The Role of Adipose Tissue as an Endocrine Gland

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Until recently, adipose tissue was regarded as a passive depot for lipids, but increasing evidence points to an important role of adipocytes as a complex and active endocrine organ whose metabolic and secretory products (eg, hormones, prohormones, cytokines, and enzymes) play a major role in whole-body metabolism. Over the past decade, it became appreciated that the relationship between obesity and both insulin resistance and endothelial dysfunction (the early stage of atherosclerosis) is mediated through the release of several hormones from adipose tissue [1]. Collectively these hormones are called adipocytokines or adipokines.

Adipokines are a group of pharmacologically active low and medium molecular weight proteins that possess autocrine and paracrine effects and are known products of the inflammatory and immune systems. They also play an important role in the adipose tissue physiology and in initiating several metabolic and cardiovascular abnormalities, not only in overweight and obese individuals but also in several lean persons with higher visceral fat mass. These cytokines include adiponectin, leptin, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), resistin, plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, and monocyte chemoattractant protein. An increased amount of adipose tissue or its disproportionate distribution between central and peripheral body regions is related to altered serum levels of these cytokines. Except for leptin and adiponectin, other cytokines are produced not only from fat cells but are also produced from adipose-tissue resident macrophages, found in the stromal tissues surrounding fat cells. For unknown reasons, the increase in the amount of body fat is associated with an increase in the amount of adipose-tissue resident macrophages and their cytokine production.

Human adiponectin contains 244 amino acid residues and is relatively abundant in plasma, where it accounts for 0.01% of total plasma proteins. Two adiponectin receptors (AdipoR1, AdipoR2) have been cloned. AdipoR1 is abundantly expressed in skeletal muscle, whereas AdipoR2 is predominantly expressed in the liver. They serve as receptors for globular and full-length adiponectin and mediate increased adenosine monophosphate (AMP) kinase, peroxisome proliferator-activated receptor (PPAR)-α ligand activity, fatty acid oxidation, and glucose uptake [2]. Adiponectin concentration is generally higher among women versus men [3]. Low fasting adiponectin concentration is associated with low insulin-stimulated skeletal muscle insulin receptor tyrosine phosphorylation. Although adiponectin gene expression in adipose tissue is associated with obesity, insulin resistance, and type 2 diabetes, hypoadiponectinemia is more strongly related to the degree of insulin resistance than to the degree of adiposity or glucose intolerance [4]. Genetic polymorphisms may be involved in the regulation of adiponectin, taking into account the existing linkage in the region of the adiponectin gene with type 2 diabetes [5].

Several human studies showed that increased adiponectin levels protect against later development of type 2 diabetes and point to the possible future use of adiponectin as an indicator of diabetes risk. Low plasma concentrations of adiponectin are also found in patients with coronary artery disease (CAD). Interestingly, diabetic patients with CAD had lower adiponectin levels than diabetic patients without CAD. In obese people, a weight reduction of 10% leads to significant increase in adiponectin level (40% to 60%) in both diabetic and nondiabetic patients. In a recent study by our group, we also found that a 7% reduction in body weight, by combined caloric reduction and increased physical activity over a 6-month period, resulted in significant increase in plasma adiponectin level in obese patients with type 2 diabetes and insulin resistance [6]. In differentiated 3T3-L1 adipocytes, the mRNA of adiponectin is also increased by administration of the synthetic PPAR-γ agonist. It has also been reported that adiponectin mRNA expression is normalized or even increased by thiazolidinediones in the adipose tissue of obese mice [7]. Thiazolidinedione administration for 3 months resulted in increased adiponectin levels in both lean, obese nondiabetic, and obese diabetic subjects. The increase in adiponectin induced by thiazolidinediones was not affected by coadministration of glyburide or metformin [8].

Adiponectin is also involved in the modulation of inflammatory responses, where it attenuates TNF-a–medi-

ated inflammatory response [9] probably through the activation of cyclic AMP protein kinase A. It has also been shown that adiponectin inhibits some functions of mature macrophage, such as phagocytosis and cytokine production [10]. Adiponectin also modulates endothelial function and has an inhibitory effect on proliferation of vascular smooth muscles induced by growth factors. The recent finding that adiponectin deficiency aggravates neointimal thickening, and that supplementation with adiponectin decreases neointimal thickening in mechanically injured arteries, suggests that increasing plasma adiponectin may be useful in preventing restenosis after vascular intervention [11].

Leptin is a 16-kDa adipocyte-derived hormone that circulates in the serum in the free and bound form. The ob mRNA encodes a 167 amino acid protein. Leptin exerts its effect on energy balance mainly by acting in the brain. Leptin acts either directly or though activating specific centers in the hypothalamus to decrease food intake, increase energy expenditure, influence glucose and fat metabolism, and alter neuroendocrine function.

