This Review is part of a thematic series on Adipocyte Signaling in the Cardiovascular System, which includes the following articles:

Adipose Tissue, Inflammation, and Cardiovascular Disease

Diabetic Cardiomyopathy
Adipocyte Signaling and Lipid Homeostasis
Adipocyte Signaling and the Vasculature
PPARγ Activation and Effects on the Vasculature

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Adipose Tissue, Inflammation, and Cardiovascular Disease
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Abstract—Mounting evidence highlights the role of adipose tissue in the development of a systemic inflammatory state that contributes to obesity-associated vasculopathy and cardiovascular risk. Circulating mediators of inflammation participate in the mechanisms of vascular insult and atheromatous change, and many of these inflammatory proteins are secreted directly from adipocytes and adipose tissue–derived macrophages. Several factors linking obesity with an increased cardiovascular risk have been identified. The adipocyte-specific secretory protein adiponectin is a particularly promising candidate in this context. Its levels are decreased in obesity. Adiponectin may mediate some of its demonstrated cardioprotective effects through its anti-inflammatory properties. In addition to decreased expression of beneficial adipokines, secretion of a host of inflammatory factors from visceral adipose tissue may contribute to the increased cardiovascular risk associated with obesity. The cardioprotective effects of many of the most popular drug regimens corroborate these conclusions, demonstrating that along with improvements in other therapeutic end points, they mediate improvements in systemic inflammation. In some cases, these improvements are attributable to direct suppression of inflammatory signaling in adipocytes. The targeted suppression of various proinflammatory cascades in adipocytes specifically represents an exciting new therapeutic opportunity for the cardiovascular disease area. (Circ Res. 2005;96:939-949.)

Key Words: adipocyte ■ secretion ■ inflammation

The Greek physician Hippocrates observed that “Sudden death is more common in those who are naturally fat than in the lean,” in 400 BC. For many centuries, this astute observation went completely unexplained. Hypercholesterolemia was, for many years, the predominating pathogenic theory of atherosclerosis. Although some aspects of this model still hold, we now know that the connections between obesity, fatty arteries, and a vulnerable heart are far more complicated and that inflammation plays a major part in disease progression. Cardiovascular disease (CVD) is associated with elevated markers of systemic inflammation, including C-reactive protein (CRP) and members of the coagulation cascades.1 Elevated levels of these proteins were also associated with infarction risk factors, such as obesity, diabetes mellitus, and angina pectoris.2 Despite these intriguing associations, the increase in systemic inflammation was generally thought to be a result of local atheromatous inflammation. The pathogenic significance of systemic inflammation was mostly eclipsed by the vigorous advances in lipid research. Subsequent studies have demonstrated the importance of systemic inflammation and demonstrated that this systemic inflammation is not merely a reactive sequelae of atherogen-
esis but is instead an important contributor. Obese hypertrophic adipocytes and stromal cells within adipose tissue directly augment systemic inflammation. This increase in systemic inflammation mediates multiple pathogenic mechanisms in the well-known but poorly understood associations between obesity, cardiovascular pathology, and the comorbidities such as dyslipidemia, type 2 diabetes mellitus, hypertension, and the metabolic syndrome. Here we review the evidence that adipose tissue is indeed an organ with properties that make it a significant contributor to systemic inflammation. We also review the studies linking obesity to subclinical inflammation, mention the studies showing that this increase in inflammation translates into accelerated atherogenesis, and illustrate these mechanisms by dissecting specific secreted inflammatory factors implicated in mediating these connections. Finally, we briefly discuss clinical implications of these recent discoveries for our treatment of obesity- and inflammation-associated diseases.

Adipose Tissue Is a Mediator of Inflammation and Innate Immunity

A total of 99% of the world’s metazoan species rely solely on innate immunity to defend themselves from infection. For insects, an organ called the fat body mostly mediates this response. The fat body has a receptor for bacterial and fungal cell wall constituents called the Toll receptor. This receptor activates the nuclear factor κB (NF-κB) signaling cascade and induces the secretion of antibacterial peptides and other defense mechanisms. The insect fat body simultaneously manages the animal’s liver functions and the storage of lipids. At some point during evolution, vertebrates split these metabolic duties between the liver and adipose tissue. But what happened to the functions of innate immunity? Since the discovery of innate immunity and the acute phase response in humans, it has been thought that these functions were primarily the domain of the liver, but more recent evidence shows that when fat storage was delegated to adipose tissue, the ability to fulfill some aspects of innate immunity was preserved in adipose tissue as well.

