Increased Fat Mass Compensates for Insulin Resistance in Abdominal Obesity and Type 2 Diabetes
A Positron-Emitting Tomography Study

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To evaluate the relative impact of abdominal obesity and newly diagnosed type 2 diabetes on insulin action in skeletal muscle and fat tissue, we studied 61 men with (n = 31) or without (n = 30) diabetes, subgrouped into abdominally obese or nonobese according to the waist circumference. Adipose tissue depots were quantified by magnetic resonance imaging, and regional glucose uptake was measured using 2-[18F]fluoro-2-deoxyglucose/positron emission tomography during euglycemic hyperinsulinemia. Across groups, glucose uptake per unit tissue weight was higher in visceral (20.5 ± 1.4 μmol·min⁻¹·kg⁻¹) than in abdominal (9.8 ± 0.9 μmol min⁻¹·kg⁻¹, P < 0.001) or femoral (12.3 ± 0.6 μmol·min⁻¹·kg⁻¹, P < 0.001) subcutaneous tissue and ~40% lower than in skeletal muscle (33.1 ± 2.5 μmol·min⁻¹·kg⁻¹, P < 0.0001). Abdominal obesity was associated with a marked reduction in glucose uptake per unit tissue weight in all fat depots and in skeletal muscle (P < 0.001 for all regions). Recent type 2 diabetes per se had little additional effect. In both intra-abdominal adipose (r = −0.73, P < 0.0001) and skeletal muscle (r = −0.53, P < 0.0001) tissue, glucose uptake was reciprocally related to intra-abdominal fat mass in a curvilinear fashion. When regional glucose uptake was multiplied by tissue mass, total glucose uptake per fat depot was similar irrespective of abdominal obesity or type 2 diabetes, and its contribution to whole-body glucose uptake increased by ~40% in obese nondiabetic and nonobese diabetic men and was doubled in obese diabetic subjects. We conclude that 1) in abdominal obesity, insulin-stimulated glucose uptake rate is markedly reduced in skeletal muscle and in all fat depots; 2) in target tissues, this reduction is reciprocally (and nonlinearly) related to the amount of intra-abdominal fat; 3) mild, recent diabetes adds little insulin resistance to that caused by abdominal obesity; and 4) despite fat insulin resistance, an expanded fat mass (especially subcutaneous) provides a sink for glucose, resulting in a compensatory attenuation of insulin resistance at the whole-body level in men. Diabetes 54: 2720–2726, 2005
contribution of total fat mass versus its distribution and sensitivity to insulin in the genesis of whole-body insulin resistance and hyperglycaemia is not well defined. To evaluate the role of adipose tissue insulin resistance in obesity and type 2 diabetes, we applied the $[^{18}F]^{FDG}$-PET method to measure insulin-stimulated glucose uptake in nonobese and moderately obese men who were either normoglycemic or had a recent diagnosis of type 2 diabetes.

**RESEARCH DESIGN AND METHODS**

Sixty-one men participated in the study (Table 1). The diabetic subjects ($n = 31$) had recently been diagnosed with type 2 diabetes according to the World Health Organization criteria (10), and they were on diet treatment. A complete medical history and physical examination were carried out to exclude other diseases as well as diabetic complications (by retinal photography, autonomic nervous system function tests, and overnight urinary albumin excretion rate measurement). These patients had participated in a trial of antidiabetic therapy (29). The abdominal and femoral regions were imaged with a 0.23 T Outlook GP (Marconi Medical Systems, Vantaa, Finland) magnetic resonance imager (110) and by a $110$ min) was synthesized with an automatic apparatus by Wallac, Turku, Finland) in each time frame. The abdominal and femoral regions were imaged with a 0.23 T Outlook GP (Marconi Medical Systems, Vantaa, Finland) magnetic resonance imager as described previously (9). Adipose tissue masses in the abdominal region were measured at the level of L2/L3 intervertebral disc, as described by Abate et al. (13). In the femoral region, the adipose tissue area was always measured exactly at the middle of the thigh from an area 10 cm in length. Fat volume was then converted into fat weight using an adipose tissue density of 0.9106 ml/g.

The regions of interest (ROIs) were drawn on MRI images and were located in subcutaneous (16 ROIs per analysis per patient) and visceral (12 ROIs per analysis per patient) regions in the abdominal area. In the femoral region, ROIs were drawn in the antero-lateral muscle compartments and in the subcutaneous adipose tissue (18 ROIs per analysis per patient). The ROIs were copied into the $[^{18}F]^{FDG}$ images to cross-sectional slices from identical planes.

