SEE LEBOVITZ AND BANERJI (P. 2322)

Counterpoint: Visceral Adiposity Is Not Causally Related to Insulin Resistance

It has been known for over half a century that accumulation of fat in the upper body is associated with metabolic complications of obesity. The mechanism responsible for this association is widely believed to be insulin resistance, which is frequently present in individuals with upper-body obesity (1) and is associated with increased cardiovascular risk (2). The upper-body obesity phenotype is accompanied by increased free fatty acid (FFA) flux and concentration, whereas individuals with predominantly lower-body obesity tend to have normal FFA kinetics (3). Increased FFA concentrations, in turn, are thought to be a major mediator of insulin resistance (4) and have been shown to cause endothelial dysfunction (5), impair pancreatic β-cell function (6), and acutely raise blood pressure (7). Increased delivery of FFA to skeletal muscle can result in insulin resistance in that tissue, either directly or via accumulation of increased intramyocellular triglyceride stores (8). Similarly, increased delivery of FFA to the liver may be responsible for hepatic insulin resistance (9), accumulation of intrahepatocellular triglyceride (10), and increased synthesis and secretion of VLDL (11). Hormone-sensitive lipase in adipocytes is exquisitely sensitive to the antilipolytic effect of insulin in lean healthy individuals (12). However, impaired insulin suppression of adipose tissue lipolysis is a feature of, and may even be the primary cause of, insulin resistance (13). To our knowledge, insulin resistance has not been reported in individuals with normal sensitivity to the antilipolytic effects of insulin.

What is visceral obesity?

The degree of upper-body obesity can be estimated by measurement of waist circumference, which is predictive of cardiovascular risk (14). However, nonobese individuals exhibit considerable variability in insulin sensitivity (15) that is not necessarily explained by differences in waist circumference (16). It is possible that differences in the distribution of upper-body fat could explain variability in insulin sensitivity at a given BMI and a given waist circumference. Waist circumference reflects total truncal fat, which consists of both subcutaneous and intra-abdominal (predominantly mesenteric and omental, also referred to as visceral) fat. It has been suggested that adipose tissue in the visceral compartment has greater lipolytic potential than subcutaneous adipose tissue (17). Although the visceral fat depot is relatively small compared with subcutaneous fat mass, the possibility that it is more lipolytically active on a per-unit-mass basis and the fact that the release of FFA directly into the portal vein creates a "first pass" effect in the liver means that that organ may be exposed to higher FFA concentrations than peripheral tissues, especially in those with visceral obesity. A recently published study found that the amount of FFAs released by visceral fat does in fact correlate with visceral fat mass (18). There is a strong correlation between the amount of visceral fat present and circulating VLDL triglyceride concentrations (19), which are thought to correlate in turn with the delivery of FFA to the liver (11). Increased visceral fat mass is associated with glucose intolerance (19), and several studies have shown that insulin sensitivity correlates with visceral fat mass in normal subjects (20) and people with type 2 diabetes (21).

Relationship between visceral obesity and insulin resistance

It seems logical that an increase in visceral fat mass could result in greater FFA release into the portal circulation, and the association between visceral fat mass and insulin sensitivity seems clear. However, whether increased visceral fat mass plays a true causal role in insulin resistance is not as obvious. Some of the same studies that demonstrate a strong correlation between insulin sensitivity and visceral fat mass also show that insulin sensitivity is strongly associated with subcutaneous fat mass (20). There is actually considerable variability in results regarding the relationship between insulin sensitivity and regional fat depots in humans (22). This could be due to technical issues related to measurement of the visceral fat depot (22) and/or variability in the relationship between the size of a fat depot and its lipolytic activity (23). The latter phenomenon could occur, for example, if a given fat depot contained fewer adipocytes of larger size in one subject than in another. One would expect greater lipolysis and greater resistance to the antilipolytic effect of insulin when fat cells are larger and fewer in number (24).

Other studies that have been cited as evidence for a key role of visceral fat in insulin resistance have ambiguities that make their interpretation difficult. Surgical removal of perinephric fat in obese rats produced improvement in insulin-mediated glucose disposal (25). This should not be interpreted as an indication that visceral lipolysis has an impact on systemic insulin action, however, because the venous drainage of perinephric fat in the rat is caval, not portal. In humans, individuals undergoing vertical-banded gastroplasty and omentectomy simultaneously had a greater improvement in insulin action than those who had only vertical-banded gastroplasty (26). However, the subjects who underwent omentectomy ($n = 19$) had a 9-kg greater weight loss than those who did not ($n = 18$), a difference that, although not statistically significant with this relatively small number of subjects, is likely important.

The contribution of visceral and subcutaneous fat to portal and peripheral FFA

Insulin-resistant states are marked by insulin resistance in both skeletal muscle and liver (27). It has been suggested that increased delivery of FFA to the liver produces hepatic insulin resistance by stimulating gluconeogenesis (9). Since the rate of visceral lipolysis correlates with visceral fat mass (18), and in view of the "first pass" effect, it seems logical to speculate that increased visceral fat could be responsible for hepatic insulin resistance. However, if the majority of FFAs delivered to the liver were to come from subcutaneous fat, then abnormalities in subcutaneous lipolysis could be more important than visceral lipolysis as a cause of hepatic insulin resistance, especially con-

sidering that subcutaneous fat stores tend to be increased in individuals who have increased visceral fat mass, even when all of the subjects studied are of normal weight (28). Relatively little information on the contribution of visceral lipolysis to FFA delivery to the liver is available.

