Skeletal muscle lipid oxidation and obesity: influence of weight loss and exercise

Jason R. Berggren,1,2 Kristen E. Boyle,1,2 William H. Chapman,4 and Joseph A. Houmard1,2,3

1Human Performance Laboratory, 2Department of Exercise and Sport Science, 3Diabetes and Obesity Center, and 4Department of Surgery, East Carolina University, Greenville, North Carolina

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Obesity is one of the leading causes of preventable death in the United States and is associated (6) with conditions such as insulin resistance, the metabolic syndrome, and type 2 diabetes. A metabolic disturbance evident with obesity is a decrement in the ability of skeletal muscle to oxidize lipid. The purpose of this investigation was to determine whether either of these treatments can reverse the existing defect in lipid oxidation. The purpose of the present study was to determine whether exercise training or weight loss altered FAO in the skeletal muscle of obese individuals. Weight loss was studied in extremely obese individuals before and after gastric bypass surgery, which produced a body mass decrease of ~50 kg. We (12, 13, 19) previously reported that muscle lipid oxidation is depressed in this population. Endurance-oriented exercise training has been demonstrated to increase mitochondrial content in skeletal muscle, which in turn may enhance the ability to oxidize lipid. However, it is not clear whether this training-induced effect occurs in individuals with an initial decrement in the capacity to oxidize lipid, such as extremely obese subjects. Muscle lipid oxidation was thus studied before and after a short-term (10 days) exercise training protocol previously demonstrated to increase markers of mitochondrial content (10, 34) and enhance whole body fat utilization (3).

METHODS

Experimental Design and Subjects

The effect of weight loss on FAO in the skeletal muscle of obese individuals was examined using both cross-sectional and longitudinal designs. The cross-sectional experiment compared muscle FAO in three groups of subjects: 1) lean, 2) extremely obese (BMI ≥40 kg/m² or ≥100 lbs. over ideal body weight), and 3) extremely obese subjects who had undergone weight loss (decrease of ~50 kg) via gastric bypass surgery. The extremely obese patients were examined ≥12 mo postsurgery, because at this time body mass stabilizes and remains significantly depressed compared with the presurgery condition (27, 28). The prospective arm of the weight loss experiment measured FAO in the skeletal muscle of extremely obese women before and ~1 yr after gastric bypass surgery.

The effect of exercise training on muscle FAO was studied in three groups: 1) lean, 2) obese, and 3) previously extremely obese women who had undergone bariatric surgery and lost weight. Previously extremely obese individuals who had lost weight were examined, as our findings demonstrated a defect in FAO similar to extremely obese.
subjects and it was of interest to determine whether exercise training could effectively overcome this obesity-linked defect. The obese and weight loss subjects were selected to possess similar BMIs.

Subjects reported to the laboratory in the morning (~0800) after an overnight fast. Body mass and stature were measured while subjects were clothed and their shoes removed. A muscle sample was obtained from the vastus lateralis using the needle biopsy technique and venous blood obtained for measuring fasting glucose and insulin as an index of subject characteristics. Biopsies were obtained ~16 h after the final exercise bout in the exercise training study. All procedures were approved by the East Carolina University Policy and Review Committee on Human Research, and signed, informed consent was obtained before any experimental procedures were performed.

Participants were not taking any medications or ergogenic aids known to alter metabolism. Women were studied because they comprise a majority of the gastric bypass population. Data from some of the subjects in the exercise training intervention have previously been presented (5). Obese subjects were recruited by advertisement or during clinical visits concerning their gastric bypass surgery. Lean subjects were recruited by advertisement.

**Weight Loss**

The weight loss group was comprised of extremely obese individuals (BMI ≥40 kg/m² or 100 lbs. over ideal body weight) who had or were going to voluntarily undergo gastric bypass (Roux-en-Y) surgery as a means to reduce body mass. With this intervention there is a mean decrease in body mass of ~50 kg, with patients reaching a stable weight at ~1-year postsurgery, which is chronically maintained (27).

