Why Visceral Fat is Bad: Mechanisms of the Metabolic Syndrome

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A consensus has emerged that fat stored in the central segment of the body is particularly damaging in that it portends greater risk for diabetes, cardiovascular disease, hypertension, and certain cancers (1–3). It is also accepted that insulin resistance is a related characteristic that may be an essential link between central fat and disease risk. Additionally, it is possible that the hyperinsulinemia that accompanies insulin resistance in non-diabetic but at-risk individuals may magnify, or even mediate, some of the detrimental effects of visceral adiposity (4–6).

However, there is less information regarding the mechanisms that may link visceral fat with risk for disease. For example, there is controversy regarding the specific mechanisms by which fat in the visceral compartment confers greater risk than subcutaneous fat. Many investigators have suggested that one or more moieties secreted by the visceral adipocyte might mediate insulin resistance. Among the so-called "bad actors" are free fatty acids (FFAs)[1] themselves ("portal theory") (7–9) or the adipose tissue–released cytokines (adipokines) such as interleukin-1, interleukin-6, tumor necrosis factor-α, resistin, or a reduction in adiponectin, which has been repeatedly shown to be associated with reduced insulin resistance (10–13). Of course, insulin itself could be involved, as other adipose-secreted protein compounds not yet identified.

But why visceral fat? Is it because of the unique anatomical position of the visceral fat depot, with effluent entering the liver, or is it because of molecular characteristics of visceral fat itself, which may favor release of damaging molecules into the systemic circulation? These questions remain unanswered. However, in our laboratory, we have developed the obese dog model, which has led to some understanding of the pathogenesis of the metabolic syndrome. The dog model has not been widely used for the study of the metabolic syndrome, but we have found it to have several important characteristics that we have been able to exploit: the ability to make longitudinal measurements and the ability to access the portal vein. In that sense the dog is a unique model, in that these latter measurements are daunting in rodents, and carrying out repetitive, invasive clinical measurements in non-human primates is challenging. Also, the dog with visceral obesity has turned out to be a reasonable model for a similar syndrome in humans (Figure 1). In fact, the dog is genetically more similar to humans than is the rodent.

Here we summarize a significant amount of evidence in which we examined what we considered to be the simplest hypothesis composed of two postulates: 1) that FFAs per se are among the most important products of the visceral adipocyte to cause insulin resistance (and hence the metabolic syndrome) and 2) that the anatomical position of the visceral adipose depot (i.e., portal drainage into the liver) plays an important role in the pathogenesis of the metabolic syndrome. While we cannot say that these postulates are proven, there are data that support them, and Occam's razor instructs us to accept them until proven untrue. Whether true or not, it appears that examining them has led us to a deeper understanding of the physiological basis for the metabolic syndrome itself.

One similarity between dogs and humans is the wide variance in fat deposition in a "wild" or "natural" population. We measure distribution of fat about the truncal region using magnetic resonance imaging [Figure 2; 11 axial slices: 1-cm landmark slice at the umbilicus (left renal artery) $\pm$ 5 cm]. Similar to human subjects (14,15), there is surprising variability in distribution. Some animals are strikingly lean, with total fat varying over a factor of 5, from 10 to 50 cm^3/cm^3 non-fat tissue. Interestingly, there is a tendency for visceral adiposity to increase rapidly as one examines animals with increasing body fat; the visceral fat depot tends to plateau, and subcutaneous fat increases more rapidly with overall obesity. This tendency for visceral fat to

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[1] Nonstandard abbreviations: FFA, free fatty acid.

Animal models of obesity

MODEL	GENETIC HOMOLOGY	ADVANTAGES
Mouse	~75%	Genetics
Rat	~85%	Physiological measures
Dog	~90%	Longitudinal studies Portal access
Monkey	~95%	Primate model
Human	100%	The real deal!

Figure 1: Different animal models of obesity and their relative homology to the human genome.

increase and plateau may be responsible for the sharp reduction in insulin sensitivity in leaner individuals, with insulin resistance being similar in human subjects with BMI levels >30 kg/m^2 (16).

Regardless of basal adiposity, increasing the content of fat in the diet induces visceral as well as subcutaneous fat in the dog model. In fact, an isocaloric diet with increased fat from 35% to 43% had a potent effect on insulin sensitivity—but the effect was almost totally on liver sensitivity to insulin (Figure 3) (17). In fact, 12 weeks of an isocaloric but elevated fat diet induced virtually total hepatic insulin resistance with respect to glucose—that is, hyperinsulinemia during glucose clamps failed to suppress liver glucose production. On the contrary, sensitivity of peripheral tissues remained surprisingly sensitive to hyperinsulinemia. Thus, we concluded that increased visceral adiposity induced by fat feeding causes a primary insulin resistance of the liver. Increasing fat in the diet to achieve an hypercaloric intake induced both hepatic and peripheral insulin resistance. We propose the "overflow hypothesis" (Figure 4): extremely lean individuals are insulin sensitive at the liver and in muscle tissue. Increasing fat in the diet is proposed to store visceral and subcutaneous fat, but the liver is exquisitely sensitive to fat in the visceral depot, leading to hepatic insulin resistance primarily (17,18). Hepatic resistance (i.e., effect of physiological insulin to suppress glucose output) is observed with moderate visceral adiposity; further fat intake results in systemic (i.e., muscle) insulin resistance associated with fat deposition in the subcutaneous tissues. We have seen an increase in liver triglycerides with isocaloric but increased fat intake, but we have not observed substantial deposition in muscle or other tissues (e.g., pancreas) as in rodents. We believe that rodent models of obesity may represent extreme obesity in human subjects, and it is in the extreme case that one may see lipid accumulating in tissues such as the endocrine pancreas. The dog model may be representative of "garden variety" obesity of the normal human population, without morbid obesity.

