Obesity and the role of adipose tissue in inflammation and metabolism\textsuperscript{1–4}

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ABSTRACT
Recent discoveries, notably of the hormones leptin and adiponectin, have revised the notion that adipocytes are simply a storage depot for body energy. Instead, adipocytes are also endocrine organs, with multiple metabolic roles in regulating whole-body physiology. Small adipocytes in lean individuals promote metabolic homeostasis; the enlarged adipocytes of obese individuals recruit macrophages and promote inflammation and the release of a range of factors that predispose toward insulin resistance. Exercise activates the AMP-activated protein kinase (AMPK) in muscle and other tissues, a pathway that increases fat oxidation and glucose transport. Importantly, the adipocyte hormones leptin and adiponectin also activate AMPK; remarkably, the same pathway is activated by certain antidiabetic agents such as thiazolidinediones. Increasingly, our understanding of the adipocyte as an endocrine organ is leading to new insights into obesity and health. Am J Clin Nutr 2006; 83(suppl):461S–5S.

KEY WORDS
Leptin, adiponectin, thiazolidinediones, exercise, obesity, hypertension, stroke, hypercholesterolemia, hypertriglyceridemia, BMI, body mass index, adipose tissue

INTRODUCTION
Obesity is the epidemic of the 21st century. In developing countries, the prevalence of obesity continues to rise, and obesity is occurring at younger ages. The World Health Organization estimates that globally there are >1 billion overweight adults [body mass index (BMI; in kg/m\textsuperscript{2}) > 27], 300 million of whom are obese (BMI > 30) \textsuperscript{(1)}. In the United States in 2001, 20.9\% of adults were classified as obese \textsuperscript{(2)}. This poses a major public health issue: obesity and overweight increase the risk of several serious chronic diseases, such as type 2 diabetes, cardiovascular disease, hypertension and stroke, hypercholesterolemia, hypertriglyceridemia, arthritis, asthma, and certain forms of cancer \textsuperscript{(1, 2)}.

Until relatively recently, the role of fat itself in the development of obesity and its consequences was considered to be a passive one; adipocytes were considered to be little more than storage cells for fat. What we now know, however, is that adipocytes are a critical component of metabolic control and endocrine organs that have both good and bad effects. This remarkable understanding is allowing us to more clearly define the role of adipocytes play in health and in obesity and how inflammatory mediators act as signaling molecules in this process. Moreover, on a molecular level, we are beginning to comprehend how such variables as hormonal control, exercise, food intake, and genetic variation interact and result in a given phenotype.

We will discuss 4 major themes. First, adipocytes are critical for health as well as being repositories of free fatty acids (FFAs). Second, adipocytes release hormones that, in lean individuals at least, modulate body fat mass. Third, as a person gets heavier and the adipocytes enlarge, these control mechanisms become dysregulated, macrophages accumulate in the adipose tissue, and inflammation ensues. Finally, the regulators of FFA storage and oxidation in adipocytes and the periphery are critical regulators of metabolic homeostasis.

IMPORTANT OF ADIPOSE TISSUE FOR HEALTH
The importance of adipocytes for health was shown very elegantly through the use of the mouse model of lipoatrophic diabetes \textsuperscript{(3, 4)}. These mice were genetically altered so they had virtually no white fat tissue. They also had characteristics similar to those seen in humans with severe lipoatrophic diabetes: insulin resistance, hyperglycemia, hyperlipidemia, and fatty livers. Transplantation of adipose tissue from healthy mice into these lipoatrophic mice resulted in a dramatic reversal of the hyperglycemia, accompanied by lowered insulin concentrations and improved muscle insulin sensitivity, decreased serum triacylglycerols, decreased hepatic gluconeogenesis, and decreased amounts of fat deposited in muscle and liver. These beneficial effects were dependent on the presence of transplanted adipose tissue. In other words, the introduction of adipocytes into these mice completely reversed the characteristic phenotype. Thus, the absence of adipocytes is metabolically detrimental. These experiments provided an elegant platform for the argument that fat cells play a role in health \textsuperscript{(3)}.

