Metabolic syndrome, hyperinsulinemia, and cancer[1–3]

Isabel R Hsu, Stella P Kim, Morvarid Kabir, and Richard N Bergman

ABSTRACT

The term *metabolic syndrome* describes the association between obesity, insulin resistance, and the risk of several prominent chronic diseases, including cancer. The causal link between many of these components remains unexplained, however. What is clear are the events that precede the development of the syndrome itself. In animal models, a fat-supplemented diet causes *1*) lipid deposition in adipose depots, *2*) insulin resistance of liver and skeletal muscle, and *3*) hyperinsulinemia. One hypothesis relating fat deposition and insulin resistance involves enhanced lipolysis in the visceral depot, which leads to an increase in free fatty acid (FFA) flux. Increased mass of stored lipid and insulin resistance of visceral adipocytes favors lipolysis. Additionally, hypersensitivity of visceral adipose cells to sympathetic nervous system stimulation leads to increased lipolysis in the obese state. However, little evidence is available for enhanced plasma FFA concentrations in the fasting state. We measured FFA concentrations over a 24-h day in obese animals and found that plasma FFAs are elevated in the middle of the night, peaking at 0300. Therefore, it is possible that nocturnal lipolysis increases exposure of liver and muscle to FFAs at night, thus causing insulin resistance, which may play a role in hyperinsulinemic compensation to insulin resistance. Nocturnal lipolysis secondary to sympathetic stimulation may not only cause insulin resistance but also be responsible for hyperinsulinemia by stimulating secretion and reducing clearance of insulin by the liver. The resulting syndrome—elevated nocturnal FFAs and elevated insulin—may synergize and increase the risk of some cancers. This possible scenario needs further study. *Am J Clin Nutr* 2007;86(suppl):867S–71S.

KEY WORDS Metabolic syndrome, obesity, insulin resistance, hyperinsulinemia, free fatty acids, nocturnal lipolysis, sympathetic nervous system, cancer

INTRODUCTION

Recent evidence supports the concept that there are risk factors in common for several chronic illnesses. These factors include obesity (primarily truncal obesity), insulin resistance, and hyperinsulinemia (1–3). The latter factors appear to be associated with increased risk of glucose intolerance, type 2 diabetes, polycystic ovarian syndrome, dyslipidemia, hypertension, and cardiovascular disease. It remains controversial whether these relations are causal or are simply reflective of clusters of risk factors in certain persons (4). What is more clear is the causal association between adiposity in the visceral fat depot, hyperinsulinemia, and insulin resistance. Thus, whereas possibly not all chronic diseases prevalent in Western society are necessarily related, it is reasonable to assume that adiposity, particularly central adiposity, poses greater risk. Strong evidence suggests that reductions in obesity will reduce risk (5, 6).

More recently, epidemiologic associations have emerged between adiposity and some forms of cancer: colon, breast, and epithelial. These associations provoke speculation that the mechanisms that link adiposity with insulin resistance may also be implicated in some cancers. Although the mechanisms of this link remain obscure, it is not impossible that insulin itself is important in linking insulin resistance to cancer. Insulin is a known growth factor (7) and has been put forth as a causative factor in cardiovascular disease (8). Additional mechanisms may include chronic inflammation and oxidative stress associated with obesity (9, 10). Adipocytes are known to release a family of so-called *adipokines*, including free fatty acids (FFAs). In fact, evidence exists that FFAs themselves play an important role in the pathogenesis of insulin resistance.

It is challenging to understand the causal relations between insulin resistance and disease risk. In humans, because of the slow development of disease, most of the available data are cross-sectional. Reversal of obesity is challenging (11, 12) and is associated with a high rate of recidivism, thus making it problematic to observe reductions in risk, not to mention in disease. The latter situation calls for study of the relation between obesity and disease risk in animal models. Small mammals have been useful, but it is not always clear whether obesity in rodents is representative of obesity in primates, including humans, which is associated with disease. For the past several years, our group has used a canine model to study the longitudinal development of obesity and insulin resistance. This animal model develops visceral and subcutaneous fat deposition when the diet is enriched with fat, even without an increase in total calories (13, 14). The degree of obesity is reminiscent of that seen in "garden variety" obesity in humans, which is associated with increased risk. Thus, whereas some animal models remind us of massive obesity, with ectopic fat storage outside the usual fat depots (15), the model in dogs has potential for examining the widespread obesity in the US population.

