# Effect of Bariatric Surgery on Adipose Tissue Glucose Metabolism in Different Depots in Patients With or Without Type 2 Diabetes

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## OBJECTIVE

**We investigated fat distribution and tissue-specific insulin-stimulated glucose uptake (GU) in seven fat compartments (visceral and subcutaneous) and skeletal muscle in morbidly obese patients with (T2D) and without (ND) type 2 diabetes before and 6 months after bariatric surgery.**

## RESEARCH DESIGN AND METHODS

**A total of 23 obese patients (BMI 43.0 ± 3.6 kg/m$^2$; 9 T2D and 14 ND) were recruited from a larger, randomized multicenter SLEEVEPASS study. MRI (for fat distribution) and [$^{18}$F]-fluorodeoxyglucose PET (for GU) studies were performed for the obese patients before and 6 months postsurgery; 10 lean subjects served as control subjects and were studied once.**

## RESULTS

**At baseline, visceral fat GU was 30 ± 7% of muscle GU in control subjects and 57 ± 5% in obese patients. Visceral and deep subcutaneous fat were more abundant (despite same total fat mass) and less insulin sensitive in T2D than ND; in both, GU was impaired compared with control subjects. Postsurgery, visceral fat mass decreased (∼40%) more than subcutaneous fat (7%). Tissue-specific GU was improved, but not normalized, at all sites in T2D and ND alike. The contribution of visceral fat to whole-body GU was greater in T2D than ND but decreased similarly with surgery. Subcutaneous fat made a fourfold greater contribution to whole-body GU in obese versus lean subjects (15% vs. 4%) both before and after surgery.**

## CONCLUSIONS

**Bariatric surgery leads to sustained weight loss and improves tissue-specific glucose metabolism in morbidly obese patients. We conclude that *1*) enhanced visceral fat accumulation is a feature of T2D, *2*) severe obesity compromises muscle insulin sensitivity more than fat insulin sensitivity, and *3*) fat mass expansion is a sink for plasma glucose.**


Visceral fat (VF) and subcutaneous fat (SC) are structurally, metabolically, and functionally distinct, albeit both contribute to obesity (1). Abdominal SC fat has clearly defined, metabolically distinct deep and superficial layers separated by the Scarpa fascia (2,3). Research suggests that the deep layers are metabolically more active

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and, hence, heavily linked to metabolic complications, particularly to insulin resistance and type 2 diabetes (T2D) (4,5). The concentration of saturated fatty acids in the deep layer is higher compared with the superficial layer, providing additional evidence of its higher metabolic activity (6).

Accumulation of abdominal VF is an independent risk factor for obesity-related metabolic abnormalities (7). VF can be partitioned into intraperitoneal and extraperitoneal compartments using anatomical reference points such as the kidneys and ascending and descending colon (8). The release of free fatty acids (FFAs) from the intraperitoneal depot drains into the portal system, interfering with hepatic glucose metabolism (9), leading to hyperinsulinemia and insulin resistance. Extraperitoneal fat, on the other hand, drains into the systemic circulation and thus is not directly involved in hepatic glucose metabolism (8).

Absolute quantification of fat mass is achieved by MRI, whereas tissue-specific glucose metabolism can be noninvasively assessed using positron emission tomography (PET) with [$^{18}$F]-fluorodeoxyglucose ([$^{18}$F]-FDG) (10). Combined PET/MRI thus provides anatomical and functional information on specific tissue compartments. Bariatric surgery leads to major, sustained weight loss and improves metabolic and lipid profiles in obese individuals with or without T2D (11). We hypothesized that bariatric surgery may have differential effects on metabolism in different adipose tissue compartments in severely obese patients. We therefore combined PET/MRI to assess the effect of bariatric surgery on fat distribution and glucose uptake (GU) in different fat compartments in severely obese patients with or without diabetes.

## RESEARCH DESIGN AND METHODS

### Patients

Patient population and study design have previously been described (12). Briefly, a total of 23 morbidly obese patients (BMI $\geq$40 kg/m$^2$ or $\geq$36 kg/m$^2$ with an additional obesity-related comorbid condition) were recruited from the SLEEVEPASS study, a larger randomized controlled clinical trial comparing different surgical techniques for the treatment of morbid obesity (ClinicalTrials.gov, NCT00793143). All subjects gave informed consent and were screened before they were included in the study. The exclusion and inclusion criteria followed international guidelines as previously reported (13). The obese patient population consisted of 3 men and 20 women, of whom 9 were postmenopausal. By the criteria of the American Diabetes Association (14), 9 patients had T2D and 14 did not have diabetes (ND) (of whom 5 had impaired glucose tolerance and 4 impaired fasting glucose). Four of the nine patients with T2D were newly diagnosed and were treated with metformin, and five patients had been treated for an average of 3 years with combinations of oral glucose-lowering drugs (metformin in two patients and metformin/sulphonylurea/gliptin, metformin/pioglitazone/gliptin, and metformin/pioglitazone for each of the remaining three patients). Thirteen (7 T2D and 6 ND) obese patients underwent Roux-en-Y gastric bypass (RYGB) and 10 (2 T2D and 8 ND) patients received sleeve gastrectomy. Ten lean healthy volunteers with normal oral glucose tolerance test (OGTT) results who were recruited through advertisement in local newspapers served as control subjects.

