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Severe Obesity: Evidence for a Deranged Metabolic Program in Skeletal Muscle?

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Abstract

Severe obesity is increasing at a disproportionate rate compared to milder grade obesity. Our research group has obtained evidence indicative of an “obesity metabolic program” in the skeletal muscle of severely obese individuals which may be genetically or epigenetically determined. We believe this represents a paradigm shift in thinking about metabolic regulation in obesity.

Keywords

Bariatric surgery; Exercise training; Fat oxidation; Class III obesity; Insulin action; Mitochondria; Obesity

INTRODUCTION

Obesity is a chronic disease which is increasing at epidemic proportions. Our research group has been studying skeletal muscle metabolism in severely obese patients for more than 25 years. These studies were initially possible due to collaborating surgeons providing abdominal muscle (rectus abdominus) biopsies which were examined in muscle strip preparations. These *in-vitro* incubation studies were complimented with experiments using needle biopsies of a leg muscle (vastus lateralis) and skeletal muscle cell cultures derived from the tissue of lean and severely obese donors (11, 26). In these preparations we have observed a consistent metabolic profile in severely obese individuals (body mass index, BMI 40 kg/m²) which has lead us to hypothesize that a constitutive “obesity metabolic program” which contributes to positive lipid balance and insulin resistance is involved. This review will focus on our findings implicating the existence of a metabolic program in the skeletal muscle of the severely obese.

THE METABOLIC PROFILE OF SKELETAL MUSCLE OF THE SEVERELY OBESE

Fat Metabolism

To determine if a reduction in fatty acid oxidation (FAO) in skeletal muscle was evident with obesity, we measured the rate of production of labeled carbon dioxide ($^{14}\text{CO}_2$) from ^{14}C -labeled palmitate as an index of fat oxidation in rectus abdominus muscle strips (27). To our surprise, FAO did not differ between the muscle of lean (BMI, $23.8 \pm 0.6 \text{ kg/m}^2$) and obese ($30.2 \pm 0.8 \text{ kg/m}^2$) individuals but only exhibited a significant reduction ($\sim 60\%$) in tissue from severely obese (BMI, $53.8 \pm 0.4 \text{ kg/m}^2$) subjects (27). Similarly, in needle biopsies from the vastus lateralis FAO (^{14}C -labeled palmitate) was reduced by $\sim 60\%$ with severe obesity (3, 29). These congruent findings in two muscle groups is suggestive of a relatively global defect as the tissues sampled were from distinct anatomical areas (abdominal vs. leg) with differing functions and recruitment patterns (i.e. postural (rectus) vs. locomotion (vastus)). We feel that these consistent findings (3, 27, 29) provide strong evidence for a reduction in FAO in the skeletal muscle of severely obese individuals. These data are summarized in Figure 1.

Our subsequent research focused on identifying cellular mechanisms which could contribute to this reduction in FAO. Proteome analyses revealed an increase in glycolytic enzyme content which was hypothesized to reflect a metabolic shift towards glycolytic energy production to compensate for the decrement in FAO with severe obesity (24). In support, we reported that the ratio of phosphofructokinase to citrate synthase enzyme activities, a surrogate for muscle glycolytic capacity, was elevated in the skeletal muscle of severely obese subjects (29). We also observed an elevated generation of lactate from incubated muscle strips, again suggesting an overall metabolic shift (17).

To directly examine processes involved in FAO, muscle biopsy samples were incubated with distinct fatty acids to study the carnitine-mediated transport of fatty acids into the mitochondria at carnitine palmitoyltransferase (CPT1) and downstream (29). With severe obesity, long-chain (palmitate) oxidation was depressed in conjunction with CPT-1 activity indicating a possible defect at this step (29). However, the oxidation of palmitoyl carnitine, which enters the mitochondria independently of CPT-1, was also depressed indicating that processes subsequent to CPT-1 such as β -oxidation and/or the tricarboxylic acid cycle (TCA) also contribute to the reduction in FAO. In support of this tenant, citrate synthase (a TCA cycle enzyme) and β -hydroxyacyl-CoA dehydrogenase (β -HAD, an enzyme involved with β -oxidation) activities were lower in the muscle of the severely obese (29). These findings are suggestive of a relatively encompassing metabolic program in the skeletal muscle of severely obese individuals where multiple processes are affected with a resultant decrement in FAO.