In addition to adipocytes, adipose tissue contains fibroblasts, preadipocytes, tissue resident macrophages, and vascular constituents. Macrophages are known to be crucial contributors to inflammation but more recently, it has been recognized that adipocytes demonstrate significant intrinsic inflammatory properties as well. Like macrophages, the adipocyte is exquisitely sensitive to infectious disease agents and cytokine-mediated inflammatory signals; it expresses a host of receptors, enabling it to sense the presence of pathogens and inflammation, and on stimulation of these receptors, it activates multiple inflammatory signal transduction cascades, and induces and secretes a number of potent inflammatory cytokines and acute phase reactants. Adipocytes are sensitive to the effects of tumor necrosis factor-α (TNF-α), which, through its p55 and p75 TNF receptors, stimulates NF-κB, extracellular signal-regulated kinase, and P38 mitogen-activated protein kinases PI-3 kinase and jun-N-terminal kinase cascades. The mammalian toll-like lipopolysaccharide (LPS) receptor TLR4 is expressed in tissue and in vitro cultured adipocytes. When stimulated with endotoxin, these receptors activate p65/p50 and p68/p52 NF-κB signal transduction pathways. In turn, these pathways induce the expression of inflammatory mediators such as interleukin-6 (IL-6), TNF-α, and serum amyloid A3 (SAA3). At the same time, endotoxin further sensitizes the adipocyte to infectious pathogens, inducing expression of the toll-like receptor for fungal wall components (TLR2). It has been demonstrated that adipocytes are responsive to IL-1β, IL-4, IL-6, IL-11, interferon-γ (IFN-γ), and fungal cell wall components, with a downstream activation of inflammatory signaling cascades. These inflammatory signaling pathways are differentially regulated during adipogenesis; adipocyte differentiation entails a dramatic induction of expression of NF-κB subunits p65, p68, p52, and the inhibitor of NF-κB (IκB), as well as changes in NF-κB constitutive nuclear localization/promoter binding, constitutive IL-6 secretion, and modulation of LPS responsiveness. The induction of p52 and p68, their constitutive nuclear localization and increased activity, and a decrease in LPS-inducible p65/p50 activity after differentiation is reminiscent of activated dendritic cells, suggesting a similar immunomodulatory switch and inflammatory function for these 2 cell types.

In response to infectious and inflammatory signals, adipocytes have been shown to induce expression and secretion of several acute phase reactants and mediators of inflammation, including TNF-α, plasminogen activator inhibitor-1 (PAI-1), IL-1β, IL-6, IL-8, IL-10, and IL-15, leukemia inhibitory factor, hepatocyte growth factor, SAA3, macrophage migration inhibitory factor, haptoglobin, complement factors B, D, C3, prostaglandin E2, and potential inflammatory modulators such as leptin, adiponectin, and resistin. Although many of these activities are restricted to autocrine and paracrine effects, some of these cytokines secreted from adipocytes and adipose-resident macrophages make significant contributions to systemic inflammation.

Obesity Is Associated With Increased Local Adipose Inflammation

Discovery of the contribution of adipose tissue toward inflammation during acute infections prompted the question as to whether this physiological response to infection may also be dysregulated in obesity. In 1993, it was discovered that TNF-α expression was upregulated in adipose tissue of obese mice. The induction of inflammatory mRNA transcripts in adipose tissue can originate in either adipocytes or their surrounding resident macrophages, and adipocytes and resident macrophages not only contribute independently to the local adipose inflammatory output, they each synergistically stimulate inflammatory activity of the other. Heterotypic signaling experiments using cultured adipocyte conditioned media have demonstrated that the inflammatory signals secreted by unstimulated adipocytes induce a dramatic increase of IL-6 and TNF-α secretion by otherwise unstimulated cultured macrophages in vitro. This autocrine and paracrine signaling becomes particularly pronounced in obese states. Although adipose is usually populated with only 5% to 10% macrophages, diet-induced weight gain causes a significant macrophage infiltration, with macrophages constituting up to 60% of all cells found in adipose tissue.
relationship between the adipocyte and the macrophage is also reflected in the transcriptional program of obese adipose tissue cells. In mice fed a high-fat diet, weight gain is associated with induction of many adipose tissue inflammatory pathways: as many as 59% of the total adipose tissue mRNA transcripts induced during diet-induced weight gain are inflammation-related genes. In addition to induced mRNA levels, protein secretion of IL-6, TNF-α, PAI-1, angiotensinogen, complement factor C3, tissue factor, and other inflammatory cytokines is elevated in adipose explants from obese patients.

Adipose tissue is not usually thought of as an immune or inflammatory organ. However, the discovery of elevated secretion of these factors from obese adipose tissue provided the first evidence of a direct connection between obesity and systemic inflammation.