### Study Design

Studies in obese patients were performed twice: before and 6 months after bariatric surgery; the baseline studies were carried out before the patients started a 4-week very low-calorie diet. Healthy subjects were studied only once. Two MRI/PET acquisitions, one in fasting condition and the other during euglycemic clamp, were performed at baseline and repeated postsurgery. MRI was performed after 2–3 h of fasting, and PET after an overnight fast. Vigorous physical activity was prohibited from the preceding evening. Glucose-lowering treatment and all diabetes medications were withheld 24–72 h before the onset of metabolic studies. The flowchart of the study design is shown in Supplementary Fig. 1. The PET/MRI results in the obese group were compared with those from the lean healthy control subjects. All studies were performed in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of the Hospital District of the Southwestern Finland.

### Whole-Body GU

Whole-body GU rate was determined using the euglycemic hyperinsulinemic clamp technique as previously described (15). Insulin infusion rate was 1 mU $\cdot$ min$^{-1}$ $\cdot$ kg$^{-1}$ (Actrapid; Novo Nordisk, Copenhagen, Denmark). During hyperinsulinemia, plasma glucose levels were maintained at 5 mmol/L using a variable infusion of 20% glucose based on arterialized glucose measurements every 5–10 min. The rate of whole-body GU was calculated over the same time period that the measurements of adipose tissue GU were made and expressed both in total amount (mmol/min) and normalized by kilogram of fat-free mass ($M_{ffm}$) (in $\mu$mol $\cdot$ min$^{-1}$ $\cdot$ kg$_{ffm}$$^{-1}$).

### PET Protocol and Data Acquisition

The PET studies were conducted both in the fasting condition and during the clamp (15) on separate days $<$2 weeks apart using the GE advanced PET camera (General Electric Medica Systems, Milwaukee, WI). Subjects were in a supine position, and two catheters, one for infusion of glucose and insulin and for tracer injection and the other for arterialized blood sampling, were inserted into an antecubital vein of each arm. At the time point 100 $\pm$ 10 min of the clamp, [$^{18}$F]-FDG (187 $\pm$ 9 MBq i.v.) was injected over 15 s. Dynamic PET scanning was started in the thoracic region at 60 min (5 $\times$ 180 s frames), followed by abdominal region at 80 min (5 $\times$ 180 s frames) and then femoral region at 100 min (3 $\times$ 300 s frames). After the injection of [$^{18}$F]-FDG, blood samples were obtained throughout the PET scanning time. Plasma radioactivity level was measured using an automatic $\gamma$ counter (Wizard 1480; Wallac, Turku, Finland).

All PET image data were corrected for time decay and photon attenuation. Carimas (version 2.8; Turku PET Centre) was used for the analysis of the PET images. PET and MRI images were coregistered using the normalized mutual information (16). Three-dimensional volumes of interest were manually drawn in the different adipose tissue compartments while avoiding bone, muscle, and skin and in skeletal muscles without intermuscular fat. The fractional uptake rate, like the influx constant ($K_i$), was calculated for each voxel drawn using the tissue and plasma input time activity curves (17). GU for adipose tissue and skeletal muscle

were calculated at the voxel level by multiplying the $K_i$ by the plasma glucose concentration and dividing this by a lumped constant of 1.14 for adipose tissue (10) and 1.2 for skeletal muscle (18). The depot-specific GU was calculated by multiplying tissue-specific GU ($\mu mol \cdot L^{-1} \cdot min^{-1}$) by the size of the fat depot (in kg) corrected for tissue density. Supplemental Fig. 2 is a representative example of MRI and insulin-stimulated [$^{18}$F]-FDG PET images in abdominal fat regions of obese patients before (left) and 6 months after (right) surgery. Regions of interest are outlined with black in SC and VF. MRI and PET images were obtained at the level of the umbilicus. In the lower panel are PET images with the scale bar showing levels of activity (Bq/mL) in the various regions.