As indicated by these data, the metabolic program with severe obesity generally involves decrements in oxidative and increases in glycolytic metabolism. We have also reported that the skeletal muscle of severely obese individuals are comprised of a lower percentage of type I muscle fibers (22, 33). Type I, or red, muscle fibers are typically insulin-sensitive and favor oxidative metabolism compared to type II (white) muscle fibers; in support, insulin action in our strip preparation was positively related to the percentage of type I muscle fibers (22). This predominance of type II fibers with severe obesity is again suggestive of a phenotype which favors a low capacity for lipid oxidation and insulin resistance. However, it is important to note that fiber type, as determined by histochemical staining for myosin adenosine triphosphatase (ATPase) activity (22, 33) may not always reflect specific metabolic processes. For example, we have reported that muscle fiber type is not altered in

severely obese subjects after the substantial weight loss induced by gastric bypass surgery despite a marked improvement in insulin action (20, 25). Such findings indicate that contractile (i.e. fiber type) and metabolic characteristics may not always be congruent.

Insulin Action

We and others have reported that severely obese individuals have whole body insulin resistance (32). Skeletal muscle comprises approximately 45% of body mass in a normal person and is responsible for approximately 75% of the glucose disposal after a meal. Therefore, it was reasonable to investigate mechanisms of insulin resistance in human muscle.

Using the muscle fiber strip preparation (14) we found that glucose transport was stimulated approximately 2.5-fold by insulin in tissue from lean controls, but there was little or no stimulation of glucose transport in muscle from severely obese patients either with or without type 2 diabetes. Glucose transport in the muscle of severely obese patients, both diabetic and non-diabetic, was also resistant to the action of insulin-like growth factor-1 (IGF-1) (13). Cumulative data demonstrated that glucose transport was stimulated by approximately 3–4 fold for individuals with a BMI ≤ 20 kg/m², but there was a progressive decline in insulin responsiveness in individuals with a BMI of about 30 kg/m², after which there was virtually no insulin-induced stimulation (16). In addition to glucose transport, insulin stimulation of glycogen formation, glucose oxidation, and non-oxidized glycolysis were also depressed in muscle of severely obese patients (10). Lactate release was not stimulated by insulin but basal (absence of insulin) lactate release was much higher in obese than non-obese controls suggesting a preferential utilization of carbohydrate as a fuel source (17).

Muscle contraction stimulates glucose transport in a manner similar to insulin; i.e., translocation of glucose transporters to the cell membrane. Thus, we asked the question whether muscle from obese individuals was also “resistant” to stimulation by muscle contraction. In obese Zucker rats, muscle contraction stimulated glucose transport normally, even though there was severe insulin resistance (15). We were not able to make human muscle fiber strips contract but did observe that hypoxia and vanadate, two stimuli that are believed to function through pathways also activated with muscle contraction, stimulated glucose transport normally in muscle strips from severely obese, insulin-resistant individuals (1, 9). From these data we concluded that the mechanism for the translocation of the insulin-sensitive glucose transporter (GLUT4) was functional and the defect must be upstream and within the signaling pathway leading to insulin-mediated glucose transport. To investigate the effects of obesity on insulin signal transduction we again used the muscle fiber strip preparation in the presence and absence of insulin. Insulin stimulation of insulin receptor and insulin-receptor substrate-1 (IRS-1) tyrosine phosphorylation as well as activation of phosphatidylinositol 3-kinase (PI-3 kinase) and Akt (also known as protein kinase B, PKB) were all substantially reduced with severe obesity (8, 19).