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THE METABOLIC SYNDROME: USEFUL CONCEPT?

The concept of the pleurometabolic syndrome emerged many years ago and was introduced into the modern lexicon by Gerald Reaven as syndrome X (16). The concept of a relation between insulin resistance and cardiovascular risk has been generalized to the metabolic syndrome, and this inclusive concept includes the risk of many chronic diseases, such as visceral obesity, diabetes, hypertension, stroke, and cancer (17, 18). Recently, this concept has come under fire, and it was suggested by Kahn et al (4) that risks of several diseases may occur independently but in common in certain individuals. We believe that the confusion regarding the metabolic syndrome emerges from the difference between an epidemiologic concept and a pathophysiologic concept. Observed epidemiologically, it is difficult to discern causality because most data are cross-sectional. However, if it is possible to observe the emergence of a condition longitudinally, evidence for causality may emerge. Thus, we suggest the term *metabolic syndrome* be used to represent the causal relation among obesity, insulin resistance, and hyperinsulinemia. Specifically, for the purposes of this review, we define the metabolic syndrome as visceral and subcutaneous adiposity associated with hepatic insulin resistance, elevated FFAs, adipokines, and hyperinsulinemia. The resultant hyperinsulinemia may well represent a risk factor for cancer and cardiovascular disease (19, 20). But, this concept focuses on the pathophysiologic relations leading to the insulin-resistant, hyperinsulinemic state, while leaving open for further study the importance of hyperinsulinemia in disease pathogenesis.

WHY DOES OBESITY LEAD TO HYPERINSULINEMIA?

Insulin resistance results from storage of lipid, and it appears from cross-sectional studies that the visceral fat depot is particularly egregious in this regard. A few instances have been noted in which reduction in visceral fat per se in animal models has been shown to increase insulin sensitivity (21), but more evidence is needed. What is more obvious is that feeding a high-fat diet causes fat deposition in the visceral depot, and insulin resistance follows. In the canine model, even a modest increase in the fat content of the diet, without increasing calories, results in visceral fat deposition and insulin resistance (**Figure 1**). Insulin sensitivity was measured with glucose clamps, which showed that reduction in the sensitivity of the liver to insulin was the primary defect in the development of insulin resistance; insulin infused during clamps failed to depress glucose production, even though the effect of insulin on glucose disposal (primarily skeletal muscle) remained almost normal (13). The time course of changes indicates a rapid shift to an insulin-resistant state (1–2 wk). Interestingly, the plasma insulin response increases slowly, not peaking until 5–6 wk. Presumably, this represents an increase in either β-cell sensitivity to stimulation by nutrients or an increase in β-cell mass due to proliferation of β-cells or a reduction in β-cell apoptosis (14). Equally important was a reduction in clearance of insulin by the liver. In lean dogs, the liver extracts more than one-half of the insulin presented to it (22). Increased dietary fat reduced that extraction by 30%, presenting an increased fraction of secreted insulin into the systemic circulation (23). Taken together, increased secretion and reduced clearance result in hyperinsulinemia.

The combination of modestly increased dietary fat, hepatic insulin resistance, reduced first-pass clearance of insulin by the liver, and fasting hyperinsulinemia (despite normoglycemia) recapitulates the metabolic syndrome observed in overweight humans. In humans, it is known that a reduction in body fat by dietary restriction or exercise or by therapy (24, 25) will reduce insulin resistance and plasma insulin. Such approaches reduce the risk of diabetes (26, 27) and may well reduce the risk of cardiovascular disease and colon and breast cancers. Sensitizers such as thiazolidinediones have been used but have side effects (28) that may limit their long-term use. Better insulin sensitizers are needed. Possible candidates are compounds that reduce fat storage such as rimonabant (29, 30).

