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Minireview: Adiposity, Inflammation, and Atherogenesis

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Adipose tissue is a dynamic endocrine organ that secretes a number of factors that are increasingly recognized to contribute to systemic and vascular inflammation. Several of these factors, collectively referred to as adipokines, have now been shown regulate, directly or indirectly, a number of the processes that contribute to the development of atherosclerosis, including hypertension, endothelial dysfunction, insulin resistance, and vascular remodeling. Several adipokines are preferentially expressed in visceral adipose tissue, and the secretion of proinflammatory adipokines is elevated with increasing adiposity. Not surprisingly, approaches that reduce adipose tissue depots, including surgical fat removal, exercise, and reduced caloric intake, improve proinflammatory adipokine levels and reduce the severity of their resultant pathologies. Systemic adipokine levels can also be favorably altered by treatment with several of the existing drug classes used to treat insulin resistance, hypertension, and hypercholesterolemia. Greater understanding of adipokine regulation, however, should result in the design of improved treatment strategies to control disease states associated with increase adiposity, an important outcome in view of the growing worldwide epidemic of obesity. (*Endocrinology* 144: 2195–2200, 2003)

Adipose Is a Proinflammatory Tissue

INCREASING EVIDENCE INDICATES that adipose tissue is an important source of cytokines (1) and that adiposity contributes to a proinflammatory milieu (2). Fat is both a dynamic endocrine organ, as well a highly active metabolic tissue. Fat produces and secretes inflammatory factors, which are well known to play important roles in the atherosclerotic process (Fig. 1). Collectively, these factors are called adipocytokines or adipokines. These include TNFα, leptin, plasminogen activator inhibitor-1 (PAI-1), IL-6, resistin, and angiotensinogen (1). Serum adipokine levels are elevated in humans and animals with excess adiposity (2–5), and visceral fat appears to produce several of these adipokines more actively than sc adipose tissue (6–9). Reduction in fat mass correlates with decrease in the serum levels of many of these adipokines (10–14), implying that approaches designed to promote fat loss should be useful in attenuating the proinflammatory milieu associated with obesity. Some of these adipokines, in addition to their proinflammatory actions, also affect insulin action. For example, TNFα inhibits tyrosine kinase phosphorylation of the insulin receptor, resulting in defects in insulin signaling and ultimately leading to insulin resistance and impaired glucose transport (15). Leptin has recently been shown to enhance cellular immune responses (16), as well as to increase blood pressure (17, 18). Leptin also tends to decrease insulin sensitivity when given to obese rats (19), although it markedly improves insulin sensitivity in patients with lipodystrophy, who tend to have low circulating levels of leptin (20). Resistin administration also markedly decreases insulin-mediated glucose uptake (21). Adiponectin (Acrp30), a recently described adipokine of emerging importance, is distinct from other known adipokines in that it alone among them appears to improve insulin sensitivity and inhibits vascular inflammation (22–24). Serum adiponectin levels are low in obese subjects but increase upon weight loss (25, 26).

Undoubtedly, other adipokines produced by fat are yet to be discovered. A potentially important therapeutic strategy for the treatment of obesity and the metabolic syndrome will be to alter the ratio of proinflammatory, insulin-desensitizing adipokines to antiinflammatory, insulin-sensitizing adipokines, to both attenuate the inflammatory milieu and improve the metabolic state.

The Monocyte and Inflammation Are Integral Components of the Atherosclerotic Process

Monocyte migration is integral to the development of atherosclerosis. Early in the process of atherosclerosis, circulating monocytes adhere to the endothelial layer of the vessel wall, migrate into the vascular interstitium, and phagocytize oxidized low-density lipoprotein cholesterol (LDLC; Ref. 27). This process results in the formation of lipid-laden foam cells, which accumulate within the arterial wall to form fatty streaks. Ultimately, these early lesions evolve into advanced atherosclerotic plaques that contain necrotic lipid cores surrounded by proteoglycan matrix and covered by a fibrous cap and thickened intima. This structure defines an organized atherosclerotic plaque.

A number of approaches have been used to cripple macrophage activity in genetically prone mouse models of atherosclerosis, all of which attenuated the atherosclerotic process. These include mouse models deficient for expression of 1) macrophage chemoattractive protein-1 (MCP-1; Ref. 28), which stimulates macrophage movement into the vessel wall; 2) chemokine receptor-2 (29), a macrophage receptor

Abbreviations: AngII, Angiotensin II; ARBs, AngII AT1 receptor blockers; CAD, coronary artery disease; CRP, C-reactive protein; hsCRP, CRP measured by a highly sensitive assay; LDLC, low-density lipoprotein cholesterol; MCP-1, macrophage chemoattractive protein-1; M-CSF, macrophage colony stimulating factor; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; PPARγ, peroxisome proliferator activated receptor γ; VSMC, vascular smooth muscle cells.

