Original Article

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-[^{18}F]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

Increased adipose tissue mass and obesity are closely related to insulin resistance and abnormalities in glucose metabolism. The risk of type 2 diabetes increases with increasing BMI (1). Patients with diabetes tend to have an android pattern of fat distribution, with accumulation of fat in the abdomen regardless of sex (2). Increased intra-abdominal adipose tissue has been suggested to contribute both to the development of peripheral insulin resistance and to the increased risk of cardiovascular events. The expansion of adipose tissue may have metabolic consequences for other tissues. For instance, release of increased amounts of fatty acids, subsequently oxidized and stored in skeletal muscle, liver, and pancreas (3), and other adipose tissue-derived mediators, such as tumor necrosis factor-α (4), with insulin-desensitizing activity may disturb the function of insulin target tissues.

In humans, computed tomography and magnetic resonance imaging (MRI) have been used to quantitate visceral fat (5–7). Obtaining direct information on intra-abdominal adipose tissue metabolism in vivo has been much more difficult. We recently reported on the use and validation of the [^{18}F]-fluorodeoxyglucose/positron emitting tomography ([^{18}F]FDG-PET) method, which provides direct depot-specific measurements of insulin-stimulated glucose uptake in subcutaneous and intra-abdominal adipose tissues (8,9). In type 2 diabetes, visceral adiposity is associated with peripheral (5,7) and hepatic insulin resistance (5), which predict and antecede overt diabetes. However, the relative

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FFA, free fatty acid; [^{18}F]FDG, [^{18}F]fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; ROI, region of interest.

TABLE 1
Clinical and metabolic characteristics

	Control subjects		Type 2 diabetes		*P**	
	Nonobese	Obese	Nonobese	Obese	Obesity	Type 2 diabetes
n	20	10	12	19	—	—
Age (years)	37 ± 3	37 ± 4	58 ± 2	58 ± 2	NS	<0.0001
Body wt (kg)	77 ± 2	103 ± 3	78 ± 2	92 ± 2	<0.0001	0.02
BMI (kg/m^2)	24.5 ± 0.6	30.9 ± 0.7	25.5 ± 0.5	29.5 ± 0.7	<0.0001	NS
Waist (cm)	84 ± 2	105 ± 2	91 ± 1	105 ± 2	<0.0001	NS
Fat-free mass (kg)	61.9 ± 1.5	73.0 ± 1.8	60.4 ± 1.4	64.9 ± 1.6	<0.0001	0.01
Body fat (%)	20 ± 1	29 ± 1	22 ± 1	29 ± 1	<0.0001	NS
FPG (mmol/l)	5.4 ± 0.1	5.4 ± 0.2	7.1 ± 0.2	7.7 ± 0.3	NS	<0.0001
A1C (%)	5.4 ± 0.1	5.5 ± 0.1	6.4 ± 0.2	6.7 ± 0.2	<0.01	<0.0001
FPI (pmol/l)	34 ± 2	63 ± 7	40 ± 3	61 ± 9	<0.0001	NS
Fasting FFA (mmol/l)	0.59 ± 0.04	0.63 ± 0.06	0.51 ± 0.07	0.55 ± 0.05	NS	NS
SSPG (mmol/l)	5.1 ± 0.1	5.1 ± 0.1	5.3 ± 0.1	5.1 ± 0.1	NS	NS
SSPI (pmol/l)	406 ± 13	478 ± 27	496 ± 22	511 ± 20	<0.05	0.003
SS-FFA (mmol/l)	0.10 ± 0.01	0.15 ± 0.02	0.09 ± 0.01	0.16 ± 0.02	0.002	NS
M (mmol/min)	2.2 ± 0.2	1.6 ± 0.3	1.8 ± 0.2	1.4 ± 0.2	0.02	NS
M/SSPI	5.7 ± 0.7	3.4 ± 0.7	3.5 ± 0.5	2.9 ± 0.4	0.02	0.03
M_{ffm} (μmol · min^{-1} · kg^{-1})	28.9 ± 2.8	15.1 ± 2.4	23.1 ± 2.5	15.2 ± 2.1	<0.002	NS
M_{ffm}/SSPI	0.09 ± 0.01	0.05 ± 0.01	0.06 ± 0.01	0.04 ± 0.01	<0.01	(0.06)

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.

contribution of total fat mass versus its distribution and sensitivity to insulin in the genesis of whole-body insulin resistance and hyperglycemia 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 medication described previously (11). Thirty nondiabetic men were used as control subjects; 12 of them were middle-aged men recruited for this study, and 18 were younger men studied previously (9). Subjects were further classified as abdominally obese (12) if their waist circumference was >94 cm. The nature, purpose, and potential risks of the study were explained to all subjects before they gave their written informed consent to participate. The ethical committee of the hospital district of Southwest Finland approved the study. The study was conducted according to the principles of the Declaration of Helsinki.

