Point: Visceral Adiposity Is Causally Related to Insulin Resistance

The relationship between obesity and insulin resistance, while well recognized for many years, has nonetheless been confusing since not all obese individuals have insulin resistance (1) and because insulin resistance occurs in individuals who have BMIs that are within the normal or mildly overweight categories (2).

Early attempts to understand the relationships between obesity, type 2 diabetes, and cardiovascular disease focused on the waist-to-hip ratio as a means of distinguishing those individuals who were at increased risk from those who were not (3,4). A high waist-to-hip ratio is a surrogate for masculine distribution of obesity (central obesity). Cross-sectional studies by Kissebah et al. (5) and Krotkiewski et al. (6) in the 1980s demonstrated that hypertension, hypertriglyceridemia, hyperinsulinemia, and glucose intolerance were increased in subjects with a high waist-to-hip ratio. Long-term longitudinal population-based studies of men (13.5 years) and women (12 years) in Gothenburg, Sweden, showed that the waist-to-hip ratio was a predictor of the future development of diabetes, myocardial infarction, angina pectoris, stroke, and death independent of BMI (3,4).

Technology developed in the 1990s, including computer tomography scans and MRI, made it possible to precisely measure specific adipose tissue depots such as total body adipose tissue mass, abdominal subcutaneous adipose tissue mass, visceral adipose tissue mass, and hepatic and intramuscular triglyceride content (7,8). Utilizing those techniques, many studies have examined the relationship between total adipose tissue, abdominal subcutaneous adipose tissue, and visceral adipose tissue mass and insulin resistance, the components of the metabolic syndrome, and the development of type 2 diabetes or clinical cardiovascular events (9–21).

Despite the much smaller size of the visceral adipose tissue depot compared with the total subcutaneous adipose tissue depot or total adiposity, many investigations demonstrated that the visceral adipose tissue mass and not the subcuta-

neous or total adipose tissue mass was significantly correlated in multivariate analyses with insulin resistance, type 2 diabetes, and cardiovascular events (9–11,13,14,16,19,20). The hypothesis that visceral adiposity and not total adiposity was the cause of the components and clinical consequences of the metabolic syndrome has been challenged by several studies that found either that abdominal subcutaneous adipose tissue mass and not visceral adipose tissue mass was independently correlated with insulin resistance or that they were both equally correlated (8,12,17,18,21). Studies using isotopic techniques have calculated that the majority of circulating free fatty acids are derived from peripheral adipose tissue (22) and that if free fatty acids are postulated to be responsible for the insulin resistance associated with obesity, then total adiposity rather than visceral adiposity should be responsible for insulin resistance.

Several lines of evidence support the hypothesis that visceral adipose tissue and not subcutaneous adipose tissue is the major contributor in causing insulin resistance and the metabolic syndrome. They are discussed in the below sections.

Correlation between adipose tissue depots and insulin resistance

Numerous investigators have examined the relationship between insulin resistance, as measured by the euglycemic-hyperinsulinemic clamp, and various adipose tissue depots, such as total adiposity, visceral adipose tissue, abdominal subcutaneous adipose tissue, and intramyocellular triglyceride. The techniques used to estimate the various pools have varied considerably. The most commonly used technique is a computed tomography scan or a magnetic resonance imaging (MRI) done at one level, such as L4-5. The area of the visceral adipose tissue is then compared with the area of the subcutaneous adipose tissue. The most rigorous technology involves scanning the abdomen with multiple slices using a computer program to calculate the total volume or mass of the visceral and abdominal subcutaneous depots. Some investigators have separated the visceral

adipose tissue pool into a retroperitoneal adipose tissue compartment that presumably drains into the systemic circulation and an intraperitoneal compartment that drains into the portal circulation (23). Other investigators have separated the abdominal subcutaneous adipose tissue into deep and superficial compartments and found that the superficial compartment had no relationship with insulin resistance, whereas the deep compartment was as highly correlated with insulin resistance as the visceral compartment (17).

