SSF, superficial subcutaneous fat area at L₄–₅; DSF, deep subcutaneous fat area at L₄–₅; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
BW=107 kg; BMI=32.6 kg/m²
VF=76 cm²; SF=391 cm²; DSF=201 cm²; SSF=190 cm²

BW=79 kg; BMI=32.9 kg/m²
VF=114 cm²; SF=530 cm²; DSF=262 cm²; SSF=268 cm²

Fig. 1. Transverse cross-sectional magnetic resonance image at the L₄₋₅ vertebral level was used to evaluate visceral fat area (VF), abdominal subcutaneous fat area (SF), and abdominal deep (DSF) and superficial subcutaneous fat (SSF) areas in male (A) and female (B) subjects. The fascia (arrows) separating the superficial subcutaneous and deep subcutaneous depots is easily visualized. BW, body wt; BMI, body mass index.

abdominal) fat areas were determined using histograms specific to the visceral regions. The histograms were summed over the range of pixel values designated as fat by fitting two normal analysis distribution curves to them.

Euglycemic-hyperinsulinemic clamp. Insulin sensitivity was assessed with a two-step euglycemic insulin clamp, as previously described (15). Upon subjects' arrival (8:00 AM) at the Clinical Research Center, blood for measurement of FPG, HbA₁c, and the lipid profile was obtained, and a prime (25 mCi × FPG/100)-continuous (0.25 mCi/min) infusion of [3-³H]glucose was started via a catheter placed in an antecubital vein. The [3-³H]glucose infusion was continued throughout the 7-h study. A second catheter was placed retrogradely in a vein on the dorsum of the hand, which was maintained by appropriately adjusting a variable infusion of 20% dextrose. Throughout the insulin clamp, blood samples for determination of plasma glucose concentration were drawn every 5 min, and blood samples for determination of plasma insulin and [3-³H]glucose radioactivity were collected every 10–15 min.

Assays. Plasma glucose was measured at bedside using the glucose oxidase method (Glucose Analyzer 2; Beckman Instruments, Fullerton, CA). Plasma insulin (Diagnostic Products, Los Angeles, CA) was measured by RIA. HbA₁c was measured by affinity chromatography (Biochemical Methodology, Dower 4350; Isolab, Akron, OH). Plasma free fatty acid (FFA) was measured by an enzymatic calorimetric quantitation (Wako Chemicals, Neuss, Germany). Plasma total cholesterol, HDL-cholesterol, and triglycerides were measured enzymatically (Boehringer-Mannheim, Indianapolis, IN) on a Hitachi 704 autoanalyzer. LDL cholesterol was calculated from the Friedewald equation. [3-³H]glucose specific activity was determined on barium hydroxide/zinc sulfate deproteinized plasma samples.

Calculations. Under steady-state, postabsorptive conditions, the rate of endogenous glucose appearance (Ra) was calculated as the [3-³H]glucose infusion rate (dpm/min) divided by the steady-state plasma [3-³H]glucose specific activity (dpm/mg). During the insulin clamp, nonsteady conditions prevailed, and Ra was calculated from Steele’s equation (36). Endogenous glucose production (EGP) was calculated as EGP = Ra – glucose infusion rate. During the insulin clamp, total body glucose disposal (TGD) equals the sum of the residual EGP plus the glucose infusion rate. In the postabsorptive state, an index of hepatic insulin resistance was calculated as the product of EGP and the fasting plasma insulin concentration. The logic behind this calculation is as follows: 1) under basal conditions, the majority (~85–90%) of EGP is derived from liver (18); and 2) insulin is a potent inhibitor of hepatic glucose production; even very small increments in the ambient insulin concentration exert a potent inhibitory effect on hepatic glucose output (24). Moreover, within the range of fasting plasma insulin concentrations that are observed in type 2 diabetic individuals (~10–25 μU/ml), the increment in plasma insulin concentration is linearly related to the decline in EGP (24). Therefore, the product of the basal rate of EGP and the simultaneously measured fasting plasma insulin concentration provides an index of hepatic insulin resistance, and this index of hepatic insulin resistance has been validated (12, 14). We also calculated the change in (Δ) EGP/insulin during the 40 mU⋅m⁻²⋅min⁻¹ insulin clamp step to provide another index of hepatic insulin sensitivity.