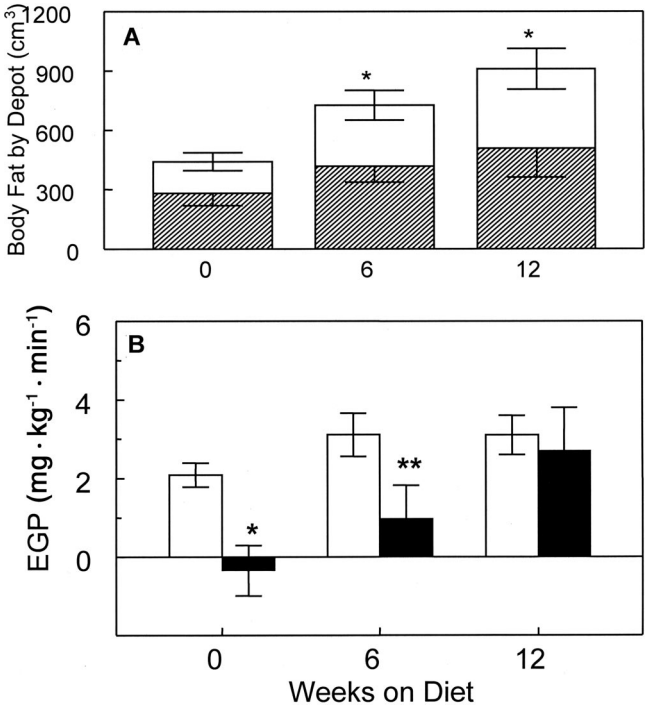

FIGURE 1. Development of adiposity and insulin resistance in an isocaloric, moderate-fat-fed dog model. (A) Mean (±SE) omental (hatched bars) and subcutaneous (white bars) fat calculated as cm^3 from the sum of 11 axial slices, the midpoint of which is shown in the figure. *Significantly different from week 0, $P < 0.05$ (ANOVA). (B) Mean (±SE) basal (white bars) and steady state (black bars) endogenous glucose production (EGP) rates as assessed during the clamp at weeks 0, 6, and 12. $^{*}P < 0.05$, $^{**}P < 0.005$ for the difference between basal and steady state (paired *t* test).

MECHANISM OF INSULIN RESISTANCE?

Belying its lethargic reputation, the adipose depot is now known to act as an active endocrine organ. It secretes a vast array of molecules, any of which may play important roles in the relation between obesity and insulin resistance. In fact, after 6 wk of feeding a high-fat diet in the canine model, we observed a marked increase in the size of adipose cells, as well as in the appearance of new cells, particularly in the visceral adipose depot. These changes could result in the appearance in the portal vein of molecules responsible for hepatic insulin resistance. Among the best candidates are the cytokines that can increase insulin resistance, including leptin, interleukin-6, tumor necrosis factor-α, or adiponectin, which is associated with reduced insulin resistance (31). An alternative candidate is fatty acid concentrations. Given the increase in stored triacylglycerols in adipocytes

