

Weight Loss and Exercise: Implications for Muscle Lipid Metabolism and Insulin Action

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ABSTRACT

BERGGREN, J. R., M. W. HULVER, G. L. DOHM, and J. A. HOUMARD. Weight Loss and Exercise: Implications for Muscle Lipid Metabolism and Insulin Action. *Med. Sci. Sports Exerc.*, Vol. 36, No. 7, pp. 1191–1195, 2004. An accumulation of intramuscular lipid has been reported with obesity and linked with insulin resistance. The purpose of this paper is to discuss: 1) mechanisms that may be responsible for intramuscular lipid accumulation with obesity, and 2) the effects of common interventions (weight loss or exercise) for obesity on skeletal muscle lipid metabolism and intramuscular lipid content. Data suggest that the skeletal muscle of morbidly obese humans is characterized by the preferential partitioning of lipid toward storage rather than oxidation. This phenotype may, in part, contribute to increased lipid deposition in both muscle and adipose tissue, and promote the development of morbid obesity and insulin resistance. Weight loss intervention decreases intramuscular lipid content, which may contribute to improved insulin action. On the other hand, exercise training improves insulin action and increases fatty acid oxidation in the skeletal muscle of obese/morbidly obese individuals. In summary, the accumulation of intramuscular lipid appears to be detrimental in terms of inducing insulin resistance; however, the accumulation of lipid can be reversed with weight loss. The mechanism(s) by which exercise enhances insulin action remains to be determined. **Key Words:** METABOLIC SYNDROME, OBESITY, PHYSICAL ACTIVITY

Obesity has become a major health care concern in the United States (7). Relative to the total population, the percentages of obese (BMI, $> 30 \text{ kg}\cdot\text{m}^{-2}$) and morbidly obese (BMI, $> 40 \text{ kg}\cdot\text{m}^{-2}$) adults are 30.5 and 6%, respectively (7). Obesity is associated with whole-body as well as skeletal muscle insulin resistance; accordingly, both obesity and insulin resistance are risk factors for the development of cardiovascular disease, hypertension, and Type 2 diabetes. Thus, a more clear understanding of the relationship between obesity and insulin resistance is needed.

Skeletal muscle, by virtue of its mass, is the predominant site of glucose disposal. We have reported (6,13) that insulin-stimulated glucose uptake is blunted in skeletal muscle from obese individuals. The exact mechanism(s) responsible for this defect has yet to be determined. An attractive hypothesis involves the accumulation of intramuscular lipids inducing the insulin-resistant state (9,12,19,29). In support of this hypothesis, intramuscular triacylglycerol (IMTG) content is elevated with obesity (9); however, recent findings suggest that other lipid intermediates (long-

chain fatty acyl-CoA (LCACoA), diacylglycerols, ceramides) are more directly linked with the insulin resistance itself, whereas IMTG is relatively inert (5,29). Recent work has thus focused upon determining the cellular mechanism(s) by which intramuscular lipids induce insulin resistance; however, relatively little is known regarding the mechanisms that initiate the accumulation of lipid within the muscle cell. The purpose of this paper is to discuss mechanisms we believe may contribute to intramuscular lipid accumulation with obesity. In addition, commonly employed interventions for obesity (i.e., weight loss or exercise) and their effects on intramuscular lipid accumulation and lipid metabolism are discussed.

THE ROLE OF SKELETAL MUSCLE LIPID METABOLISM IN OBESITY

Part of the insulin resistance of obesity, particularly morbid obesity, may be due to differences in muscle fiber type. Type I fibers, often referred to as slow-twitch or red fibers, are the more oxidative, insulin-sensitive fiber type, whereas Type II fibers (fast-twitch, white fibers) are glycolytic, relatively insulin-resistant, and have a lower capacity to oxidize fats. We have reported that morbidly obese subjects possess a significantly lower percentage of Type I (42% vs 55%) and a higher percentage of Type IIb (25% vs 14%) muscle fibers compared with lean individuals (13,31). Moreover, the percentage of Type IIb muscle fibers was positively correlated with BMI (13). These findings suggest that skeletal muscle fiber type may play a role in the reduced muscle oxidative capacity and insulin resistance reported with obesity. It is not evident whether the increased expres-

