Impaired plasma fatty acid oxidation in extremely obese women

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Thyfault, John P., Raymond M. Kraus, Robert C. Hickner, Amy W. Howell, Robert R. Wolfe, and G. Lynis Dohm. Impaired plasma fatty acid oxidation in extremely obese women. Am J Physiol Endocrinol Metab 287: E1076–E1081, 2004.—Skeletal muscle from extremely obese individuals exhibits decreased lipid oxidation compared with muscle from lean controls. It is unknown whether this effect is observed in vivo or whether the phenotype is preserved after massive weight loss. The objective of this study was to compare free fatty acid (FFA) oxidation during rest and exercise in female subjects who were either lean [n = 7; body mass index (BMI) = 22.6 ± 2.2 kg/m2] or extremely obese (n = 10; BMI = 40.8 ± 5.4 kg/m2) or postgastric bypass patients who had lost >45 kg (weight reduced) [n = 6; BMI = 33.7 ± 9.9 kg/m2] with the use of tracer (113C)palmitate and (14C)acetate method and indirect calorimetry. The lean group oxidized significantly more plasma FFA, as measured by percent fatty acid uptake oxidized, than the extremely obese or weight-reduced group during rest (66.6 ± 14.9 vs. 41.5 ± 16.4 vs. 39.9 ± 15.3%) and exercise (86.3 ± 11.9 vs. 56.3 ± 22.1 vs. 57.3 ± 20.3%, respectively). BMI significantly correlated with percent uptake oxidized during both rest (r = −0.455) and exercise (r = −0.459). In conclusion, extremely obese women and weight-reduced women both possess inherent defects in plasma FFA oxidation, which may play a role in massive weight gain and associated comorbidities.

Obesity is a widespread epidemic in many industrialized countries. Of particular concern is the direct impact that obesity has on the development of other comorbidities, including type 2 diabetes, hypertension, and cardiovascular disease. Not only is the rate of obesity increasing (from 13 to 27% in the last three decades), but the severity of obesity is increasing as well. Currently, 5% of the United States population is extremely obese, indicated as a body mass index (BMI) > 35, and this rate is continually rising (5). Unfortunately, as the severity or level of obesity increases, so does the risk of disease (7).

Skeletal muscle plays an important role in utilizing lipids supplied to the circulation. Thus a defect in the ability of skeletal muscle to oxidize plasma fatty acids could lead to increased triglyceride storage in both adipose tissue and skeletal muscle. Intramuscular triglycerides and lipid metabolites (fatty acyl-CoA, diacylglycerol, and ceramide) are directly linked to insulin resistance in skeletal muscle (2, 21). To examine why intramuscular triglyceride and lipid metabolites accumulate with obesity, we previously investigated fatty acid oxidation and lipid storage patterns with intact skeletal muscle strips obtained during surgery from normal-weight (BMI = 23.8) and extremely obese (BMI = 53.8) patients (11). Muscle from extremely obese patients showed a significant decrease in palmitate oxidation compared with normal and overweight/obese subjects. Our laboratory also investigated in vitro fat oxidation (muscle biopsy and homogenate technique) from normal-weight and extremely obese female subjects and found that muscle from the extremely obese subjects showed a significant decrease in both palmitate and palmitoyl carnitine oxidation (14). In addition, carnitine palmitoyltransferase 1 (CPT I) and citrate synthase enzyme activities were negatively correlated with increased adiposity, suggesting that there is a lower mitochondrial oxidative capacity in muscle of extremely obese individuals. Therefore, we have observed a phenotype of depressed skeletal muscle lipid oxidation with extreme obesity; however, we did not know whether this also occurs in vivo.

The defect of lipid oxidation in intact skeletal muscle from extremely obese subjects shows that the severity of obesity is related to a depressed ability of skeletal muscle to readily handle lipids. These factors led us to question whether extremely obese individuals possess a phenotype of decreased lipid oxidation that contributes to becoming obese and whether this defect would still be present after massive weight loss. We measured plasma free fatty acid (FFA) oxidation via infusion and recovery of labeled [13C]palmitate during both rest and exercise [50% of maximum oxygen consumption (V̇O2 max)] in female subjects who were lean or extremely obese or had previously undergone gastric bypass surgery and had lost >45 kg and were weight stable. It was our hypothesis that the subjects who had undergone gastric bypass would oxidize FFA at a rate similar to the extremely obese and that both of these groups would have significantly lower rates of FFA oxidation than normal-weight subjects.