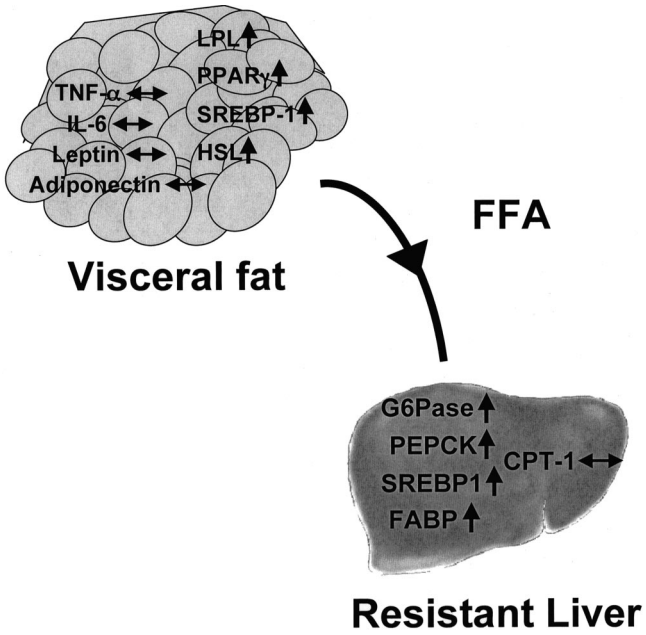

FIGURE 2. Changes in gene expression with the development of visceral adiposity in the fat-fed dog model. CPT-1, carnitine palmitoyltransferase-1; FABP, fatty acid binding protein; FFA, free fatty acids; G6Pase, glucose-6-phosphatase; HSL, hormone sensitive lipase; IL-6, interleukin-6; LPL, lipoprotein lipase; PEPCK, phosphoenolpyruvate carboxykinase; PPARγ, peroxisome proliferator-activated receptor-γ; SREBP-1, sterol regulatory element-binding transcription factor-1; TNF-α, tumor necrosis factor-α.

associated with obesity, it makes logical sense that the product of the degradation of triacylglycerols, FFAs, might be implicated in causing obesity-related insulin resistance. Administration of lipid causes an acute insulin-resistant state associated with increased plasma FFAs and also a compensatory hyperinsulinemia (32). However, increases in systemic FFA concentrations appear modest in obesity, which argues against an important role.

We have examined the possible roles of adipokines versus FFAs in the insulin resistance of the fat-fed canine model (33). To our surprise, we did not see increases in the enzyme expressions of several potential adipokines in visceral fat, despite the onset of insulin resistance in the fat-fed model. In contrast, we measured changes in expression of enzymes related to the visceral turnover of FFAs consistent with the release of FFAs into the portal vein in the insulin-resistant state (**Figure 2**). Also, we observed significant deposition of triacylglycerols in the liver, which suggests the transport of FFAs from the visceral depot to the liver. These data show that FFAs could be responsible for the hepatic insulin resistance observed with elevated fat intake in the dog model. However, data that fasting FFA concentrations change little during fat feeding (which were confirmed in our experiments) appear to discount the importance of FFAs. However, further studies have supported the role of FFAs in the development of insulin resistance.

SYMPATHETIC NERVOUS SYSTEM

The relation between obesity and hypertension led Landsberg et al (34) to propose that obesity activates the sympathetic nervous system. Experiments done in our laboratory, in which we measured directly the rate of release of FFAs from the omental adipose depot (by using arteriovenous differences), showed the pulsatile nature of such release (35). In fact, we observed a burst of lipolysis (coordinated net portal appearance of FFAs and glycerol) every 10–11 min in the fasting state. These pulses were almost totally suppressed by the high-affinity β-3 blocking agent bupranolol (36). Thus, it is apparent that the sympathetic nervous system is responsible for at least part of the visceral lipolysis in the fasting state. In recent studies, we observed that pulsatile octanoate is more potent than constant FFA administration in stimulating endogenous (hepatic) glucose production (37). Therefore, it is reasonable to suppose that the sympathetic nervous system plays a role in the pathogenesis of temporal increases in FFAs in blood, which in turn may render the liver resistant to insulin.