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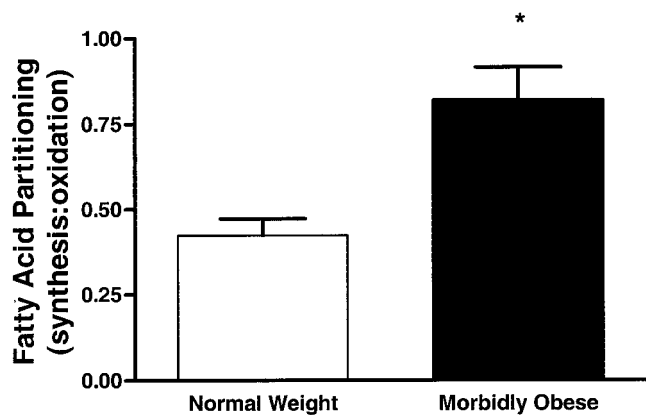


FIGURE 1—Fatty acid partitioning (ratio of palmitate synthesized to palmitate oxidized) in rectus abdominus strips from nonobese and morbidly obese women. Data expressed as mean \pm SE. *Significantly different from nonobese group ($P < 0.05$). Data are redrawn from Hulver et al. (17).

sion of Type II fibers is developed during the course of obesity or an inherent part of the morbidly obese state. However, we observed no change in muscle fiber type with dramatic weight loss (>40 – 50 kg) in morbidly obese subjects, which suggests that fiber type is not a direct function of body mass (10).

When considering that muscle from morbidly obese individuals appears to have a higher percentage of Type II, glycolytic fibers, it is logical to hypothesize that the oxidative capacity of the tissue will be blunted compared with lean controls. Previous work from Kelly and colleagues (12) demonstrated a reduced activity of enzymes responsible for lipid degradation in concert with higher IMTG content in obese skeletal muscle. In support of these data (12), our laboratory (22), reported that the activities of enzymes pertinent to mitochondrial fatty acid oxidation [carnitine palmitoyl transferase-I (CPT-1), citrate synthase, β -hydroxyacyl-CoA dehydrogenase] were significantly reduced with obesity. Furthermore, $^{14}\text{CO}_2$ production from [1 - ^{14}C] palmitoyl-carnitine, a compound that is CPT-1 independent, was also suppressed in skeletal muscle from primarily morbidly obese subjects. Together, these findings (12,22) suggest that the ability to oxidize lipid is compromised in skeletal muscle with obesity. This notion is supported by data demonstrating decreased mitochondrial size and function in the skeletal muscle of obese subjects (21).

To more clearly characterize the nature of the defect in skeletal muscle fatty acid metabolism with obesity, we employed an *in vitro* model using intact human muscle strips to examine lipid degradation and deposition in non-obese (BMI < 25.0 kg·m $^{-2}$), moderately obese/overweight (BMI, 25–34.9 kg·m $^{-2}$), and morbidly obese (BMI > 35.0 kg·m $^{-2}$) individuals (17). Relative to nonobese controls, we observed blunted fatty acid oxidation and elevated levels of IMTG in muscle from the very obese subjects. In addition, when calculating a synthesis/oxidation ratio, fatty acids were preferentially partitioned towards lipid synthesis as opposed to oxidation in the morbidly obese tissue (Fig. 1). These findings suggest that multiple steps involved in lipid

metabolism are altered in skeletal muscle with morbid obesity, which are manifested as a reduction in fat oxidation and increased lipid accumulation. These alterations were not evident in the moderately obese/overweight subjects, suggesting a different mechanism for lipid accumulation in the skeletal muscle of these individuals.

To determine whether this preferential partitioning of lipid towards storage may contribute to the accumulation of intramuscular lipid intermediates in skeletal muscle from morbidly obese subjects, we measured LCACoA concentration in the same skeletal samples where lipid metabolism was observed to favor deposition vs oxidation (Fig. 1). Long-chain fatty acyl-CoA are detrimental to insulin signaling as they can directly and indirectly activate protein kinase C (PKC) (5,29,30), which impairs insulin signal transduction leading to insulin resistance (2). Total LCA-CoA concentrations were significantly higher in both the moderately obese/overweight and morbidly obese subjects compared with nonobese controls despite a blunted fatty acid oxidation only in the morbidly obese muscle (17). These findings suggest that the accumulation of LCACoA in obesity may be due to some, yet to be defined, mechanism other than reduced fatty acid oxidation. Investigations are currently underway in our laboratory examining fatty acid uptake. Regardless, in contrast to obese/overweight subjects, a defect in lipid oxidation in morbidly obese skeletal muscle may contribute to lipid deposition in skeletal muscle and the development of insulin resistance. A reduced oxidative capacity in skeletal muscle may also partition lipid towards storage in adipose tissue, thus contributing to the development of the morbidly obese state itself.