To investigate differences in the insulin signaling pathway in severely obese subjects we partially purified insulin receptors from biopsy tissue and found that the insulin receptors of severely obese subjects had lower tyrosine kinase activity than those of non-obese controls (10). When the insulin receptors from muscle of obese individuals were treated with a serine phosphatase, the tyrosine kinase activity was restored to normal. This suggests that insulin receptors are highly serine phosphorylated in muscle of the severely obese and this inhibits activity, which is restored when the phosphate is removed (28, 35). Phosphorylation of the insulin receptor and IRS-1 on tyrosine residues activates the signaling pathway, while serine phosphorylation inhibits signal transduction. IRS-1 from muscle of severely obese patients was also found to be hyper-phosphorylated, especially on serine 312 which would inhibit

activity (4). These changes in serine phosphorylation were accompanied by increased activities of several serine kinases, including protein kinase C (PKC) (28, 35). PKC is activated by diacylglycerol, which is one of the lipids stored in muscle of obese individuals. The involvement of PKC was also implicated by the finding that insulin resistance could be induced by a phorbol ester, which activates PKC, and insulin sensitivity restored in obese muscle with a PKC inhibitor (12). Based on these findings our hypothesis is that several kinases are activated in the muscle of severely obese individuals with subsequent serine phosphorylation of the insulin receptor and IRS-1 which in turn reduces activity. These modifications depress insulin signal transduction and stimulation of glucose transport, glycogen synthesis, glucose oxidation and non-oxidized glycolysis.

CHARACTERISTICS OF MYOTUBES RAISED IN CULTURE FROM SEVERELY OBESE INDIVIDUALS

Satellite cells from muscle biopsy samples can be cultured into myoblasts and subsequently myotubes which closely resemble mature muscle fibers. In this preparation, the influence of factors such as neural input, hormonal concentrations, and physical activity level on metabolic characteristics are essentially removed due to the length and nature of the proliferation and differentiation phases; findings obtained in human skeletal muscle cells raised in culture (HskMC) are thus thought to reflect a phenotype resulting from a specific DNA sequence (i.e. genetic) and/or from changes to the genome that do not involve a change in the nucleotide sequence (i.e. epigenetic). We initiated studies with the intent of determining if characteristics evident *in-vivo* and *in-vitro* were retained in HskMC with severe obesity. This model also permitted the experimental manipulation of variables to discern cellular mechanisms that could not be accomplished in intact humans.

Fat Metabolism

Our initial experiments were designed to determine if the decrement we reported in FAO (3, 27, 29) was retained in HskMC. As presented in Figure 1, the magnitude of the reduction in FAO with severe obesity was virtually identical in HskMC compared to intact muscle strips or muscle homogenates (2, 3, 11, 26). In addition, an index of oxidation efficiency (incomplete oxidation divided by complete oxidation) was similar between HskMC and *in-vitro* measurements in skeletal muscle (2, 3, 11, 26). Indices indicating increased lipid partitioning towards storage (i.e. ^{14}C incorporation into triacylglycerol, phospholipid and diacylglycerol) were also approximate and even slightly elevated in HskMC (2, 3, 11, 26). These findings indicate that the metabolic signature evident in the skeletal muscle of severely obese individuals in relation to FAO is maintained in HskMC (Figure 1).

Gene arrays and PCR analyses indicted multiple differences in gene expression with severe obesity with one of the more pronounced being a 2-fold elevation in stearoyl-CoA desaturase-1 (SCD-1) expression; this elevation in SCD-1 mRNA content was also evident in HskMC (26). SCD-1 is a lipogenic enzyme which directs palmitoyl-CoA (C16:0) and stearoyl-CoA (C 18:0) towards lipid synthesis but has no readily discernible effects on FAO. To mimic the severely obese state, we over-expressed SCD-1 in HskMC from lean subjects. This treatment elicited a reduction in FAO and concomitantly increased lipid storage both of which are characteristics of HskMC from severely obese individuals (26). The fact that both FAO and lipid storage were altered with overexpression suggests that SCD-1 may impart a multi-tiered level of control with the ultimate result of lipid accumulation.

In terms of other cellular mechanisms, there are conflicting findings of whether a reduction in mitochondrial content or a decrement in mitochondrial function is responsible for the lower FAO evident with obesity. In HskMC from severely obese donors, mitochondrial

content, as determined by mitochondrial DNA copy number (mtDNA) and cytochrome c oxidase IV (COXIV) protein content, was significantly reduced (11). However, FAO was equivalent between lean and obese individuals after correcting for these indices of mitochondrial content (i.e. FAO/mtDNA; FAO/COXIV) (11). These data suggest that the mitochondria of severely obese individuals function normally and that the overall reduction in FAO can be primarily attributed to a reduction in mitochondrial content (11).