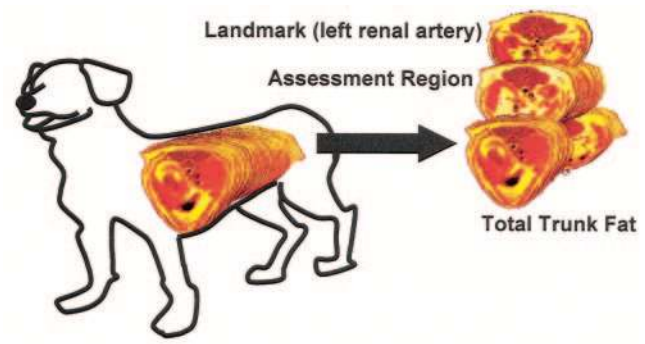

Figure 2: Illustration of fat distribution taken by magnetic resonance imaging in the truncal region in the dog model. The axial image at the level where the left renal artery branches from the abdominal aorta is used as the midpoint landmark slice. Contribution of omental vs. subcutaneous fat is assessed within the region ± 5 cm from this landmark slice. Approximately 20 axial images (depending on the relative torso length of the animal) are used for assessment of total trunk fat.

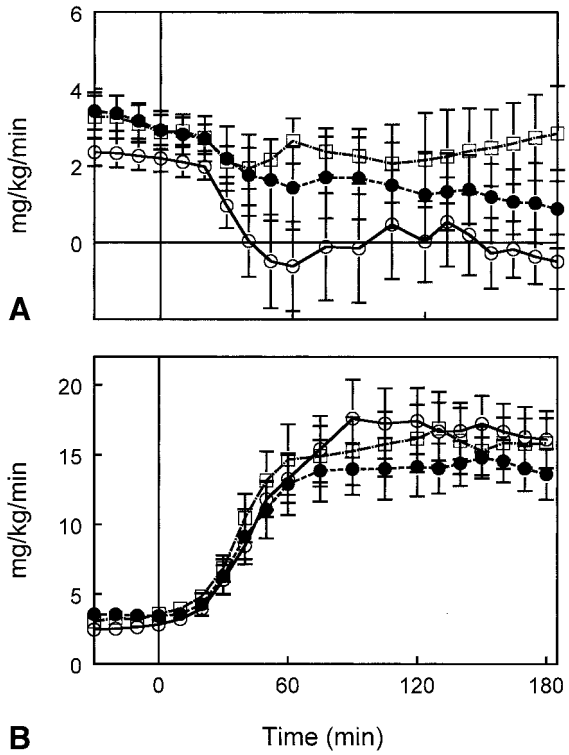

Figure 3: Time-course data of (A) glucose production and (B) glucose uptake during a standard euglycemic-hyperinsulinemic clamp in dogs fed an isocaloric, moderate fat diet at weeks 0 (○), 6 (●), and 12 (□) (17).

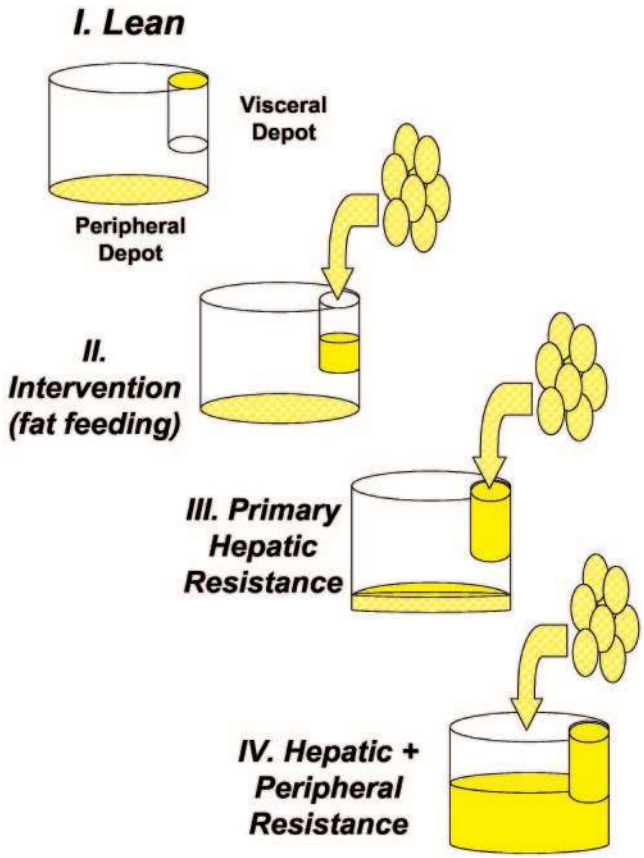

Figure 4: "Overflow hypothesis." Lean animals have little fat in visceral or subcutaneous compartment (I). Moderate fat feeding (II) increases fat in the visceral compartment primarily, resulting in visceral fat deposition and hepatic insulin resistance (III). Increased amounts of dietary fat (IV) result in visceral and subcutaneous fat deposition and hepatic and peripheral insulin resistance.