FAT AS AN ENDOCRINE ORGAN
One of the insights that has changed our appreciation of the role of adipocytes so dramatically over recent years has been the

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discovery of their hormonal role in the regulation of metabolism, energy intake, and fat storage. Adipose tissue is currently known to secrete a large number of proteins termed adipokines that act in an autocrine, paracrine, or endocrine fashion to control various metabolic functions. Although >50 adipokines have been identified with diverse functional roles, adiponectin and leptin have been most closely studied.

Adiponectin

Adiponectin, a hormone also known as adipQ or adipocyte complement-related protein, is specifically and very highly expressed in adipose tissue. This hormone enhances insulin sensitivity in muscle and liver and increases FFA oxidation in several tissues, including muscle fibers (5–7). It also decreases serum FFA, glucose, and triacylglycerol concentrations: if normal, lean mice are given injections of adiponectin in conjunction with a meal high in fat and sugar, the normal postprandial increase in plasma glucose, FFA, and triacylglycerol concentrations are smaller as the result of an increased rate of clearance from the blood rather than a reduced rate of absorption from the gut (5). In contrast, if insulin-resistant mice are treated with physiologic concentrations of adiponectin, glucose tolerance is improved and insulin resistance is reduced (6).

In humans, plasma adiponectin concentrations fall with increasing obesity, and this effect is greater in men than in women (8). Reduced adiponectin concentrations correlate with insulin resistance and hyperinsulinemia (9, 10). In addition, several polymorphisms of the adiponectin gene (APM1, mapped to chromosome 3q27) have been identified that are associated with reduced plasma adiponectin concentration (11–13) and that increase the risk of type 2 diabetes, insulin resistance, or the metabolic syndrome (11, 12, 14).

Interestingly, adiponectin appears to be implicated in the development of atherosclerosis. Adiponectin concentrations are reduced in patients with coronary artery disease (9), and adiponectin inhibits tumor necrosis factor α (TNF-α)-induced expression of adhesion molecules and the transformation of macrophages to foam cells, both of which are key components of atherogenesis (15, 16). Finally, in mice deficient in apolipoprotein E (and thus susceptible to atherosclerosis), treatment with human adiponectin inhibits lesion formation in the aortic sinus by 30% compared with that in untreated control animals (P < 0.05) (17).

Leptin

Leptin, the first adipocyte hormone identified, influences food intake through a direct effect on the hypothalamus (18, 19). In humans and rodents, plasma leptin concentrations are highly correlated with BMI (20). Mice lacking the gene coding for leptin (ob/ob mice) are very obese and diabetic, and if ob/ob mice are treated with regular injections of leptin, they reduce their food intake, increase their metabolic rate, and lose weight (18, 21). Mice and rats with a genetic mutation affecting the leptin receptor in the hypothalamus exhibit a similar phenotype to ob/ob mice (19, 22).

However, as animals and humans become obese, the role of leptin in regulating body weight becomes more complex. There are certainly rare cases where mutations affecting the genes coding for either leptin or its receptor have been found in families with a high prevalence of morbid obesity (23–25), and leptin therapy does have a beneficial effect in children with congenital leptin deficiency (26, 27). However, in most obese individuals, leptin concentrations are already high because of the increased amount of leptin-secreting adipose tissue (28). It appears that with increasing leptin concentrations, the hormone induces target cells to become resistant to its actions. In mice that became obese after being fed a high-fat diet, leptin concentrations increased, and this increase was accompanied by an increased expression of SOCS-3 (suppressor-of-cytokine-signaling), a potent inhibitor of leptin signaling (29). Thus, the central effects of leptin are blocked by SOCS-3 produced as a result of the increasing concentrations of leptin found in obesity.

But what about the effects of leptin on peripheral metabolism? In a mouse model of congenital lipodystrophy (with little or no fat) and resulting insulin resistance, hyperinsulinemia, hyperglycemia, and enlarged fatty liver, leptin therapy reversed the insulin resistance and diabetes (4). Humans with a rare disorder called lipodystrophic diabetes have little or no fat mass, reduced serum adipokines such as leptin, and very elevated serum triacylglycerol concentrations. In fact, triacylglycerol concentrations tend to be in the thousands, so high that some individuals require regular plasmapheresis to reduce serum triacylglycerol. These elevated lipid concentrations lead to an enlarged fatty liver, which can lead to severe liver disease, and some individuals die secondary to liver complications. In a pioneering study, administration of exogenous leptin to individuals with lipodystrophic diabetes resulted in marked reductions in triacylglycerol concentrations, liver volume, and glycated hemoglobin and discontinuation of or a large reduction in antidiabetes therapy (30).