WEIGHT LOSS

Surgically induced weight loss, via gastric bypass surgery, is an effective intervention for treating morbid obesity and the associated insulin resistance. Briefly, the gastric bypass procedure involves decreasing the size of the stomach, which dramatically reduces caloric intake and induces substantial weight loss (28). It has been reported that most patients have a complete reversal of diabetes/insulin resistance and a significant alleviation of related co-morbidities after gastric bypass surgery (28). Generally, patients lose approximately 100 lb and retain this weight loss for years after the surgery (25,27). Insulin sensitivity increases 100–360% after weight loss while fasting insulin levels tend to decrease between 85 and 100% (16). The effect of weight loss on skeletal muscle lipid oxidation and accumulation is less understood. Thus, we have used surgically induced weight loss as a model to investigate how skeletal muscle lipid metabolism is modulated with weight reduction (10,16). In our studies, we examine subjects 1 yr after surgery as they are weight stable at this time (indicating energy balance) and remain so as long as the reduced stomach size is intact (28).

As previously discussed, morbidly obese individuals tend to have a lower percentage of Type I muscle fibers relative to nonobese controls. Weight loss does not appear to have

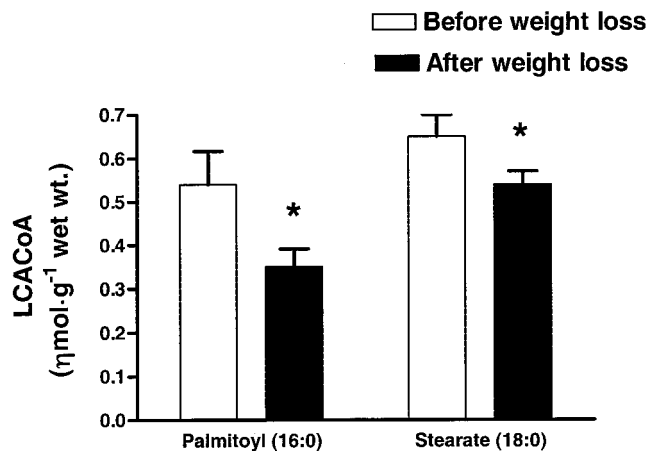


FIGURE 2—Changes in skeletal muscle (vastus lateralis) saturated long chain fatty acyl CoA content (LCACoA) in response to weight loss. Data are expressed as mean \pm SE. *Significantly different ($P < 0.01$) from before weight loss. Data are redrawn from Houmard et al. (16).

an impact on fiber type distribution (10). Furthermore, neither oxidative nor glycolytic capacity is changed in response to weight loss. However, we observed that the initial percentage of Type I (%) muscle fibers were positively correlated with weight loss, which suggests that patients with a higher initial percentage of Type I muscle fibers were prone to lose more weight (31). It is well established that Type I muscle fibers have greater oxidative potential. Thus, our data suggest individuals with a higher skeletal muscle oxidative capacity may be more successful at weight loss, which is in accordance with the general hypothesis that the oxidative capacity of skeletal muscle is related to obesity.

In support of an obesity/muscle oxidative capacity relationship, Kelley et al. (20) suggested that impaired skeletal muscle fatty acid oxidation is a predisposing factor to the development of obesity as well as weight regain after weight loss. To determine whether the ability to oxidize lipid is altered after pronounced weight loss, we compared fatty acid oxidation (RER from expired gases) during submaximal exercise in formerly morbidly obese patients after weight loss with controls matched for age, race, and BMI (11). Our findings indicated that even in a weight-reduced state, formerly morbidly obese women had a reduced capacity to utilize fat for energy. This reduced ability to oxidize lipids may predispose individuals to excess muscle lipid accumulation and weight gain or regain after weight loss, as hypothesized by others (20).

As discussed previously, the accumulation of muscle lipids, particularly bioactive lipid species such as LCACoA, ceramide, and diacylglycerol, is related to insulin resistance. In our model of weight loss, morbidly obese gastric-bypass patients decreased total LCACoA content by $\sim 20\%$ ($P = 0.09$), which occurred in concert with improved insulin action but no change in muscle oxidative capacity (16). In relation to specific LCACoA species, there was a decline in palmitoyl (16:0) and stearoyl CoA (18:0) by 35% and 15%, respectively, with weight loss (Fig. 2). The decline in palmitoyl CoA tended to be associated with increased insulin sensitivity ($r = -0.58$, $P = 0.08$). This is important as

saturated lipids are detrimental to insulin action (1,4,26,33). In support of this notion, diets high in saturated fatty acids induce insulin resistance in both animal and human models (33). Reductions in LCACoA content, specifically the saturated species may thus be a factor contributing to improvements in insulin action in morbidly obese individuals with weight loss.