$[^{18}F]^{FDG}$ ($t_{1/2} = 110$ min) was synthesized with an automatic apparatus by a modified method of Hamacher et al. (14). The specific radioactivity at the end of the synthesis was more than 75 GBq/mmol, and the radiochemical purity exceeded 95%. The subject was positioned supine in a 15-slice ECAT 931/08-tomograph (Siemens/CTI, Knoxville, TN) with the femoral or abdominal region within the gantry. Before the emission scan, a 5-min transmission scan for correction of photon attenuation was performed in both the femoral and abdominal regions with a removable ring source containing $^{68}$Ge. All data were corrected for dead time, decay, and measured photon attenuation and reconstructed in a $256 \times 256$ matrix. For image processing, a Bayesian iterative reconstruction algorithm using median root prior with 150 iterations and the Bayesian coefficient of 0.3 was applied (11,15). PET counts were converted into radioactivity concentration values (Bq/ml) using a calibration factor derived from phantom studies.

Plasma and tissue time activity curves for skeletal muscle and adipose tissue were analyzed graphically to quantify the fractional rate of tracer uptake, $K_r (S,16,17)$. Linear regression was used to determine the slope of the time–activity points between 2 and 18 min after the injection of the $[^{18}F]^{FDG}$ tracer in the first area scanned and between 27 and 41 min after tracer injection in the following area. The rate of regional glucose uptake during insulin stimulation was calculated by multiplying fractional $[^{18}F]^{FDG}$ uptake ($K_r$) by plasma glucose concentration divided by a lumped constant value of 1.14 in adipose tissue (5) and 1.2 in skeletal muscle (18).

Whole-body glucose uptake ($M$ value) was calculated according to the euglycemic-hyperinsulinemic clamp technique as previously described (19). Whole-body insulin sensitivity was calculated as the ratio of $M$ to the steady-state plasma insulin concentrations achieved during the clamp.

**TABLE 1**

**Clinical and metabolic characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Type 2 diabetes</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonobese</td>
<td>Obese</td>
<td>Nonobese</td>
</tr>
<tr>
<td>$n$</td>
<td>20</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37±3</td>
<td>37±4</td>
<td>58±2</td>
</tr>
<tr>
<td>Body wt (kg)</td>
<td>77±2</td>
<td>103±3</td>
<td>79±2</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>24.5±0.6</td>
<td>30.9±0.7</td>
<td>25.5±0.5</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>84±2</td>
<td>105±2</td>
<td>91±1</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>61.9±1.5</td>
<td>73.0±1.8</td>
<td>60.4±1.4</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>20±1</td>
<td>29±1</td>
<td>22±1</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td>5.4±0.1</td>
<td>5.4±0.2</td>
<td>7.1±0.2</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>5.4±0.1</td>
<td>5.5±0.1</td>
<td>6.4±0.2</td>
</tr>
<tr>
<td>FPI (pmol/l)</td>
<td>34±2</td>
<td>63±7</td>
<td>40±3</td>
</tr>
<tr>
<td>Fasting FFA (mmol/l)</td>
<td>0.59±0.04</td>
<td>0.63±0.06</td>
<td>0.51±0.07</td>
</tr>
<tr>
<td>SSPG (nmol/l)</td>
<td>5.1±0.1</td>
<td>5.1±0.1</td>
<td>5.3±0.1</td>
</tr>
<tr>
<td>SSPi (pmol/l)</td>
<td>406±13</td>
<td>478±27</td>
<td>496±22</td>
</tr>
<tr>
<td>SS-FFA (mmol/l)</td>
<td>0.10±0.01</td>
<td>0.15±0.02</td>
<td>0.09±0.01</td>
</tr>
<tr>
<td>$M$ (mmol/min)</td>
<td>2.2±0.2</td>
<td>1.6±0.3</td>
<td>1.8±0.2</td>
</tr>
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<td>$M$/SSPi</td>
<td>5.7±0.7</td>
<td>3.4±0.7</td>
<td>3.5±0.5</td>
</tr>
<tr>
<td>$M_{\text{SSF}}$ (mmol $\cdot$ min$^{-1}$ $\cdot$ kg$^{-1}$)</td>
<td>28.9±2.8</td>
<td>15.1±2.4</td>
<td>23.1±2.5</td>
</tr>
<tr>
<td>$M_{\text{SSF}}$/SSPi</td>
<td>0.09±0.01</td>
<td>0.05±0.01</td>
<td>0.06±0.01</td>
</tr>
</tbody>
</table>