To examine if skeletal muscle from the severely obese is resistant to stimuli for mitochondrial biogenesis, PGC-1 α , a transcriptional coactivator that stimulates mitochondrial biogenesis, was overexpressed in HSkMC (11). This manipulation increased mitochondrial content and FAO in myotubes from severely obese individuals; however, FAO remained depressed compared to lean controls, which suggests that the severely obese state limits both mitochondrial biogenesis and oxidative capacity via mechanisms that are independent of PGC-1 α abundance (11). Together, these data obtained in HSkMC (11, 26) suggest that lipid oxidation is inherently reduced in the skeletal muscle of severely obese individuals due to impairments at several levels of lipid metabolism (i.e. increase SCD-1 expression, reduced mitochondrial content).

Insulin Action

We questioned whether the insulin resistance and changes in insulin signal transduction that we observed in muscle tissue biopsies and in *in-vitro* incubated muscle fiber strips of severely obese individuals would extend into primary cell culture. Insulin stimulation of IRS-1 tyrosine phosphorylation and Akt phosphorylation, both of which would increase signal transduction, were significantly blunted in HSkMC from severely obese patients (2, 5). This “blunting” of insulin-stimulated IRS-1 tyrosine phosphorylation in muscle fiber strips of severely obese individuals was approximately 60% compared to lean controls and was essentially reproduced in HSkMC, while the degree of blunting of Akt activation was even greater in HSkMC than in intact muscle (2, 5, 8, 19).

As mentioned in a previous section, IRS-1 becomes serine phosphorylated in insulin-resistant muscle which inhibits downstream signaling. Therefore, serine 312 phospho-IRS-I can be a useful marker of insulin resistance. Muscle serine 312-phospho-IRS-I was elevated in both intact tissue biopsies and in HSkMC from severely obese subjects, compared to lean controls (Figure 2). These data suggest that there are constitutive changes in insulin signaling in the skeletal muscle of severely obese patients that are retained in human skeletal muscle cells raised in culture.

THE IMPACT OF LIPID EXPOSURE ON THE METABOLIC PROGRAM

A high fat, energy-rich diet is likely one of the primary factors contributing to the development of obesity and ectopic lipid accumulation. However, there is evidence that lean and obese individuals differ in respect to their ability to increase fatty acid oxidation in the face of an increased lipid load which can in turn influence the magnitude of positive lipid balance. Lipid alone also appears to be detrimental, as relatively acute exposures can inhibit processes such as insulin signal transduction in skeletal muscle. As the effects of lipid exposure are encompassing and relevant to the obese condition, we have examined the ability of lipid exposure to increase FAO and induce insulin resistance in lean and severely obese individuals.

Fat Metabolism

Metabolic flexibility is defined as the ability to adjust fuel utilization in respect to fuel availability. The capacity for metabolic flexibility is an important trait in the free-living

environment, as not responding appropriately to dietary lipid or temporary excursions where dietary lipid is elevated could result in positive lipid balance and accumulation.

To examine metabolic flexibility, HSkMC from lean and severely obese subjects were incubated with a fatty acid mixture (palmitate:oleate) for 24 hours and FAO determined with high-resolution respirometry (7). State 3 (ADP stimulated) respiration with lipid (palmitate) as the substrate increased after the 24 h lipid exposure in HSkMC from lean subjects reflecting metabolic flexibility; this increase in FAO was accompanied by an elevation in mtDNA and a trend for an increase in COX-IV protein content both of which suggest that mitochondrial content increased (7). In contrast, there were no comparable responses to increased lipid presence in HSkMC from the severely obese (7). These findings suggest an impaired capacity for metabolic flexibility in response to lipid in the skeletal muscle of the severely obese.

