

Skeletal Muscle Triglyceride

An aspect of regional adiposity and insulin resistance

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Recent evidence derived from four independent methods indicates that an excess triglyceride storage within skeletal muscle is linked to insulin resistance. Potential mechanisms for this association include apparent defects in fatty acid metabolism that are centered at the mitochondria in obesity and in type 2 diabetes. Specifically, defects in the pathways for fatty acid oxidation during postabsorptive conditions are prominent, leading to diminished use of fatty acids and increased esterification and storage of lipid within skeletal muscle. These impairments in fatty acid metabolism during fasting conditions may be related to a metabolic inflexibility in insulin resistance that is not limited to defects in glucose metabolism during insulin-stimulated conditions. Thus, there is substantial evidence implicating perturbations in fatty acid metabolism during accumulation of skeletal muscle triglyceride and in the pathogenesis of insulin resistance. Weight loss by caloric restriction improves insulin sensitivity, but the effects on fatty acid metabolism are less conspicuous. Nevertheless, weight loss decreases the content of triglyceride within skeletal muscle, perhaps contributing to the improvement in insulin action with weight loss. Alterations in skeletal muscle substrate metabolism provide insight into the link between skeletal muscle triglyceride accumulation and insulin resistance, and they may lead to more appropriate therapies to improve glucose and fatty acid metabolism in obesity and in type 2 diabetes.

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Nearly all individuals with type 2 diabetes are markedly insulin resistant, and the majority of them are obese. This review examines mechanisms that might contribute to the association between insulin resistance and obesity, emphasizing 1), established and newer concepts of regional adipose tissue distribution, and 2), triglyceride content within skeletal muscle. Physiological and cellular mechanisms that lead to an excess accumulation of lipids within skeletal muscle will also be examined. The hypothesis that is addressed in this review is that tissue accumulation of triglyceride makes a major contribution to skeletal muscle insulin resistance and occurs due

to reduced reliance on free fatty acid oxidation during postabsorptive conditions.

Abdominal Adipose Tissue Distribution and Insulin Resistance

Obesity, even if not complicated by diabetes, is associated with insulin-resistant glucose metabolism in skeletal muscle. Considerable insight into the link between obesity and insulin resistance has been gained from studies of adipose tissue distribution. Omental and mesenteric adipose tissue, so-called *visceral adiposity*, is recognized as a depot strongly associated with insulin resistance of skeletal muscle (1), as well as with dyslipidemia (2) and increased risks for hypertension

and glucose intolerance (1,3,4). For example, Banerji et al. (5) observed that variance in visceral adiposity accounted for much of the inter-individual variation in insulin resistance among a cohort of African-American individuals with type 2 diabetes, some of whom manifested an “insulin-sensitive” subtype of type 2 diabetes. In a recent weight-loss intervention trial, our laboratory found that among nondiabetic obese subjects, the decrease in visceral adiposity was the body composition change that best predicted the improvement in insulin sensitivity after weight loss (6). However, emerging findings suggest that other aspects of regional adiposity also contribute to the link between obesity and insulin resistance.

In type 2 diabetes, there is an increased prevalence of hepatosteatosis (increased lipid accumulation in the liver) that appears to be related to adiposity, particularly visceral adiposity. A recent clinical investigation in insulin-treated patients with type 2 diabetes indicates that hepatic triglyceride content is a strong determinant of hepatic insulin resistance (7–9). Fatty acid flux to the liver may be a determinant of rates of hepatic glucose production (10). Patterns of hepatic fatty acid metabolism and hepatocyte triglyceride concentrations are potentially important areas warranting additional investigation so that there may be better understanding of the relationship between regional lipid distribution and insulin resistance in obesity and type 2 diabetes.

Lower-Extremity Adipose Tissue and Insulin Resistance

There is considerable adipose tissue in the lower extremities; however, subcutaneous adipose tissue in the legs is generally regarded as a relatively weak marker of insulin resistance (11). In a recent study from our laboratories, Goodpaster et al. (12) used cross-sectional computed tomography (CT) imaging to measure the quantity and distribution of adipose tissue in the thigh. The investigators followed the novel body composition approach of using anatomic criteria to

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Abbreviations: CPT, carnitine palmitoyl transferase; CT, computed tomography; FABP, fatty acid-binding protein; FFA, free fatty acid; leg RQ, respiratory quotient across the leg; MRS, magnetic resonance spectroscopy; UCP2, uncoupling protein 2.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

subdivide adipose tissue planes into adipose tissue present above the fascia lata (termed *subcutaneous adipose* tissue) and adipose tissue present below the fascia lata (termed *subfascial adipose* tissue). Their findings confirm the prior perception that subcutaneous adiposity of the legs—although it is greatly increased in obesity and comprises >90% of thigh adipose tissue, even in lean individuals—is not correlated with rates of insulin-stimulated glucose metabolism. However, several novel observations were made concerning adipose tissue contained beneath muscle fascia. Variance in the amount of adipose tissue beneath muscle fascia correlated with insulin resistance (Fig. 1). Moreover, adipose tissue dispersed within muscle and identifiable by CT imaging as distinct from muscle itself also was strongly correlated to insulin resistance. Interestingly, the quantities of these fat depots contained beneath the fascia and within muscle tissue were substantially smaller than the amount of adipose tissue located subcutaneously, comprising ~10% of leg adipose tissue. These observations suggest that in the lower extremities, the location of adiposity is a key determinant of the link between insulin resistance and obesity. Conceptually, this is analogous to regional distribution of abdominal adipose tissue and its relation to insulin resistance.