We (7, 11, 35) have previously used this model as a means to study the effects of weight loss with respect to skeletal muscle metabolism and obesity.

**Exercise Training**

Lean, previously extremely obese subjects who had lost weight via gastric bypass surgery and obese individuals with a similar BMI to the weight loss group were studied before and after 10 consecutive days of endurance-oriented exercise training. An incremental, maximal stress test was initially performed to 1) screen for underlying cardiovascular disease and 2) determine the workload [%peak oxygen consumption (V̇O₂ peak) and heart rate peak] for the exercise training. V̇O₂ peak was determined on an electronically braked cycle ergometer (Lode; Diversified, Brea, CA) in the upright position, with oxygen consumption measured via open-circuit spirometry (Parvomedics, Sandy, UT). Twelve-lead EKG tracings were monitored continuously during the stress tests, with physician oversight. The training program was based upon previous exercise prescriptions that improved whole body fat oxidation (3) or increased mitochondrial content (34). Participants exercised 60 min/day at 70% V̇O₂ peak for 10 consecutive days on a cycle ergometer. All training was performed in the Human Performance Laboratory under direct supervision. Subjects were initially permitted to take a rest break (5 min) during exercise; by day 5 all subjects exercised continuously. Heart rate was monitored during training and exercise intensity verified by measuring oxygen consumption. Participants were instructed to maintain their current diet and body mass and repeat the same meals the day before each biopsy.

**Muscle and Plasma Analyses**

Skeletal muscle (~100 mg) was obtained from the vastus lateralis after a 12-h overnight fast and utilized for the in vitro determination of FAO. Muscle palmitate oxidation was measured as previously described (14, 19, 20). Approximately 50–60 mg of tissue was collected in 200 µl of a modified sucrose-EDTA medium containing 250 mM sucrose, 1 mM EDTA, and 10 mM Tris·HCl, pH 7.4. Samples were minced thoroughly with scissors and then diluted 20-fold with additional sucrose-EDTA buffer. Tissue was placed on ice and homogenized with a Teflon pestle on glass for ~30 s. Forty microliters of homogenate was added to incubation wells on a sealed, modified, 48-well plate with a channel cut between the adjacent trap wells. The trap wells contained 200 µl of 1 N sodium hydroxide for the collection of liberated 14CO₂. Incubation buffer (final concentrations were as follows: 0.2 mM palmitate ([1-14C]palmitate at 0.5 µCi/ml), 100 mM sucrose, 10 mM Tris·HCl, 5 mM potassium phosphate, 80 mM potassium chloride, 1 mM magnesium chloride, 0.1 mM malate, 2 mM ATP, 1 mM dithiothreitol, 0.2 mM EDTA, 1 mM L-carnitine, 0.05 mM coenzyme A, and 0.5% fatty acid-free bovine serum albumin, 160 µl, pH 7.4) was added to the wells to initiate the reaction. Following 30 min of incubation at 37°C, 100 µl of 70% perchloric acid was added to terminate the reaction. The trap wells were sampled for label incorporation into 14CO₂, which was determined by scintillation counting using 4 ml of Unisint BD (National Diagnostics, Atlanta, GA). In addition to complete oxidative products (14CO₂), incomplete oxidative products [acid-soluble metabolites (ASM)] were also measured as described previously (19). The ratio of incomplete (ASM) to complete (14CO₂) radiolabeled products was determined to provide an index of incomplete to complete FAO.

