Insulin Resistance in Morbid Obesity
Reversal With Intramyocellular Fat Depletion

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Obesity is a frequent cause of insulin resistance and poses a major risk for diabetes. Abnormal fat deposition within skeletal muscle has been identified as a mechanism of obesity-associated insulin resistance. We tested the hypothesis that dietary lipid deprivation may selectively deplete intramyocellular lipids, thereby reversing insulin resistance. Whole-body insulin sensitivity (by the insulin clamp technique), intramyocellular lipids (by quantitative histochemistry on quadriceps muscle biopsies), muscle insulin action (as the expression of Glut4 glucose transporters), and postprandial lipemia were measured in 20 morbidly obese patients (BMI = 49 ± 8 [mean ± SD] kg · m^{-2}) and 7 nonobese control subjects. Patients were restudied 6 months later after biliopancreatic diversion (BPD; $n = 8$), an operation that induces predominant lipid malabsorption, or hypocaloric diet ($n = 9$). At 6 months, BPD had caused the loss of 33 ± 10 kg through lipid malabsorption (documented by a flat postprandial triglyceride profile). Despite an attained BMI still in the obese range (39 ± 8 kg · m^{-2}), insulin resistance (23 ± 3 μmol/min per kg of fat-free mass; $P < 0.001$ vs. 53 ± 13 of control subjects) was fully reversed (52 ± 11 μmol/min per kg of fat-free mass; NS versus control subjects). In parallel with this change, intramyocellular—but not perivascular or interfibrillar—lipid accumulation decreased (1.63 ± 1.06 to 0.22 ± 0.44 score units; $P < 0.01$; NS vs. 0.07 ± 0.19 of control subjects), Glut4 expression was restored, and circulating leptin concentrations were normalized. In the diet group, a weight loss of 14 ± 12 kg was accompanied by very modest changes in insulin sensitivity and intramyocellular lipid contents. We conclude that lipid deprivation selectively depletes intramyocellular lipid stores and induces a normal metabolic state (in terms of insulin-mediated whole-body glucose disposal, intracellular insulin signaling, and circulating leptin levels) despite a persistent excess of total body fat mass. *Diabetes* **51:144–151, 2002**

Obesity is associated with type 2 diabetes, cardiovascular complications, and premature death in both men and women (1). Morbidity and risk of premature death are directly related to the amount and distribution of excess body fat (2). Mainstays of obesity treatment include caloric restriction, increased physical activity, and cognitive restructuring therapy (3). In obese women, moderate weight loss (10% of initial body weight) has been shown to reduce mortality by 20% (4). Most obese patients, however, find it difficult to comply with low-energy diets, particularly in the long run. Morbidly obese patients who do not respond to weight control programs and those who have disabling joint disease, pulmonary insufficiency, hypertension, or diabetes are eligible for surgical treatment. Bariatric surgery usually produces substantial weight loss, often achieving a stable near-normal weight (5,6). In obese patients with diabetes, biliopancreatic diversion (BPD) (7) induces a normalization of insulin sensitivity that persists for up to 2 years (8,9).

Insulin resistance is common in obesity (10,11), as evidenced by low rates of whole-body glucose uptake during euglycemic-hyperinsulinemic clamping (12). Weight loss has been shown to improve insulin-mediated glucose disposal by enhancing both oxidation and storage of glucose in skeletal muscle (13–15). The mechanisms whereby weight loss, by diet or surgery, improves insulin resistance are incompletely understood. Recently, attention has focused on the content, localization, and composition of fat within skeletal muscle as determinants of insulin resistance. Several studies have reported an inverse relationship between insulin action and the fatty-acid composition of skeletal muscle phospholipids (16), muscle triglyceride levels (17–20), and saturated fatty acids in muscle triglycerides (21). Less information is available on the localization, intracellular or interfibrillar, of lipids in human skeletal muscle and its specific impact on insulin action. Muscle attenuation on computed tomography scans, believed to reflect intramuscle lipid content, has been reported to be accentuated in obese women (22) and to be reciprocally related to insulin sensitivity (20). Proton magnetic resonance spectroscopy has been validated against a chemical extraction method and used to establish a reciprocal relationship between intramyocellular lipid accumulation and insulin sensitivity in healthy individuals (23). The accuracy of this approach in obese patients or obese patients with diabetes has not been

TABLE 1
Clinical characteristics

	Control subjects	Obese participants
n	7	20
M/F	3/4	6/14
Age (years)	35 ± 11	39 ± 12
Height (cm)	167 ± 7	162 ± 12
Weight (kg)	74 ± 8	130 ± 29*
BMI (kg/m^2)	26.5 ± 1.1	49.4 ± 7.8*
FFM (kg)	52 ± 10	71 ± 17*
FM (kg)	22 ± 5	60 ± 15*
Waist (cm)	76 ± 3	135 ± 20*
WHR	0.92 ± 0.06	0.95 ± 0.08†

*$P < 0.001$ by Mann-Whitney U test. †$P = 0.02$ by analysis of covariance (adjusted by sex).

established, however. By quantitative histochemistry, Phillips et al. (18) found an inverse relationship between intracellular lipids in the gastrocnemius of nondiabetic women and muscle glycogen synthase activity but not insulin sensitivity. In another ex vivo study using histochemistry, lipid accumulation was demonstrated within muscle fibers of the vastus lateralis in obese individuals (24).

