Obesity is a heterogeneous disorder of multi-factorial etiology. Excess adipose tissue can accumulate in specific regional patterns which have been broadly classified as upper body vs. lower body in distribution. Upper body obesity also varies and can result from either excess subcutaneous or deep abdominal visceral fat deposition. Upper body obesity with visceral fat localized to mesenteric and omental tissues and drained by the portal vein is more often associated with a constellation of metabolic disturbances that include insulin resistance and glucose intolerance.

Exactly how visceral obesity is associated with insulin resistance and glucose intolerance is unknown but substantial evidence implicates a potential role for increased portal or splanchnic FFA (1). Omental fat cells have high lipolytic activity and resistance to the antilipolytic action of insulin. Hepatic metabolism of elevated portal FFA concentrations could enhance glucose output by inducing hepatic insulin resistance, stimulating gluconeogenesis, and reducing hepatic clearance of portal insulin. Plasma FFA levels are usually elevated in obese individuals and women with upper body obesity are reported to have greater basal FFA turnover than those with lower body distribution. Enlarged visceral fat depots could contribute significantly to increased systemic FFA concentrations and utilization. The most plausible mechanism to explain how FFA induce insulin resistance in muscle tissue is by substrate competition between glucose and FFA for entry into the glucose–fatty acid cycle. Thus, FFA released from visceral fat have the potential to induce insulin resistance in liver and skeletal muscle, the two principal tissues involved in glucose intolerance and type 2 diabetes.

Although visceral obesity is accompanied by abnormalities of fatty acid metabolism and may cause insulin resistance, a growing body of evidence indicates that the sequence may be reversed. Skeletal muscle is the largest tissue in the body and is responsible for the majority of lipid oxidation and insulin-stimulated glucose utilization. In non-obese individuals, fatty acids account for ~80% of substrate oxidation in the postabsorptive state. As such, muscle is the principal site of thermogenesis and a major determinant of resting metabolic rate and daily energy expenditure in sedentary adults. Reduced rates of energy expenditure are a risk factor for weight gain and a high 24-h RQ or low ratio of fat to carbohydrate oxidation independently predicts subsequent weight gain (2). Consistent with this indirect evidence of low fat oxidation in muscle, an inverse correlation has been demonstrated between skeletal muscle lipoprotein lipase (LPL) activity and 24-h RQ (3). Low muscle LPL activity would limit fatty acid or lipid oxidation and favor its deposition in adipose tissue. Insulin resistance, again occurring principally in skeletal muscle, is also associated with reduced risk of weight gain (4). Thus, the available evidence suggests that defects of both fat and glucose exist in skeletal muscle of individuals predisposed to develop obesity.

In this issue of *The Journal*, Colberg and colleagues (5) have directly evaluated the interaction of fat and glucose metabolism in whole-body and leg tissue of premenopausal women over a wide range of visceral obesity. Interestingly, and contrary to what one might predict, this study provides additional support that skeletal muscle may have a primary role in the genesis of visceral obesity. If leg balance data accurately reflects events in leg muscle, a strong correlation was found during moderate hyperinsulinemia between visceral obesity and both systemic and muscle glucose storage, probably in the form of glycogen. These observations were present despite the absence of a relationship between visceral obesity and insulin-stimulated glucose uptake in either leg or whole body.

There are several important implications of the above findings. First, evidence of insulin resistance was present without corresponding increases in leg FFA uptake or oxidation during either mild or moderate hyperinsulinemia implying that glucose–fatty acid substrate competition was not involved in causing this defect. Second, visceral obesity is a risk factor for type 2 diabetes and insulin resistance and decreased non-oxidative glucose metabolism has been reported to be present in family members of individuals with diabetes. Therefore, the identification of defects in muscle glucose storage without decreased glucose uptake may indicate that this is the initial lesion which predisposes those with visceral obesity to develop type 2 diabetes.

The other important finding of this study is the negative relationship between visceral obesity and fasting rates of FFA uptake across the leg. This was not due to reduced FFA availability since neither fasting arterial FFA levels or systemic FFA appearance were reduced with increasing visceral fat. More likely, reduced fasting FFA uptake was due to an intrinsic muscle defect since carnitine palmitoyl transferase (CPT), the rate-limiting enzyme for long chain acyl CoA ester transfer into mitochondria, correlated positively with fasting FFA leg uptake and negatively with visceral fat content. Although basal leg lipid oxidation was not decreased with increasing visceral fat content, a strong correlation was present between basal leg lipid oxidation and insulin-stimulated leg glucose storage. These findings indicate that defects in postabsorptive fatty acid uptake and insulin-stimulated glucose storage co-exist in muscle and could contribute to the development of visceral obesity. By this scenario, fatty acids that cannot be taken up by muscle would be stored in visceral depots.

These are provocative findings that are preliminary in nature and require confirmation. However, these results support other data which suggests that, like type 2 diabetes, the initial lesion for visceral obesity may begin in skeletal muscle. It is anticipated that further investigations in this area of muscle metabolism will provide greater insight into the possible mechanisms linking visceral obesity with altered fat utilization, insulin resistance and type 2 diabetes.

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