While the results of the studies from various investigators differ, there is remarkable consistency of results from the same investigator. The studies of Fujimoto and colleagues (13,16) in Japanese Americans over the last 10 years show that visceral adiposity is associated with and predicts the development of type 2 diabetes, coronary heart disease, and hypertension. The numerous studies emanating from the laboratories of Després and Bouchard (9,10) since 1990 have reproducibly shown that visceral adiposity is the component of adiposity that is the independent risk factor for insulin resistance, glucose intolerance, and cardiovascular risk factors. Abate and Garg and their associates (8,23) have devised a procedure for measuring regional adiposity by multiple MRIs and consistently find that it is abdominal subcutaneous adipose tissue that is associated with insulin resistance. Goodpaster et al. (12) reported in 1997 that subcutaneous abdominal fat predicted insulin sensitivity independently of visceral fat. However, when they subsequently examined the effects of weight loss on regional fat distribution and insulin sensitivity in obesity, they found that the reduction in visceral adiposity was the only adipose tissue parameter that predicted the improvement in insulin sensitivity (15). Banerji and colleagues (11,14), using multiple abdominal computed tomography slices to measure visceral and abdominal subcutaneous adipose tissue volumes and euglycemic-hyperinsulinemic clamps to measure insulin sensitivity, have found visceral adiposity to be independently associated with insulin resistance in type 2

diabetic African-American men and women and in nondiabetic Southeast-Asian men. Visceral obesity has been reported to be an important correlate of sex differences in cardiovascular disease risk (24).

In obese children and adolescents with impaired glucose tolerance, intramyocellular and visceral lipid deposits are increased and the abdominal subcutaneous adipose tissue depot is decreased, as indicated by MRI. These abnormalities are associated with the development of severe peripheral insulin resistance (25).

Absence of insulin resistance in overweight and obese individuals with lower body obesity
Individuals with lower body obesity have an increase in total adiposity that is predominately in subcutaneous adipose tissue; visceral adipose tissue is not significantly affected.

In near-normoglycemic African-American men with the same BMI ($\sim$26.5 kg/m^2), insulin resistance is present in those with increased visceral adipose tissue mass (4.71 $\pm$ 1.85 l) but not in those with normal visceral adipose tissue mass (2.49 $\pm$ 2.3 l) (26).

Lemieux et al. (10) followed a cohort of women for 7 years to assess changes in total obesity, regional adiposity, and measures of glucose and insulin homeostasis. They compared two subgroups of women with similar mean increases in body fat mass but with either small or large increases in visceral fat mass. The greatest deterioration of glucose tolerance and increases in insulin secretion occurred in those with the large increase in visceral adiposity. In contrast, when they compared two subgroups with similar increases in visceral fat mass but with small or large changes in body fat mass, they found no difference in the changes in glucose tolerance and insulin secretion between the groups. They concluded that visceral fat mass and not total fat mass was the determining factor in regulating glucose homeostasis.

Adipose tissue composition and metabolic status in patients with the Prader-Willi syndrome
The Prader-Willi syndrome is a genetic disorder characterized by hyperphagia, marked obesity from childhood, mental retardation, short stature from growth hormone deficiency, and hypogonadism.

It is thought to be due to developmental abnormalities in the hypothalamus. Of particular interest has been the observations that they don't seem to have many of the obesity-related metabolic abnormalities. Goldstone et al. (27) compared total and regional adipose tissue depots in patients with the Prader-Willi syndrome with comparable obese individuals and nonobese control subjects. BMI (36.6 $\pm$ 9.9 kg/m^2), total adipose tissue volume (55.7 $\pm$ 25.8 l), percent body fat (46.9 $\pm$ 6.9), and abdominal subcutaneous adipose tissue as percent of total body fat (25.9 $\pm$ 3.2) were the same in the Prader-Willi syndrome patients as in the obese subjects. In contrast, their visceral adipose tissue mass (5.7 $\pm$ 1.3%) was the same as the nonobese individuals (5.7 $\pm$ 1.7%) and $\sim$60% that of the obese individuals (9.1 $\pm$ 1.6%). The values of metabolic factors that characterize the obese phenotype, such as plasma insulin levels, insulin sensitivity, and plasma triglyceride levels, were proportional to visceral adipose tissue mass and not to total fat mass. In the Prader-Willi syndrome, the increase in total fat mass does not cause insulin resistance and the metabolic syndrome.