Several factors support a putative role for FFAs in the development of insulin resistance during the several months of fat feeding. The fat diet induces significant deposition of stored triacylglycerol in the visceral fat depot as well as in subcutaneous depots. In recent studies (M Kabir, unpublished observations, 2006), we discovered that the deposition patterns are not alike. Whereas subcutaneous deposition increases the volume of individual adipocytes, in the visceral depot, additional fat-laden cells are also recruited. These findings support the significance of the visceral depot. Also, direct evidence obtained in vivo, as well as study of omental and subcutaneous cells in vitro, confirms that cellular lipolysis of omental tissue is resistant to insulin, compared with subcutaneous cells (ie, insulin is less able to suppress lipolysis in visceral fat). Additionally, omental cells are more sensitive to stimulation by adrenergic agonists, which supports the concept that sympathetic stimulation would have a greater role in stimulating lipolysis in the visceral fat depot. These data support the idea that the sympathetic nervous system would increase FFA flux from the omental depot to the liver and that insulin would be comparatively impotent to reverse the lipolysis. But, these data do not necessarily implicate FFAs, because fasting concentrations of FFAs in the obese model are only modestly elevated. Is it possible that the effects of FFAs are maximized at other times of the day?

We recently examined concentrations of glucose and FFAs in healthy animals over 24 h (38). We compared lean animals with animals fed a hypercaloric, elevated-fat diet for 6 wk. As expected, the latter diet induced weight gain (about 10%) and doubling of fat deposition in both omental and subcutaneous depots. Also as expected, plasma insulin concentrations increased 50%. Much to our surprise, however, although there was a modest and insignificant trend for fasting concentrations of FFAs to increase, we observed a striking and highly significant enhancement of FFA concentrations in the middle of the night (**Figure 3**). FFA concentrations at 0300 approached 1000 μmol/L. Therefore, although little evidence exists that fasting FFA concentrations increase after feeding a high-fat diet, these data support the concept that there is a 60% increase in 24-h exposure of the tissues to FFAs, and that this increase takes place predominantly overnight. We do not yet know the role of the sympathetic nervous system in this nocturnal increase in FFAs, although we do have evidence for changes in the patterns of pulsatile FFA release at night. We also continue to examine the extent to which the omental fat depot is responsible for the observed increase in plasma FFAs. These data are consistent with the hypothesis that there is a massive increase in exposure of the liver to FFAs after fat feeding, and that most of this exposure occurs at night.

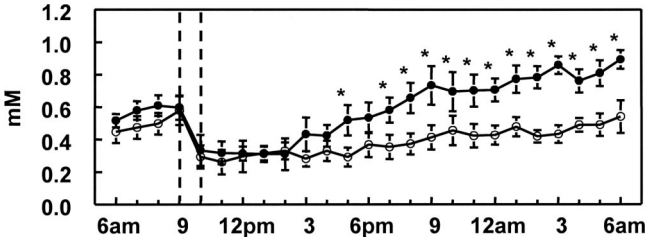

FIGURE 3. Increase in nocturnal free fatty acids from week 0 (white circles) and week 6 (black circles) of fat feeding as shown over a 24-h period. Dashed lines represent time of meal presentation and meal removal. Repeated measures analysis of variance with Bonferroni post-test was used to compare all time course data. Paired *t* tests (*$P < 0.05$ versus week 0) were used to determine significantly different time point pairs between week 0 and week 6. Reprinted from the *American Journal of Physiology, Endocrinology and Metabolism* (38). Used with permission.

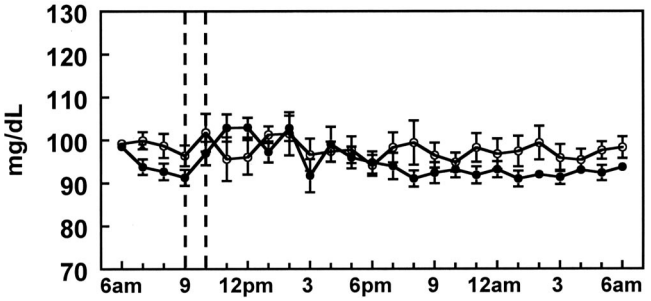

FIGURE 4. Plasma glucose concentrations during a 24-h observation period before (white circles) and after (black circles) fat feeding. Dashed lines represent time of meal presentation and meal removal. Reprinted from the *American Journal of Physiology, Endocrinology and Metabolism* (38). Used with permission.