### Measurement of Adipose Tissue Mass

Body fat content was measured using bioelectric impedance (Omron BF400). The volumes of different adipose depots were measured using 1.5 Tesla MRI (Tesla Intera system; Philips Medical Systems, Best, the Netherlands). Thorax and upper arm, abdominal, and femoral regions were acquired with axial T1-weighted dual fast field echo images (echo time 2.3 and 4.6, repetition time 120 ms, slice thickness 10 mm without gap). The different fat regions were analyzed using sliceOmatic (Tomovision, Montreal, Quebec, Canada). SC adipose tissue compartment was defined as the adipose tissue between the skin and the outermost regions of the muscle wall. Femoral SC mass was calculated from the femoral head to the patella surface, humeral SC from humeral head to the region of the capitulum, thoracic SC from the clavicle to the diaphragm, and abdominal SC from diaphragm to the head of the femur. The abdominal SC compartment was divided into anterior and posterior regions by drawing a line along the coronal plane passing through the anterior surface of the vertebral bodies (19). The posterior region was further divided into deep and superficial areas using the Scarpa fascia as a guide (20). Abdominal VF region was separated into the intraperitoneal and extraperitoneal compartments using specific anatomical reference points (2). Fat volumes ($cm^3$) were converted to mass (kg) by taking into account the tissue density (8).

### Statistical Analysis

Data analysis was performed using SPSS (version 22; SPSS, Chicago, IL), with $P \leq 0.05$ considered statistically significant. Continuous variables are expressed as mean ± SD. Normality of distribution was assessed using the Shapiro-Wilk test. Variables that were not normally distributed were log transformed before analysis. Pearson correlation analyses were performed to investigate the univariate associations between fat distribution and tissue-specific GU with metabolic and lipid variables. Two-way repeated-measures ANOVA was used to assess the interaction of T2D status with surgery.

## RESULTS

### Anthropometric and Metabolic Characteristics

There was no difference in age between obese and control subjects, but the obese T2D patient group was older than the ND group (53.3 ± 4.4 vs. 43.0 ± 9.2 years, $P = 0.01$). Altogether, the MRI-scanned fat regions constituted >90% of the total fat mass as assessed by bioelectric impedance. Compared with sex-matched control subjects, the obese group as a whole had expanded fat depots at all locations, subcutaneous and visceral alike, and displayed insulin resistance, hyperinsulinemia, dyslipidemia, and elevated hs-CRP as a marker of subclinical inflammation. In the T2D group, VF mass was larger (Table 1) than in the ND group (7.4 ± 0.7 vs. 4.7 ± 0.3 kg, $P < 0.01$) and insulin resistance was worse ($M_{ffm}$ 19.2 ± 1.2 vs. 28.0 ± 0.8 $\mu mol \cdot min^{-1} \cdot kg_{ffm}^{-1}$, $P < 0.03$).

T2D patients were classified as remitters if they achieved 2-h glucose levels <7.8 mmol/L on the OGTT and fasting glucose levels <7.0 mmol/L

**Table 1—Anthropometric and metabolic characteristics of control and obese subjects**

| | Control subjects ($n$ = 10) | Obese patients ($n$ = 23) | | |
|---|---|---|---|---|
| | | Before surgery | After surgery | $P$ |
| Age (years) | 47.3 ± 6.0 | 46.5 ± 9.0#,[a] | 46.8 ± 8.9 | — |
| Sex (female/male) | 8/2 | 19/4 | 19/2 | ns |
| Body weight (kg) | 69.2 ± 6.7 | 121.9 ± 11.6† | 93.2 ± 12.9† | <0.001 |
| BMI ($kg/m^2$) | 23.7 ± 1.8 | 43.1 ± 3.6† | 33.2 ± 4.1† | <0.001 |
| Waist (cm) | 81.4 ± 10.1 | 123.9 ± 8.3† | 104.3 ± 10.6† | <0.001 |
| WHR (cm/cm) | 0.8 ± 0.1 | 0.9 ± 0.1 | 0.9 ± 0.1 | ns |
| Percent body fat | 31.4 ± 6.5 | 48.0 ± 7.0† | 42.0 ± 6.4† | <0.001° |
| Fat mass (kg) | 21.7 ± 4.5 | 57.8 ± 8.7† | 39.1 ± 7.6† | <0.001 |
| Fat-free mass (kg) | 47.6 ± 7.5 | 63.2 ± 12.2† | 54.2 ± 10.8 | <0.001 |
| Total abdominal SC (kg) | 6.8 ± 2.4 | 26.7 ± 6.0† | 15.9 ± 4.7† | <0.001 |
| Total abdominal VF (kg) | 2.2 ± 1.2 | 5.6 ± 2.0#,[a] | 3.5 ± 2.0 | <0.001° |
| Thoracic SC (kg) | 1.3 ± 0.4 | 4.7 ± 0.7† | 3.2 ± 0.8† | <0.001 |
| Femoral SC (kg) | 7.1 ± 2.8 | 16.4 ± 4.2† | 11.5 ± 4.0† | <0.001 |
| Humeral SC (kg) | 0.5 ± 0.2 | 1.0 ± 0.2† | 0.7 ± 0.1† | <0.001 |
| Posterior deep SC (kg) | 1.3 ± 0.6 | 5.7 ± 1.9#,[b],† | 3.4 ± 1.3† | <0.0001 |
| Fasting FFA (mmol/L) | 0.5 ± 0.2 | 0.6 ± 0.2 | 0.5 ± 0.1 | <0.04 |
| Triglycerides (mmol/L) | 0.8 ± 0.3 | 1.3 ± 0.5† | 0.9 ± 0.2 | <0.001 |
| HDL cholesterol (mmol/L) | 2.0 ± 0.5 | 1.3 ± 0.5† | 1.5 ± 0.3† | 0.001 |
| LDL cholesterol (mmol/L) | 2.7 ± 0.6 | 2.4 ± 0.6 | 2.2 ± 0.6† | ns |
| $HbA_{1c}$ (%) | 5.7 ± 0.2 | 5.9 ± 0.7#,[a] | 5.6 ± 0.3 | 0.01° |
| $HbA_{1c}$ (mmol/mol) | 39.0 ± 2.4 | 47.1 ± 7.4#,[a] | 37.8 ± 3.7 | 0.01° |
| Fasting glucose (mmol/L) | 5.5 ± 0.4 | 6.5 ± 1.4#,[a] | 5.4 ± 0.6 | <0.001° |
| Fasting insulin (mmol/L) | 6.7 ± 3.7 | 17.4 ± 13.1† | 6.5 ± 3.0 | <0.001 |
| hs-CRP (mg/L) | 1.1 ± 0.8 | 4.6 ± 4.1† | 1.7 ± 1.5 | <0.001 |
| 2-h glucose (mmol/L) | 5.7 ± 1.2 | 9.4 ± 3.4#,[a],† | 6.4 ± 2.9 | <0.001° |
| $M_{ffm}$ ($\mu mol \cdot min^{-1} \cdot kg_{ffm}^{-1}$) | 58.9 ± 13.6 | 24.6 ± 11.8#,[b],† | 40.9 ± 15.4† | <0.001 |
| Whole-body M (mmol/min) | 2.77 ± 0.61 | 1.50 ± 0.66#,[b],† | 2.13 ± 0.66† | <0.001 |