Data are means ± SE. *P value for the effect of obesity and type 2 diabetes by two-way ANOVA. FPG, fasting plasma glucose; FPI, fasting plasma insulin; SS, steady state; SSPG, steady-state plasma glucose; SSPi, steady-state plasma insulin.
Calculations were performed using the SAS statistical program package, significant differences between the four groups. Linear, nonlinear, and multi-

*Obesity and their interaction were tested using two-way ANOVA. Post hoc

grams of fat-free mass (M) the clamp than nondiabetic, nonobese subjects. During the

subjects, whereas diabetes had no statistically significant

association with these variables (Table 1).

In association with abdominal obesity, whole-body insulin-mediated glucose uptake was reduced by −35%, whether expressed as total rate or normalized per kilogram of fat-free mass (Mffm). The presence of diabetes had a small additional effect to reduce M, which reached full statistical significance when normalizing M or Mffm by the steady-state plasma insulin concentration (Table 1).

**Regional metabolism.** Intra-abdominal fat represented roughly 10% of total body fat, with no significant differences across groups, and was directly related to total fat mass (r = 0.72, P < 0.0001). Intra-abdominal fat was directly related to waist circumference in a linear fashion (y = −3.083 + 0.054x; r = 0.72, P < 0.0001). All fat depots (abdominal visceral, abdominal subcutaneous, total subcutaneous, and total) as well as skeletal muscle mass were greater in obese than nonobese subjects regardless of diabetes (Table 2). Across groups, the rate of insulin-stimulated adipose tissue glucose uptake per unit tissue weight was approximately twice as high in visceral (20.5 ± 1.4 μmol · min⁻¹ · kg⁻¹) than in abdominal (9.8 ± 0.9 μmol · min⁻¹ · kg⁻¹, P < 0.0001) or femoral subcutaneous tissue (12.3 ± 0.6 μmol · min⁻¹ · kg⁻¹, P < 0.0001) and ~40% lower than in skeletal muscle (33.1 ± 2.5 μmol · min⁻¹ · kg⁻¹, P < 0.0001) (Fig. 1). Abdominal obesity was associated with reduced glucose uptake in visceral adipose tissue (P < 0.001); in subcutaneous abdominal and femoral fat depots, this effect was modified by type 2 diabetes (diabetes × obesity interaction, P = 0.02 and P = 0.04, respectively; Fig. 1). In these tissues, in fact, the presence of type 2 diabetes blunted the difference in glucose uptake due to abdominal obesity. In none of the adipose regions did type 2 diabetes per se affect glucose uptake in a statistically significant manner. With regard to skeletal muscle, insulin-stimulated glucose uptake in the femoral skeletal muscle was significantly reduced by abdominal obesity (P < 0.01), whereas diabetes per se did not affect glucose uptake (Fig. 1). In both intra-abdominal adipose tissue (Fig. 2) and skeletal muscle tissue (Fig. 3), glucose uptake per kilogram was inversely related to the mass of the intra-abdominal fat depot in a curvilinear fashion.

When regional glucose uptake rates were multiplied by the corresponding tissue mass, neither abdominal obesity nor type 2 diabetes affected total glucose uptake per fat depot, whereas obesity was associated with reduced muscle glucose uptake (Table 2). In contrast, the contribution of total fat glucose uptake to whole-body glucose uptake was increased independently by obesity and type 2 diabetes.
tes, whereas the contribution of total muscle glucose uptake to whole-body glucose disposal was similar across groups (Fig. 4). The sum of whole-body fat and muscle glucose uptake (Table 2) represented 74% of total \( M \) (Table 1), with no major differences between obese and nonobese and between diabetic and nondiabetic subjects.