MATERIALS AND METHODS

Experimental design. Labeled [13C]palmitate and [14C]acetate were infused for measurement of FFA oxidation and acetate recovery factor, respectively. Blood and breath samples were taken during 90 min of rest and 60 min of cycling exercise (50% of V̇O2 max) and measured for 13C and 14C enrichment, carbon dioxide production (VCO2), oxygen consumption (V̇O2), and plasma insulin, glucose, and nonesterified fatty acids in female subjects who were normal weight or extremely obese or had previously undergone gastric bypass surgery and lost at least 45 kg and were weight stable.

Human subjects. Twenty-three female subjects participated in this investigation: 7 normal-weight lean controls (lean; age 38.6 ± 2.5 yr, BMI 22.6 ± 0.9 kg/m2), 10 extremely obese subjects (obese; age
the subjects were sedentary as classified by V\(^{\text{dot}}\)\(\text{O}_2\) max (19) as well as to be assured with a metabolic cart (True Max 2400; Parvo Medics, Salt Lake City, UT). Plasma was extracted after centrifugation. Plasma palmitate \(^{13}\text{C}\) (98% enriched; Cambridge Isotopes, Andover, MA) and \(^{14}\text{C}\) acetate (0.020 \(\mu\text{Ci/kg}) was administered. This was immediately followed with a constant (0.02 \(\mu\text{mol/kg} \cdot \text{min}^{-1}\) ) infusion of \(^{13}\text{C}\) palmitate (98% enriched; Cambridge Isotopes, Andover, MA) bound to albumin and \(^{14}\text{C}\) acetate (0.50 \(\mu\text{Ci/kg} \cdot \text{min}^{-1}\) ) (ICN Pharmaceuticals, Irvine, CA) with syringe pumps (Harvard Apparatus, Cheshire, UK). At the same time points, expired breath was collected in a 3-liter bag and \(^{14}\text{CO}_2\) carbon was measured by means of a metabolic cart into 15-ml Vacutainers (Becton Dickinson,Franklin Lakes, NJ) for analysis of breath \(^{14}\text{CO}_2\). Total lipid oxidation rates were calculated from indirect calorimetry with stoichiometric equations (6). V\(^{\text{dot}}\)\(\text{O}_2\) and V\(^{\text{dot}}\)\(\text{CO}_2\) values were measured with a metabolic cart (True Max 2400; Parvo Medics, Salt Lake City, UT). The maximal exercise test was used to determine whether the subjects were sedentary as classified by V\(^{\text{dot}}\)\(\text{O}_2\) max (19) as well as to prescribe the appropriate exercise intensity used in later testing.

**Preliminary exercise testing.** Subjects underwent preliminary testing, which included measurements of body mass and height. Subjects were then tested for V\(^{\text{dot}}\)\(\text{O}_2\) max and 12-lead electrocardiogram during an incremental exercise test on an electronically braked cycle ergometer (Lode; Excalibur Sport, Groningen, The Netherlands). V\(^{\text{dot}}\)\(\text{O}_2\) was measured with a metabolic cart (True Max 2400; Parvo Medics, Salt Lake City, UT). After completion of the infusion studies, subjects remained rested in a bed for 90 min while serial samples of breath and plasma were collected at 15, 30, 45, and 60 min of rest and the last 20 min of the 60-min exercise period. The average enrichment values for the last 30 min of rest and the last 20 min of exercise were used for the calculation of FFA oxidation.

The rate of appearance (\(R_p\)) of palmitate in plasma [which is equal to the rate of disappearance (\(R_d\)) in steady-state conditions] was calculated as

\[
R_p = \frac{F_{\text{palm}}}{E_p}
\]

where \(F_{\text{palm}}\) is the palmitate tracer infusion rate, and \(E_p\) is the palmitate-derived \(^{13}\text{CO}_2\) carbon enrichment (tracer-to-tracee ratio) in plasma above the fasting baseline, corrected for the additional carbon added with methylation. FFA \(R_d\) was calculated by dividing palmitate \(R_p\) by the ratio of palmitate in the plasma FFA pool, which equaled 0.23 for lean, 0.24 for extremely obese, and 0.23 for weight-reduced subjects.