The contribution of visceral fat to systemic FFA availability also has been uncertain. Recently, Nielsen et al. (18) measured regional fat depots and visceral and systemic lipolysis in 44 obese and 24 lean subjects using combined isotope dilution and arteriovenous sampling (leg, splanchnic) techniques. Visceral lipolysis was responsible for only 5–10% and 20–25% of total FFA delivery to the liver in lean and obese subjects, respectively, although the contribution of visceral fat was proportional to the size of the visceral fat depot. Importantly, however, the contribution of visceral lipolysis to systemic (i.e., extrahepatic) FFA availability was very small—generally <5% (18).

It remains possible that isolated visceral "hyperlipolysis" could be a factor in systemic insulin resistance. For this to be the case, however (considering that the contribution of visceral fat to the peripheral FFA pool is so small and assuming that FFAs are the chief mediators of insulin resistance), systemic insulin resistance would have to result from FFA-mediated hepatic insulin resistance in the absence of insulin resistance in peripheral tissues. Parenthetically, in this scenario, one would not expect to see the lipotoxicity that may be responsible for decline in β-cell function when systemic FFAs are increased (29). A recent study in dogs receiving a moderately high-fat diet demonstrated an increase in both visceral and subcutaneous fat, with insulin resistance primarily due to impaired insulin suppression of endogenous glucose production (30). There was no change in plasma FFA concentrations. Does isolated visceral obesity or isolated hepatic insulin resistance occur in humans? There are no data to suggest that this is the case. Moreover, it seems unlikely considering that increased fat stores are the common denominator for abnormally high rates of lipolysis, and subcutaneous fat mass tends to be increased when visceral fat mass is increased (28). If isolated visceral obesity exists, individuals with it would be expected to be at normal or near-normal weight because the visceral fat depot is relatively small, even in the viscerally obese. A potential model for isolated visceral obesity is the individual who is "metabolically obese" but of normal weight (MONW), as described by Ruderman et al. (31). Unfortunately, no studies are available that relate FFA metabolism to insulin sensitivity in normal-weight individuals. Dvorak et al. (28) reported body composition data in 13 MONW women and 58 insulin-sensitive control subjects. They found that MONW women had higher visceral and upper-body subcutaneous fat than control subjects; moreover, the MONW individuals had slightly higher BMIs than control subjects (22.5 vs. 21.5 kg/m^2, $P = 0.08$). A study in nonobese Japanese subjects found insulin resistance (using the euglycemic clamp) and greater visceral fat in MONW compared with lean control subjects (32). However, the MONW subjects were selected for visceral obesity, and they had both significantly higher BMIs and greater subcutaneous fat than the control group (both $P < 0.01$). Thus, isolated visceral obesity is not known to occur in humans.

The RISC (Relationship between Insulin Sensitivity and Cardiovascular disease risk) study, now underway in 20 European centers, provides preliminary observations of potential interest. Among 625 individuals with BMI values <25 kg/m^2, there was marked variation in insulin sensitivity (measured by the euglycemic clamp) and waist circumference. Distinct groups of individuals were identified with insulin resistance alone, increased waist circumference alone, both, and neither (E. Ferrannini, personal communication). Although FFAs and regional fat mass were not measured in the RISC study, these findings underscore the potential complexity of the relationship between the size of body fat depots and insulin resistance.

Non-FFA mediators of insulin resistance

Increased delivery of FFAs is thought to be the primary effector of insulin resistance in extrahepatic tissues, primarily skeletal muscle (4,13). Based on the study of Nielsen et al. (18), it seems unlikely that visceral fat could contribute in any significant way to increased FFA supply to skeletal muscle. It is possible that visceral fat could mediate peripheral insulin resistance via another mechanism, such as the release of adipocytokines. However, direct evidence to support this idea is lacking. Moreover, a recent study in type 2 diabetic patients who were given acipimox for 7 days to lower plasma FFA concentrations makes this notion less attractive. In that study, FFA concentrations were reduced and a significant improvement in insulin action was observed in the absence of changes in adiponectin, resistin, interleukin-6, and tumor necrosis factor-α levels (33). This observation does not necessarily mean that adipocytokines are not mediators of insulin resistance. It does suggest, however, that FFAs are important. Additional research is needed to delineate the relative importance of FFAs and adipocytokines in this regard.

Summary

The data on the role of increased visceral fat as a cause of insulin resistance are conflicting. There are probably several reasons for the confusion. Methodologic imprecision in the measurement of body fat depots and real biological variation in lipolytic activity of fat depots may both play a role. It appears that visceral fat has very little if any role in the oversupply of FFAs to extrahepatic tissues in insulin-resistant states. Instead, subcutaneous fat, especially in the upper body, is the major contributor to this known mediator of insulin resistance. Increases in visceral fat mass, even among normal-weight individuals, are accompanied by increases in subcutaneous fat mass. Thus, the weight of evidence suggests that visceral fat may be responsible for hepatic insulin resistance in some circumstances but is no more than a marker for insulin resistance in extrahepatic tissues. Future studies should focus on the relationship between upper-body subcutaneous and visceral fat depots, regulation of FFA metabolism, and the relative contribution of insulin resistance in liver versus that in skeletal muscle to systemic insulin resistance.

JOHN M. MILES, MD
MICHAEL D. JENSEN, MD

From the Endocrine Research Unit, Division of Endocrinology, Metabolism and Nutrition, Mayo Clinic, Rochester, Minnesota.

Address correspondence and reprint requests to John M. Miles, MD, Endocrine Research Unit, Mayo Clinic, Rochester, MN 55905. E-mail: miles.john@mayo.edu.

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