**Obesity Is Associated With Increased Systemic Inflammation**

A growing body of evidence demonstrates that increased adipose tissue mass contributes directly toward an increase in systemic inflammation. The earliest indications of this phenomenon were reported in 1985, when an article noted positive correlations between body mass and peripheral leukocyte counts. Since then, a large number of studies have found that increased body mass index (BMI) correlates with increases in systemic circulating levels of inflammatory proteins such as CRP, IL-6, PAI-1, P-selectin, vascular cell adhesion molecule 1 (VCAM-1), fibrinogen, angiotensinogen, SAA3, and α1-acid glycoprotein. Considering that adipose and adipocytes produce all of these factors, it can be inferred that adipose itself is a large contributor to these systemic increases.

The systemic inflammation observed in obesity is undoubtedly derived not only from adipose tissue but also from the liver and other important inflammatory tissues. The relative contributions of each tissue vary a great deal. For example, SAA3 is upregulated in adipose tissue but not in the liver of obese mice. Although α1-acid glycoprotein is expressed in adipose tissue, it is upregulated primarily in the liver under conditions of increased obesity. However, even for some of the proteins derived from the liver, it is believed that adipose tissue is the initial driving force for upregulation. One of the best examples of this is the clinical marker of systemic inflammation CRP. The regulation of this protein in the liver is believed to be driven by IL-6. It may be IL-6 derived from visceral adipose tissue draining directly into the portal system that causes the obesity-associated rise of liver CRP production. Furthermore, in addition to liver-derived CRP, newer data show that adipose tissue itself may contribute to obesity-associated increased CRP levels. Although the direct contributions of adipose tissue toward systemic CRP levels may be limited, it is clear that adipocyte- and adipose tissue stroma–derived factors have a strong impact on the production of CRP in other tissues.

**Weight Loss Decreases Systemic Inflammation**

Evidence for a connection between obesity and inflammation has also been found in the context of clinical weight loss studies. Whether the weight loss is attributable to decreased dietary intake, increased fuel use through exercise, liposuction, or bariatric surgery, loss of adipose tissue is associated with a decrease in markers of inflammation. Weight loss achieved through dietary intervention alone or diet and exercise resulted in decreased circulating IL-6, CRP, PAI-1, TNF-α, soluble TNF receptor, P-selectin, intercellular adhesion molecule 1 (ICAM-1), VCAM-1, and IL-18 in men and women of various age groups and BMIs.

Weight loss by liposuction in obese patients was associated with significant decreases in circulating CRP, IL-6, IL-18, and TNF and sustained (6 months postoperative) improvements in insulin resistance. In contrast, Klein et al reported recently that large-volume subcutaneous abdominal liposuction did not significantly alter plasma concentrations of CRP, IL-6, TNF-α, and adiponectin, and did not significantly affect other risk factors for coronary heart disease and insulin sensitivity. The main lesson from this latter study is that liposuction of subcutaneous fat pads may not have as strong an impact as surgical removal of visceral adipose tissue.

In another form of dietary weight loss, gastric bypass surgery resulted in improved insulin sensitivity, amelioration of diabetes, and significant decreases in circulating IL-6 and CRP levels 14 months after the procedure. Not only do these findings strengthen the evidence for the direct contribution of obese adipose tissue to systemic inflammation, they also imply that many of the health benefits of weight loss are attributable to these decreases in inflammatory signals.

**Systemic Inflammation Is Associated With Increased Cardiovascular Risk**

Systemic inflammation has been reported to be present before any evidence of myocardial infarction. This was first interpreted as an inflammatory response to the developing atherosclerotic vascular damage. However, an alternative explanation could be offered by suggesting that systemic inflammation is causing atherosclerosis rather than being the result of it. This interpretation is supported by the observation that patients with pre-existing inflammatory diseases have a dramatically increased risk of CVD at younger ages. Patients with autoimmune diseases such as rheumatoid arthritis and lupus have accelerated rates of atherosclerosis. Systemic inflammation resulting from untreated indolent infections like periodontal disease is also correlated with increased cardiovascular risk. One of these studies found that serological evidence of past or ongoing chlamydial infection had increased amounts of carotid arteriosclerosis and demonstrated that empiric antimicrobial antibiotic treatment in these patients actually slowed their carotid arteriosclerotic narrowing over the next 3 years compared with untreated controls.

Because there was no evidence of direct infectious infiltration of these patients’ atheromatous lesions, these studies made conclusions similar to the studies on rheumatoid arthritis (ie, that systemic inflammation, per se, was mediating these vasculopathic effects).