The relation of intramyocellular fat depots to total body fat and their physiological regulation are not well known. In rats fed a high-fat diet, acute dietary lipid withdrawal is associated with an improvement of muscle insulin resistance (25). Likewise, reducing tissue lipid availability in rats by peroxisome proliferator–activated receptor-γ agonism has been reported to enhance insulin sensitivity (26). On these grounds, it has been hypothesized that selective depletion of intracellular fat depots in skeletal muscle is the key metabolic change that leads to reversal of insulin resistance independent of fat mass (FM) loss. To test this hypothesis, we measured insulin sensitivity and the distribution of intramuscle fat in a group of morbidly obese patients in whom BPD caused chronic lipid malabsorption, and compared the results with those of patients in whom weight loss was achieved by conventional caloric restriction.

RESEARCH DESIGN AND METHODS

Participants. The study group included 20 morbidly obese patients (BMI >40 kg/m^2) and 7 nonobese control subjects. None of the study participants had impaired glucose tolerance, diabetes, or other endocrine or nonendocrine

disease. At the time of study, all participants were on a free diet (the Italian diet typically consists of 55% carbohydrate, 30% fat, and 15% protein). After the initial set of studies, patients were assigned either to BPD ($n = 10$, consisting in a partial gastrectomy with a distal Roux-en-Y reconstruction (7,8) or to a hypocaloric, balanced diet regimen (1,200 kcal/day, $n = 10$). All patients were asked to return for a repeat study 6 months later; 3 refused, and 17 patients underwent the follow-up studies (9 in the diet group and 8 in the BPD group) and are therefore included in the present report. The study protocol was approved by the Ethics Committee of the Catholic University of Rome; the nature and purpose of the study were carefully explained to all participants before obtaining their written consent to participate.

Body composition. Total-body water (TBW) was determined by using ^3H_2O as previously described (27), with a correction (5%) for nonaqueous hydrogen exchange (28). The within-participant coefficient of variation for this method is 1.5% (29). Fat-free mass (FFM) was obtained by dividing TBW by 0.732 (30). FM was obtained as the difference between body weight and FFM. Waist circumference was measured at the narrowest part of the torso, and the hip circumference was measured in a horizontal plane at the level of the maximum extension of the buttocks. The waist-to-hip ratio (WHR) was also calculated.

Postprandial lipemia. On a separate day, all study participants spent 24 h in the hospital, where they received four meals for a total caloric intake of 30 kcal/kg$_{ffm}$ (20% breakfast, 40% lunch, 10% afternoon snack, and 30% dinner). Blood samples were drawn hourly for the measurement of serum triglyceride concentrations.

Insulin sensitivity. Insulin sensitivity was determined after an overnight fast by the insulin clamp technique using an insulin infusion rate of $1 \text{ mU} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (31); steady-state insulin-mediated whole-body glucose disposal (M) was expressed in $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}_{ffm}^{-1}$. Tracer glucose, to monitor suppression of endogenous glucose output by exogenous insulin, was not used in these studies. However, in previous studies using an identical clamp technique, we found that residual endogenous glucose production was similar in lean (BMI = 23 ± 2 kg/m^2, $n = 183$) and very obese nondiabetic participants (BMI = 37 ± 6 kg/m^2, $n = 68$) (-0.9 ± 5.0 vs. 0.4 ± 2.4 $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}_{ffm}^{-1}$; $P = 0.06$) despite very different whole-body insulin sensitivity (50 ± 15 vs. 38 ± 15 $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}_{ffm}^{-1}$; $P < 0.0001$ (11 and unpublished data thereof).

Plasma glucose was measured by the glucose oxidase method (Beckman, Fullerton, CA). Plasma insulin and leptin concentrations were assayed by specific radioimmunoassays (Linco Research, St. Charles, MO). Serum triglycerides were determined by enzymatic colorimetric methods (Boehringer Mannheim, Mannheim, Germany).

Muscle biopsy. Participants were instructed not to perform strenuous physical exercise for 48 h before the muscle biopsy procedure. Biopsies were obtained from the middle region of the quadriceps muscle by a percutaneous needle. Muscle specimens were trimmed free of fat, mounted, and frozen in isopentane cooled at −160°C by liquid nitrogen and stored at −80°C.