**Labeled \(^{14}\text{CO}_2\) excretion resulting from the oxidation of \(^{14}\text{C}\)-palmitate was calculated as**

\[
\text{\(^{14}\text{CO}_2\) excretion} = \frac{V_{\text{\(^{14}\text{CO}_2\)}}}{(E_{\text{\(^{14}\text{CO}_2\)}} - E_{\text{\(^{2}\text{CO}_2\)}})}
\]

where \(E_{\text{\(^{14}\text{CO}_2\)}}\) is breath \(^{14}\text{CO}_2\) found from the carbon enrichment (\(^{14}\text{C}/\text{C}\)) and \(E_{\text{\(^{2}\text{CO}_2\)}}\) is the natural abundance of breath \(^{12}\text{CO}_2\) obtained during baseline samples (\(^{12}\text{C}/\text{C}\)).

The acetate recovery factor (AR) derived from the infusion and subsequent oxidation of \(^{14}\text{C}\)-acetate was

\[
\text{AR} = \frac{E_{\text{\(^{14}\text{CO}_2\)}} \times V_{\text{\(^{14}\text{CO}_2\)}}}{(\text{SA of infusate} \times F_{\text{\(^{14}\text{C}\)}})}
\]

where \(E_{\text{\(^{14}\text{CO}_2\)}}\) is breath \(^{14}\text{CO}_2\) carbon enrichment (dpm/ml), \(V_{\text{\(^{14}\text{CO}_2\)}}\) is exhaled \(^{14}\text{CO}_2\) (ml/min), SA is specific activity of infusate (dpm/ml), and \(F_{\text{\(^{14}\text{C}\)}}\) is the acetate tracer infusion rate (ml/min).

The oxidation rate of plasma FFA was calculated as

\[
\text{plasma palmitate oxidation} = \left(\frac{\text{\(^{14}\text{CO}_2\) excretion}}{E_p} \times \text{AR} \times 16\right)
\]

where the acetate correction factor equaled 0.22 at rest and 0.74 during exercise as averaged across all groups (due to early measurement errors, acetate correction factor was accurately measured in 4 lean, 6 extremely obese, and 4 weight-reduced subjects). We found no statistical differences measured between groups for acetate correction factor. Multiplication of the denominator by 16 accounts for uniformly labeled \(^{14}\text{C}\)-palmitate, which has 16 labeled carbons. Plasma FFA oxidation was determined by dividing the rate of oxidation of palmitate by the ratio of palmitate in the plasma FFA pool.

The percentage of labeled plasma FFA taken up by tissues and then oxidized was calculated as

\[
\text{percent uptake oxidized} = \left(\frac{\text{FFA oxidation/FFA} R_d}{100}\right)
\]

Total lipid oxidation rates were calculated from indirect calorimetry with stoichiometric equations (6). V\(^{\text{dot}}\)\(\text{O}_2\) and V\(^{\text{dot}}\)\(\text{CO}_2\) values were averaged from the collection periods at points equal to 70, 80, and 90
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Lean (n = 7)</th>
<th>Obese (n = 10)</th>
<th>Weight Reduced (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>38.6 ± 2.3</td>
<td>38.9 ± 1.9</td>
<td>45.3 ± 1.5</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>61.8 ± 2.9</td>
<td>111.3 ± 5.6*</td>
<td>91.4 ± 10.9</td>
</tr>
<tr>
<td>BMI</td>
<td>22.6 ± 0.8</td>
<td>20.8 ± 1.7*</td>
<td>33.7 ± 3.8*</td>
</tr>
<tr>
<td>(\dot{V}O_2\max), l/min</td>
<td>1.58 ± 0.1</td>
<td>1.91 ± 0.1</td>
<td>1.73 ± 0.1</td>
</tr>
<tr>
<td>(\dot{V}O_2\max), ml kg(^{-1}) min(^{-1})</td>
<td>25.8 ± 1.9</td>
<td>17.4 ± 1.1*</td>
<td>19.2 ± 1.8*</td>
</tr>
<tr>
<td>HOMA</td>
<td>0.7 ± 0.1</td>
<td>2.4 ± 0.3†</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>156.0 ± 9.6</td>
<td>156.6 ± 7.8</td>
<td>141.0 ± 9.8</td>
</tr>
<tr>
<td>Triglyceride, mg/dl</td>
<td>85.1 ± 8.8</td>
<td>162.3 ± 31.44</td>
<td>80.3 ± 12.97</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>19.0 ± 8.6</td>
<td>83.6 ± 5.7</td>
<td>82.1 ± 8.5</td>
</tr>
<tr>
<td>VLDL, mg/dl</td>
<td>16.9 ± 1.8</td>
<td>32.0 ± 6.3</td>
<td>15.7 ± 2.6</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>44.4 ± 3.9</td>
<td>40.1 ± 3.7</td>
<td>42.4 ± 5.0</td>
</tr>
</tbody>
</table>