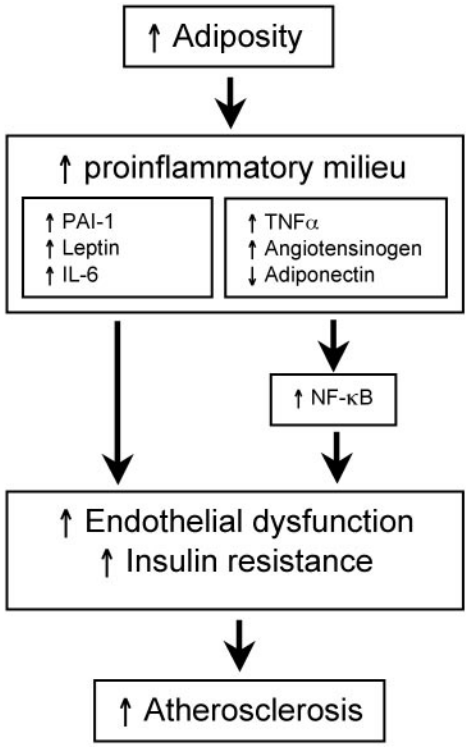

FIG. 1. Many of the adipokines whose expressions are altered during obesity promote inflammation and can promote insulin resistance, endothelial dysfunction, and, ultimately, atherosclerosis.

that binds MCP-1; 3) macrophage colony stimulating factor (M-CSF; Ref. 30), which enhances conversion of monocytes to macrophages; 4) macrophage osteopontin, which may prevent macrophage apoptosis, similar to its effects on endothelial cell survival (31). These observations underscore the prominent role of the macrophage in the pathogenesis of atherosclerosis.

Adipokines enhance the attachment and migration of monocytes into the vessel wall and their conversion into macrophages. In particular, TNFα activates the transcription factor nuclear factor-$\kappa\beta$, which orchestrates a series of inflammatory changes in vascular tissue, including expression of adhesion molecules on the surface of the endothelial cells and vascular smooth muscle cells (VSMC). This includes elevated expression of intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 (32–35), which enhance monocyte adhesion to the vessel wall (36–40); endothelial cells and VSMC production of MCP-1 and M-CSF (32, 41–43); and activation of a proinflammatory macrophage state resulting in increased macrophage expression of inducible nitric oxide (NO) synthase, interleukins, superoxide dismutase, *etc.* (44–47). T lymphocytes are also activated and enhance macrophage atherosclerotic activity (48). Leptin is also reported to stimulate cholesterol accumulation by the macrophage, particularly in the presence of high glucose (49). The cytokine, IL-6, also has proinflammatory activity by itself and through increasing the levels of IL-1 and TNFα; all of these have been implicated in atherogenesis (CRP; Ref. 50). Importantly, IL-6 stimulates liver production of CRP (51). Serum CRP measured by a highly sensitive assay (hsCRP) has become an important marker of vascular inflammation and predictor of atherosclerosis (52–56). Recent data suggest that hsCRP is as important a predictor of atherosclerosis as circulating LDLC (57). Thus, inflammation may be potentially as important as cholesterol in contributing to atherosclerosis. High levels of hsCRP in obesity also predict later development of diabetes (58).

Angiotensinogen is a precursor to a major vasconstrictive, proatherogenic peptide, angiotensin II (AngII). This product of the renin-angiotensin system enhances multiple steps leading to foam cell formation. AngII directly stimulates intracellular adhesion molecule-1, vascular cell adhesion molecule-1, MCP-1, and M-CSF expression in the cells of the vessel wall (59). When infused into animal models, an early increase in arterial macrophage accumulation occurs in the vessel wall (60). In addition, another important affect of AngII is to enhance the metabolism of NO into oxygen free radicals, which damage the vascular tissue. AngII accomplishes this effect by stimulating nicotinamide adenine dinucleotide phosphate (reduced) oxidase, resulting in decreased bioavailability of NO (61). Importantly, NO is not only a vasodilator, but protects the vessel wall from macrophage adhesion and accumulation (62), decreases VSMC growth (63), and decreases platelet adherence to the endothelium (64). An imbalance between AngII and NO leads to endothelial dysfunction with not only a loss of vasodilator capacity, but also increased monocytes/macrophage platelet activity in the vessel wall.

PAI-1 has two important actions in the vessel wall. First, it inhibits the breakdown of fibrin clots and, therefore, plays a key role in promoting thrombus formation upon rupture of unstable atherosclerotic plaques (65). In addition, elevated PAI-1 activity, by altering the fibrinolytic balance, also contributes to remodeling of the vascular architecture (66–69). In human population studies, circulating PAI-1 levels correlate with atherosclerotic events and mortality, and some studies suggest that PAI-1 may be an independent risk factor for coronary artery disease (CAD; Ref. 70–72). Hyperglycemia (73, 74), AngII (75, 76), and very LDLC (77), in addition to obesity (78), contribute to elevated serum PAI-1 levels. All of these factors increase PAI-1 gene expression (79–83). High levels of PAI-1 in patients with diabetes are a major contributor to the prothrombotic state in diabetes, which leads to enhanced atherosclerotic mortality (84). Use of aspirin to attenuate this prothrombotic state is associated with attenuation of CAD (85).