Total body water was calculated from the mean plasma [³H₂O] radioactivity measured at 90, 105, and 120 min after the intravenous bolus of [³H₂O]. Plasma [³H₂O] specific activity was calculated assuming that plasma water represents 93% of total plasma volume. FFM was calculated by dividing total body water by 0.73 (25).

Statistical analysis. Statistics were performed with StatView for Windows (version 5.0; SAS Institute, Cary, NC). Comparisons between groups were performed using ANOVA with Bonferroni/Dunn post hoc testing when appropriate. Linear or logarithmic (for nonlinearly distributed data) regression analysis was used to examine the relationships
between hepatic/peripheral insulin sensitivity and specific fat depots. All results are presented as means ± SE. A P value <0.05 was considered to be statistically significant.

RESULTS

Fat distribution. BMI and FM were similar in male and female subjects (Table 1). Despite similar BMI and FM, the SF and the SSF measured at L4–5 were significantly greater in female than in male subjects. The greater SF at L4–5 in female subjects was due entirely to a greater SSF. No differences in DSF at L4–5 or intra-abdominal VF area were observed between females and males.

Metabolic variables. FPG and HbA1c were slightly higher in male subjects than female subjects. The fasting plasma insulin concentration was similar in males and females. Basal EGP, EGP and TGD during the first insulin clamp step, and TGD during the second insulin clamp step were similar in male and female subjects (Table 1). Plasma insulin concentrations during the first insulin clamp step (67 ± 3 vs. 76 ± 5 μU/ml) and second insulin clamp step (330 ± 12 vs. 361 ± 19 μU/ml) were similar in male and female subjects.

Relationship between fat distribution and peripheral/hepatic insulin resistance. In male subjects, TGD during the first insulin clamp step correlated with total body FM (r = −0.37, P < 0.05) and with the BMI (r = −0.39, P < 0.05; Fig. 2). Hepatic insulin resistance (basal EGP × fasting plasma insulin concentration) also correlated with total body FM (r = 0.62, P < 0.0001) and with the BMI (r = 0.51, P < 0.01; Fig. 2).

In male subjects, TGD during the first insulin clamp step correlated inversely with visceral (VF; r = −0.45, P < 0.01), subcutaneous (SF; r = −0.46, P < 0.01), DSF (r = −0.46, P < 0.01), and superficial subcutaneous (SSF; r = −0.39, P < 0.05) fat areas (Fig. 3). TGD during the second insulin clamp step correlated only with VF (r = −0.37, P < 0.05) and not with SF, DSF, or SSF in male subjects. Expression of the data as the rate of glucose disposal per increment in plasma insulin concentration did not alter the relationships with any measure of body fat distribution. The hepatic insulin resistance index correlated with VF (r = 0.37, P < 0.05), SF (r = 0.47, P < 0.01), DSF (r = 0.49, P < 0.01), and SSF (r = 0.33, P < 0.05) in male subjects (Fig. 3). In male subjects, the fasting plasma FFA concentration did not correlate with any abdominal fat area, TGD, or hepatic insulin resistance index.

In female subjects, we failed to observe significant correlations between total body FM or BMI and TGD or the hepatic insulin resistance index (Fig. 4). VF correlated with TGD during the first and second insulin clamp steps (both r = −0.45, P < 0.05) and with the hepatic insulin resistance index (r = 0.49, P < 0.05; Fig. 5). There were no correlations between TGD or the hepatic insulin index and any measure of SF in female subjects (Fig. 5). In female subjects, the fasting plasma FFA concentration was positively correlated with total SF (r = 0.50, P = 0.009) and SSF (r = 0.51, P = 0.008) but not with DF, DSF, TGD, or hepatic insulin resistance.

When a combined analysis was performed using all subjects (males and females), TGD during the first
insulin clamp step was inversely correlated with total body FM ($r = -0.49$, $P < 0.001$), VF ($r = -0.45$, $P < 0.001$), and DSF ($r = -0.27$, $P < 0.05$; Fig. 6). TGD during the second insulin clamp step was inversely correlated only with VF ($r = -0.41$, $P < 0.01$). The hepatic insulin resistance index correlated with VF ($r = 0.39$, $P < 0.01$), SF ($r = 0.34$, $P < 0.01$), and DSF ($r = 0.41$, $P < 0.01$), but not with SSF. VF also was correlated with the EGP/insulin during the 40 mU·m$^{-2}$·min$^{-1}$ insulin clamp step ($r = 0.35$, $P < 0.01$). In stepwise multiple-regression analysis using gender, age, FFA concentration, VF, DSF, SSF, and total body FM as independent factors, only VF was a significant predictor of TGD during the first insulin clamp step ($r = -0.45$, $P < 0.01$), and total FM was the best predictor of hepatic insulin resistance ($r = 0.49$, $P < 0.001$).