Skeletal Muscle Triglyceride and Insulin Resistance

In the study of adipose tissue distribution in the thigh conducted by Goodpaster et al. (12), it was also observed that there was an altered composition of skeletal muscle in obese patients with type 2 diabetes. Skeletal muscle composition, as assessed by CT imaging and expressed on the basis of the distribution of CT attenuation values of muscle, differed in obese patients with type 2 diabetes compared with the skeletal muscle of lean volunteers, as shown in Fig. 2. Attenuation values are the units of measure used in CT imaging to denote tissue density and are referenced to the properties of water to attenuate the transmission of radiation. These findings confirm results from previous studies in which muscle attenuation values were lower in obese patients, particularly those with type 2 diabetes (13,14). Recent studies using chemical phantoms (surrogate “limbs” of known lipid concentration) and tissue biochem-

ical studies (using muscle biopsy samples) confirm that increased lipids are a key determinant of reduced attenuation characteristics of skeletal muscle (15). These findings are of interest because of the potential metabolic implications of altered muscle composition.

Reduced muscle attenuation has been found to correlate significantly with insulin resistance, even after adjusting for the amount of visceral adiposity or overall obesity (13). Indeed, among a cohort of 40 nondiabetic individuals with a BMI >30 kg/m², muscle attenuation was the strongest body composition correlate of insulin resistance. Additionally, muscle attenuation has been found to correlate negatively with aerobic fitness (13) and with the oxidative enzyme capacity of skeletal muscle (16).

Another elegant approach recently developed to investigate the metabolic significance of muscle lipid content is magnetic resonance spectroscopy (MRS). Aside from the noninvasive nature of MRS, an advantage of this approach appears to be the capability of MRS to distinguish the signal attributable to protons of the lipids contained within muscle fibers from those located outside the mus-

cle fibers (17). Subsequent validation studies demonstrated that proton MRS of muscle in animals and humans can be used to observe intracellular lipid (18). Perseghin et al. (19) used this method to report that lipids contained within muscle fibers were strongly correlated with the severity of insulin resistance. Moreover, it was observed that this depot was increased among first-degree relatives of type 2 diabetic individuals and was related to the expression of insulin resistance in this high-risk group (19).

The link between insulin resistance and triglyceride content measured in human muscle biopsy samples has also been established. Pan et al. (20) determined the triglyceride content in vastus lateralis muscle among 38 nondiabetic Pima Indian men, an ethnic group with a pronounced disposition for obesity and type 2 diabetes. Insulin sensitivity, measured using the hyperinsulinemic-euglycemic clamp technique, was inversely related to skeletal muscle triglyceride content, as shown in Fig. 3. Moreover, the relation between insulin resistance and muscle triglyceride was independent of total adiposity. In animal studies, it was previously observed that a high-fat diet

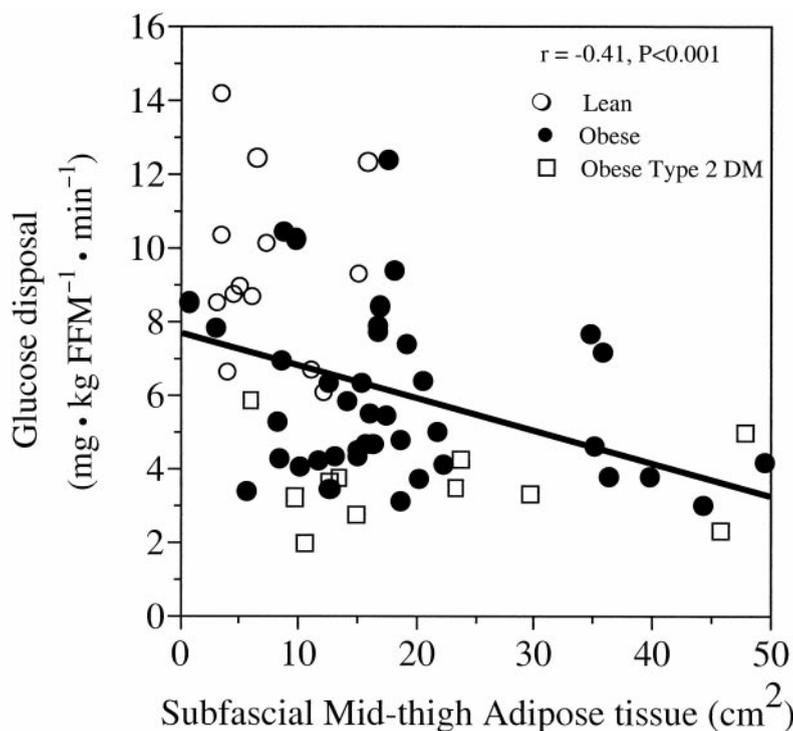


Figure 1—Associations of adipose tissue located beneath the fascia lata in the mid-thigh among lean glucose-tolerant (GT) subjects, obese GT subjects, and obese subjects with type 2 diabetes (n = 68).