The mRNA content of genes involved in FAO was also determined in an attempt to aid in interpreting the FAO data. Genes selected were pyruvate dehydrogenase kinase-4 (PDK4), carnitine palmitoyltransferase I (CPT I), and peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α). Total RNA was isolated from ~10 to 20 mg of muscle using an RNasey mini kit (Qiagen, Valencia, CA) with on-column DNase digestion using the RNase-free DNase set (Qiagen) to remove residual DNA. Following isolation, RNA was quantified using the RiboGreen RNA quantification kit (Molecular Probes, Eugene, OR). Total RNA was reverse transcribed into cDNA using the Superscript III reverse transcriptase protocol (Invitrogen, Carlsbad, CA). Prior to RT-PCR analysis, cDNA was quantified in triplicate with Quant-IT PicoGreen reagents (Invitrogen). Predesigned and validated primer/probe sets were obtained from Applied Biosystems/ABI (Foster City, CA). Real-time quantitative PCR was conducted using an ABI Prism 7700 sequence detection system with Taqman Universal PCR Master Mix in accordance with the manufacturers’ instructions (Applied Biosystems/ABI). Relative gene expression levels were determined using the number of cycles necessary to reach threshold (CT). The CT values from RT-PCR were compared with a standard curve that was run on each plate, which consisted of a serially diluted pool from each of the samples. All samples from a particular subject were run on the same plate and values normalized to the amount of cDNA that was originally added to each reaction well.

A fasting venous blood sample was taken before each biopsy in the prospective weight loss study; fasting blood was obtained at only the initial visit in the cross-sectional weight loss and exercise training experiments and used as an index of subject characteristics. Plasma was separated and frozen at ~80°C for subsequent analyses of glucose (YSI 2300 STAT Plus Glucose and Lactate Analyzer; YSI, Yellow Springs, OH) and insulin (Access Immunonassay System; Beckman Coulter, Fullerton, CA). A homeostasis model assessment (HOMA) value [fasting glucose (mg/dl)/0.05551 × fasting insulin (µU/ml)/22.1] was calculated (1).

**Statistical Analysis**

Comparison between lean, obese, and obese subjects after weight loss was performed with a between-groups ANOVA. Repeated-measures ANOVA was utilized to examine variables before and after weight loss or exercise training. Post hoc testing was performed with contrast-contrast analyses. Statistical significance was set at P ≤ 0.05. Values are expressed as means ± SE.
RESULTS

Weight Loss Intervention

Subjects. Subject characteristics for the cross-sectional comparisons between lean, extremely obese, and extremely obese subjects after weight loss (wt. loss) are presented in Table 1. There were statistically significant (P < 0.05) differences between each of the groups in body mass and BMI in the order of obese > wt. loss > lean. Fasting glucose was significantly higher in the extremely obese individuals compared with the lean and wt. loss groups. There were no differences in stature, fasting insulin, or HOMA between the groups (Table 1). The extremely obese (38.5 ± 1.9 yr) and wt. loss (42.3 ± 1.5 yr) groups were older than the lean (24.9 ± 1.5 yr) group.

Demographics for the longitudinal weight loss experiment are presented in Table 2. Mean age prior to weight loss was 37.4 ± 2.2 yr, and patients were examined a mean of 1.4 ± 0.2 yr after gastric bypass surgery. Over this period ~55 kg of body mass was lost; BMI was reduced by a mean of 20 kg/m², and subjects approached being clinically defined as overweight rather than obese (Table 2). Fasting plasma insulin, glucose, and HOMA all decreased with weight loss, in agreement with other reports that studied this intervention (7, 11). Subjects in the cross-sectional and longitudinal experiments were distinct populations; i.e., no data from any subject in the prospective studies were included in the cross-sectional comparison (Table 1).

FAO. FAO data for the cross-sectional weight loss experiment are presented in Fig. 1. Complete palmitate oxidation (14CO2 production) was significantly (P < 0.05) lower, by ~50%, in the in the extremely obese and previously extremely obese subjects after weight loss compared with the lean subjects (Fig. 1A). The concentration of ASM was similar between the lean, obese, and wt. loss groups (236.6 ± 52.9, 240.8 ± 49.2, and 226.8 ± 12.8 nM·g protein−1·min−1, respectively). The ratio of incomplete (ASM) to complete (14CO2 production) oxidation products was significantly elevated in the extremely obese and weight loss groups (Fig. 1B).