To gauge the capacity for metabolic flexibility in response to dietary lipid, we placed lean and severely obese individuals on a 5-day HFD (65% of total energy from fat) and examined the responsiveness of genes controlling FAO and mitochondrial content in skeletal muscle (6). mRNA content for peroxisome proliferator-activated receptor alpha (PPAR α), a broad transcriptional regulator which up-regulates FAO, increased in lean subjects after a single high-fat meal; in contrast, there was no change in PPAR α expression in severely obese subjects (6). After the 5 d HFD, PPAR α and the expression of other genes linked with enhancing lipid oxidation (*PDK4*, *PGC-1 α*) increased in the lean subjects; however, we observed no concomitant changes in gene expression in the muscle of the severely obese (6). With the HFD, acylcarnitine derivatives from long-chain fatty acids were not altered, indicating no adaptation at the level of CPT-1 in either the lean or severely obese individuals. However, shorter-chain acylcarnitine (6–12 carbons) species decreased in the lean subjects with the HFD, suggestive of an increase in FAO. These findings (6, 7) indicate an inability to increase FAO in skeletal muscle in response to lipid exposure with severe obesity. This impairment may be an underlying defect contributing to the lower mitochondrial content evident with severe obesity as muscle is constantly subjected to elevated lipid concentrations during normal activities such as an overnight fast and dietary fat consumption. An inability to appropriately increase FAO with lipid exposure also results in positive lipid balance which may predispose an individual to weight gain. This lack of metabolic flexibility may thus be a critical component of the metabolic program evident with severe obesity.

Insulin Action

Muscle cells in culture are an excellent tool to investigate the mechanisms of insulin resistance. We have been interested in what treatments might cause insulin resistance in HSkMC from lean individuals and how we might reverse the insulin resistance in cells of severely obese subjects. Because high-fat diets cause insulin resistance in skeletal muscle, we investigated the effects of incubating HSkMC from lean and severely obese subjects in fatty acids for 12 to 48 hours. Consistent with our hypothesis, fatty acids caused insulin resistance in HSkMC from lean controls, increased IRS-1 serine 312 phosphorylation, and decreased insulin-stimulated IRS-1 tyrosine phosphorylation and Akt activation in cells from lean controls to values approximating those in myotubes from severely obese subjects (5). Since cells from severely obese subjects were already insulin resistant there was no further effect of fatty acid incubation.

Activation of adenosine monophosphate kinase (AMPK) is known to reverse insulin resistance in animal models and metformin may increase insulin sensitivity in humans through this mechanism. Therefore, we tested whether activation of AMPK could reverse insulin resistance in HSkMC from severely obese individuals. AICAR (an activator of

AMPK) incubation rescued insulin signal transduction in HSkMC from severely obese subjects or cells from lean controls treated with fatty acids (5). These results suggest that treatment of insulin-sensitive skeletal muscle with fatty acids induces insulin resistance to a degree equivalent to HSkMC from severely obese subjects. Likewise, insulin resistance caused by either fatty acid treatment or severe obesity can be reversed through the activation of AMPK.

CAN THE METABOLIC PROGRAM OF SEVERE OBESITY BE EFFECTIVELY TREATED?

If our obesity metabolic program hypothesis is correct, a related question is whether the program can be “turned off” and metabolism returned to values similar to lean individuals. Two interventions that were available for us to test this question were weight loss induced by gastric bypass surgery and physical activity.

Fat Metabolism and Weight Loss

When examining the decrement in FAO with severe obesity, the classic “chicken or egg” question arises, i.e. is FAO impaired prior to developing severe obesity and thus possibly contribute to weight gain or does the reduction in FAO develop as a consequence of being severely obese? One way of addressing this issue was using the HSkMC model as already discussed. However, another approach is to reverse the condition of severe obesity to the pre-severely obese state and determine if FAO is in turn is normalized. From a clinical perspective it is also important to examine the effectiveness of weight loss in addressing the deficits in metabolism evident with severe obesity.

To determine if weight loss normalizes FAO, Berggren et al. (3) compared FAO in severely obese women that were weight stable 1 year after gastric bypass surgery to lean controls and severely obese individuals. FAO in skeletal muscle (vastus lateralis) did not differ between the gastric bypass surgery/weight loss (BMI, $36.5 \pm 3.5 \text{ kg/m}^2$) and severely obese ($50.7 \pm 3.9 \text{ kg/m}^2$) groups and was depressed compared to the lean ($22.8 \pm 1.2 \text{ kg/m}^2$) women. Studying individuals using a repeated measures design prior to and ~1 y after gastric bypass surgery, we also observed that FAO remained depressed in women who lost 55 kg to achieve a mean BMI of $30.5 \pm 2.3 \text{ kg/m}^2$ (3). Tracer methodology (^{13}C palmitate and ^{14}C acetate) was used to compare FAO in lean, severely obese, and post-gastric bypass patients who had lost > 45 kg to achieve a BMI of $33.7 \pm 9.9 \text{ kg/m}^2$ (34). Similar to skeletal muscle, whole-body FAO was depressed in the gastric bypass/weight loss and severely obese women both during rest and mild (50% $\text{VO}_{2\text{max}}$) exercise (34). A comparison of fat utilization during submaximal exercise with indirect calorimetry also indicated that whole-body lipid oxidation was depressed in previously severely obese women who had lost weight via gastric bypass surgery compared to weight-matched controls (21).