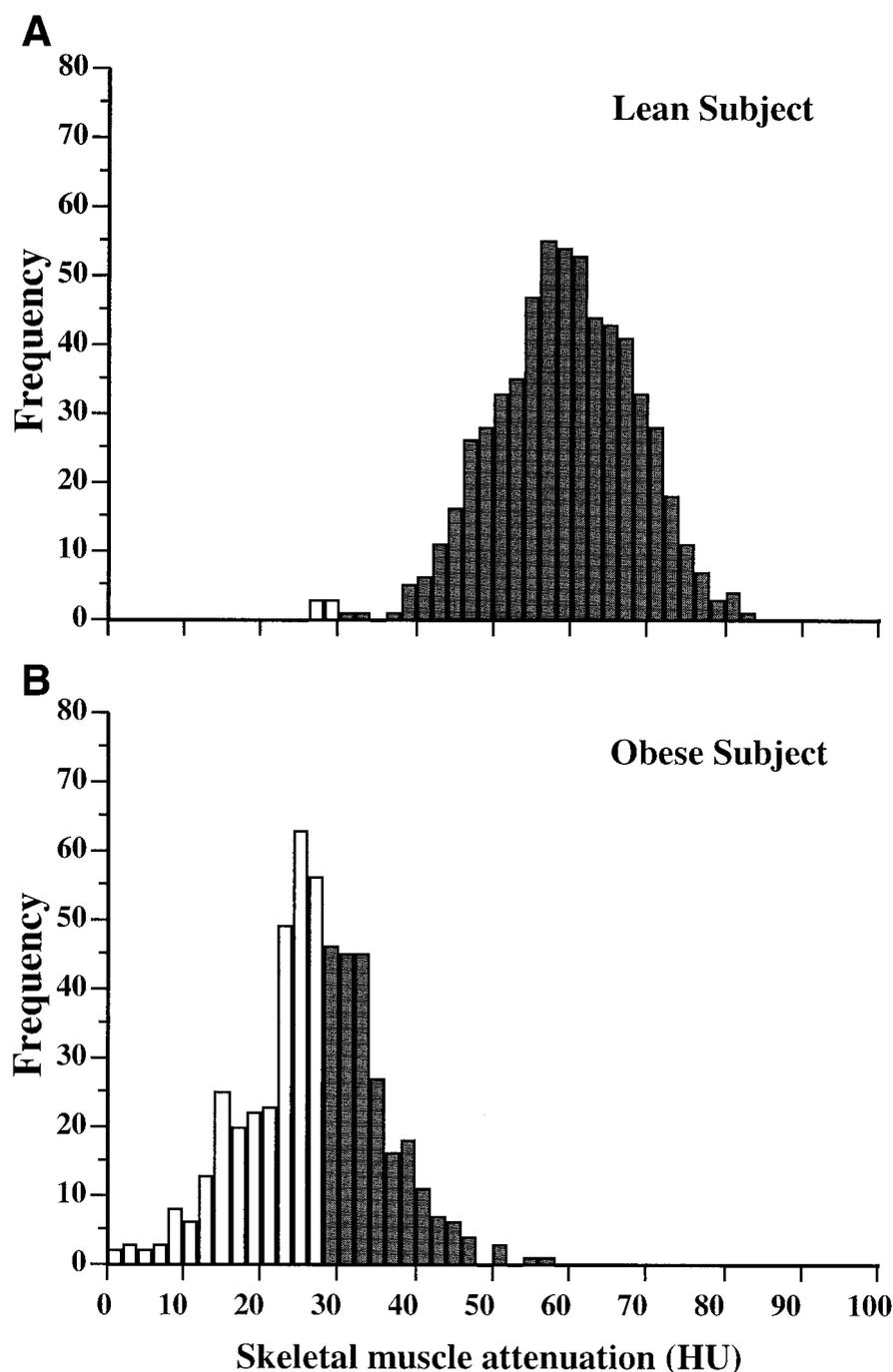


Figure 2—Histograms of the distribution and frequency of pixels across the range of adipose skeletal muscle (0–100 HU) in a representative lean (A) and obese (B) subject. Open bars represent the frequency of pixels from 0 to 29 HU as “low-density muscle” (i.e., ≥ 2 SDs below the mean attenuation value for normal lean skeletal muscle); filled bars represent the frequency of pixels from 30 to 100 HU as “normal-density muscle.” In the obese individual, more skeletal muscle is represented as low-density muscle. Adapted from *Diabetes* 48:839–847, 1999.

induced insulin resistance in skeletal muscle and that this was related to the fat content of muscle (21). Accordingly, selective muscle triglyceride depletion by leptin administration reversed insulin resistance in animals (22).