DISCUSSION

In the present study, we have examined the relationship between fat distribution and peripheral (muscle) and hepatic insulin resistance in men and in women with type 2 diabetes mellitus. Previous studies that examined these relationships examined men only (1, 2, 5, 6, 22), women only (3, 8–10, 33), or included men and women in a single combined group analysis (11, 23, 31). We also have separated the SF into its deep and superficial components on the basis of its normal facial separation plane (30). The deep and SSF layers are histologically distinct (34), and recent data suggest that, in nondiabetic subjects, these fat depots may be metabolically distinct (27, 31). No published study has examined the relationship between superficial/deep subcutaneous adipose tissue and indexes of hepatic/peripheral insulin resistance in type 2 diabetic subjects. Basu et al. (7) measured deep superficial abdominal fat with computerized topography in 14 type 2 diabetics (5 females and 9 males) but presented a combined analysis of nondiabetic and diabetic subjects. Although an inverse correlation between deep subcutaneous abdominal fat and insulin-mediated whole body glucose disposal was found, when VF was included in a multivariate analysis, the deep subcutaneous abdominal fat no longer was a predictor of insulin resistance. Unlike the present study, these investigators used a combined hyperglycemic-hyperinsulinemic clamp so that a pure measure of insulin-mediated glucose disposal could not be obtained.

As expected, the percent body fat was significantly greater in type 2 diabetic female compared with male subjects (Table 1). When viewed in absolute amounts or as a percentage of total FM, there were no significant differences in VF between males and females. All of the increase in total body fat in female subjects was accounted for by an increase in subcutaneous fat area and, in particular, by an increase in the SSF (Table 1). Despite the significant differences in FM and fat topography (i.e., SSF) between females and males, peripheral and hepatic sensitivity to insulin was similar in
both groups. These observations underscore the importance of examining females and males separately when exploring the relationship between FM/topography and measures of insulin-mediated glucose disposal.

In male subjects, regression analysis demonstrated that TGD (primarily muscle) in response to a physiological increment in the plasma insulin concentration (~70 μU/ml; first insulin clamp step) was inversely

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**Fig. 4.** Relationship between total body fat mass (left)/BMI (right) and TGD during the 1st insulin clamp step (top) and the hepatic insulin resistance index (bottom) in female subjects.

**Fig. 5.** Relationship between VF area, abdominal SF, DSF, and SSF at L₄–₅ and TGD during the 1st insulin clamp step (top) and the hepatic insulin resistance index (bottom) in female subjects. NS, not significant.
correlated with total FM, BMI, VF, SF, SSF, and DSF area (Figs. 2 and 3). Simple correlation coefficients between first TGD and total FM, BMI, VF, SF, SSF, and DSF were of similar magnitude. These results are consistent with the majority of previous studies that have been carried out in male subjects (1, 2, 6, 23, 31) and indicate that the total amount of fat predicts the presence of peripheral (primarily muscle) insulin resistance in male type 2 diabetic subjects and any specific fat depot. In multivariate analysis, the visceral plus DSF are the best predictors of peripheral insulin resistance in male type 2 diabetic patients ($r = 0.54$, $P = 0.003$). Addition of total body FM does not significantly improve the $r$ value (0.56). This result is similar to that reported by Kelley et al. (31) in nondiabetic male subjects. The hepatic insulin resistance index (basal EGP × fasting plasma insulin concentration), like peripheral insulin resistance, also was correlated with total body FM, BMI, VF, SF, SSF, and DSF in male diabetic subjects (Figs. 2 and 3). In multivariate analysis, the total amount of FM per se, i.e., obesity, rather than the distribution of fat within the body, is the best predictor of hepatic insulin resistance in male subjects with type 2 diabetes mellitus. These results are very similar to those reported by Abate et al. (1) in nondiabetic males.