Together, these observations, as summarized in Figure 1, indicate that the decrement in FAO with severe obesity remains evident despite pronounced weight loss and reversal of the severely obese state. If an impairment in FAO is linked with weight gain, an inability to normalize FAO with weight loss intervention may explain why some individuals are predisposed to weight-regain after dietary interventions. In the severely obese, the mechanical limitations imposed by the gastric bypass procedure may be the only practical and effective intervention to insure long-term weight loss.

Insulin Action and Weight Loss

Results from a number of laboratories have reported that weight loss is associated with an improvement in insulin action. However, the degree of obesity and insulin resistance in

those studies was not as severe as in our patients. To test whether weight loss after gastric bypass could reverse the insulin resistance of severe obesity we studied a group of women who lost approximately 50 kg after surgery and were weight stable for at least 3 months (surgery/weight loss group) (4). Because the experimental subjects still had a BMI of approximately 30 kg/m², the surgery/weight loss group was compared to: (1) severely obese women; (2) weight- and age-matched women who were never severely obese, and (3) age-matched, but lean (BMI < 25 kg/m²) women. Whole-body insulin sensitivity (insulin sensitivity index, (S_I) determined from a frequently sampled intravenous glucose tolerance test) was much lower in the severely obese compared to the other groups (4). The S_I of the surgery/weight loss group was not different than the lean group and was higher than in the weight-matched women. Likewise, muscle IRS-1 serine 312 phosphorylation in the surgery/weight loss group matched that of the lean group and was significantly lower than that of the severely obese or the weight-matched groups. Thus, the weight loss induced by gastric bypass not only reverses insulin resistance, but actually improves insulin sensitivity to a degree that is superior to that seen in weight-matched controls. This improvement in insulin action cannot be attributed to increased physical activity after gastric bypass which is equivalent between previously severely obese surgery patients and weight-matched sedentary controls (21). Prospective studies have confirmed that gastric bypass surgery dramatically enhances insulin action in severely obese patients (20, 25).

In terms of possible mechanisms, we observed no change in the concentration of the insulin-sensitive glucose transporter (GLUT4) with weight loss (18). Insulin receptor concentration, however, doubled which may contribute to the improvement in insulin action seen with the intervention (31). Gene array and real time polymerase chain reaction (RT-PCR) analyses indicated that growth factor receptor-bound protein 14, glycerol-3-phosphate dehydrogenase, and myostatin were elevated with severe obesity and reduced with weight loss (30). Pathway analyses indicated the involvement of these genes in weight-loss responsive networks which could improve insulin signaling, decrease triglyceride synthesis, and increase muscle mass (30). The predominance of insulin-resistant, glycolytic muscle fibers evident with severe obesity (22) was not altered with gastric bypass surgery (20), although a higher initial percentage of type I fibers was associated with a greater rate of weight reduction (33). In contrast, intramuscular triacylglycerol (TAG) and long-chain fatty acyl-CoA concentrations (palmitoyl, stearate, and linoleate CoA) were dramatically reduced (20, 25). This reduction in intramuscular lipid content could contribute to the improvement in insulin action seen with gastric bypass surgery as intracellular lipids can induce insulin resistance.