Another approach to directly examine lipid content in muscle fibers is histochemical staining, which provides visual information on the distribution of lipids within myocytes. Phillips et al. (23) used a neutral lipid stain and semiquantitative

histological scoring to assess intramuscular lipid in percutaneous biopsy samples from vastus lateralis obtained from 27 nondiabetic women. Neutral lipid staining in skeletal muscle correlated with reduced insulin activation of the enzyme glycogen synthase, a marker enzyme for insulin action and one regarded as rate limiting for glucose storage. Using a more quantitative imaging approach to histological sections of vastus lateralis muscle stained by Oil red O, Goodpaster et al. (24) found that the triglyceride content of myocytes was especially increased in obese patients with type 2 diabetes. Thus, in summary, four distinct methods have been used to support the finding that triglyceride content is increased in skeletal muscle in obesity and type 2 diabetes and is correlated with insulin resistance.

One caution in the interpretation of these data is that an increased muscle triglyceride content is not invariably linked to insulin resistance. Exercise training has been reported to increase muscle triglyceride content (25,26), and chronic exercise increases insulin sensitivity (27,28) as well as the capacity for fatty acid oxidation (29). Studies of exercise physiology indicate that skeletal muscle triglyceride can contribute substantially to the mixture of substrates oxidized by exercising skeletal muscle (30–32). Moreover, type 1 skeletal muscle fibers, which manifest increased oxidative enzyme capacity and may have increased insulin sensitivity, increased capacity for fatty acid uptake, and increased triglyceride stores (33). These findings should not be interpreted as contradictory to the findings cited above regarding the link between muscle triglyceride and insulin resistance in obese patients with type 2 diabetes. Rather, the data point to the importance of relating muscle triglyceride content with its capacity for fatty acid metabolism. Muscle triglyceride may not have adverse metabolic consequences in muscle that has the capacity for efficient lipid utilization. Perhaps an excess level of muscle triglyceride merely represents a surrogate for other lipid metabolites in muscle, such as fatty acyl CoA, which are known to confer insulin resistance (34). It is also conceivable that periodic depletion and repletion of muscle triglyceride, as might occur with regular exercise, is not associated with insulin resistance. The inability or failure to periodically deplete triglyceride in muscle, as likely occurs in

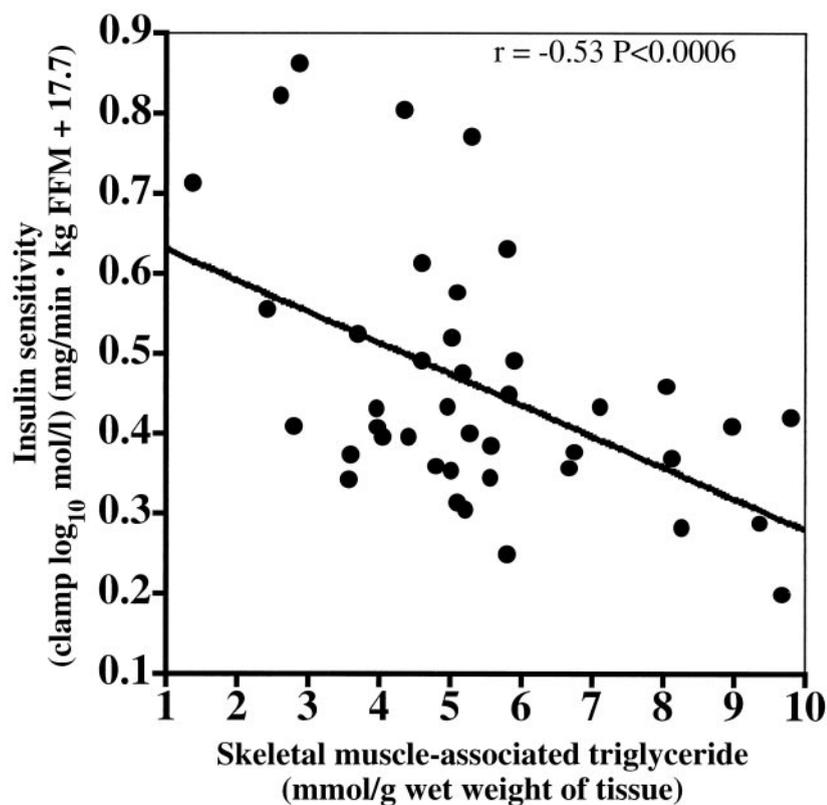


Figure 3—Relationship between skeletal muscle triglyceride content and insulin sensitivity. Adapted from *Diabetes* 46:983–988, 1997.

sedentary individuals, however, is associated with insulin resistance.