Data are mean ± SD or $n/n$. 2-h glucose, levels after a standard OGTT. $P$ value for presurgery vs. postsurgery comparisons. #$P \leq 0.05$ for the difference between ND and T2D at baseline; †$P \leq 0.05$ for the comparison with control subjects; °$P \leq 0.05$ for the interaction surgery × T2D; [a]T2D > ND; [b]T2D < ND. ns, nonsignificant; WHR, waist-to-hip ratio.

without diabetes medication (14). Based on this criterion, five of the nine T2D subjects achieved remission at 6 months postsurgery.

Six months after surgery, T2D and ND patients had lost similar amounts of body weight (30 ± 3 and 27 ± 2 kg, respectively), and fat depots and fat-free mass were all reduced in size, although they were still larger than in control subjects. At this time, metabolic parameters had improved significantly in both groups; $HbA_{1c}$ and glucose levels declined more in the T2D group, while whole-body insulin sensitivity remained subnormal in both groups.

At baseline, extraperitoneal fat mass was significantly larger in T2D than in ND (2.8 ± 1.2 vs. 1.8 ± 0.6 kg, $P = 0.02$). Similarly, T2D patients had increased amounts of intraperitoneal fat than ND (4.5 ± 0.8 vs. 2.9 ± 0.7 kg, $P < 0.001$). After surgery, total VF mass remained higher in T2D than in ND (4.7 ± 0.9 vs. 2.8 ± 0.3 kg, $P = 0.02$), while abdominal deep SC was higher in ND than T2D (6.3 ± 2.1 vs. 4.5 ± 0.8 kg, $P = 0.03$).

There were no differences between the two types of surgery on the remission of T2D postsurgery. Preoperatively, the prediabetic group (impaired glucose tolerance and impaired fasting glucose) had higher intraperitoneal (3.5 ± 0.7 vs. 2.5 ± 0.4 kg, $P = 0.01$) and extraperitoneal (2.3 ± 0.6 vs. 1.5 ± 0.4 kg, $P = 0.01$) fat mass than the normoglycemic group. These differences in fat mass were no longer there postoperatively. Menopausal status of obese women was associated with postsurgery total VF mass (β −0.70, $P < 0.001$, $R^2$ = 50%) but not with the other fat regions. Drug regimen did not influence postoperative fat distribution and tissue-specific GU in the obese group.

### Insulin-Stimulated GU

Before surgery, all obese subjects had severe skeletal muscle insulin resistance, which improved markedly after surgery, although it remained lower than in control subjects (Table 2 and Fig. 1*A*). Presurgery, insulin-stimulated tissue-specific GU was impaired in obese compared with control subjects in all fat compartments (though falling short of statistical significance for humeral and thoracic depots) and increased significantly in all subjects postsurgery (remaining subnormal only in extraperitoneal VF). Within the obese group, VF and abdominal deep SC adipose tissue GU was lower in T2D than in ND (Fig. 1*B*).