In support of the cross-sectional data, complete palmitate oxidation also did not change in extremely obese subjects examined before and after weight loss (Fig. 2A). There was also no statistically significant change in ASM with weight loss (261.3 ± 71.5 before vs. 386.9 ± 41.0 nM·g protein−1·min−1 after weight loss); the ratio of incomplete to complete oxidation products thus remained unaltered (Fig. 2B). The relatively low capacity for FAO in either extremely obese or extremely obese after weight loss subjects (Figs. 1 and 2) remained consistent across both the cross-sectional and longitudinal experiments, with FAO averaging ~35 nM·g protein−1·min−1 with no differences (P > 0.05) between these independent observations. As presented in Fig. 3, there was a statistically significant negative relationship (P < 0.01, r = −0.51) between BMI and complete palmitate oxidation when data from the lean and obese subjects prior to any intervention (exercise training or weight loss) were combined (n = 28). There were no changes with weight loss in PDK4, CPT I, and PGC-1α expression.

Table 1. Characteristics of the lean (BMI <25 kg/m²), extremely obese (BMI ≥40 kg/m²), and weight loss groups

<table>
<thead>
<tr>
<th></th>
<th>Lean (n = 7)</th>
<th>Obese (n = 6)</th>
<th>Weight Loss (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, m</td>
<td>1.7±0.02</td>
<td>1.7±0.02</td>
<td>1.7±0.01</td>
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<tr>
<td>Mass, kg</td>
<td>63.7±3.5</td>
<td>138.4±12.5*</td>
<td>99.2±8.8*†</td>
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<tr>
<td>BMI, kg/m²</td>
<td>22.8±1.2</td>
<td>50.7±3.9†</td>
<td>36.5±3.5†</td>
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<tr>
<td>Insulin, pmol/ml</td>
<td>35.4±9.7</td>
<td>107.0±34.0</td>
<td>37.5±13.2</td>
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<tr>
<td>Glucose, mmol/l</td>
<td>4.8±0.1</td>
<td>5.7±0.2*</td>
<td>4.7±0.3†</td>
</tr>
<tr>
<td>HOMA</td>
<td>1.1±0.3</td>
<td>4.0±1.4</td>
<td>1.2±0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. Weight loss group refers to extremely obese subjects after weight loss. BMI, body mass index; HOMA, homeostatic model assessment. *Significantly (P < 0.05) different from the lean group. †Significantly (P < 0.05) different from the obese group.

Table 2. Characteristics of the extremely obese subjects before and after weight loss

<table>
<thead>
<tr>
<th></th>
<th>Pre-Weight Loss</th>
<th>Post-Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, m</td>
<td>1.7±0.02</td>
<td>1.7±0.02</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>140.9±11.3</td>
<td>85.1±7.7*</td>
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<tr>
<td>BMI, kg/m²</td>
<td>51.0±3.5</td>
<td>30.5±2.3*</td>
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<tr>
<td>Insulin, pmol/l</td>
<td>86.8±14.6</td>
<td>26.4±5.6*</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>5.1±0.1</td>
<td>4.5±0.2*</td>
</tr>
<tr>
<td>HOMA</td>
<td>2.8±0.5</td>
<td>0.7±0.2*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8. *Significantly (P < 0.05) different from pre-weight loss.
mRNA content in skeletal muscle from subjects in the prospective weight loss study.

Exercise Training Intervention

Subjects. Characteristics for the lean, obese, and previously extremely obese subjects after weight loss (wt. loss) who performed the 10-day exercise training intervention are presented in Table 3. Any subject from the weight loss experiments (Tables 1 and 2) could volunteer for the exercise training arm; seven lean subjects, two obese subjects, and five of the extremely obese individuals after weight loss participated in both the weight loss and exercise training experiments. The lean subjects were younger (lean 26.8 ± 2.4 yr, obese 34.8 ± 2.5 yr, wt. loss 42.4 ± 2.2 yr; P = 0.05) and had a lower body mass and BMI than the obese and wt. loss groups (Table 3). BMI did not differ between the weight loss and obese groups (Table 3). Fasting glucose was significantly higher in the obese compared with the lean and wt. loss subjects. There were no differences in stature, fasting insulin concentration, HOMA, or absolute VO₂peak (Table 3); relative VO₂peak was significantly (P = 0.05) greater in the lean than the obese or wt. loss groups.