Values are means ± SE; \(n\) = no. of subjects. BMI, body mass index; \(\dot{V}O_2\max\), maximum oxygen consumption; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein. Significantly different from lean (*) and weight-reduced (†), and rest to exercise (‡), \(P \leq 0.05\).

RESULTS

Subject characteristics. Subject characteristics are found in Table 1. BMI was significantly higher in the obese and weight-reduced group than in the lean group, but no differences were found between the obese and weight-reduced groups. The weight-reduced group lost an average of 67.2 ± 11.2 kg after gastric bypass surgery, which reduced their mean BMI from 59.5 ± 5.2 to 33.7 ± 3.8 kg/m\(^2\). Homeostasis model assessment was significantly higher in the obese group compared with the lean or weight-reduced groups, respectively. The weight-reduced group was equally as insulin sensitive as the lean group, despite having a higher BMI.

Exercise variables. The lean group had a significantly higher \(\dot{V}O_2\max\) than the obese and weight-reduced groups, expressed per kilogram body weight, but no differences were found when \(\dot{V}O_2\max\) was expressed in absolute terms (Table 1). The lean, obese, and weight-reduced groups cycled at the same relative intensities (48 ± 8 vs. 51 ± 3 vs. 49 ± 5% \(\dot{V}O_2\max\), respectively).

DISCUSSION

The major finding of this study is that extremely obese individuals and those who were previously extremely obese
LIPID OXIDATION IN EXTREME OBESITY

Table 3. Plasma and total fatty acid kinetics and oxidation at rest and exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
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<th>Exercise</th>
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<tr>
<td></td>
<td>L</td>
<td>OB</td>
<td>WR</td>
<td>L</td>
<td>OB</td>
<td>WR</td>
</tr>
<tr>
<td>Plasma FFA oxidation</td>
<td>0.89±0.15</td>
<td>0.70±0.06</td>
<td>0.52±0.13</td>
<td>1.05±0.13</td>
<td>0.89±0.12</td>
<td>0.64±0.14</td>
</tr>
<tr>
<td>Total FFA Ra</td>
<td>1.32±0.14</td>
<td>1.94±0.29</td>
<td>1.26±0.16</td>
<td>1.18±0.15</td>
<td>1.74±0.24</td>
<td>1.17±0.19</td>
</tr>
<tr>
<td>Nonplasma lipid oxidation</td>
<td>0.16±0.11</td>
<td>0.38±0.16</td>
<td>0.43±0.22</td>
<td>1.20±0.43‡</td>
<td>1.46±0.22‡</td>
<td>1.39±0.49‡</td>
</tr>
<tr>
<td>RER</td>
<td>0.85±0.02</td>
<td>0.76±0.02</td>
<td>0.82±0.03</td>
<td>0.91±0.02‡</td>
<td>0.86±0.01‡</td>
<td>0.88±0.02</td>
</tr>
<tr>
<td>Total lipid oxidation</td>
<td>0.92±0.08</td>
<td>1.07±0.18</td>
<td>0.92±0.14</td>
<td>2.53±0.43‡</td>
<td>2.40±0.23‡</td>
<td>2.03±0.40‡</td>
</tr>
</tbody>
</table>

Values are means ± SE in μmol·kg⁻¹·min⁻¹; n = 7 lean, 10 extremely obese, and 6 weight-reduced subjects. Ra, rate of appearance; RER, respiratory exchange ratio. ‡Significantly different from rest to exercise, P ≤ 0.05.

possess a decreased ability to oxidize plasma FFA compared with lean controls. This defect was measured via percent plasma FFA uptake oxidized during both basal and exercise (50% VO₂ max) conditions.