Clearly, both adiponectin and leptin are important hormones with both central and peripheral effects on metabolism and energy balance. Recent data suggest that at least some of their actions to reduce circulating fatty acids and triacylglycerol are due to increased fat oxidation. The increase in fat oxidation is mediated by activating the enzyme AMP-activated protein kinase (AMPK), which also increases glucose transport in muscle (31, 32). Interestingly, exercise activates AMPK, which also increases fat oxidation and reduces insulin resistance (33). Thus, the adipocyte hormones and exercise act via a similar signal transduction pathway to increase fat oxidation and promote insulin sensitivity.

EFFECT OF OBESITY ON ADIPOCYTES

As individuals become obese and their adipocytes enlarge, adipose tissue undergoes molecular and cellular alterations affecting systemic metabolism. First, fasting whole-body FFA and glycerol release from adipocytes is increased in obese women compared with lean women (34, 35), which probably promotes insulin resistance. Increased FFAs are well known to promote insulin resistance in tissues such as muscle (36). One underlying cause for the increased release of FFAs is secondary to alterations in perilipin expression. Perilipins are phosphoproteins found in adipocytes on the surface of triacylglycerol droplets that act as gatekeepers, preventing lipases from hydrolyzing triacylglycerol to facilitate the release of FFAs (37). Obese individuals have a deficiency of perilipins even if their fat cells are larger, hence their increased basal rate of lipolysis (38).

Second, several proinflammatory factors are produced in adipose tissue with increasing obesity. Compared with that of lean
individuals, adipose tissue in obese persons shows higher expression of proinflammatory proteins, including TNF-α, interleukin 6 (IL-6), monocyte chemotactic protein 1, inducible nitric oxide synthase, transforming growth factor β1, procoagulant proteins such as plasminogen activator inhibitor type 1, tissue factor, and factor VII (39–49). Macrophage numbers in adipose tissue also increase with obesity (50, 51), where they apparently function to scavenge moribund adipocytes, which increase dramatically with obesity (52). Macrophages are responsible for most of the cytokine production in obese adipose tissue (49–51). In fact, adipose tissue macrophages are responsible for almost all adipose tissue TNF-α expression and significant amounts of IL-6 and inducible nitric oxide synthase expression (50). Of particular note, Xu et al (51) reported that the increased expression of inflammation-specific genes by macrophages in the adipose tissue of obese mice preceded a dramatic increase in insulin production. Furthermore, when those mice were treated with rosiglitazone, an insulin-sensitizing drug, the expression of these genes declined. Thus, the chronological appearance of these inflammatory molecules before the development of insulin resistance, as well as their known ability to promote insulin resistance and other complications of obesity, strongly suggests adipose tissue inflammation as an important protagonist in the development of obesity-related complications.

Inflammation is thought to contribute to the development of the sequelae of obesity. Certain cytokines are thought to reduce adiponectin expression (53). As discussed above, adiponectin production is reduced with obesity. This is significant for the inflammatory response in that adiponectin is a potent inhibitor of TNF-α–induced monocyte adhesion and adhesion molecule expression (15). This may be an important link between obesity and the development of atherosclerosis.

Adipose tissue TNF-α concentrations are correlated with obesity and insulin resistance in patients with and without type 2 diabetes (54, 55). In obese women, TNF-α messenger RNA expression in adipose tissue is correlated with fasting plasma glucose, insulin, and triacylglycerol concentrations (39). TNF-α increases adipocyte lipolysis, and this appears to be mediated at least in part by its effects on perilipin (56, 57). Thus, TNF-α may increase systemic insulin resistance by promoting the release of fatty acids from adipose tissue into the bloodstream to act on tissues such as muscle and liver. Thus, adipose tissue TNF-α can act locally in adipose tissue, which ultimately promotes insulin resistance in peripheral tissues.

IL-6 expression is also increased in obese adipose tissue; IL-6 expression in adipose tissue from obese individuals is 10-fold that in adipose tissue from lean individuals if normalized for the number of adipocytes present (49). Also, IL-6 expression varies between adipose tissue sites: expression is higher in visceral than in peripheral adipocytes, and >90% of IL-6 expressed in adipose tissue is produced by cells other than adipocytes (49).