Fat Metabolism, Insulin Action, and Exercise

Classic responses to endurance-oriented exercise training include an increase in the capacity of skeletal muscle for FAO and an improvement in insulin action. Our laboratories have used relatively acute programs (7 to 10 consecutive days) to discern the effects of endurance-oriented exercise training upon insulin action and FAO. This model is used as 1) there is little to no loss in body mass thus minimizing the effect of this potentially confounding factor and 2) it facilitates the recruitment and retention of populations typically not accustomed to exercise training. To examine the impact of exercise on insulin action, severely obese men trained for 7 consecutive days (60 min/day, ~65% VO_{2peak}) with insulin action determined via an oral glucose tolerance test (OGTT) in the sedentary condition and ~16 h after the final exercise bout (23). Exercise training reduced fasting and two-hour insulin concentrations as well as the insulin area under the curve during the OGTT, indicating improved insulin action.

A similar training prescription (10 consecutive days, 60 min/day, ~70% VO_{2peak}) was utilized to examine the effect of exercise on FAO (3). We studied previously severely obese

individuals who had lost weight via gastric bypass surgery due to their ability to effectively ambulate and achieve and maintain the desired exercise intensity. In agreement with our previous findings, FAO was reduced and incomplete FAO elevated in the gastric bypass/weight loss compared to lean and a group of obese, but not severely obese subjects. The 10 days of exercise training increased FAO by ~2-fold in the lean and obese groups and, despite the initial impairment, also increased FAO in the gastric bypass/weight loss group to the extent that there was no difference between the lean, obese, and weight loss groups after the intervention. Incomplete oxidation was also normalized after exercise training (3). These findings (3, 23) indicate that exercise training can be used to effectively alleviate the phenotype/metabolic program of insulin resistance and reduced FAO evident with severe obesity, although the cellular mechanism(s) remain to be defined (see Figure 1).

CONCLUSIONS

Severe obesity (BMI ≥ 40 kg/m²) is associated with insulin resistance and a reduced capacity for fatty acid oxidation in skeletal muscle. These characteristics remain intact in human skeletal muscle cells (HskMC) raised in culture which has lead us to hypothesize that the skeletal muscle of severely obese individuals displays an inherent global metabolic program (see Figure 3). We believe this concept represents a paradigm shift in our perception of obesity. For example, the deficit in FAO and inability to increase FAO appropriately in response to ingested lipid (lack of metabolic flexibility) may predispose an individual towards ectopic lipid accumulation and weight gain and possibly the development of the severely obese state. The present findings also indicate that the metabolic program linked with insulin resistance can be induced by fatty acid exposure.

As presented in Figure 3, weight loss via gastric bypass surgery can “turn off” components of this metabolic program as insulin sensitivity is restored or even enhanced compared to weight-matched controls. However, gastric bypass/weight loss does not rescue the decrement in FAO which may explain a propensity for weight-regain after or a resistance to diet-induced weight loss and why the mechanical limitations imposed by the gastric bypass procedure are needed for an effective intervention. Endurance-oriented exercise training can improve FAO and insulin action in severely obese individuals, indicating that this patient population is not “exercise resistant”; exercise should thus be considered as an adjunct to weight loss intervention. The biological mechanisms linked with these perturbations and interventions are largely yet to be discerned. In conclusion, it is hoped that the research summarized in this review can aid in preventing and/or treating the severely obese condition.

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Figure 1.

Decrement in fatty acid oxidation (FAO) using various methodologies with severe obesity in skeletal muscle and inability of weight loss (Weight Reduced columns) to restore FAO. Only exercise training in severely obese individuals who have lost weight appears to be effective for increasing FAO. Abbreviations: Rectus Adom, rectus abdominus muscle; HSkMC, human skeletal muscle cells raised in culture. FAO for the columns titled "Vastus Lateralis" and "Weight Reduced + Exercise" were determined in biopsy samples with the muscle homogenate technique.

Figure 2. Serine 312 phospho-IRS-I in muscle biopsies and in primary muscle cell cultures (HskMC) from severely obese and lean control subjects. Values are expressed as a percent of the lean control muscle analyzed under identical conditions with dotted line at 100% indicating lean control.

Figure 3.

Summary of the metabolic program in human skeletal muscle with severe obesity in relation to fat and carbohydrate (CHO) metabolism. In the top panel, arrows represent processes elevated or depressed compared to lean controls either *in-vivo* or in *in-vitro* muscle preparations or humans skeletal muscle cells raised in culture (HSkMC). The lower panel represents increases, decreases, or no change compared to the severely obese condition with the respective intervention.