Interaction Between Glucose and Fatty Acid Metabolism in Type 2 Diabetes

Plasma fatty acids are an important substrate for skeletal muscle in healthy individuals, as has been recognized for many years, based on the now-classic human physiology studies of Andres et al. (35), and their importance was reconfirmed in more recent clinical investigations (36–38). During postabsorptive conditions, such as those that occur after an overnight fast, skeletal muscle has a high fractional extraction of plasma fatty acids, and lipid oxidation accounts for the majority of energy production. It has been postulated that uptake of fatty acids into skeletal muscle may be a saturable process regulated by fatty acid-binding proteins (FABPs) (39). Thus, in addition to its important role as a site for insulin-stimulated glucose utilization, skeletal muscle has a key role in systemic fatty acid utilization, which manifests especially during fasting conditions.

The capacity of skeletal muscle to utilize either lipid or carbohydrate fuels, as well as the potential for substrate competition between fatty acids and glucose, has maintained the interest of investigators of insulin resistance (37,38,40–45). A potential implication of the glucose–fatty acid cycle, which was originally postulated by Randle et al. (46), is that increased lipid availability could interfere with muscle-glucose metabolism and contribute to insulin resistance of obese patients with type 2 diabetes. Studies by several investigators support the concept of impaired insulin-stimulated glucose metabolism by elevated free fatty acids (FFAs) (40,43,45,47). Recent investigations have begun to delineate postreceptor signaling mechanisms that might contribute to fatty acid-induced insulin resistance, with several studies reporting an impact on signaling via the protein kinase C pathway (48–52), a component of the insulin signaling pathways that has an impact on insulin-stimulated glucose transport.

A collateral concept has emerged, however; it purports that substrate com-

petition might not only operate in the direction of lipid-inducing, insulin-resistant glucose metabolism, but that provision of glucose inhibits oxidation of lipids. Evidence supporting this notion has arisen from studies by Kelley and Mandarino (53) of patients with type 2 diabetes under conditions of fasting hyperglycemia. By using the limb-balance technique, they found that the respiratory quotient across the leg (leg RQ) was elevated (0.92) in type 2 diabetes, denoting increased glucose oxidation and a greatly reduced reliance on fatty acid oxidation. Subsequent reduction of glycemia by a low-dose insulin infusion designed to suppress hepatic glucose output in patients with type 2 diabetes led to a reduction in leg glucose oxidation and increased leg fat oxidation. In lean healthy volunteers, hyperglycemic clamp studies performed while suppressing insulin to basal conditions also caused a rise in leg RQ similar to that found in patients with type 2 diabetes (54). These effects of hyperglycemia were accentuated in obese patients (55). Kelley et al. (43) and Kelley and Simoneau (44) found that skeletal muscle uptake of fatty acids was reduced in obese patients with type 2 diabetes (53) during fasting hyperglycemia, with lower fractional extraction across the leg. More recently, Sidossis et al. (38) confirmed these findings by implicating inhibition of the entry of fatty acids into the mitochondria as the mechanism by which insulin and hyperglycemia inhibit the oxidation of lipids. Cortez et al. (56) and Torgan et al. (57) found increased glucose oxidation in the skeletal muscle of obese insulin-resistant rats. These studies suggest that hyperglycemia perturbs the normal fasting reliance on fatty acid oxidation within skeletal muscle, a finding with potential implications for the pathogenesis of lipid accumulation within skeletal muscle and for obesity in general.

Patients with type 2 diabetes have reduced efficiency in the uptake of plasma FFAs by skeletal muscle (36,44,53). This result has been found using limb-balance methods (44,58) and, more recently, using positron emission tomography imaging in lower-extremity muscle of individuals with impaired glucose tolerance (59). However, reduced fractional extraction of plasma FFAs does not appear to be the sole mechanism that limits fat oxidation. This finding suggests that factors intrinsic to muscle may contribute to

decreased fatty acid oxidation and increased storage of fat within muscle.

Mechanisms of Skeletal Muscle Triglyceride Accumulation in Type 2 Diabetes

Plasma concentrations of FFAs play an important role in determining the rate of FFA uptake by skeletal muscle (60). Nonetheless, plasma FFA availability is not the sole factor determining FFA uptake into tissues. One potential site for the regulation of fatty acid metabolism in muscle is fatty acid transport. Multiple proteins have been identified as putative transporters of fatty acids in muscle (60), namely FABP, fatty acid translocase, and fatty acid transport protein, but their role in the regulation of fat metabolism is unclear. In studies of human skeletal muscle, neither the content of cytosolic FABP nor that of the sarcolemmal FABP was diminished in obese subjects with obesity (61). However, Blaak et al. (62) reported reduced FABP in the muscle of diabetic individuals. Further investigation may reveal unidentified mechanisms by which these transport proteins contribute to increased skeletal muscle triglyceride storage in obese patients with type 2 diabetes.