Histochemistry. Samples of skeletal muscle were removed and immediately fixed overnight in 4% paraformaldehyde in 0.1 mol/l phophate buffer (pH 7.4), dehydrated in ethanol, postfixed in osmium, and paraffin-embedded (32). Transverse sections were stained with hematoxylin-eosin and analyzed for the presence of lipid droplets in the perivascular spaces (perivascular lipid), between fibers (interfibrillar lipid), and inside fibers (intramyocellular lipid). In each location, lipid content was scored as follows: 0, none; 0.5, just distinguishable, with focal distribution; 1, detectable in restricted areas of the parenchyma but in scarce amount; 2, well evident in different areas of the parenchyma; and 3, numerous and/or voluminous, generally confluent drop-

TABLE 2
Anthropometric and metabolic data before and after treatment

	Control subjects	Obese pre-Tx		Obese post-Tx	
		BPD	Diet	BPD	Diet
Body weight (kg)	74 ± 8	137 ± 25*	130 ± 36*	104 ± 20†	117 ± 27†
BMI (kg/m^2)	26.5 ± 1.1	51.2 ± 8.0*	48.2 ± 8.9*	39.0 ± 8.3†	43.6 ± 7.1†
FFM (kg)	52 ± 10	75 ± 15*	71 ± 21*	59 ± 15†	60 ± 17†
FM (kg)	22 ± 5	62 ± 14*	59 ± 17*	45 ± 13†	57 ± 14
Waist (cm)	76 ± 3	143 ± 14*	131 ± 25*	119 ± 15†	121 ± 15†
WHR	0.92 ± 0.06	0.98 ± 0.07	0.93 ± 0.10*	0.98 ± 0.08	0.93 ± 0.08
Fasting glucose (mmol/l)	5.65 ± 0.56	5.04 ± 0.77	4.99 ± 0.91	5.72 ± 1.09	6.25 ± 0.73
Plasma leptin (ng/ml)	11 ± 3	46 ± 12*	46 ± 7*	19 ± 5†	43 ± 10
Fasting insulin (pmol/l)	88 ± 11	298 ± 140*	274 ± 128*	84 ± 41†	305 ± 181
M value ($\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}_{ffm}^{-1}$)	53 ± 13	23 ± 3*	28 ± 10*	52 ± 11†	36 ± 20

*$P < 0.05$ or less versus control subjects; †$P < 0.05$ or less for the effect of treatment. Tx, treatment.
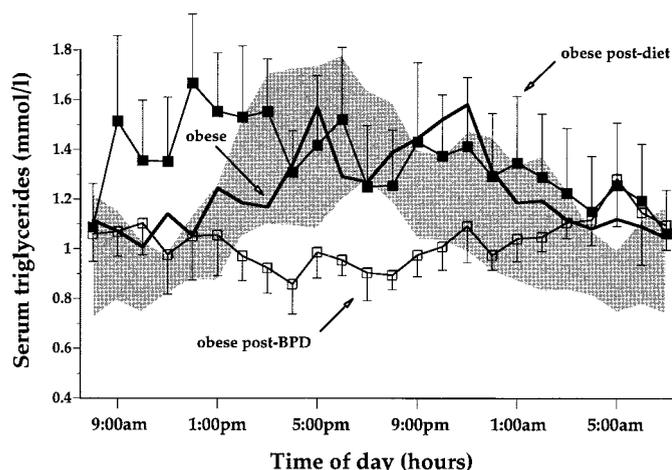
FIG. 1. Day-long profile of serum triglyceride concentrations in obese patients before treatment (heavy line) and after diet (■) or BPD (□) in comparison with control subjects (shaded area = ± 1 SE). Meals were breakfast between 7:30 and 8:00 A.M., lunch between 12:00 and 1:30 P.M., snack at 4:00 P.M., and dinner between 7:30 and 8:00 P.M. Data are mean values, bars are 1 SE.

lets in diffuse areas of the parenchyma. The quantitative assessment was carried out by two authors (M.M. and S.C.), who were blinded to the participant group and metabolic data; the results were tested in repeated measurements of the same specimen and were found to be reproducible within 10%.

RNA extraction and reverse transcriptase–polymerase chain reaction assay. In five of the obese patients who underwent BPD and four control subjects, enough muscle tissue was available to measure the expression of the insulin-regulatable glucose transporter isoform Glut4 using previously described methodology (33).

Statistical analysis. Data are given as mean ± SD. The Mann-Whitney U test was used for between-group comparisons of means, whereas paired comparisons were performed using the Wilcoxon test. Spearman correlation coefficients, analysis of covariance, and regression analyses were used to examine associations. Results were considered significant at $P \leq 0.05$.

RESULTS

At baseline, obese patients had a 40% greater FFM, a threefold greater FM, and a twofold larger waist circumference than control subjects (Table 1), with no significant differences between the patients allocated to diet and those who underwent BPD (Table 2). At the 6-month follow-up, the BPD group had lost significantly ($P < 0.003$) more weight (33 ± 10 kg, or 24 ± 5% of initial weight) than the diet group (14 ± 12 kg, or 9 ± 8%). The composition of the lost weight was different between the two groups; a significant reduction of FM was observed only in the BPD group (17 ± 10 vs. 3 ± 10 kg; $P = 0.01$). The waist circumference was significantly, if slightly, reduced in both group, whereas the WHR was not.

Before treatment, fasting plasma insulin and leptin con-

centrations were elevated in both obese groups as compared with the control subjects. After treatment, a significant reduction in both plasma insulin and leptin was seen only in the BPD group (Table 2). The baseline 24-h profile of serum triglyceride concentrations in the obese group was essentially normal; at 6 months, the profile showed postprandial hyperlipemia in the diet-treated patients as compared with the response in the BPD group, which was essentially flat (Fig. 1).