Leptin serum levels increase exponentially with increased fat mass. It was found that the mean serum leptin concentrations are 7.5 ng/mL in normal weight subjects and 31.3 ng/mL in obese subjects, indicating that obese individuals may be resistant to endogenous leptin production. Leptin mRNA is expressed predominantly by subcutaneous rather than visceral fat cells. This suggests a role for leptin in modulating adipose tissue mass and distribution. After adjustment of body mass index, women also seem to have higher leptin levels than men. This could be either related to the increased percentage of peripheral body fat in women, or a result of stimulation of leptin production by estrogen/progesterone and/or by androgens. It was found that fat mass and gender are the main independent predictors of leptin concentration in patients with type 2 diabetes [12], and that insulin secretion and the degree of insulin resistance contribute significantly to leptin levels.

Leptin therapy in lipodystrophic patients was shown to improve glycemic control, improve insulin-stimulated hepatic and peripheral glucose metabolism, and to reduce hepatic and muscle triglyceride content, suggesting that leptin acts as a signal that contributes to regulation of total body sensitivity to insulin [13]. It was also found that leptin was independently associated with cardiovascular mortality. In obese patients, administration of thiazolidinediones for 12 weeks resulted in a significant increase in insulin sensitivity but had no effect on plasma leptin concentrations.

Although both adiponectin and leptin are integrally related to the insulin resistance syndrome, adiponectin was more strongly related to visceral abdominal fat, whereas leptin was more closely related to subcutaneous fat content [14]. Many aspects of that association are still unclear. The coming years may shed light on the relationships between them and offer the prospect of their use in treatments of overweight and obese subjects with insulin resistance or the metabolic syndrome.

Adipose tissue is also a major source of TNF-α, a cytokine that is known to possess a wide range of proinflammatory activities. It acts as a higher-order cytokine that influence synthesis, secretion, and activity of other cytokines. It was observed that obesity in animals and humans is associated with increased production of TNF-α and its receptors from adipocytes and that gene expression and protein production of TNF-α do not appear to be different in subcutaneous or visceral fat. In contrast, only 30% of total circulating IL-6 originates from adipose tissue in humans and that visceral adipose tissue produces two to three times more IL-6 compared with the subcutaneous adipose tissue. In addition, circulating IL-6 concentrations correlate better with adiposity in comparison to circulating levels of TNF-α.

Levels of these proinflammatory cytokines were shown to be correlated with all measures of obesity and were strongly related to insulin resistance. Several studies had demonstrated a possible link between TNF-α and cardiovascular disease. Plasma levels of TNF-α were shown to be increased in individuals with premature cardiovascular disease independent of insulin sensitivity. Conversely, circulating levels of TNF-α decrease after weight reduction in parallel with the improvement in endothelial function [15].

Resistin is a unique adipocyte-derived signaling cysteine-rich molecule that was first identified in obese mice. In mice, resistin is expressed predominantly in white adipose tissue and is detectable in serum, suggesting that it may act at distant sites similar to other adipokines. Several observations showed increased resistin serum level in genetic and diet-induced obese mice. The observation that reduction in resistin levels in ob/ob and Zucker diabetic obese mice treated with PPAR-γ agonists was associated with improved insulin sensitivity raised the assumption of a possible link between resistin and insulin resistance. Subsequent data failed to confirm this association.

PAI-1 is another important bioactive substance produced by adipose tissue. Although PAI-1 mRNA was detected in both subcutaneous and visceral fat, it correlates better with visceral adiposity. In humans, it has been shown that improvement in insulin sensitivity by either weight reduction or medications lowers circulating levels of PAI-1. The decrease in PAI-1 serum level with weight reduction was found to correlate with the amount of weight loss and the decline in serum triglycerides.

Many recent studies showed significant variation in the gene expression of different cytokines between visceral and subcutaneous fat and point to the difference in the endocrine function between them. Removal of a significant amount of subcutaneous fat by liposuction in obese individuals with and without diabetes resulted in a reduction in serum leptin and did not change the serum levels of other cytokines. It also did not improve insulin sensitivity

or decrease the high serum insulin level that was observed initially in those individuals. In animal models, removal of subcutaneous fat resulted in an increase in mesenteric fat volume and increased production of TNF-α by visceral fat. Although surgical removal of visceral fat has not been attempted in humans, two studies in rodent models of aging showed that removal of visceral fat improved glucose tolerance and insulin sensitivity, and reduced adipokine production. These interesting observations point to the possible need for a new definition of obesity based on the location of fat rather than on its volume, especially when the endocrine function and the metabolic risk are considered. The reference to increased volume of visceral fat as "metabolic obesity" may better identify more subjects at risk for cardiovascular disease than does the current definition of obesity.

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