During resting postabsorptive conditions, ~30% of fatty acid flux in the plasma pool is accounted for by oxidation, with the remaining 70% of flux recycled into triglyceride, indicating a physiological reserve that exceeds immediate tissue needs for oxidative substrates. The equilibrium between oxidation and reesterification within muscle is paramount in determining fatty acid storage within tissue. After transport in the sarcoplasm by FABP, and before oxidation, long-chain fatty acids must be activated to long-chain acyl CoA, then translocated into mitochondria by the enzyme complex, carnitine palmitoyl transferase (CPT) I and II. Activity of CPT I is regarded as a key step in the regulation of fatty acid oxidation within muscle (63). The muscle isoform of CPT I is highly sensitive to allosteric inhibition by malonyl CoA, the precursor of fatty acid synthesis (63). Insulin and glucose increase skeletal muscle content of malonyl CoA, suggesting that insulin and glucose inhibit lipid oxidation (64). In animal models of insulin resistance, Ruderman et al. (34) found increased skeletal muscle content of malonyl CoA during postabsorptive conditions, which was consistent with the

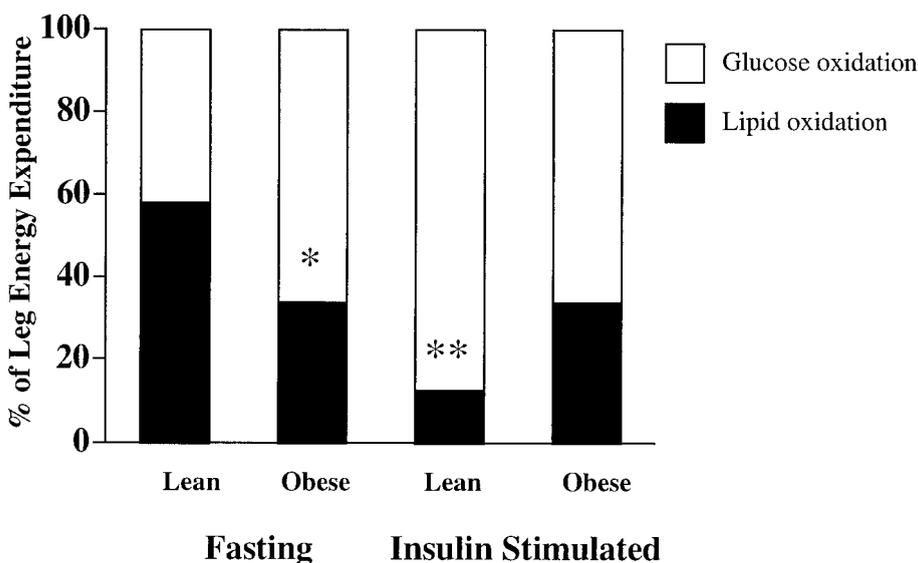


Figure 4—Contributions of lipid and glucose oxidation to resting energy expenditure of the leg. Obese subjects derived relatively less energy from lipid oxidation during basal conditions (* $P < 0.01$). Lean subjects have greater suppression of lipid oxidation during insulin-stimulated conditions (** $P < 0.01$). Adapted from Am J Physiol 277:E1130–E1141, 1999.

inhibition of fatty acid oxidation. Simoneau et al. (61) found reduced CPT activity in skeletal muscle of insulin-resistant obese volunteers, who also exhibited reduced rates of fat oxidation across the leg (37). This reduced CPT activity was proportional to an overall reduction in activities of citrate synthase, cytochrome C oxidase, and hydroxyacyl dehydrogenase; enzymes of the tricarboxylic acid cycle; electron transport; and β -oxidation, respectively (61). Moreover, reduced oxidative enzyme activity has been associated with insulin resistance and with the presence of type 2 diabetes (65–67). Thus, the reduction in CPT activity may reflect reduced mitochondrial content, resulting in a reduced capacity for lipid oxidation. Additional evidence pertinent to mitochondrial metabolism in skeletal muscle is the finding of increased content of uncoupling protein 2 (UCP2) in obese patients, and an association between lower rates of fatty acid oxidation across the leg with UCP2 content (68). Taken as a whole, the biochemistry of skeletal muscle in obese patients with type 2 diabetes suggests impairments centered at the mitochondria that direct fatty acids in skeletal muscle toward esterification and storage rather than oxidation.

Impaired Fatty Acid Utilization in Insulin Resistance: Metabolic Inflexibility

Healthy skeletal muscle has substantial metabolic flexibility (69) and switches from predominantly lipid oxidation during fasting conditions, accompanied by high rates of fatty acid uptake (35), to increased glucose uptake, oxidation, and storage under insulin-stimulated conditions with suppression of lipid oxidation (58). Insulin resistance is defined as a reduced insulin stimulation of glucose metabolism. Another aspect of insulin resistance appears to be an inability to suppress lipolysis and lipid oxidation. Obese individuals and those with type 2 diabetes manifest higher lipid oxidation during insulin-stimulated conditions (41), despite lower rates of lipid oxidation during fasting conditions. These findings are actually commensurate with each other, considering that a key metabolic feature of skeletal muscle is its capacity to switch between fuels. This capacity may be lost in insulin resistance.