In a whole body setting, the Ra and availability of plasma FFA vary among individuals and will affect the rate of plasma fatty acid oxidation. It is our opinion that the best marker of whole body plasma FFA oxidation is the percentage of plasma FFA uptake oxidized, which controls for the amount of plasma FFA available to tissues. We believe that skeletal muscle is playing a primary role in the percent plasma FFA uptake oxidized. However, it is important to consider the impact of adipose tissue, as the obese group presumably had much larger adipose tissue stores than the other two groups. Because adipose tissue in the postabsorptive state can readily take up FFA for the synthesis and storage of triglycerides, there is competition for available FFA between nonoxidizing (adipose) and oxidizing (skeletal muscle) tissues. However, the same differences in percent plasma FFA uptake oxidized between groups were found during exercise, when available plasma FFA are taken up by contracting skeletal muscle and transport of FFA to nonoxidizing tissue is presumably low. We believe that the decrease in percent plasma FFA uptake oxidized in the obese and weight-reduced groups is due to a defective ability to oxidize plasma FFA taken up by skeletal muscle.

Previous work from our laboratory (11, 14) examined in vitro lipid metabolism in skeletal muscle from extremely obese and lean individuals. Using both homogenate and intact muscle techniques, we found that skeletal muscle from extremely obese individuals displayed a decreased ability to oxidize palmitate compared with muscle from lean subjects. In addition, BMI negatively correlated with rates of palmitate oxidation. This led us to conclude that a defect in skeletal muscle lipid oxidation occurred during cases of extreme obesity.

In another study from our group (9), we measured whole body substrate oxidation (indirect calorimetry) in weight-reduced women (BMI = 34.8 kg/m²; similar to the weight-reduced subjects presented in this study) who were previously extremely obese and another group of women with matching body weights (BMI = 33.8 kg/m²). The weight-reduced group had higher respiratory exchange ratio values and lower utilization of lipids during exercise compared with the weight-matched group (9). This led us to hypothesize that the weight-reduced group possessed an inherent defect in lipid metabolism and that this defect contributed to their development of extreme obesity. However, that study had limitations, as it lacked the comparison of a group of subjects who were currently extremely obese and did not use tracer methodology in combination with indirect calorimetry.

Kelley et al. (13) measured substrate oxidation with indirect calorimetry across the leg in obese and lean men and women and found results supportive of the work presented here. Obese subjects had suppressed lipid oxidation (elevated respiratory quotient) and suppressed skeletal muscle CPT I activity and oxidative enzyme activity compared with the lean subjects. They measured the same variables in a sample of individuals after weight loss (reduction of ~14 kg body mass) and found that fatty acid oxidation was still suppressed, whereas CPT I activity had not changed and oxidative enzyme activity had lowered. Goodpaster et al. (8) measured fatty acid oxidation via tracer methodology in obese and lean men during moderate-intensity exercise and found similar results. Their obese subjects demonstrated a trend for lower plasma fatty acid oxidation per kilogram of fat-free mass and significantly lower percentages of plasma FFA uptake oxidized compared with lean subjects, but the major finding reported in their study was that the obese group oxidized significantly more (50%) nonplasma FFA than the lean group. In another study, Mittendorfer et al. (17) measured lipolysis and oxidation of FFA in lean, overweight, and obese men during 90 min of exercise and found that, as percent body fat increased, there was a decrease in the oxidation of plasma FFA and an increase in the oxidation of nonplasma FFA. Our obese and weight-reduced groups also oxidized more nonplasma lipids at rest (~50%), but only

Fig. 1. Percentage of plasma free fatty acid (FFA) uptake oxidized during basal and exercise (50% maximum oxygen consumption [VO₂ max]). *Significantly decreased in extremely obese and weight-reduced compared with lean (P ≤ 0.05).
slightly higher during exercise (~15%), and neither was statistically significant.

The data presented here conflict with some previous reports showing no differences (23, 26, 29) or greater rates of lipid oxidation in obese subjects compared with lean individuals (4, 10, 12). The disparities may be a result of different factors. First, the degree of adiposity or BMI was higher in our extremely obese group than in the obese subjects studied in previous studies, and although our weight-reduced group had a BMI similar to that of the obese groups from other studies, they had been previously extremely obese and may therefore possess a distinct phenotype. Differences between genders are another possible factor, as many of the previous studies were conducted in men. We are not aware of a study that has compared FFA oxidation between obese men and women by use of tracer methodology, although there is evidence that substrate utilization is different between normal-weight men and women (1, 18).