In female subjects, only VF displayed a significant association with TGD (1st and 2nd insulin clamp steps) and the hepatic insulin resistance index (Figs. 4 and 5). This result is consistent with a previous report in female subjects from our laboratory (8) and reports from other laboratories (3, 9, 10, 33). In contrast to the report by Kelley et al. (31), we failed to find any association between DSF, SSF, or SF and TGD in female diabetic subjects. However, it should be noted that these investigators (31) combined female and male subjects into a single group in their analysis. Examination of the scattergram plotting insulin-stimulated glucose disposal vs. total SF and SSF (31) suggests that all of the significance is accounted for by the male subjects. If there is a significant association between insulin-mediated glucose disposal and total SF or SSF, it must have been very weak (31). In contrast, the DSF (as well as VF) was associated inversely with insulin-mediated glucose disposal in the report by Kelley et al. (31). It should be noted, however, that Kelley et al. studied only nondiabetic females, whereas in the present study only type 2 diabetic females were examined. Moreover, the severity of insulin resistance in our diabetic females was much greater than in the nondiabetic subjects studied by Kelley et al. Our results suggest that, in insulin-resistant type 2 diabetic females, increased VF is the best correlate of whole body insulin resistance (Fig. 5). This observation may explain why increased total body FM (which primarily is accounted for by increased subcutaneous adipose tissue; Table 1) in female type 2 diabetic subjects does not correlate with insulin-mediated TGD (Fig. 2).
observation is consistent with previously published results from our laboratory (8).

In both males and females, VF was correlated with the hepatic insulin resistance index. In males, but not in females, the DSF also correlated with the hepatic insulin resistance index. It has been suggested that an increased release of FFA from the more lipolytically active visceral adipose tissue (26) in the portal vein might augment hepatic glucose production, impair the suppression of hepatic glucose production by insulin, and cause peripheral (muscle) insulin resistance (20). However, in the present study, we failed to observe any relationship between the circulating plasma FFA concentration and VF, SF, SSF, DSF, TGD, or the hepatic insulin resistance index in male diabetic subjects. In female diabetic subjects, the fasting plasma FFA concentration was positively correlated with total SF ($r = 0.50, P = 0.009$) and SSF ($r = 0.51, P = 0.008$). The fasting plasma FFA concentration was not correlated with VF, DSF, TGD, or hepatic insulin resistance. Multiple-regression analysis including all subjects demonstrated that VF and total body FM are the best predictors of peripheral and hepatic insulin resistance, respectively, independent of plasma FFA concentration, gender, and age. Based on these results, it is unlikely that elevated plasma FFA levels can account for the significant relationship between intra-abdominal VF/total body FM and peripheral (muscle)/hepatic tissue resistance to insulin. In recent years, it has become recognized that mature adipocytes can synthesize and secrete a number of proteins that exert local (paracrine) or distant (autocrine) effects on other tissues. Tumor necrosis factor (TNF)-α, which is secreted by mature adipocytes, has been shown to cause hepatic and peripheral insulin resistance (28). Most recently, Steppan et al. (37) reported a new adipocyte-derived factor, resistin, that is secreted by well-differentiated larger adipocytes and causes insulin resistance in vivo and in vitro in mice. These secretory factors were not measured in the present study, but it is possible that they may, in part, explain the association between insulin resistance and intra-abdominal VF/total body FM. Nonetheless, because subcutaneous adipose tissue accounts for ~80% of all body fat (4), whereas visceral adipose tissue represents only ~10% of all adipose tissue, the mechanism(s) responsible for the correlation between visceral adiposity and peripheral insulin resistance remain unknown. TNF-α gene expression and the rate of TNF-α secretion by adipocytes have been reported to be similar in subcutaneous and visceral adipose tissue (17, 19, 35), whereas regional differences in resistin and adiponectin production are unknown. Visceral adipocytes are lipolitically more active than SF cells, but fasting plasma FFA levels did not correlate with either total body or hepatic insulin resistance in the present study. Further investigations will be needed to elucidate the etiological factors responsible for the relationship between VF and total body/hepatic insulin resistance.

In summary, we measured abdominal SSF, DSF, and VF using MRI and examined the relationship between these fat depots and peripheral (muscle)/hepatic insulin sensitivity measured with the euglycemic insulin clamp/[3-3H]glucose technique in male and female type 2 diabetic patients. Strong correlations between visceral adiposity/total body FM and peripheral/hepatic insulin resistance, respectively, were observed, independent of gender. In male, but not in female type 2 diabetic subjects, abdominal subcutaneous adiposity, especially increased deep subcutaneous adipose tissue, also was associated with peripheral/hepatic insulin resistance. The explanation for the different relationship between fat topography and insulin resistance in males and females remains to be elucidated but may be explained by differences in fat cell size and/or in the release of adipocyte secretory factors that induce insulin resistance.

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