The concept of metabolic inflexibility in insulin resistance has been demonstrated in recent studies using limb-balance methods to examine rates of substrate uptake and oxidation (37). As shown in Fig. 4, obese subjects had lower fasting rates of lipid oxidation, yet during insulin infusions, rates of lipid oxidation

by muscle were higher than in lean subjects. Clearly, lean subjects demonstrated the ability to shift from a reliance on lipid oxidation during fasting to glucose oxidation during insulin infusions. In contrast, obese subjects lacked the capacity to modulate substrate selection during either condition, demonstrating metabolic inflexibility. Lipid oxidation does not increase in all conditions; rather, it is part of an inflexible response to either insulin or fasting in the modulation of substrate oxidation. The diminished capacity of obese individuals to augment lipid oxidation during fasting conditions also predicts the severity of insulin resistance. Thus, lower rates of fatty acid oxidation during fasting are likely a key mechanism leading to excess lipid accumulation within skeletal muscle, which in turn contributes to insulin-resistant glucose metabolism through processes of substrate competition and other mechanisms (70).

On the basis of these findings, we propose that the mechanisms for an excess lipid accumulation within myocytes in obesity and in type 2 diabetes are related to defects in fatty acid oxidation. We posit that reduced fatty acid oxidation, rather than an increased fatty acid uptake, mediates lipid accumulation. The biochemical mechanism responsible for lower fatty acid oxidation may be diminished entry of acyl CoA into mitochondria secondary to a reduced CPT activity and potentially due to increased malonyl CoA concentrations.

Effect of Weight Loss on Skeletal Muscle Lipid Metabolism

Weight loss can be a highly effective treatment for overweight patients with type 2 diabetes and other cardiovascular risk factors, and indeed it is advocated as the first line of therapy. Weight loss may also play a role in the prevention of type 2 diabetes (71,72). In overweight patients with type 2 diabetes, weight loss can reduce hepatic glucose production (73,74), insulin resistance (73–76), and fasting hyperinsulinemia (74–76), and it can improve glycemic control (73–76). Weight loss in type 2 diabetes is also associated with a reduction in blood pressure and an improvement in the lipid profile (77). These benefits can occur with as little as 5–10% weight loss (74,78,79). Moreover, preventing obesity in primates with long-term caloric restriction mitigates the development of insulin resistance (80).

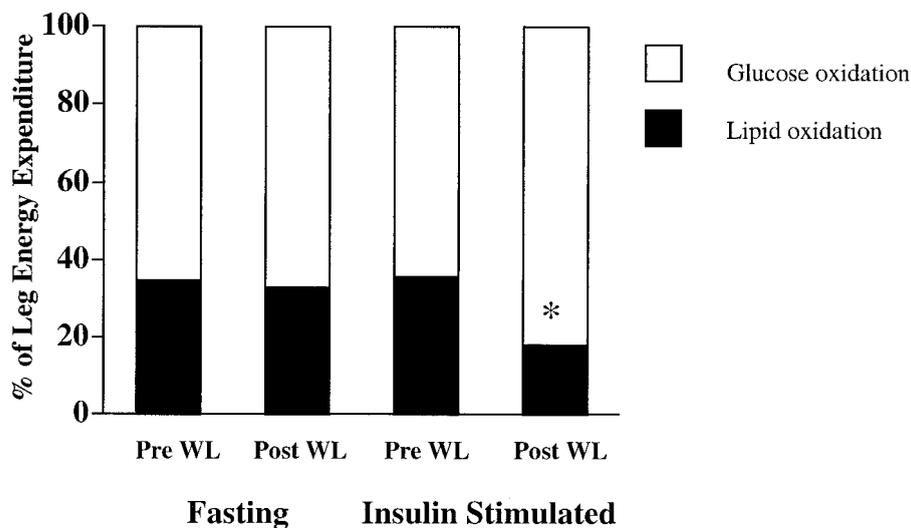


Figure 5—During fasting conditions, the proportion of energy derived from lipid oxidation was not changed with weight loss (WL), whereas during insulin-stimulated conditions, weight loss resulted in a greater suppression of lipid oxidation (* $P < 0.01$). Adapted from *Am J Physiol* 277:E1130–E1141, 1999.

Less is known concerning the effects of weight loss on the pattern of muscle fatty acid metabolism and the accumulation of lipid within muscle. Thus, it is important to consider whether impairments within the pathways of fatty acid utilization in skeletal muscle are primary defects in obese individuals or arise secondarily, after an individual has become obese. This issue is difficult to effectively address by cross-sectional comparisons of lean and obese subjects. One prospective clinical study indicated that lower rates of lipid oxidation were a predisposing factor for greater weight gain (81), and collateral studies revealed that skeletal muscle enzyme activities were implicated in impaired lipid oxidation (82,83). A reduced reliance on lipid oxidation has also been identified as a risk factor for weight regain after weight loss (84). These data raise the possibility that a potential impairment in the capacity for lipid oxidation might be a primary defect in obesity. Weight loss can markedly improve insulin-resistant glucose metabolism in skeletal muscle. When patient response indicates a substantial acquired or secondary component of obesity-related insulin-resistant glucose metabolism, it is important to address whether weight loss can modulate patterns of skeletal muscle metabolism of fatty acids, including the content of fat within muscle.