Because of fat mass expansion, presurgery depot-specific GU was increased in obese compared with control subjects in all compartments (except for extraperitoneal VF and femoral SC sites). Compared with ND subjects, T2D patients had higher uptake in the intraperitoneal VF depot and lower uptake in abdominal deep and femoral SC depots. After surgery, depot-specific GU in intraperitoneal VF decreased significantly in both T2D and ND, whereas GU in all other depots was unchanged.

We did not find differences in tissue-specific GU in any of the studied regions between the normoglycemic and prediabetic (impaired glucose tolerance and impaired fasting glucose) groups. Menopause in obese women did not influence insulin-stimulated GU in skeletal muscle or any fat regions after the surgical intervention.

### Fasting GU

Presurgery, fasting tissue-specific GU rates were lower than in the insulin-stimulated state at all sites and did not show major differences between obese patients and control subjects (except for significantly lower extraperitoneal VF uptake in obese vs. control subjects); surgery did not alter these rates of GU significantly. On the other hand, depot-specific GU was larger in obese than in control subjects in all compartments and was higher in T2D than in ND (18.7 ± 7.0 vs. 11.1 ± 4.9, $P = 0.01$); surgery decreased depot-specific GU at all sites (except for the humeral depot) (Supplementary Table 1).

### Contribution of Different Fat Depots to Whole-Body Glucose Disposal

Before surgery, the contribution of VF GU to whole-body insulin-mediated glucose disposal was twice as high in ND and four times as high in T2D patients ($P < 0.05$ between ND and T2D) as in control subjects (Fig. 1*C*). All SC depots,

**Table 2—Insulin-stimulated GU in fat compartments and skeletal muscle***

| | Control subjects ($n$ = 10) | Obese patients ($n$ = 23) | | $P$ |
|---|---|---|---|---|
| | | Before surgery | After surgery | |
| Tissue-specific GU ($\mu mol \cdot L^{-1} \cdot min^{-1}$) | | | | |
| Extraperitoneal VF | 26.7 ± 11.7 | 8.3 ± 2.7#† | 13.5 ± 5.1† | <0.0001 |
| Intraperitoneal VF | 17.9 ± 7.5 | 10.1 ± 2.7#,[b],† | 13.8 ± 3.9 | 0.0002 |
| Abdominal deep SC | 17.3 ± 9.1 | 6.3 ± 1.9#,[b],† | 11.7 ± 4.9 | <0.0001 |
| Abdominal superficial SC | 11.8 ± 5.5 | 5.8 ± 1.7† | 9.3 ± 3.4 | <0.0001 |
| Femoral SC | 10.2 ± 3.9 | 5.0 ± 1.2† | 8.9 ± 4.6 | 0.0007 |
| Humeral SC | 8.6 ± 4.4 | 6.7 ± 1.9 | 9.4 ± 3.7 | 0.0041 |
| Thoracic SC | 8.8 ± 4.4 | 7.2 ± 2.3 | 9.2 ± 3.8 | <0.03 |
| Skeletal muscle | 72.5 ± 26.2 | 22.0 ± 17.6† | 45.7 ± 31.6† | 0.003 |
| Depot-specific GU ($\mu mol \cdot min^{-1}$) | | | | |
| Extraperitoneal VF | 27.3 ± 14.6 | 19.4 ± 7.7 | 20.9 ± 10.4 | ns |
| Intraperitoneal VF | 17.5 ± 5.8 | 36.6 ± 11.2#,[a],† | 28.1 ± 12.5† | <0.0001 |
| Abdominal deep SC | 23.6 ± 16.6 | 39.8 ± 21.3#,[b],† | 44.4 ± 23.7† | ns |
| Abdominal superficial SC | 19.4 ± 13.5 | 41.3 ± 21.2† | 40.7 ± 21.8† | ns |
| Femoral SC | 89.9 ± 54.5 | 93.0 ± 34.1#,[b] | 113.3 ± 53.7 | ns |
| Humeral SC | 4.3 ± 3.7 | 6.9 ± 2.5† | 7.4 ± 3.5† | ns |
| Thoracic SC | 12.9 ± 7.6 | 36.1 ± 11.7† | 31.9 ± 12.3† | ns |

Data are mean ± SD. $P$ value for presurgery vs. postsurgery comparisons. #$P \leq 0.05$ for the difference between ND and T2D at baseline; †$P \leq 0.05$ for the comparison with control subjects; °$P \leq 0.05$ for the interaction surgery × T2D; [a]T2D > ND; [b]T2D < ND. ns, nonsignificant.