Plasma concentrations of IL-6 increase with obesity, unlike those of TNF-α, which acts in an autocrine and paracrine fashion (58); in obese individuals, adipose tissue is a major determinant of plasma IL-6 concentrations, contributing as much as 30% of total body production (58). IL-6 increases lipolysis and fat oxidation in humans (59), and plasma IL-6 concentrations correlate with insulin resistance (55). Recently, IL-6 was shown directly to cause insulin resistance in the liver (60). Elevated IL-6 concentration is a predictor for development of type 2 diabetes and for myocardial infarction (61, 62).

Some endocrinologists previously posited that obesity results from an increased endogenous production of the glucocorticoid hormone cortisol. It is well known that either endogenous overproduction of cortisol or exogenous administration of corticosteroids results in weight gain, with an increase in visceral fat deposition compared with peripheral fat (central obesity). Hypercortisolism, additionally, results in hyperphagia, central obesity, high concentrations of VLDL, insulin resistance, and predisposition to diabetes. Therefore, the obvious question is, do people who are obese have higher circulating concentrations of cortisol? The answer is no (63). However, it has been shown that concentrations and activity of 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) are elevated in adipose tissue of obese individuals (63); 11βHSD-1 converts inactive metabolites of cortisol back into cortisol. In an elegant experiment to determine the role of increased expression of 11βHSD-1 in adipocytes, a transgenic mouse model that specifically overexpressed this enzyme in adipocytes was generated and studied. These transgenic mice overexpressed 11βHSD-1 to about the same extent as is seen in obese humans, resulting in increased local adipose tissue concentrations but normal plasma concentrations of cortisol (64). Importantly, these mice developed increased visceral adiposity, insulin resistance and diabetes, increased cytokine expression, hyperphagia, hyperlipidemia, and hypertension (64). Thus, increased expression of 11βHSD-1 in mice resulted in deleterious body composition and metabolic abnormalities that mimic many of the complications observed in obese humans. Clearly, several inflammatory mediators are implicated in the development of obesity and the mechanisms responsible for the development of the chronic diseases associated with obesity.

**POTENTIAL FUTURE THERAPEUTIC OPTIONS**

How can we avoid or reverse the deleterious effects of obesity? We know about diet and exercise, and that both leptin and adiponectin act through at least one common pathway, ie, AMPK, as does exercise. What about pharmacotherapy?

The class of antidiabetic therapy called the thiazolidinediones (TZDs), for example, rosiglitazone mentioned above, activate peroxisome proliferator-activated receptor γ (PPAR-γ), a nuclear transcription factor that in turn activates many genes and that is highly expressed in adipose tissue (65). PPAR-γ, once activated, reduces plasma FFA and glucose concentrations and improves insulin sensitivity, with beneficial effects for persons with diabetes. In ob/ob mice, the TZDs inhibit leptin gene expression (66). TZDs have also been shown to decrease 11βHSD-1, increase adiponectin, decrease IL-6 and TNF-α, and increase perilipin concentrations (67). As we have discussed, all these effects are beneficial.

Remarkably, more recently, the TZDs, similar to exercise, leptin, and adiponectin, were shown to activate AMPK (68). Metformin also activates AMPK, although metformin does not increase adiponectin concentrations as the TZDs do (69). However, none of these drugs are cures for diabetes and certainly not obesity. Further therapeutic options are needed, including pharmacotherapy and nutrients and diets that promote fat oxidation, enhance insulin action, and act to regulate appetite. A combination of therapeutic agents may prove to be most efficacious.
CONCLUSION

In conclusion, it is now apparent that adipocytes are not simply a storage reservoir of fat but are active endocrine organs that play multiple roles in the body. Their metabolic role changes as they enlarge with increasing obesity. This increased understanding of the role of the adipocyte and its associated adipokines, such as leptin and adiponectin, is allowing us to dissect the all-too-prevalent metabolic syndrome and perhaps affect its course for the better. We are also beginning to understand the interplay of inflammation and obesity, although our knowledge remains incomplete. Finally, the intracellular mechanisms by which these factors affect energy intake, utilization, and metabolism are being better understood, and we are developing therapies that manipulate these pathways.

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