FFAs may directly contribute to the development of some cancers. This relation was hypothesized on the basis of the observation that FFA concentrations are elevated in some cancer patients (39). It was also shown that specific FFAs may have immunosuppressive effects (40). More importantly, the long-chain monosaturated FFA oleate was shown to stimulate the proliferation of human breast cancer cells (41). These data together suggest that FFAs may support tumorigenesis by directly stimulating cell proliferation as well as by aiding the tumor cell in evading tumor suppression. Of course, the role of these increased nocturnal FFAs in the pathogenesis of cancers is entirely speculative at this point in time.

INSULIN CONCENTRATIONS

Hyperinsulinemia has been suggested as a factor in the observed relation between insulin resistance and cancer. It appears that hyperinsulinemia is secondary to the development of obesity-induced insulin resistance. The conventional view is that insulin resistance results in subtle glucose intolerance, and that the modestly increased glucose concentrations could stimulate increases in β-cell sensitivity, cause proliferation of β-cells, and suppress β-cell apoptosis. Yet, little evidence exists to support this role for glucose. Therefore, in our overnight sampling studies, we measured 24-h glucose concentrations under control and fat-fed conditions, as well as several additional candidates that could, in principle, contribute to increased insulin release. Also, it is now clear that reduction in first-pass insulin clearance by the liver can play a significant role in enhancing insulin concentrations after fat feeding (33, 42, 43). Therefore, we added measures of insulin clearance to our observations.

Our first surprise was the extreme constancy of fasting, postprandial, and nocturnal glucose values before and after the induction of obesity (**Figure 4**). Careful observation showed absolutely no increase in glucose measured at any time in the 24-h day. If glucose were the intervening signal, even after hyperinsulinemic compensation at 6 wk of fat feeding, a slight increase in glucose should remain that would maintain the hyperinsulinemia. By contrast, there is no evidence whatsoever for increased glucose; in fact, there was a tendency for glucose reduction with the high-fat diet (Figure 4). Therefore, we believe that glycemia can be ruled out as the cause of hyperinsulinemia during fat-induced insulin resistance in this model.

Additionally, the following factors did not increase significantly with fat feeding: glucagon-like peptide-1, cortisol, and growth hormone. The only blood-borne factor that was increased in significant amounts was nocturnal FFAs. Therefore, it is possible that the FFA increment after fat feeding is a double-edged sword, responsible for both the induction of insulin resistance and the increase in insulin concentrations. FFAs are potent stimuli for insulin secretion in several species, and Nolan et al (44) also suggested that FFAs are involved in insulinemic compensation in a rat model. Therefore, FFAs could play a synergistic double role in the relation between obesity and cancer: FFA could themselves have carcinogenic potential, and this potential could be exacerbated by hyperinsulinemia, which is also stimulated by elevated FFAs.

FINAL COMMENTS

Consensus exists that the trend for increasing adiposity, which began in the West, is spreading throughout the world (45). The reason or reasons for this spread are generally assumed to be increased dietary fat and reduced energy expenditure. Keith et al (46), however, recently commented that there are a plethora of additional potentially causative factors that have increased in parallel to the so-called obesity "epidemic." Regardless of the cause of obesity, the increase in obesity has been associated with several prevalent and important chronic diseases, including diabetes, cardiovascular disease, and several forms of cancer. Yet, the causal pathway linking obesity to these diseases remains ambiguous. From experimental work done in our and other laboratories, one central factor might be plasma FFAs. FFAs cause insulin resistance, and our recent data suggest that much of the damage may be done in the middle of the night, when FFA concentrations explode. Hyperinsulinemia has also been put forth as a possible egregious factor. Data that FFAs stimulate insulin release and reduce insulin degradation by the liver suggest that there may well be a synergistic and sinister relation between FFAs and insulin, both of which are increased in obese subjects, that may enhance carcinogenesis. At present, the FFA–insulin hypothesis is mere speculation, but more data are needed to examine the importance of this hypothesis and to reveal new possible points of entry to interrupt the carcinogenic pathway.

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