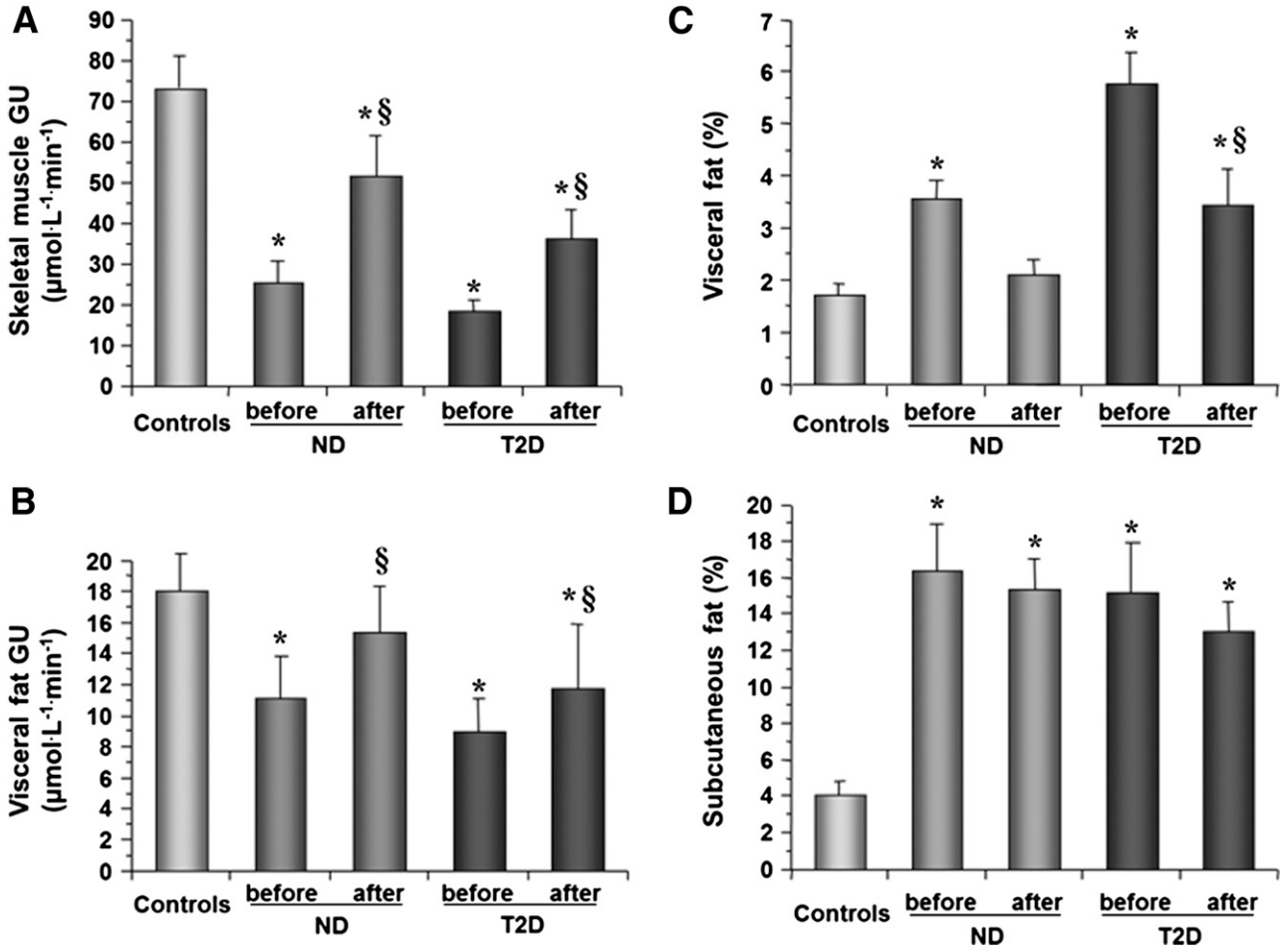


**Figure 1**—Skeletal muscle (*A*) and VF (*B*) insulin-mediated GU in lean control subjects and in obese ND and T2D patients before and 6 months after bariatric surgery. Percentage contribution of VF depots (*C*) and SC depots (*D*) to whole-body insulin-mediated GU in lean control subjects and in obese ND and T2D patients before and 6 months after bariatric surgery. Data are mean ± SEM. *$P \leq 0.05$ compared with control subjects; §$P \leq 0.05$ for the presurgery to postsurgery comparison.

on the other hand, contributed four times more in patients, ND and T2D alike, than in control subjects. Combined VF and SC fat contribution to total GU was 5.6 ± 2.5% in control subjects and 20.2 ± 9.5% in the whole patient group ($P < 0.0001$). After surgery, the contribution of VF fat was significantly reduced (but still higher in T2D than in control subjects), whereas that of SC tissue was unchanged (Fig. 1*C* and *D*).

In the whole data set, GU rate into VF (intraperitoneal plus extraperitoneal) was inversely related to both 2-h plasma glucose and suppression of lipolysis during insulin stimulation (Fig. 2). Upon categorizing obese subjects in T2D and ND groups, we found that clamped FFA levels significantly correlated with VF GU in the ND group ($r = -0.77$, $P = 0.001$) and not in the T2D group ($P = 0.22$). No significant correlation was registered between 2-h plasma glucose and VF GU in ND or T2D.