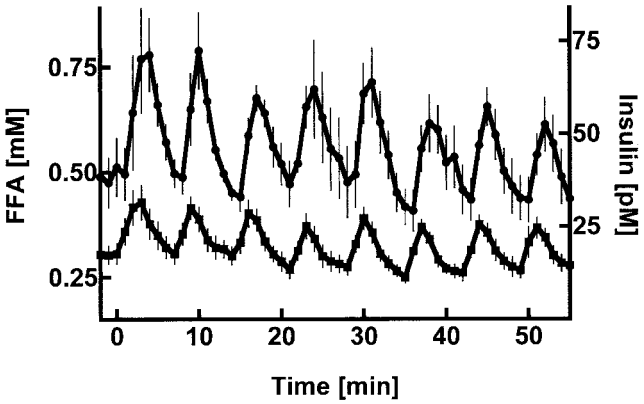

Figure 5: Effect of pulsatile intravenous injection of octanoate on plasma insulin. Squares, insulin; circles, FFAs.

What is the mechanism by which visceral fat causes insulin resistance at the liver and in muscle? We measured gene expression of a variety of important enzymes in visceral and subcutaneous fat and liver (19). In addition, we measured expression of some adipokines. The overall pattern is clear: expression of enzymes related to lipid turnover in visceral fat (e.g., lipoprotein lipase, hormone sensitive lipase, peroxisome proliferator-activated receptor γ) increase with fat feeding in visceral fat relative to subcutaneous fat. This can enhance flux of FFAs through the portal vein to the liver, as well as to other tissues. However, we have not found evidence that expression of so-called "adipokines" is increased specifically in visceral fat tissues (tumor necrosis factor α, interleukin-6, adiponectin, leptin). We believe these data support the concept that FFAs themselves are responsible for the insulin resistance of the liver, at least with moderate increases in fat intake. Of course, our results may not extrapolate to the human obese model, which usually represents years of overweight in which adipokines could contribute substantially to insulin resistance. Overall, we do not believe that FFAs have been ruled out as the putative factor, resulting in insulin resistance of the liver during increased weight gain secondary to fat intake.

An interesting feature of potentially damaging effects of moieties emanating from fat tissues is time of day. Interestingly, an increase in fasting FFA levels in obesity and insulin resistance is not always observed (20). However, the question arises of whether fasting levels reflect potentially damaging tissue exposure at all times of the day. To examine whether there is increased exposure to FFA moieties nocturnally, we again exploited the fat-fed canine model. Members of our laboratory group carried out a series of challenging experiments in which blood samples were collected every hour for 24 hours under control conditions, and the same protocol was carried out in a similar fashion after 6 weeks of an hypercaloric high fat diet (6 g/kg per day). The results were striking: total trunk fat increased by 76% (visceral and subcutaneous), whereas there was no measurable increase in fasting FFAs; 24-hour FFA profile increased by 50%. If this increase is suggested to come from visceral fat primarily, it could represent a large increase in flux of FFAs to the liver from the visceral fat depot and could be an important factor in the insulin resistance of moderate obesity. Additionally, the increase in nocturnal FFAs could play a role in stimulating the hyperinsulinemia that normally accompanies insulin resistance in non-diabetic individuals. FFAs are a potent stimulus to insulin secretion (Figure 5) and can reduce first-pass hepatic insulin clearance (21), both of which may contribute to the hyperinsulinemic compensation.

The explanation for the relationship between visceral fat deposition, in particular, and components of the metabolic syndrome, including insulin resistance, remains obscure. However, good evidence refuting a possible effect of FFAs

in this syndrome has not been produced. While the bevy of proteins secreted from adipose tissue could well play a major role, at least in pathophysiological states, in our view, there is no compelling reason to reject the concept that FFAs themselves play a part or even the majority in the role of inducing liver insulin resistance, which is the primary event in the development of the metabolic syndrome in animal models (17,22). It is certainly possible that cytokine molecules that emanate from the adipose may play important roles in pathological states of extreme insulin resistance, such as type 2 diabetes.

Acknowledgment

This study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases Grants DK-27619 and DK-29867 (R.N.B.) and NIH Training Grant AG00093 (S.P.K. and K.J.C.). M. Kabir performed this work during a postdoctoral fellowship supported by a mentor-based grant from the American Diabetes Association.

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