Anthropometric measurements. Height and weight were measured by standard procedures. Total body fat content was estimated by the electrical bioimpedance method (Bioelectrical Impedance Analysis; Akern, RJL Systems, Florence, Italy). Whole-body subcutaneous fat mass was calculated by subtracting visceral fat mass from total fat mass. Waist circumference was measured at the level of the umbilicus. Skeletal muscle mass was estimated to be 45% of the fat-free mass.

[^{18}F]FDG-PET study. [^{18}F]FDG-PET studies were performed after an overnight fast. Alcohol consumption and fatty meals were avoided for 3 days before the study, and strenuous physical activity was not allowed for 48 h before the study. All studies were performed in the supine position. Two catheters were inserted: one into the antecubital vein of the left hand for infusion of glucose and insulin and injection of [^{18}F]FDG, and another one into the radial artery of the right hand for blood sampling. Each study was performed under conditions of euglycemic hyperinsulinemia (6 pmol · min^{-1} · kg^{-1}) and lasted 140 min. Sixty minutes after the start of the clamp, after steady-state glucose concentrations had been reached, 0.18–0.19 GBq of [^{18}F]FDG was injected intravenously. First, a 20-min dynamic scan of either the femoral or abdominal region was started simultaneously with the injection (2- × 30-, 4- × 60-, and 3- × 300-s frames). Thereafter, either an abdominal or femoral dynamic scan for 18 min (6 × 180 s) was performed. Plasma radioactivity was measured using an automatic γ-counter (Wizard 1480; Wallac, Turku, Finland) in each time frame.

MRI. 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 0.9196 mg/ml. 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/μmol, 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 × 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_i (8,16,17). 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_i) by plasma glucose concentration divided by a lumped constant value of 1.14 in adipose tissue (8) 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 2
Tissue mass and insulin-mediated glucose uptake

	Control subjects		Type 2 diabetes			
	Nonobese	Obese	Nonobese	Obese	*P** obesity	Type 2 diabetes
Tissue mass (kg)						
Intra-abdominal fat	1.5 ± 0.1	2.7 ± 0.2	1.8 ± 0.2	2.6 ± 0.2	<0.0001	NS
Abdominal SC fat	3.1 ± 0.3	6.7 ± 0.7	3.3 ± 0.2	5.0 ± 0.4	<0.0001	0.02
Whole-body SC fat	14.1 ± 1.0	27.0 ± 1.4	15.6 ± 1.0	24.2 ± 1.3	<0.0001	NS
Whole-body fat	15.6 ± 1.1	29.7 ± 1.3	17.4 ± 1.0	26.8 ± 1.5	<0.0001	NS
Skeletal muscle	27.9 ± 0.7	32.9 ± 0.8	27.2 ± 0.6	29.2 ± 0.7	<0.0001	0.01
Depot GU (μmol/min)						
Intra-abdominal fat	33 ± 2	33 ± 4	34 ± 3	41 ± 5	NS	NS
Whole-body SC fat	193 ± 16	204 ± 23	183 ± 22	251 ± 18	NS	NS
Whole-body fat	226 ± 17	237 ± 26	217 ± 24	292 ± 22	NS	NS
Skeletal muscle	1,190 ± 148	756 ± 152	1,060 ± 159	717 ± 68	<0.01	NS
Sum†	1,417 ± 147	993 ± 167	1,276 ± 169	1,009 ± 68	<0.02	NS

Data are means ± SE. **P* value for the effect of obesity and type 2 diabetes by two-way ANOVA. †Sum of glucose uptake by whole-body fat and skeletal muscle. SC, subcutaneous.

Biochemical analyses. Arterial plasma glucose was measured in duplicate by the glucose oxidase method (Analox GM9 Analyzer; Analox Instruments, London, U.K.). Glycosylated hemoglobin (A1C) was measured by fast protein liquid chromatography (MonoS; Pharmacia, Uppsala, Sweden), with a normal reference range of 4.2–6.0%. Serum insulin concentrations were measured basally and at 60-min intervals during insulin infusion using a double-antibody fluoroimmunoassay (Autodelfia; Wallac). Serum free fatty acids (FFAs) were determined by an enzymatic method (ACS-ACOD Method; Wako Chemicals, Neuss, Germany).

Statistical analysis. Power analysis was made based on previous results on subcutaneous glucose uptake in adipose tissue (9). To detect a difference of 11.1 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ with a power of >80% and using a significance level (two sided) of 5%, at least 10 subjects were needed per group.

Results are expressed as means ± SE. The effect of diabetes and abdominal obesity and their interaction were tested using two-way ANOVA. Post hoc analyses were performed using the Bonferroni-Dunn test to reveal statistically significant differences between the four groups. Linear, nonlinear, and multiple regression analyses were carried out by standard techniques. Statistical calculations were performed using the SAS statistical program package, version 8.2 (SAS Institute, Cary, NC).