EXERCISE

There is a discrepancy regarding the effect of endurance-oriented exercise training on intramuscular lipid content. Although increased lipid stores are associated with obesity and insulin resistance, endurance-trained athletes, an insulin sensitive population, also have high quantities of IMTG (8). This discrepancy may be explained by an enhanced ability to oxidize intramuscular lipids and the use of IMTG as a fuel source during exercise. Thus, although IMTG content may increase, the accompanying elevation in mitochondrial content/oxidative capacity with exercise training may minimize the accumulation of potentially detrimental lipid metabolites such as LCACoA, although this remains to be determined.

One of our experiments compared characteristics of muscle lipid metabolism and lipid content in lean, sedentary individuals and endurance-trained athletes. Jong-Yeong et al. (18) reported higher rates of both long-chain (LCFA) and medium-chain (MCFA) fatty acid oxidation in muscle homogenate preparations from endurance-trained individuals. Carnitine palmitoyltransferase I activity was also elevated in the endurance trained subjects indicating that mitochondrial transport of LCFA was enhanced. The finding that MCFA oxidation was elevated in trained individuals is important as the mitochondrial transport of MCFA occurs independent of CPT-1, which suggests that mitochondrial oxidative capacity is also elevated in trained subjects. These findings were confirmed by a concomitant increase in citrate synthase activity. Thus, the increased capacity to oxidize FFA may contribute to the increased insulin sensitivity seen in endurance-trained skeletal muscle despite increased lipid content.

Although endurance training may promote increased lipid oxidation in many individuals, it remained to be demonstrated whether the skeletal muscle of morbidly obese subjects was responsive to the exercise-training stimulus. Using a short-term exercise-training model, we examined fatty acid oxidation in muscle homogenates from morbidly obese ($BMI = 40.15 \pm 0.90 \text{ kg}\cdot\text{m}^{-2}$) females (age = 32.56 ± 2.23 yr; $N = 9$). This training model has previously been shown to improve insulin action (14,32,34) and by others (3) to enhance fat oxidation in lean sedentary individuals independent of weight loss. Briefly, training involved 10 d of exercise, $1 \text{ h}\cdot\text{d}^{-1}$ at $75\% \dot{V}O_{2\text{max}}$ on a cycle ergometer. Body mass of participants was maintained by increasing energy intake to replace calories expended during exercise. Biopsies of the vastus lateralis were taken before and ~ 16 h after the last training session and fatty acid oxidation determined as previously described (22). Preliminary data (unpublished results) indicated that morbidly obese skeletal muscle is indeed responsive to exercise (Fig. 3) as palmitate

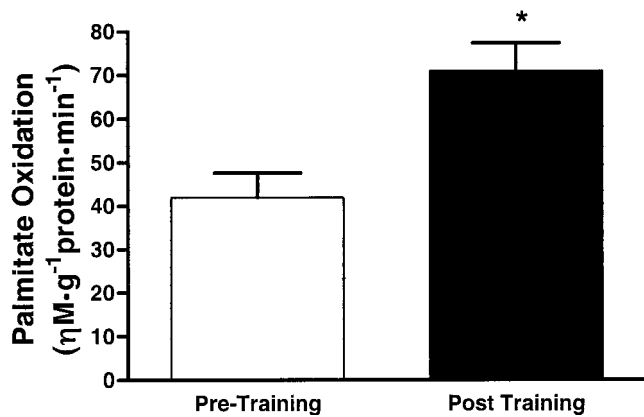


FIGURE 3—Changes in morbidly obese skeletal muscle (vastus lateralis) fatty acid oxidation in response to 10 d of exercise training (1 h·d⁻¹, ~ 75% $\dot{V}O_{2peak}$). Data are expressed as mean \pm SE. *Significantly different ($P < 0.05$) from before training.

oxidation increased approximately twofold. We have not yet determined the effect of training on bioactive lipid intermediates in skeletal muscle from morbidly obese participants; a reduction in, for example, LCACoA species with training would offer a plausible mechanism by which insulin action is improved.