On the clamp, insulin-mediated glucose uptake was markedly reduced in both patient groups before treatment, whereas in the diet group, insulin sensitivity was only marginally improved at 6 months (the change fell short of full statistical significance); insulin resistance was fully reversed in the BPD group ($P < 0.001$ versus baseline; NS versus control subjects; Table 2).

Lipid content in the perivascular, interfibrillar, and intramyocellular space of skeletal muscle is summarized in Table 3. Before treatment, large amounts of lipids were present in the muscle of obese patients at all three locations (e.g., Figs. 2A and 3A). After treatment, perivascular and, especially, intramyocellular fat was markedly decreased in BPD patients only (compare Fig. 2B with Fig. 3B).

In the five obese patients in whom it was measured, Glut4 expression was significantly reduced ($P = 0.05$) as compared with control subjects; 6 months after BPD, Glut4 expression was increased ($P = 0.06$ versus baseline) to values no longer significantly different from those of control subjects (NS; Fig. 4).

In the baseline dataset, insulin sensitivity was reciprocally related to both FM ($r = 0.62$, $P = 0.002$) and BMI ($r = 0.66$, $P = 0.0007$) in a linear manner, with predicted decrements in sensitivity of 0.5 μmol $\cdot$ min^{-1} $\cdot$ kg$_{ffm}^{-1}$ per kg of FM increase and 1 μmol $\cdot$ min^{-1} $\cdot$ kg$_{ffm}^{-1}$ per BMI unit (Fig. 5). Likewise, insulin sensitivity was inversely related to the waist circumference ($r = 0.63$, $P = 0.001$), although the association was no longer statistically significant when adjusting for BMI. For both waist circumference and BMI, the posttreatment values of insulin sensitivity in the diet group fell approximately on the regression line; in contrast, the corresponding values for the BPD group were clearly above the regression lines. A similar curvilinear pattern described the relationships between insulin sensitivity and the amount of perivascular or interfibrillar fat, whereas insulin sensitivity was inversely related to intramyocellular fat in a linear manner (Fig. 6). Fasting plasma leptin was better related to intramyocellular lipid (positively) and insulin sensitivity (reciprocally) than to total FM (Fig. 7).

TABLE 3
Skeletal muscle histochemistry

	Control subjects	Obese pre-Tx		Obese post-Tx	
		BPD	Diet	BPD	Diet
Perivascular fat (a.u.)	1.07 ± 0.73	2.87 ± 0.35*	3.00 ± 0.00*	2.22 ± 0.67†	2.50 ± 0.54
Interfibrillar fat (a.u.)	0.43 ± 0.45	1.69 ± 0.80*	2.17 ± 0.75*	1.39 ± 0.78	1.44 ± 0.98
Intramyocellular fat (a.u.)	0.07 ± 0.19	1.63 ± 1.06*	0.76 ± 0.76*	0.22 ± 0.44†	0.69 ± 0.46