RESULTS

Whole-body metabolism. Type 2 diabetic patients, whether obese or nonobese, were significantly older than nondiabetic control subjects and had higher fasting plasma glucose and serum A1C concentrations. All indexes of adiposity (BMI, waist circumference, and whole-body fat mass) were higher in abdominally obese than in nonobese subjects. Of note is that fat-free mass was significantly less in obese type 2 diabetic patients than in obese control subjects. Fasting serum insulin concentrations were higher in abdominally obese than in nonobese subjects, whereas diabetes had no statistically significant association with these variables (Table 1).

On the clamp, euglycemia was maintained in all groups with no difference among them (Table 1). However, patients with type 2 diabetes and/or abdominal obesity had higher steady-state plasma insulin concentrations during the clamp than nondiabetic, nonobese subjects. During the clamp, obese subjects had higher serum FFA concentrations than nonobese control subjects, regardless of diabetes.

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 (M_{ffm}). The presence of diabetes had a small additional effect to reduce M, which reached full statistical significance when normalizing M or M_{ffm} 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 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 $\mu mol \cdot min^{-1} \cdot kg^{-1}$) than in abdominal (9.8 ± 0.9 $\mu mol \cdot min^{-1} \cdot kg^{-1}$, $P < 0.001$) or femoral subcutaneous tissue (12.3 ± 0.6 $\mu mol \cdot min^{-1} \cdot kg^{-1}$, $P < 0.001$) and ~40% lower than in skeletal muscle (33.1 ± 2.5 $\mu mol \cdot min^{-1} \cdot kg^{-1}$, $P < 0.0001$) (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 diabe-

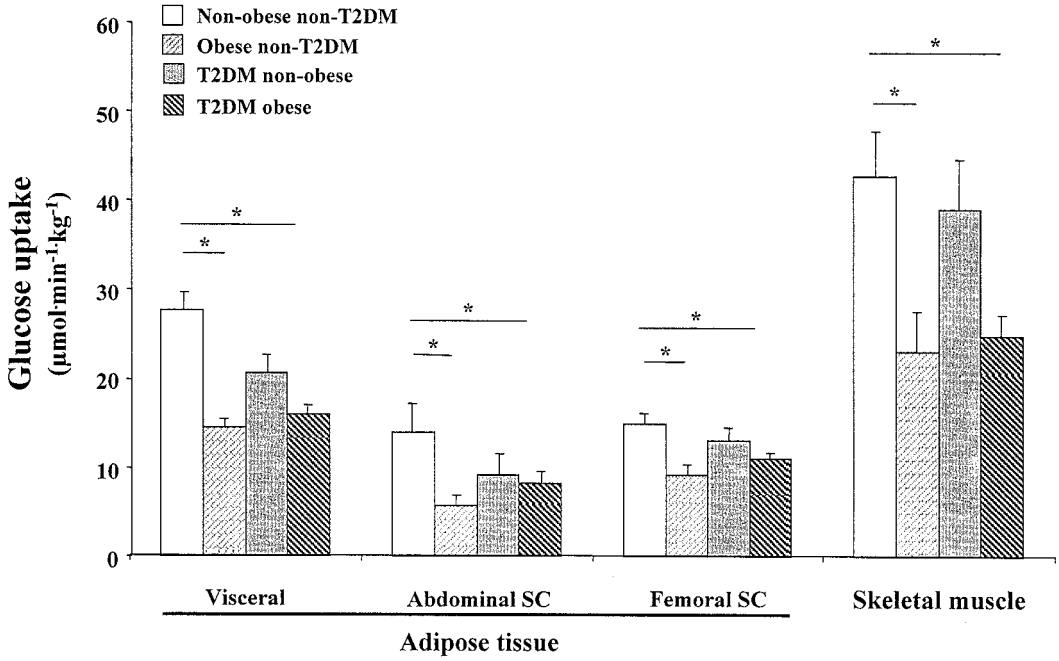

FIG. 1. Insulin-stimulated glucose uptake rate per unit tissue weight in adipose tissue and in skeletal muscle as measured directly by [^{18}F]FDG-PET. Bars denote means ± SE. *P < 0.01 by Bonferroni-Dunn test.