Further support for the linkage between lipid accumulation and insulin resistance comes from a recent exercise trial (STRIDDE) that examined the effects of exercise intensity on insulin sensitivity and comorbidities associated with cardiovascular disease (15,23,24). Sedentary overweight/obese subjects exercised at a low amount/moderate intensity [~ 12 miles walking per week at 40–55% $\dot{V}O_{2peak}$], low amount/high intensity [~ 12 miles jogging per week at 65–80% $\dot{V}O_{2peak}$], or high amount/high intensity [~ 20 miles jogging per week at 65–80% $\dot{V}O_{2peak}$] for 6 months. Regardless of training intensity, exercise training significantly improved insulin sensitivity. However, the relative improvement in insulin action differed between groups, with the low amount/rigorous intensity group showing the least amount of improvement (Fig. 4). The interesting aspect relative to lipid metabolism/accumulation was that changes in plasma triacylglycerols mirrored changes in insulin action (Fig. 4); in other words, exercise-training prescriptions that induced a greater reduction in circulating plasma TG improved insulin action to a greater extent. Thus, exercise may mediate its effects on insulin sensitivity partly through alterations in triacylglycerol levels. To date, the effect of exercise on IMTG levels in an obese population is unclear; however, in a lean sedentary population, IMTG appear to increase with training as discussed previously (8). Thus, the elevated oxidative capacity of skeletal muscle with endurance training is a likely avenue for disposal of the lipid intermediates known to induce insulin resistance.

CONCLUSIONS

Both moderate and morbid obesity is associated with impaired insulin action and an accumulation of intramuscular lipids. The skeletal muscle of morbidly obese individuals

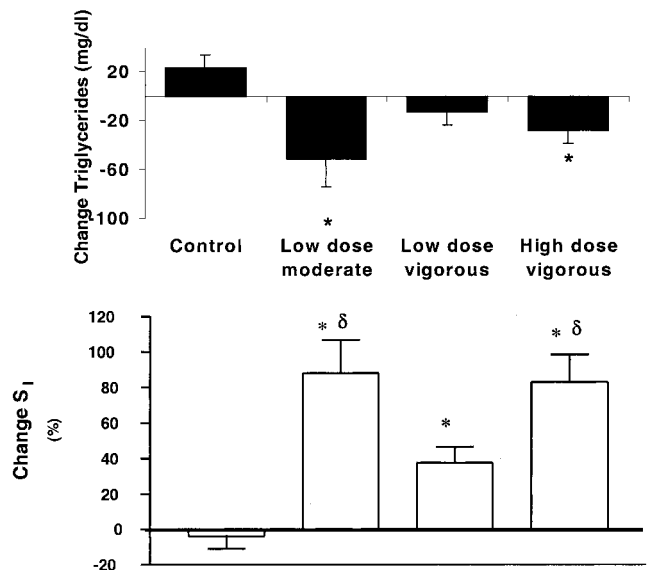


FIGURE 4—Relative changes (%) (after training/before training) in serum triglyceride (top panel) in the control and exercise (low amount/moderate intensity; low amount/high intensity; high amount/high intensity) groups from the STRRIDE study. Line at 0.0 represents no change. Relative changes (%) in S₁ (insulin sensitivity index) (bottom panel) in the control and exercise groups. Data are expressed as mean \pm SE. *Significantly different ($P \leq 0.05$) from control group. δ Significantly different ($P < 0.05$) from the low amount/high intensity group. Data are redrawn from Houmard et al. (15).

appears to have a unique metabolic phenotype that favors the deposition of lipids within the muscle cell. This phenotype is characterized, in part, by a lower distribution of Type I muscle fibers, impaired fatty acid oxidative capacity, and increased lipid deposition, all of which may contribute to the accumulation of intramuscular lipids. The mechanism by which lipid accumulates in the muscle of moderately obese/overweight individuals is not evident.

Weight loss effectively increases insulin sensitivity in morbidly obese skeletal muscle and reduces skeletal muscle lipid content (triglycerides and lipid intermediates), which may contribute to the improvement in insulin action. The reduction in muscle lipid content occurs in the absence of alterations in skeletal muscle fatty acid oxidation. Exercise, on the other hand, improves skeletal muscle insulin action and increases fatty acid oxidation, which may serve as a protective mechanism against the accumulation of harmful lipid species. The effect of exercise on overall intracellular lipid content and specific bioactive lipid species (i.e., saturated LCACoA species) in obese individuals, however, has yet to be clearly defined. Although both weight loss and exercise are effective in ameliorating insulin resistance in obese individuals, further research is needed to discern the link between changes in lipid metabolism/accumulation with these interventions and the positive effect of these intervention in enhancing insulin action.

Jason R. Berggren and Matthew W. Hulver contributed equally to the preparation of this manuscript.

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