Exercise training. All subjects trained at a mean of 74.7 ± 1.1% of absolute VO₂peak, with no significant differences between the groups. Mean heart rate during exercise training was 143.4 ± 3.5 beats/min. Body mass did not change with exercise training.

FAO. Changes in complete FAO with exercise training are presented in Fig. 4A. FAO was depressed in the wt. loss group and was normalized to the level of lean and obese subjects (Fig. 1) but rather indicates that with our methodology we do not observe a significant decrement in FAO unless extremely obese subjects either before or after weight loss are studied. Palmitate oxidation increased significantly (P ≤ 0.05) with the 10 days of exercise training in all of the groups at the post-training time point (Fig. 4A). ASM were not significantly different between groups prior to exercise training and significantly increased following training (214.8 ± 49.8 to 404.2 ± 55.9, 304.8 ± 39.3 to 475.6 ± 73.8, and 274.9 ± 35.5 to 479.0 ± 81 nM·g protein⁻¹·min⁻¹ for the lean, obese, and wt. loss groups, respectively). The ratio of incomplete to complete oxidation remained unchanged in the lean and obese groups with exercise, whereas the ratio significantly decreased in the wt. loss group and was normalized to the level of lean and obese individuals (Fig. 4B). There was a statistically significant (P < 0.02) training effect with PDK4, CPT I, and PGC-1α mRNA content increasing in each of the groups (lean, obese, wt. loss); there was no group-by-training interaction indicating that the groups responded similarly to the intervention. Relative changes (fold change, after training ÷ before training) in mRNA content are presented in Fig. 5.

Table 3. Characteristics of subjects who participated in the exercise training study

<table>
<thead>
<tr>
<th></th>
<th>Lean (n = 8)</th>
<th>Obese (n = 9)</th>
<th>Weight Loss (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, m</td>
<td>1.7 ± 0.02</td>
<td>1.6 ± 0.02</td>
<td>1.6 ± 0.02</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>62.8 ± 3.2</td>
<td>104.3 ± 3.9*</td>
<td>90.7 ± 10.2*</td>
</tr>
<tr>
<td>BMI, kg·m⁻²</td>
<td>22.8 ± 1.0</td>
<td>38.9 ± 1.2*</td>
<td>33.5 ± 4.0*</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>34.0 ± 7.6</td>
<td>57.6 ± 6.3</td>
<td>41.7 ± 16.7</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>4.7 ± 0.1</td>
<td>5.3 ± 0.1*</td>
<td>5.0 ± 0.2†</td>
</tr>
<tr>
<td>HOMA</td>
<td>1.0 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>1.4 ± 0.6</td>
</tr>
<tr>
<td>VO₂peak, l/min</td>
<td>1.8 ± 0.1</td>
<td>1.9 ± 0.1</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>VO₂peak, ml·kg⁻¹·min⁻¹</td>
<td>28.3 ± 1.3</td>
<td>18.4 ± 0.9*</td>
<td>18.6 ± 1.5*</td>
</tr>
</tbody>
</table>

Values are means ± SE. *Significantly (P < 0.05) different from the lean group. †Significantly (P < 0.05) different from the obese group.
DISCUSSION

There is an accumulating body of evidence indicating a defect in skeletal muscle mitochondrial function with obesity. Concomitant with morphological alterations such as atrophy and a reduction in mitochondrial network volume (18, 29) are decrements in the activities of enzymes involved in a wide range of oxidative processes such as nutrient partitioning (i.e., PDK4), lipid transfer (i.e., CPT I), the Krebs cycle, electron transport, and \( \alpha \)-oxidation (4, 19, 32, 33). This myriad of conditions negatively affects skeletal muscle metabolism, because the capacity for lipid oxidation, whether measured in vivo or in skeletal muscle preparations, is reduced in obese (4, 16) and extremely obese (i.e., BMI \( >40 \text{ kg/m}^2 \)) (13, 19, 36) individuals (Figs. 1–3). A low-functioning level of lipid oxidation is linked with insulin resistance, type 2 diabetes, and weight gain (9, 17, 18, 25, 26, 38); it is thus critical to determine whether commonly used clinical interventions can effectively reverse the impairment in muscle FAO seen with obesity (Figs. 1 and 2).