*$P < 0.05$ or less versus control subjects; †$P < 0.05$ or less for the effect of treatment. a.u., arbitrary units.
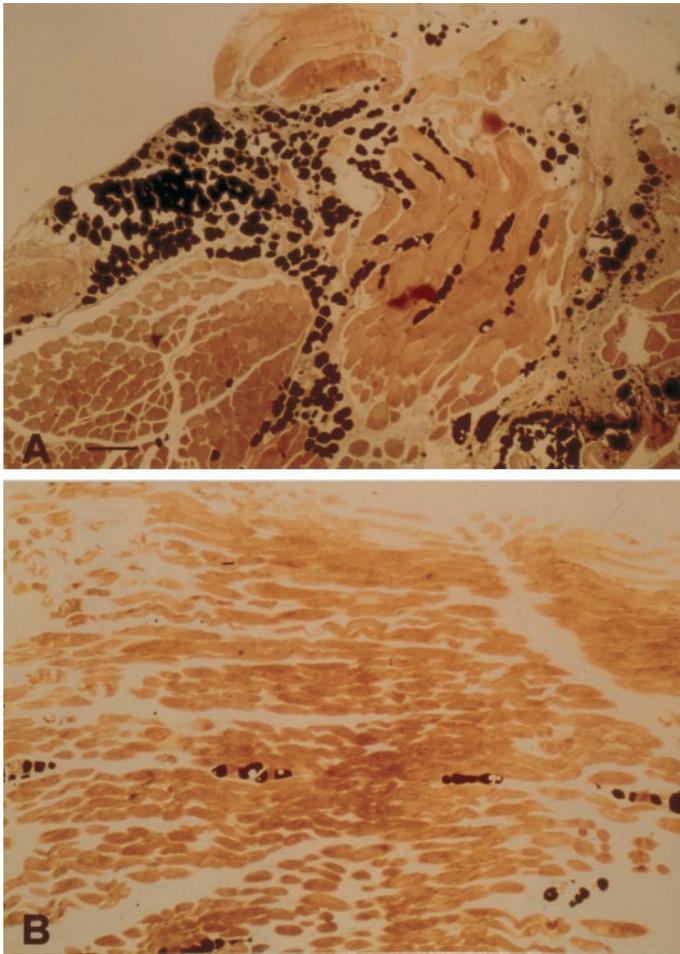
FIG. 2. Skeletal muscle sections of a patient in the BPD group. *A*: Before treatment: numerous large lipid droplets are localized in the perivascular space and between fibers. *B*: After treatment: only a few lipid droplets are visible between fibers, none intracellularly. Magnification ×43; bar = 230 μm.
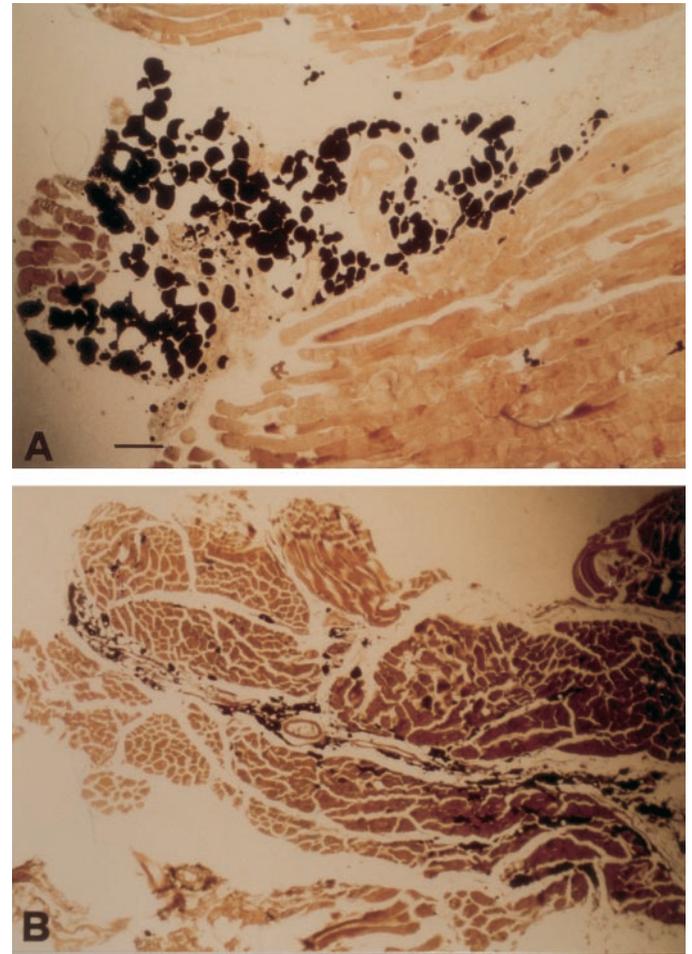

FIG. 3. Skeletal muscle sections of a patient in the diet-treated group. *A*: Before treatment: numerous, voluminous lipid droplets are present as in Fig. 2*A*. *B*: After treatment: the amount of lipids is clearly higher than found in Fig. 2*B*. Magnification ×43; bar = 230 μm.

DISCUSSION

Weight loss induced by BPD was associated with a complete reversal of insulin resistance in participants who maintained a BMI of 39 kg/m^2 and a body FM approximately twice normal. Thus, post-BPD patients were anthropometrically obese but metabolically normal. In contrast, a 9% weight loss achieved by caloric restriction, i.e., a typical outcome of reducing diets (34), led to only a small improvement in insulin sensitivity. The change in in vivo insulin action seen with the low-calorie diet could be predicted from the baseline relationships between baseline BMI and insulin sensitivity (Fig. 5). This relationship was virtually identical with that derived from the analysis of a large cohort of nondiabetic individuals with a BMI ranging from 15 to 55 kg/m^2 previously studied by the insulin clamp technique (11). Thus, by dieting, patients gained insulin sensitivity in approximate proportion to the weight they had lost. However, the BPD-treated participants clearly fell outside the prediction, as their actual insulin sensitivity was 50% higher than expected. This heterogeneous response (Fig. 5) is congruous with previous observations that *1*) the prevalence of definite insulin resistance (lowest decile of normal distribution) is relatively low (43%) in obese individuals (BMI $\geq$ 30 kg/m^2)

when obesity is defined only by the BMI (11) and *2*) that the improvement in insulin resistance seen with weight loss is only weakly correlated with the change in total FM (35). Growing evidence indicates that the anatomical site of excess fat deposition is an important determinant of
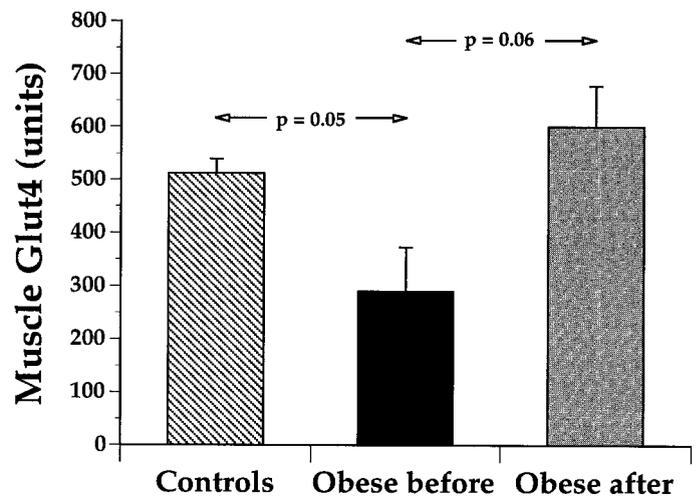