Goodpaster et al. (6,24), Kelley et al. (37), and Simoneau et al. (61) have ad-

ressed the impact of weight loss within a group of obese men and women, for whom the pre-weight loss patterns of muscle fatty acid metabolism have previously been described in this review. The weight-loss intervention decreased weight (by a mean value of ~14 kg), BMI, total fat mass, and subcutaneous and visceral abdominal adipose tissue, and it improved insulin sensitivity. Weight loss also modified the composition of muscle determined from its attenuation characteristics on CT; skeletal muscle attenuation values were increased in a direction indicative of partial reduction in muscle lipid content (6). Furthermore, the cross-sectional area of thigh muscle decreased, which was entirely due to the decrease in the area of low-density muscle, because the area of normal-density muscle did not change (12). Weight loss significantly decreased the amount of neutral lipid contained within muscle fibers (i.e., intramuscular triglycerides) in nondiabetic obese subjects and in obese patients with type 2 diabetes (24). Clearly, clinical weight-loss interventions can reduce excess lipid stored within skeletal muscle, which may mitigate insulin resistance.

The impact of weight loss on muscle fatty acid metabolism was also recently examined by Kelley et al. (37). Although insulin-stimulated glucose metabolism in skeletal muscle was improved by ~50%, the effects of weight loss on fatty acid metabolism were considerably more

blunted. The reduced reliance on lipid oxidation during postabsorptive conditions in obese patients persisted after weight loss (Fig. 5). Although rates of FFA uptake across the leg were lower after weight loss during postabsorptive conditions, rates of lipid oxidation across leg tissues continued to be lower after weight loss, resulting in a lower net storage of fatty acids within the leg. Consistent with these findings, activity of CPT did not change, whereas the oxidative enzyme capacity actually decreased after weight loss.

Weight loss, however, does seem to influence patterns of muscle fatty acid metabolism during insulin-stimulated conditions. During insulin infusions, arterial FFA levels and rates of uptake for plasma FFAs across the leg were lower after weight loss than during the same conditions before weight loss. Insulin infusions also significantly suppressed fat oxidation by leg tissues, compared with the markedly blunted response to insulin before weight loss. This finding indicates more effective insulin suppression of lipolysis in leg tissues after weight loss, a pattern similar to that observed in lean subjects. Taken together with previous reports (84–86), these data indicate that after weight loss, there is a persistent impairment of fasting patterns of fatty acid metabolism by skeletal muscle but improved insulin suppression of both lipolysis and lipid oxidation. Exercise training in lean healthy individuals increases the oxidative enzyme capacity and rates of fatty acid oxidation from intramuscular stores during exercise conditions (87). This finding suggests that impaired lipid metabolism and an increased muscle triglyceride content could be primary impairments leading to obesity, rather than merely resulting from obesity. Perhaps exercise, either alone or in combination with weight loss, can effectively improve skeletal fatty acid metabolism concomitant with improving insulin-resistant glucose metabolism.

SUMMARY — Nearly 40 years ago, Randle et al. (46) published a series of experiments that revealed that fatty acids could inhibit the utilization of glucose in skeletal muscle. Their seminal work has stimulated an ongoing interest in the hypothesis that substrate competition is a potential mechanism that contributes to insulin resistance in individuals with obe-

sity and type 2 diabetes. Their hypothesis has been substantiated, although not without important modifications. It remains clear that fatty acids can impair glucose metabolism during insulin-stimulated conditions. However, investigators over the past 10 years, both in clinical and in animal models of type 2 diabetes and obesity, have observed that skeletal muscle in these disorders can also manifest a decreased reliance on fat oxidation during fasting conditions. To some extent, impairment of the postabsorptive fat oxidation in muscle may result from glucose inhibition of fatty acid utilization—a “reverse” Randle cycle. However, biochemical examinations of skeletal muscle, as well as physiological investigations, also indicate that insulin-resistant skeletal muscle in individuals with obesity and type 2 diabetes has a reduced capacity for fat oxidation and a tendency toward increased lipid storage. Thus, the concept of insulin resistance includes impairments in fatty acid oxidation and denotes a distinct metabolic inflexibility with regard to substrate selection. These aspects of altered substrate metabolism in skeletal muscle offer new insights into the strong link between obesity and insulin resistance. These findings also pose a therapeutic challenge: How can we rectify not only glucose metabolism, but also skeletal muscle–fatty acid metabolism in obese patients with type 2 diabetes?

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