We (12) recently reported that the decrement in lipid oxidation with obesity was retained in primary skeletal muscle cells raised in culture from extremely obese donors. This finding suggests a possible genetic origin, or at the very least a robust persistence of the obesity-linked defect in FAO, as myoblasts are raised ex vivo for 6–8 wk before FAO determination (12). In the present study, skeletal muscle lipid oxidation also remained significantly depressed in extremely obese individuals despite pronounced weight loss (Figs. 1 and 2). Such resilience, coupled with the morphological and functional aberrations evident in the mitochondria of obese individuals (18, 19, 29), could be hypothesized to produce a relatively nonresponsive muscle cell in terms of the characteristic plasticity seen in response to contractile activity. Fortunately, this does

![Fig. 4. Ten consecutive days of endurance-oriented exercise training increases lipid oxidation in skeletal muscle. Fatty acid oxidation was determined in lean (BMI <25 kg/m²), obese (BMI ≥30 kg/m²), and extremely obese subjects after weight loss (BMI = 33.5 ± 4.0 kg/m²). A: skeletal muscle fatty acid oxidation (\( ^{14}\text{CO}_2 \) production from labeled palmitate) in lean, obese, and weight loss groups before and after 10 days of exercise training (60 min/day, ~70% peak oxygen consumption). B: the ratio of incomplete to complete lipid oxidation as indicated by the amount of label in the ASM fraction divided by complete oxidation (\( ^{14}\text{CO}_2 \) production) pre- and post-exercise training. Data are expressed as means ± SE. *Significantly different (\( P \leq 0.05 \)) from the lean and obese groups at pretraining. §Significant (\( P \leq 0.05 \)) increase in all groups from pre- to postraining. ‡Significantly different (\( P \leq 0.05 \)) from the postraining time point in the weight loss group.]

![Fig. 5. Changes in pyruvate dehydrogenase kinase-4 (PDK4; A), carnitine palmitoyltransferase I (CPT I; B), and peroxisome proliferator-activated receptor-\( \gamma \) coactivator-1\( \alpha \) (PGC-1\( \alpha \); C) mRNA content with 10 consecutive days of exercise training. The data are expressed as fold increase with training (after training \( / \) before training; means ± SE) in the lean, obese, and weight loss groups. There was a training effect with mRNA content increasing after training for each of the genes.]

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not appear to be the case, as relatively acute (10 days) endurance-oriented exercise physical activity increased muscle FAO, although the capacity for lipid oxidation was initially depressed due to extreme obesity (Fig. 4). Exercise training also increased the expression of genes involved in lipid oxidation (PDK4, CPT I) and the expression of a global transcriptional regulator thought to positively influence mitochondrial content (PGC-1α) by the same relative extent regardless of the degree of obesity (Fig. 5). The present data thus provide the important information that endurance-oriented physical activity provides an effective stimulus to enhance the ability of skeletal muscle to oxidize lipid in obese individuals despite the presence of an initial decrement.

We selected this 10-day exercise training paradigm because it has previously been demonstrated (3) to increase whole body lipid oxidation. Bruce et al. (2) reported that a longer (8 wk, 5 days/wk, 60 min/day at 70% \( V_{\text{O}_2}\text{peak} \) exercise training intervention with no weight loss enhanced the ability to oxidize labeled palmitate in mitochondria isolated from the skeletal muscle of obese individuals (mean BMI of 36 kg/m\(^2\)). However, in the Bruce et al. study (2) the absence of a lean group did not permit a determination of either the extent of the initial decrement in lipid oxidation with obesity or whether the enhancement in FAO with physical activity was equivalent or compromised in obese vs. lean individuals. The data from the current study (Fig. 4) provide the novel and important information that exercise training can induce an increase in FAO in individuals with an initial obesity-linked impairment and that this effect is robust and occurs to the same extent as in younger, lean subjects.