FIG. 4. Skeletal muscle Glut4 expression in obese patients before and after BPD as compared with control subjects. Bars are mean ± 1 SE
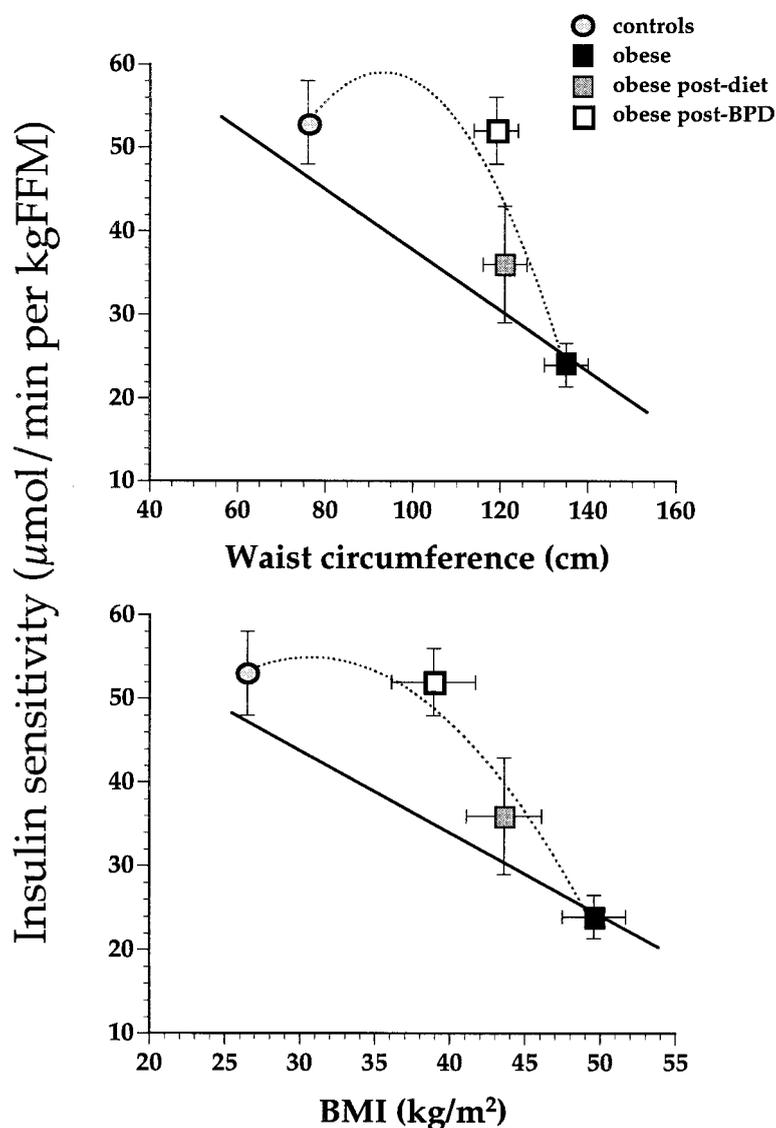
FIG. 5. Plot of insulin sensitivity against waist circumference (top) and BMI (bottom) in control subjects, obese patients at baseline ($n = 20$), and obese patients after diet ($n = 9$) or BPD treatment ($n = 8$). Symbols plot mean data ± 1 SE. The straight lines are the regression lines calculated from the baseline dataset ($n = 27$); the curves highlight the outlying position of the post-BPD group data.

obesity-related insulin resistance. Thus, visceral (1) and intramuscle (17–22,24) fat accumulation both have been implicated in the insulin resistance of both obesity and type 2 diabetes. In moderately obese, nondiabetic individuals, Goodpaster et al. (35) found that loss of visceral fat with low-calorie diets was a better predictor of improvement of insulin action than loss of total or subcutaneous abdominal fat. In the very obese participants in the present study, the waist circumference was not independently related to insulin sensitivity (when accounting for BMI) and was a poor predictor of the response to weight loss (Fig. 5). It is possible that this finding reflects that anthropometric measures are poor indexes of visceral fat accumulation. Equally conceivable is that visceral fat excess is a better marker for insulin resistance (and other cardiovascular risk factors) in moderate than in morbid obesity.

In the present study, quantitative histochemistry showed that fat accumulates in the skeletal muscle of morbidly obese individuals, both between fibers (and around blood vessels) and within myocytes. In fact, the majority of intramuscle fat is found outside myocytes, in agreement with estimates obtained by proton spectroscopy in lean volunteers (23). The novel finding is that BPD surgery selectively depleted intramyocellular lipids and that this change, rather than the changes in extramyocellular or total body fat, fully predicted reversal of the insulin resistance. These results are the mirror image of those recently obtained in rats, in which intramyocellular lipid accumulation—produced by a high-fat diet or by inhibition of fat oxidation—was found to be a close correlate of in vivo insulin-mediated glucose disposal (36).