Liposuction removal of abdominal subcutaneous adipose tissue in obese nondiabetic and type 2 diabetic subjects
If the metabolic effects of obesity are due to total body fat and contributed to by the abdominal subcutaneous adipose tissue, the removal of a large mass of abdominal subcutaneous adipose tissue should result in some amelioration of insulin resistance and components of the metabolic syndrome. Klein et al. (28) studied 15 obese patients (8 nondiabetic control subjects and 7 type 2 diabetic patients) before and 10–12 weeks after liposuction of abdominal subcutaneous adipose tissue. The type 2 diabetic patients had a mean baseline BMI of 39.9 $\pm$ 5.6 kg/m^2 and had 10.5 $\pm$ 3.3 kg fat removed, which was 28% of the depot. The nondiabetic subjects had a baseline BMI of 35.1 $\pm$ 2.4 kg/m^2 and had 9.1 $\pm$ 3.7 kg fat removed, which was 44% of the subcutaneous abdominal adipose tissue. There was no loss of visceral adipose tissue. In both groups, the removal of the abdominal subcutaneous fat had no effect on insulin resistance, plasma glucose or insulin levels, plasma adiponectin levels,

or any of the lipid or inflammatory components of the metabolic syndrome.

Peroxisome proliferator–activated receptor γ agonists increase abdominal subcutaneous adipose tissue mass but decrease insulin resistance and improve most of the components of the metabolic syndrome
Pioglitazone, rosiglitazone, and troglitazone have been shown to increase total body fat and abdominal subcutaneous adipose tissue while having no effect on or slightly decreasing visceral adipose tissue. Despite this increase in overall obesity, the thiazolidinediones improve insulin sensitivity and improve all of the components of the metabolic syndrome (29). Plasma free fatty acid levels decrease $\sim$20–25%, and hepatic fat decreases 25–50%.

This sequence of events suggests that insulin resistance and the components of the metabolic syndrome are the consequence of the metabolic effects of the products being released from the adipose tissue rather than an effect of the absolute mass of the tissue. Adipose tissue releases free fatty acids and cytokines (e.g., tumor necrosis factor α) and modulates the secretion of a large number of metabolically active adipokines (e.g., adiponectin). It is the net effect of these factors that appears to be responsible for the metabolic abnormalities of obesity.

Reflections
We have presented evidence that we believe supports the thesis that increases in visceral adipose tissue are the conduit by which obesity leads to insulin resistance and the metabolic syndrome. Further validation requires many additional pieces of the puzzle to be unraveled and explained. Visceral adipose tissue is biochemically quite distinct from subcutaneous adipose tissue, as has been reviewed by several authors (30), and it is unclear as to how the large number of adipokines, cytokines, and enzymes as diverse as adiponectin and 11β-hydroxysteroid dehydrogenase type 1 are regulated and integrated. Several recent studies involving nondiabetic Asian Indians suggest that regional adipose tissue metabolic activity may be quantitatively different depending on the ethnic background of the individual. For the same fat mass and regional distribution, Asian Indians have more insulin re-

sistance, higher plasma free fatty acids, higher C-reactive protein and plasminogen activator inhibitor-1, and lower plasma adiponectin than Caucasians (31). The relationship between visceral adipose tissue and abdominal subcutaneous tissue may be more closely linked than has been thought. There are a few studies suggesting that increases in visceral adipose tissue mass or activity may alter subcutaneous adipose cell lipolysis.

It has become increasingly evident that the effects of visceral adiposity must be mediated by multiple factors. Free fatty acid release from visceral adipose tissue in obese individuals has been reported to account for ~20% of that delivered to the liver, although in an individual it can be as high as 50% (22). As Klein (32) has commented in a recent editorial, it is unlikely that the contribution that visceral fat makes to the free fatty acid flux in the circulation is its major mechanism in causing insulin resistance.

Adiponectin and other newly discovered adipokines are likely to contribute.

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