**DISCUSSION**

The present results provide novel information on adipose tissue mass and glucose uptake in men with abdominal obesity and newly diagnosed type 2 diabetes. In the scanned volume, intra-abdominal fat mass averaged \( \approx 10\% \) of total body fat and, like subcutaneous fat, was directly related to total fat mass, confirming that weight excess is associated with a generalized expansion of fat depots. In intra-abdominal fat, insulin-stimulated glucose uptake was twice as high as in subcutaneous adipose tissue and only \( \approx 40\% \) lower than in skeletal muscle. Although the enhanced metabolic activity of intra-abdominal versus subcutaneous fat has been noted previously (9,20,21), perhaps less appreciated is the fact that the adipocyte, when stimulated by insulin in vivo simultaneously with skeletal muscle, is a very avid glucose consumer despite a cell volume that is mostly (by \( \approx 90\% \)) occupied by lipid droplets (9). Clearly, its glycolytic capacity, in terms of enzyme concentrations and/or activity, must exceed that of resting muscle (22).

In our group of subjects, abdominal obesity was defined as a waist circumference >94 cm, which corresponded to a total mass of intra-abdominal fat (sum of visceral and retroperitoneal fat) of 2 kg. This degree of intra-abdominal fat accumulation was quantitatively associated with decreased insulin-stimulated glucose uptake per unit tissue mass in all tissues scanned, i.e., subcutaneous and intra-abdominal fat, and skeletal muscle (Fig. 1). Interestingly, when drawn over a continuum, these relationships were highly curvilinear (Figs. 2 and 3), such that an increase in intra-abdominal fat mass from 0.5 to 2 kg (i.e., up to the median of the entire group) predicted a \( \approx 65\% \) drop in glucose uptake in both abdominal adipose tissue and

![Image](image_url)
skeletal muscle, with little further decrease for increments in intra-abdominal fat of up to 4.5 kg. This possibly reflects the fact that initial increases in fat mass are mostly due to adipocyte hypertrophy. Because large adipocytes are less insulin sensitive than small adipocytes (23), the expanded fat depot loses most of its ability to take up glucose in response to insulin. Further increases in fat accumulation occur by differentiation of preadipocytes into small, relatively insulin-sensitive adipocytes, such that the insulin sensitivity of the depot declines only slightly more. Notably, an inverse relationship between fat mass and fat glucose uptake was evident also in the abdominal subcutaneous depot ($r = -0.37, P = 0.003$), indicating that downregulation of insulin sensitivity in expanding fat depots may be a general phenomenon. The changes in cellular phenotype that occur as adipocytes hypertrophy include a strictly mechanical effect, whereby an enlarged lipid droplet pushes cell organelles, such as mitochondria, against the cell surface (24). The role of mitochondria may be important especially in visceral fat. In addition, endocrine and paracrine hormonal signals may also play an important role in decreasing oxidative capacity in enlarged adipocytes (24).

In contrast to fat mass, skeletal muscle mass was only slightly (~10%) increased in association with obesity, and even less so in association with diabetes (Table 2), and there was little relation between skeletal muscle mass and glucose uptake (data not shown). Therefore, the reciprocal relationship between muscle glucose uptake and intra-abdominal fat mass (Fig. 3) must reflect tissue cross-talk. Expanded, insulin-resistant adipose tissue has a reduced capacity to reesterify FFAs (which then circulate at higher levels under insulinized conditions; Table 1) and releases increased amounts of cytokines with insulin-desensitizing activity (such as tumor necrosis factor-$\alpha$ [3]) and reduced amounts of the insulin-sensitizing cytokine, adiponectin (25). By both of these mechanisms, fat accumulates intracellularly and intracellular insulin signaling is impeded, resulting in insulin resistance.

The impact of obesity on fat glucose uptake was especially strong in nondiabetic subjects; in diabetic subjects, the reduction in abdominal subcutaneous fat glucose uptake was blunted. Whether this was due to the higher steady-state plasma insulin levels achieved in diabetic subjects during the clamp (Table 1) or to some adaptation induced by chronic hyperglycemia is not clear from the data. On the other hand, when accounting for abdominal obesity, diabetes per se had little effect also on skeletal muscle or total body glucose uptake. It must be recalled, however, that the diabetic patients selected for this study were mildly hyperglycemic, newly diagnosed, and drug-naive; in more severe, long-standing diabetes, the insulin resistance may be in part independent of abdominal obesity. Another factor potentially interfering with a precise assessment of the impact of diabetes itself on insulin resistance is that our diabetic patients were ~20 years old.
older than the nondiabetic subjects. Insulin sensitivity decreases slightly with aging, however. In the European Group for the Study of Insulin Resistance study, insulin-mediated glucose uptake (using the same clamp protocol as adopted in the present study) was estimated to decrease by an average of 1.6 μmol/kg·min per decade of age (26). Thus, the age difference had but a minor quantitative effect on the insulin resistance of our diabetic group.