Diabetes is an atherosclerotic risk equivalent. Both are the end result of two important parallel pathways (Fig. 2): 1) the progression of insulin resistance to the metabolic syndrome, prediabetes, and, ultimately, diabetes and 2) the progression of endothelial dysfunction with progressive inflammation, thrombosis, and oxidation at the vessel wall to fatty streak formation and, ultimately, to development of advanced atherosclerotic plaques. Indeed, in the prediabetic state (impaired glucose tolerance), there is a 2-fold increased atherosclerosis risk, and, in frank diabetes, the risk is increased 3- to 4-fold (86). The metabolic syndrome, itself, is also associated with increased CAD risk (87). Early in the insulin resistant, hyperinsulinemic state, there is also evidence of brachial artery endothelial dysfunction, as well as abnormal

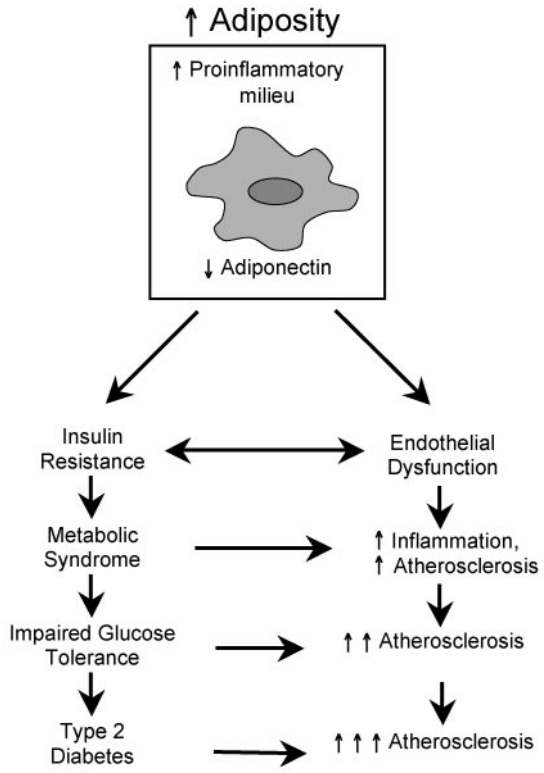

FIG. 2. Obesity promotes the parallel progression of insulin resistance to type 2 diabetes and endothelial dysfunction to atherosclerosis.

coronary artery vasomotion, which appears to result from the endothelial dysfunction (88). Thus, insulin resistance, itself, appears to be an endothelial dysfunction risk equivalent. The pathways are clearly interdigitated and sparked in obesity, in large part by excess adipokine production.

Is Decreasing Adipokine Production Useful?

Reducing adipocyte mass is associated with a reduction in proinflammatory, insulin-desensitizing adipokines and a rise in circulating adiponectin. Exercise and weight loss improve endothelial function and prevent diabetes (89–91). Thus, there is a strong association between changes in adipokines, endothelial function, and prevention of diabetes through lifestyle modifications.

Treatment with insulin-sensitizing ligands that activate the nuclear receptor, peroxisome proliferator activated receptor γ (PPARγ), is reported to decrease serum hsCRP (92), leptin (5), PAI-1 (93), and TNFα (94) levels and to increase circulating adiponectin (95, 96). These agents also improve endothelial function (97–99). The TRIPOD study suggested that an early PPARγ ligand, troglitazone, prevented type 2 diabetes in a high-risk cohort (100). The PPARγ ligands currently in clinical use, rosiglitazone and pioglitazone, are being tested in clinical trials for their ability to prevent diabetes and decrease CAD events. In mice that are genetically prone to develop atherosclerosis, PPARγ ligands consistently attenuate vascular lesions (101, 102).

Statins decrease hsCRP by 30–40%, which is not correlated with their cholesterol-lowering capability (103); they consistently improve endothelial function, decrease cardiovascular events and mortality, and in the West of Scotland study decreased new onset type 2 diabetes (104, 105). Statins are reported to have additive and possibly synergistic effects with PPARγ ligands on vascular inflammation (106). Statins have also been reported to decrease plasma TNFα (107) and may also lower plasma PAI-1 (108).

Angiotensin converting enzyme inhibitors and AngII AT1 receptor blockers (ARBs) lower hsCRP, although inconsistently, and angiotensin converting enzyme inhibitors are reportedly better at lowering serum PAI-1 than ARBs, although ARBs have been reported to have this effect (109–112). Both classes of agents improve endothelial function and reduce atherosclerosis-associated events. In the HOPE trial, Ramipril administration was associated with 32% less new-onset diabetes than placebo (113), and, in the LIFE trial, Losartan administration was associated with less new-onset diabetes than its comparator, Atenolol (114, 115). These agents tend to decrease circulating TNFα, but their effects on leptin and adiponectin are unknown (116–118). AngII is reported to increase leptin secretion from cultured adipocytes through a prostaglandin-independent mechanism but has no effect on adiponectin expression in these cells.

Clearly, much more investigation is needed, but insight into mechanisms by which the adipocyte communicates with both insulin target tissues and the vasculature allows us to better understand the relationships between obesity and cardiovascular disease. Furthermore, study of the regulation of these mechanisms will help us to develop treatment strategies to prevent diabetes and heart disease in the growing epidemic of obesity.

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