## CONCLUSIONS

The first major finding of the current study is that prior to surgery, obese T2D patients had more VF mass than did ND patients (13 ± 7% vs. 8 ± 3% of total fat mass, $P < 0.02$) despite having virtually identical total fat mass (57 ± 4 vs. 58 ± 2 kg, $P$ = nonsignificant). Furthermore, insulin-stimulated GU in VF tissues was more impaired in T2D than in ND (Table 2). Therefore, the presence of T2D (and ~10-year older age) was associated with a selective visceral deposition of extra adipose tissue more resistant to insulin action. In addition to the endogenous glucose overproduction and β-cell dysfunction typical of T2D, the metabolic impact of this abnormal adipose tissue phenotype is reflected in the reciprocal relation of VF GU to both 2-h glucose levels and circulating FFA concentrations (Fig. 2).

The second major finding is that VF GU was 30 ± 7% of skeletal muscle GU in control subjects but twice that (57 ± 5%) in obese patients, whether T2D or ND. Thus, the presence of severe obesity compromises skeletal muscle insulin sensitivity more than adipose tissue insulin sensitivity. The cellular basis of this discrepancy, which to our knowledge has not been reported before, remains to be investigated. In any event, as a combined result of less compromised insulin sensitivity and the expanded VF pool size, the contribution of VF to whole-body glucose disposal under insulinized conditions was twice as much in ND obese and four times as much in T2D obese patients as in control subjects (Fig. 1*B*). Moreover, SC fat GU averaged

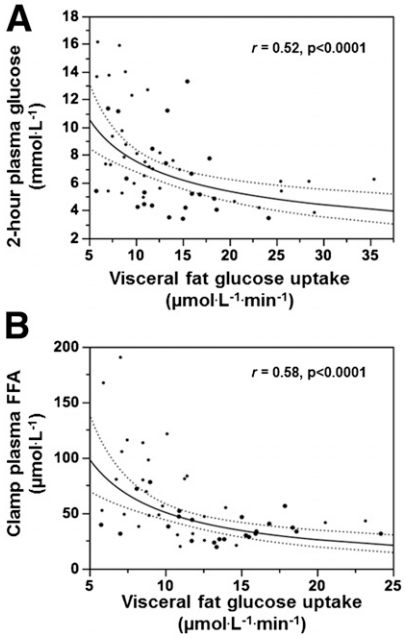


**Figure 2—**Nonlinear, reciprocal relationship between VF GU and 2-h plasma glucose concentrations (*A*) and steady-state plasma FFA on the clamp (*B*) in the pooled presurgery and postsurgery data set. Lines are best fit with 95% CIs.

15% of whole-body glucose disposal in obese patients versus 4% in control subjects (Fig. 1*D*). Therefore, despite the insulin resistance, fat expansion in the obese provides a sink for glucose, which would otherwise accumulate in the bloodstream and further impair glucose tolerance. The converse problem, namely, the inability of adipose tissue to expand, is also conducive to reduced glucose tolerance and dyslipidemia (21).

Surgically induced major weight loss brought about improved insulin sensitivity and, in the T2D group, improved glucose tolerance, as expected. However, skeletal muscle insulin-mediated GU was still subnormal in the obese group, especially in T2D patients, and VF insulin sensitivity was still impaired in the T2D group (Fig. 1*B*). Whether insulin action would eventually normalize with further weight loss cannot be determined from the current data because these very obese patients rarely regain lean body weight. What is remarkable is that despite the massive reduction in fat mass, SC depots continued to make a threefold greater contribution to total insulin-mediated glucose disposal—compared with lean control subjects—as a result of more efficient glucose utilization. Thus, in the postsurgical state, residual obesity continues to protect glycemia from rising higher.

Of note is that percentagewise, bariatric surgery induced a greater loss of VF (~40% of presurgery size) than SC fat (7%) equally in ND and T2D. This phenomenon was also reported by Gray et al. (22), who found that subjects with more intra-abdominal fat at baseline tended to lose more fat from this depot during weight loss. Studies by Kim et al. (23) likewise suggested that weight loss after bariatric surgery preferentially targets VF in T2D patients. Although there are well-established links between increased intra-abdominal fat accumulation and T2D (5,22), previous studies did not separate intraperitoneal from extraperitoneal fat compartments and did not quantify intra-abdominal fat for the whole abdominal region. Upon accurately compartmentalizing intra-abdominal VF, we found that T2D patients had increased amounts of both intra- and extraperitoneal fat compared with obese ND patients and control subjects.

That increased amounts of total VF heighten risk of developing insulin resistance seems to be well established (24). However, Kobayashi et al. (25) found no difference in intra-abdominal VF between T2D men and women with similar BMI. Abate et al. (26) stated that intraperitoneal fat volume in males with T2D tends to be similar to that in healthy control subjects with similar BMI. The apparent contradictions with our results may stem from sex differences because Abate et al. studied only males, whereas 80% of the current study subjects were female.