The mechanisms underlying the association of intramyocellular lipid with insulin resistance in obesity are incompletely understood. Intracellular triglycerides may feed back on insulin action on glucose metabolism through the release of long-chain fatty acyl-CoA (LC-CoA) (37,38). An increase in the cytosolic pool of LC-CoA could directly inhibit glycogen synthase as well as interfere with insulin signaling and glucose transport (25). Because entry of LC-CoA into mitochondria is restrained by cytosolic
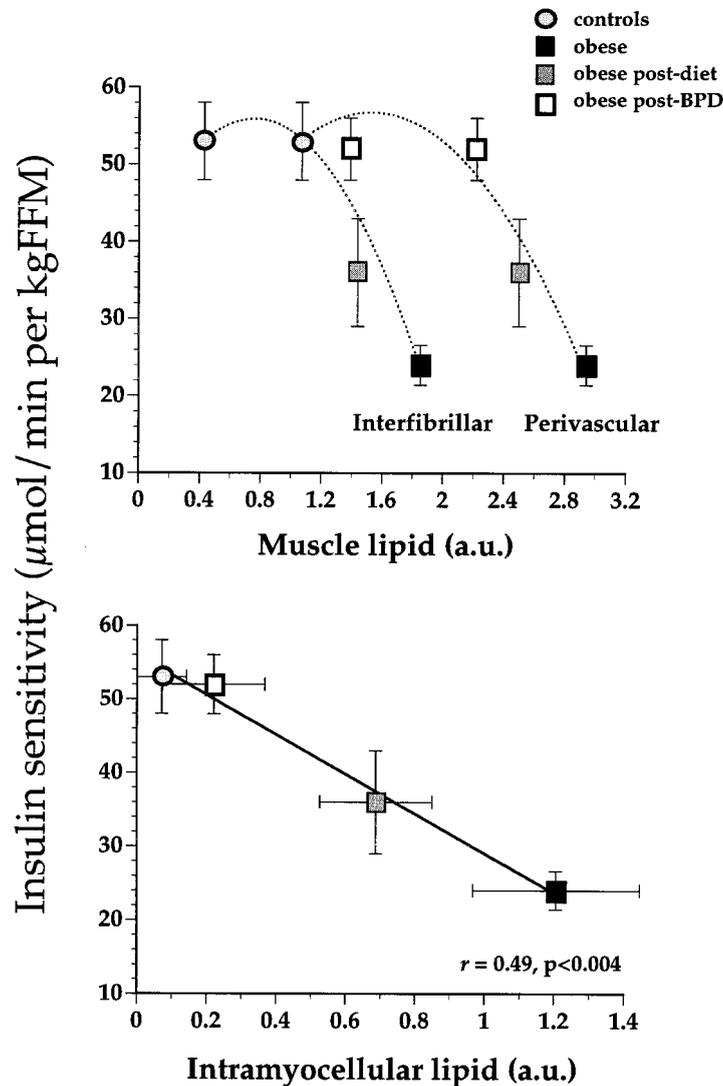
FIG. 6. Plot of insulin sensitivity against perivascular or interfibrillar fat (top) and intramyocellular fat (bottom) in control subjects, obese patients at baseline, and obese patients after diet or BPD treatment. Symbols and codes as in Fig. 5 (horizontal error bars omitted for clarity).

malonyl-CoA (through inhibition of carnitine-palmitoyl-transferase I), a general regulatory role for malonyl-CoA has been proposed in cellular fuel sensing and insulin action (the malonyl-CoA hypothesis) (39). In support of a cause-effect relationship between intramyocellular lipid accumulation and insulin signaling, we found that Glut4 expression was low in the skeletal muscle of obese patients and was fully reversed by BPD (Fig. 4).

In morbidly obese individuals, BPD surgery induces rapid and large losses in body weight and FM (at average rates of 2 kg and 1.3 kg per month, respectively) by causing severe lipid malabsorption. In the long run, BPD can achieve normal body weight, body composition, glucose tolerance, substrate utilization, and energy expenditure (5,6,40). In the current study, lipid malabsorption was documented by measuring postprandial lipemia: in contrast to the diet-treated obese patients and to the nonobese control subjects, post-BPD patients showed essentially no increment in serum triglyceride concentrations after meals (Fig. 1). In a rat model of diet-induced obesity and insulin resistance, acute dietary lipid withdrawal ameliorated muscle insulin resistance (25). In an experimental model

of internal biliary diversion, tolerance to intravenous or oral glucose and to fasting-feeding cycles was consistently improved in diverted rats in comparison with sham-operated controls in the absence of major differences in body weight (41). Thus, BPD in obese humans seems to be the full equivalent of experimental lipid deprivation, especially in terms of its effects on muscle insulin sensitivity and glucose tolerance. It is of note that the striking effects of fat starvation—whether achieved by removing lipids from the diet or by impeding their absorption—stand in contrast to the small and erratic changes in insulin sensitivity that have been observed after less drastic manipulations of dietary lipids (rev. in 42).