When calculated per tissue depot, the differences in adipose tissue glucose uptake between obese and nonobese subjects vanished. Thus, glucose uptake in each scanned fat depot, intra-abdominal, subcutaneous, and total, was similar irrespective of obesity or diabetes. This sort of compensation was more evident when expressing fat glucose uptake as a percentage of total glucose disposal (Fig. 4): percent fat glucose uptake was increased by ~40% in obese nondiabetic and nonobese diabetic subjects (in comparison with nonobese nondiabetic subjects) and was doubled in obese diabetic patients. Thus, in insulin-resistant states, glucose disposition is impaired, but the effect at the whole-body level is mitigated by an expanded fat mass. In obese diabetic patients, fat glucose uptake may amount to one-half the rate of skeletal muscle glucose uptake (Table 2). This phenomenon has been previously surmised to occur in obese subjects (27) in whom insulin-stimulated glucose uptake, when expressed not per unit fat-free mass but as total M, declined only at BMIs in the range of morbid obesity. The present study demonstrates (and extends to diabetes) this phenomenon by directly measuring regional glucose disposal and total body glucose uptake. To draw up the full balance of insulin-stimulated glucose disposal, it is worth noting that the fraction of total M that was unaccounted for by the sum of regional (total fat and skeletal muscle) glucose uptake averaged 0.57 ± 0.07 mmol/min in the whole study group. This “residual” amount matches rather closely the glucose consumption of non–insulin-dependent tissues (brain, erythrocytes, kidney, etc.), which has been estimated to range 0.5–0.7 mmol/min (28).

The present study was conducted in men. We have previously shown that skeletal muscle insulin sensitivity is higher in lean women than in men (29), but unfortunately adipose tissue was not evaluated. Our current preliminary data in obese women and men does not support any sex-related differences in adipose tissue glucose uptake between obese and nonobese subjects. When calculated per tissue depot, the differences in adipose tissue glucose uptake between obese and nonobese subjects vanished. Thus, glucose uptake in each scanned fat depot, intra-abdominal, subcutaneous, and total, was similar irrespective of obesity or diabetes. This sort of compensation was more evident when expressing fat glucose uptake as a percentage of total glucose disposal (Fig. 4): percent fat glucose uptake was increased by ~40% in obese nondiabetic and nonobese diabetic subjects (in comparison with nonobese nondiabetic subjects) and was doubled in obese diabetic patients. Thus, in insulin-resistant states, glucose disposition is impaired, but the effect at the whole-body level is mitigated by an expanded fat mass. In obese diabetic patients, fat glucose uptake may amount to one-half the rate of skeletal muscle glucose uptake (Table 2). This phenomenon has been previously surmised to occur in obese subjects (27) in whom insulin-stimulated glucose uptake, when expressed not per unit fat-free mass but as total M, declined only at BMIs in the range of morbid obesity. The present study demonstrates (and extends to diabetes) this phenomenon by directly measuring regional glucose disposal and total body glucose uptake. To draw up the full balance of insulin-stimulated glucose disposal, it is worth noting that the fraction of total M that was unaccounted for by the sum of regional (total fat and skeletal muscle) glucose uptake averaged 0.57 ± 0.07 mmol/min in the whole study group. This “residual” amount matches rather closely the glucose consumption of non–insulin-dependent tissues (brain, erythrocytes, kidney, etc.), which has been estimated to range 0.5–0.7 mmol/min (28).

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In conclusion, the present study shows that 1) in abdominal obesity insulin-stimulated glucose uptake rate is markedly reduced not only in skeletal muscle but also in all fat depots; 2) in target tissues, this reduction is reciprocally (and nonlinearly) related to the amount of intra-abdominal fat; 3) mild, recent diabetes adds little insulin resistance to that caused by abdominal obesity; and 4) despite fat insulin resistance, an expanded fat mass (especially subcutaneous) provides a sink for glucose, resulting in a compensatory attenuation of insulin resistance at the whole-body level.

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ADIPOSE TISSUE GLUCOSE METABOLISM IN MEN