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 ~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 ~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 >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 ~65% drop in glucose uptake in both abdominal adipose tissue and

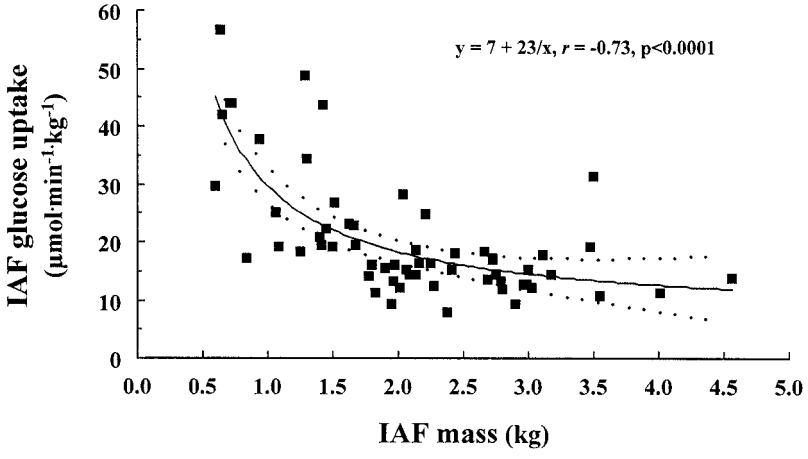

FIG. 2. Relationship between intra-abdominal fat (IAF) mass and intra-abdominal fat glucose uptake. The solid line is the line of best fit, and the dotted lines enclose its 95% CI.

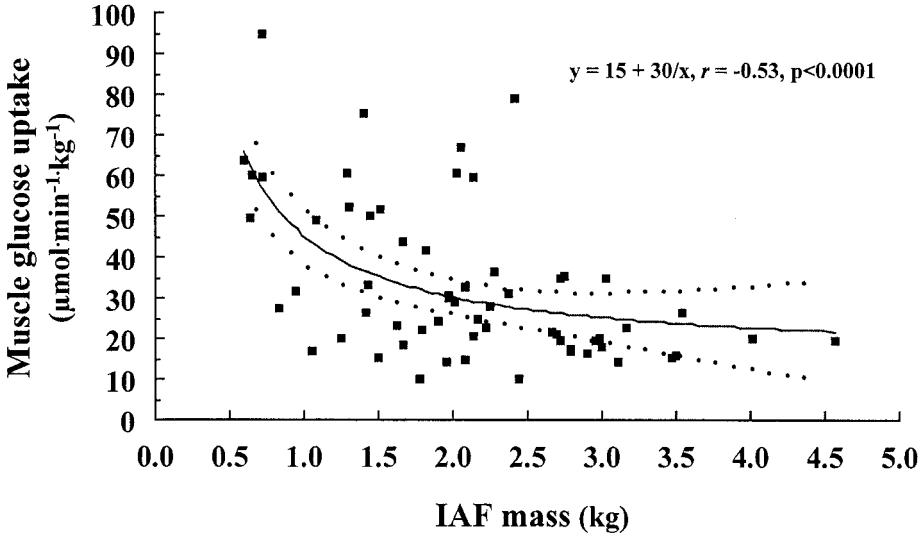

FIG. 3. Relationship between intra-abdominal fat (IAF) mass and skeletal muscle glucose uptake. The solid line is the line of best fit, and the dotted lines enclose its 95% CI.

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).

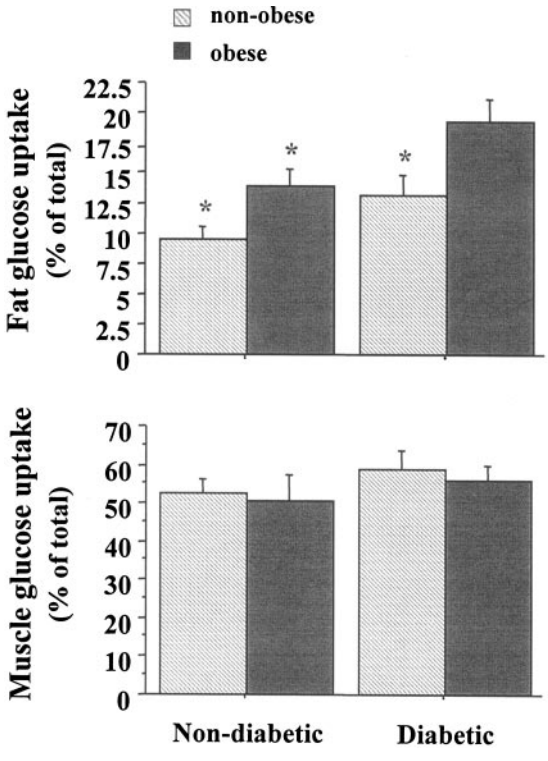

FIG. 4. Contribution of fat glucose uptake (*top*) and skeletal muscle glucose uptake (*bottom*) to whole-body glucose uptake by presence of abdominal obesity and diabetes. Bars are means ± SE. *$P < 0.01$ vs. obese diabetic subjects by Bonferroni-Dunn test.

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-α [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

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$_{ffm}$ 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 per adipose mass unit (data not shown).

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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