The mechanisms by which lipid withdrawal affects intramyocellular fat depots are not entirely clear. In the present studies, intramyocellular fat was effectively normalized in post-BPD patients at a time when extracellular muscle fat and whole-body fat stores were still abundant. This indicates not only that intramyocellular fat is controlling insulin action but also that its response to fat deprivation is sensitive. One component of this chain of events is leptin. In healthy volunteers infused with a triglyceride
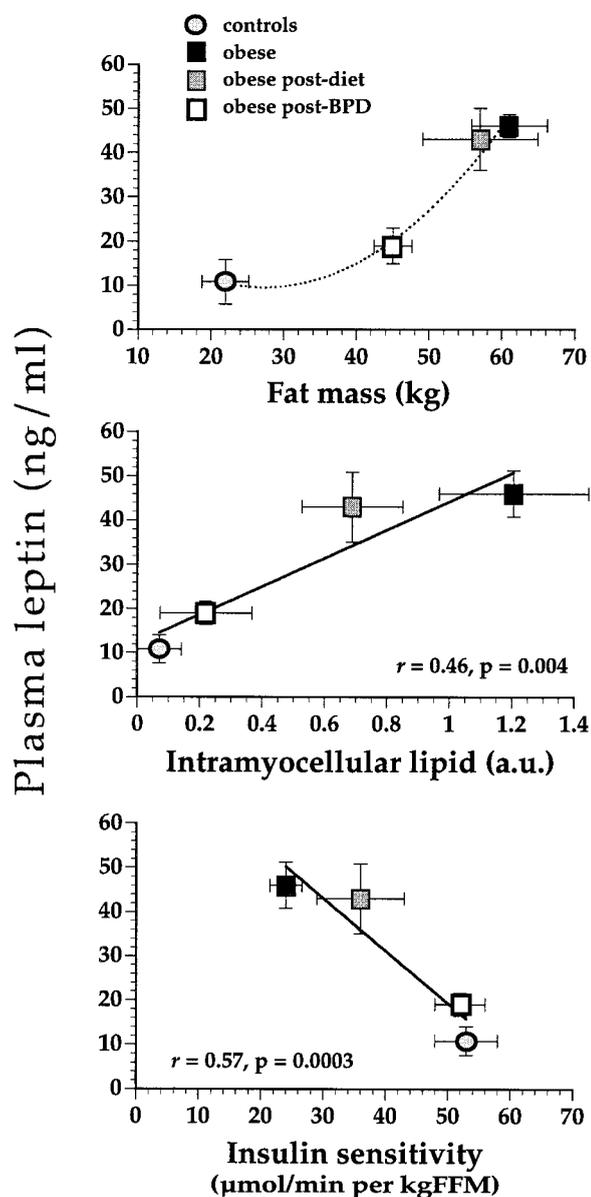
FIG. 7. Plot of plasma leptin concentrations against total FM (top), intramyocellular fat (middle), and insulin sensitivity (bottom) in control subjects, obese patients at baseline, and obese patients after diet or BPD treatment. Symbols and codes as in Fig. 5.

emulsion for 5 h, the subcutaneous adipose tissue expression of leptin is increased by 110% (43). The converse of this phenomenon presumably underlies our finding that plasma leptin concentrations were nearly normalized post-BPD but not after diet (Table 2). Furthermore, leptin levels were best related across treatments to intramyocellular fat and insulin sensitivity than to whole-body fat (Fig. 7). This result further suggests that the three observed effects of fat malabsorption—intramyocellular lipid depletion, decrease in circulating leptin levels, and increase in insulin sensitivity—may be interrelated. Thus, by inhibiting leptin gene expression, dietary lipid starvation may restore tissue sensitivity to leptin, thereby promoting intracellular triglyceride depletion (44). In turn, the reduced flux of LC-CoA (and other signal molecules) that emanates from intramyocellular fat stores may upregulate insulin signaling and restore muscle insulin sensitivity. Thus, metabolic

normalization can occur before and, in part, independent of FM normalization by virtue of physiological links between circulating lipids and intramyocellular fat storage, with an amplifying loop involving leptin release and action.

Bariatric surgery is increasingly considered for the treatment of morbidly obese patients who have serious comorbidity or fail on medical and/or behavioral weight reduction therapies. In 1991, the National Institutes of Health Consensus Conference made a recommendation for surgery in patients who have a BMI >40 kg/m^2 and exhibit a strong desire for substantial weight loss to improve quality of life (45). Of the two main surgical approaches to morbid obesity, both vertical banded gastroplasty and BPD aim at a stable reduction in total caloric assimilation, but only BPD induces predominant lipid malabsorption. No standard criteria exist to judge the success of surgery for morbid obesity in terms of weight loss, although an accepted goal is a reduction to within 50% of ideal body weight (46). In the choice of the optimal therapeutic strategy for the individual patient with morbid obesity, the postsurgical complications associated with BPD (47) may be weighed against the possibility of attaining a major and stable weight reduction and a reversal of insulin resistance.

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