\( \text{VO}_2 \) is an important determinant in the ability to oxidize lipids during exercise. We found that \( \text{VO}_{2\text{max}} \) significantly correlated with percent plasma FFA uptake oxidized during exercise (\( r = 0.51, P = 0.015 \)). Earlier studies (8, 10) compared fatty acid oxidation between groups of lean and obese subjects who were matched for \( \text{VO}_{2\text{max}} \). Although we did not purposely match our groups on the basis of \( \text{VO}_{2\text{max}} \), we found no differences in absolute \( \text{VO}_2 \) among our three groups. The relative \( \text{VO}_{2\text{max}} \) was significantly lower in the extremely obese and weight-reduced groups than in the lean, but because the exercise was performed on a cycle ergometer, we believe absolute \( \text{VO}_{2\text{max}} \) is the appropriate comparison.

Other investigators have reported plasma FFA oxidation expressed per kilogram of fat-free mass; however, the data reported here are expressed per kilogram of body mass. As reported in a recent study (3), it is difficult to accurately assess body composition in extremely obese individuals, as traditional methods (hydrostatic weighing and dual-energy X-ray absorptiometry) are inaccurate or impractical for extremely obese patients (3). Because of this, we did not measure body composition in this study. However, the study of Das et al. (3) measured body composition in extremely obese and weight-reduced subjects who had body weight and BMI similar to those of the subjects from our study. To ensure that our measurements would hold true when expressed per fat-free mass, we extrapolated their measurements for percent body fat to our subjects and found that the data (not shown) displayed the same relationships when expressed per fat-free mass as they did when expressed per kilogram body weight.

Figure 2 shows the current data alongside those of our previous in vitro study (11) (all data are expressed as percentage of FFA oxidation for the control nonobese group). Figure 2 demonstrates that a similar decrement in FFA oxidation is found with both in vitro skeletal muscle incubations and in vivo tracer methodology. As stated earlier, we have shown that previously extremely obese women have reduced lipid utilization during exercise compared with healthy women of the same BMI. Therefore, the weight-reduced group (BMI = 33.7 kg/m²) seems to possess different characteristics than obese subjects with a similar BMI level. The weight-reduced group in this study had a BMI before surgery of 59.5 ± 5.2 kg/m² and a mean body weight loss of 67.2 ± 11.2 kg, which is similar to the surgery-induced weight loss in other studies (9, 20, 28).

There are existing data demonstrating that some individuals in a positive energy balance possess a body weight set point where they become overweight/obese, whereas others gain excessive amounts of weight and become extremely obese (15). The data we have collected, in vitro and in vivo, demonstrate that the development of extreme obesity could be related to a reduced ability to oxidize plasma fatty acids. Of great interest would be the ability to assess fatty acid oxidation in the preobesity condition; however, this would take a large prospective study design.

One possible explanation for depressed plasma FFA oxidation seen in extreme obesity is the composition of skeletal muscle fibers. Our group has previously shown (25) that obese individuals possess more type II nonoxidative muscle fibers and fewer type I oxidative muscle fibers than lean controls. When gastric bypass patients are followed after surgery, the percentage of type I skeletal muscle fibers positively correlated with the amount of total weight lost over time. A study by Sun et al. (24) overfed young men for a long period and found that the amount of body fat gained was inversely proportional to the amount of type I muscle fibers and directly proportional to the amount of type II muscle fibers. Therefore, skeletal muscle fiber composition, which is primarily controlled by genetic factors, most likely plays a part in the suppressed plasma FFA oxidation found with extreme obesity.

In conclusion, extremely obese and weight-reduced women possess a deficit in plasma FFA oxidation as measured by percent plasma FFA uptake oxidized. Although we have not measured FFA oxidation in the preobese state, we believe that suppressed plasma FFA oxidation plays a strong role in the advent of extreme obesity and its related comorbidities.

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Fig. 2. All data are expressed as percent fat oxidation compared with control (±SD) for 2 methods: in vitro skeletal muscle (palmitate oxidation expressed in nmol·g wet wt·h⁻¹) (11) and in vivo tracer (present data; plasma FFA oxidation expressed in pmol·kg⁻¹·min⁻¹). Extremely obese subjects (body mass index (BMI) >40 kg/m²), weight-reduced subjects (lost >45 kg of body mass; BMI = 34 kg/m²), and nonobese controls were examined.
REFERENCES