Differences in the partitioning of abdominal SC fat into deep and superficial layers in obese and lean subjects and their metabolic implications have previously been elucidated by He, Engelson, and Kotler (20). In our data, obese ND patients have increased posterior deep SC fat mass compared with T2D (6.3 $\pm$ 2.1 vs. 4.5 $\pm$ 0.8 kg, $P < 0.05$). One could therefore speculate that expanded deep SC fat might be metabolically protective, although few studies have established a direct association between abdominal deep SC depots (27,28), posterior SC abdominal fat (2), and metabolic complications such as insulin resistance. According to Marinou et al. (29), expanded deep SC fat is a major feature of increased adiposity in men but not women. Furthermore, Miyazaki et al. (5) showed that deep SC fat is associated with peripheral and hepatic insulin resistance in men but not women. It is therefore conceivable that sex-specific differences in the distribution of abdominal SC fat subcompartments may account for these discrepant findings.

To our knowledge, there are relatively few studies that have explored the use of dynamic [$^{18}$F]-FDG PET to quantitatively analyze tissue-specific GU in VF and SC fat (10,30) and skeletal muscle (31). Based on the current data, obese T2D have decreased GU in skeletal muscles compared with ND and control subjects; this confirms previous results by our group (31). The decreased skeletal muscle GU in T2D in response to insulin may be due, at least in part, to increased FFA levels (32), i.e., a model of substrate competition.

With regard to fat glucose metabolism, research suggests that VF depots tends to have higher rate of insulin-stimulated GU compared with SC compartments (33). In obese individuals, GU in visceral and SC compartments is lower than in nonobese subjects (10). Our findings confirm that expanded fat mass leads to decreased GU, particularly in the VF fat regions.

Dividing the abdominal SC fat into deep and superficial regions and VF into intraperitoneal and extraperitoneal yielded interesting results. We observed that obese ND patients tended to have significantly higher GU in intraperitoneal VF fat and deep SC fat than T2D patients did. The relatively higher metabolic activity in abdominal VF fat compared with SC fat depot is well documented (34), but the metabolic potential in deep SC depots has been likened to VF fat (29,35). This metabolic similarity is attributed to the restricted capacity of peripheral fat depot to store excessive energy, leading to overflow of energy into other fat depots such as deep SC and VF compartments (36). Research has shown that adipocytes from the abdominal deep depots are metabolically superior to superficial SC compartments (29), thereby contributing significantly to global GU. Indeed, Abate et al. (26) reported that intraperitoneal, but not extraperitoneal, fat is a better correlate of metabolic complications. It is worth mentioning that the expanded

VF in T2D is accompanied by increased adipocyte size, which tends to correlate positively with insulin resistance (37).

The use of [$^{18}$F]-FDG PET to assess inflammation in adipose tissue has been reported on previously (38). Higher fasting FDG uptake represents glucose utilization not only by adipocytes but also by infiltrating macrophages and other cells in the stromovascular fraction (39). Based on this assumption, inflammatory signals from intraperitoneal fat were higher in ND, whereas T2D had higher inflammatory signals from abdominal SC fat. In addition, T2D had enhanced inflammatory signals from skeletal muscle compared with ND, in line with reports of increased levels of inflammation in skeletal muscle of T2D patients (40).

Some strengths and limitations of this study should be acknowledged. Strengths are that within the same study, we performed a hyperinsulinemic-euglycemic clamp to assess whole-body insulin sensitivity; MRI for absolute quantification of fat in thoracic, humeral, abdominal, and femoral regions; and FDG PET to quantify tissue-specific GU in skeletal muscle in the above-mentioned fat regions. Limitations of the current study are the small sample size of 23 obese patients. The patients and control groups were predominantly females, and fat distribution and metabolic activities may have been different if equal numbers of both sexes had been studied. There is lack of data for the assessment of GU at the molecular and cellular level. Bioelectric impedance analysis may not be an accurate measure of body fat content in morbidly obese subjects. The weight of the patient was not fully stabilized at 6 months of follow-up.

In conclusion, our study confirms the metabolic variations in different fat compartments in obese patients. Bariatric surgery improves insulin-stimulated glucose in skeletal muscle and in all fat compartments of obese subjects independent of diabetes status.

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**Author Contributions**. P.D. analyzed fat distribution from MRI and performed FDG-PET image analysis in abdominal, thoracic, and humeral regions. L.L. analyzed FDG uptake in the femoral region. P.D. and L.L. wrote the manuscript. M.H. and P.S. were involved in the study design, patient recruitment, and surgical procedures. J.C.H., H.I., N.S., M.S., and R.P. were involved in data acquisition and contributed to the discussion of the results. M-J.H. and M.B. contributed to and made corrections to the manuscript. J.P. and P.I. contributed to and edited the manuscript. E.F. compiled the results, performed the statistical analysis, and contributed to and edited the manuscript. P.N. is the principal investigator of this study and was involved in the project planning, analysis, and writing of the manuscript. P.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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