Other work (9, 23, 37) has documented positive improvements in indexes linked with FAO, such as mitochondrial volume and electron transport chain activity during combined weight loss and physical activity programs in obese subjects. The present study differed from these investigations by 1) utilizing an exercise intervention where weight loss was minimized to specifically discern the effect of contractile activity and 2) directly measuring lipid oxidation in skeletal muscle. Although we did not attempt to extensively study the specific cellular mechanisms explaining the improvement in FAO with exercise, we did observe that the previously extremely obese individuals exhibited an elevated ratio of labeled carbons in the acid soluble fraction (ASM) compared with complete oxidation (Figs. 1 and 4), which suggests a reduced rate of flux with obesity through pathways associated with FAO. The fraction of incompletely oxidized fatty acids was normalized to the level of lean subjects with exercise training (Fig. 4), which again supports an enhanced capacity for lipid oxidation with physical activity that is likely due to positive adaptations at multiple steps of lipid oxidation processes, as suggested by our mRNA data (Fig. 5). This normalization did not occur with weight loss (see Figs. 1 and 2 and RESULTS).

The effect of weight loss on FAO in skeletal muscle was studied in extremely obese individuals before and ~1 yr after gastric bypass surgery and by comparing these patients after weight loss with lean and extremely obese subjects that had not lost weight (Figs. 1 and 2). We have reported previously that muscle lipid oxidation is depressed in extremely obese individuals (13, 19) and that with weight loss insulin action is enhanced along with a reduction in intramyocellular lipid content (7, 11). An increase in the capacity for FAO with weight loss would provide a logical mechanism for the reduction in lipid content and improvement in insulin action that we have reported previously (7, 11). However, both our cross-sectional and prospective experiments consistently revealed no effect of pronounced weight loss (Tables 1 and 2) on FAO in skeletal muscle. This observation is in agreement with one study (8) indicating a decrement in whole body fat utilization in severely obese patients after weight loss compared with weight-matched controls and provides the additional information that no benefit in FAO is gained specifically in skeletal muscle with weight loss.

Although the focus of the current study was on FAO in skeletal muscle, the findings obtained may provide insight into factors that control insulin action with exercise training or weight loss. An increase in FAO with endurance-oriented exercise training may enhance insulin action in skeletal muscle either through reducing intracellular lipid levels (2) or by a yet-undefined mechanism linked with the increase in FAO itself (9, 24). This is in contrast to weight loss, where FAO was not altered (Figs. 1 and 2), yet insulin action is enhanced along with a decrease in saturated long-chain acyl-CoA species (palmityl and stearate CoA) and intramuscular triglyceride (7, 11). Such information reveals the complexity of determining the mechanisms in skeletal muscle that ultimately influence insulin action with either weight loss or exercise interventions, whether individually or in combination.

In conclusion, skeletal muscle from extremely obese individuals exhibits an impaired capacity for FAO. This decrement in FAO persists even after pronounced weight loss (~50 kg). In contrast, the ability to oxidize lipid significantly improved after relatively acute (10 days) exercise training in extremely obese individuals where lipid oxidation was initially depressed. Exercise training enhanced FAO to the same extent as in lean subjects, indicating the efficacy of this intervention in effectively overcoming the obesity-linked defect in lipid oxidation in skeletal muscle. These findings suggest that the commonly utilized clinical interventions of weight loss and exercise training each have distinct effects on the capacity for lipid oxidation in the skeletal muscle of obese individuals.

GRANTS

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REFERENCES


LIPID OXIDATION AND OBESITY