**Mechanisms of Cardiovascular Pathology by Systemic Inflammation**

Obesity contributes to CVD via all of the proven mechanisms of coronary vasculopathy: atherosclerosis, hypercholesterolemia,
C-Reactive Protein

The first observations of the well-known association between CRP and cardiac risk was in 1954, when it was found that after myocardial infarction, there was a dramatic rise in circulating CRP levels and the amplitude of this rise correlated with poor prognosis. Subsequently, it was also found that preinfarct-elevated levels correlated with an increased risk of future cardiac events as well. Not only were preinfarction CRP levels correlated with increased risk for later adverse cardiac events and sudden death, elevated circulating levels of IL-6, IL-18, α1-antitrypsin, SAA3, and ICAM-1 were as well, and increased IL-6 levels have been correlated recently with increased risk of congestive heart failure development in elderly patients even before evidence of CVD.

There is currently great excitement surrounding the acute-phase reactant CRP for the insights it is providing into the etiologic relationships between inflammation and clinical vasculopathic syndromes, its usefulness as a clinical marker, and evidence for a direct pathogenic involvement. Elevated CRP levels are unquestionably associated with obesity and increased risk of CVD. Numerous additional studies have further strengthened the association of elevated CRP levels with nearly all the important cardiovascular risk factors, including insulin resistance and diabetes, metabolic syndrome, hypertension, smoking, and dyslipidemia. Numerous ongoing studies have demonstrated a linear relationship between circulating levels of CRP and CVD risk. They revealed that elevated CRP levels in obese patients are not only prognostic for the development of CVD but also predictive of the risk of progression to type 2 diabetes mellitus. Elevated CRP levels in obesity and the decreases associated with weight loss provide another suggestive link between CRP and obesity-associated risks for CVD and diabetes. Finally, the contribution of CRP to atherogenesis has been demonstrated in apolipoprotein E (apoE)–deficient mice; although apoE knockout mice are already predisposed to atherosclerosis, crossing them with transgenic mice overexpressing CRP significantly exacerbated atherosclerotic progression. Most intriguingly, a number of pharmacological interventions aimed at improving insulin sensitivity (with thiazolidinediones or metformin), hypertension (angiotensin inhibitors), or cholesterol biosynthesis (statins) have also been shown to cause significant reductions in CRP levels. Together, these results show such reciprocity between all variables that suggest not so much a linear path of causality but rather a linked matrix with inflammation and CRP at the nexus.

In addition to epidemiological and mouse model data demonstrating CRP to be a useful clinical marker for CVD risk, there is in vitro evidence demonstrating that it also may be an active mediator of inflammatory vasculopathy. After myocardial infarction, CRP accumulates within damaged myocardium, and it is thought to participate in the opsonization of necrotic tissue. Because of the correlation between circulating CRP levels and postinfarction prognosis, it was proposed that the complement-activating and opsonizing activities of CRP actually participate in the postinfarction pathology. However, even before infarction, circulating CRP has atherogenic activities on vascular endothelium and smooth muscle. Elevated CRP levels have been associated with endothelial dysfunction in the form of inappropriate vascular constriction/relaxation. CRP has been shown to cause induction of endothelial adhesion proteins ICAM-1, VCAM-1, E-selectin, P-selectin, and angiostatin type 1 receptor. Additionally, CRP has been implicated in the activation of endothelial NF-κB, induction of endothelial IL-1β, PAI-1, IL-6, TNF-α, monococyte chemoattractant protein-1 (MCP-1), endothelin-1, and tissue factor, and inhibition of endothelial NO synthase and NO signaling. Furthermore, many of these factors regulate CRP levels reciprocally; thus, even in the absence of tissue damage, CRP seems to be an amplifier of vascular inflammation. Increased expression of these adhesion proteins and cytokines results in increases in leukocyte adherence, chemotaxis, and extravasation into the inflamed subendothelial intima, with cellular inflammation and eventual foam cell accumulation. They also induce loss of endothelial and smooth muscle NO generation and proper vascular relaxation. Combined with increased vascular contractile signals by endothelin-1 and angiotensin II (AT-II), this results in inappropriate vascular contraction/relaxation and contributes to hypertension. Other effects include increased smooth muscle cell migration, proliferation, and vascular remodeling. Finally, the above-mentioned effects on NO and induction of endothelin-1 and P-selectin have proaggregating effects on platelets. These multiple molecular mechanisms for vasculopathic effects by CRP may explain the central position of CRP within the context of cardiovascular risk factors.

Plasminogen Activator Inhibitor-1

PAI-1 is a regulatory protein of the coagulation cascade, which is elevated in inflammatory and obese states as well as in the metabolic syndrome; and although it usually is primarily derived from platelets and endothelium, there is evidence to show that much of the elevation in obesity is attributable to upregulated production by adipose tissue itself. Obesity is also associated with increased circulating levels of the procoagulant factors tissue factor, fibrinogen, von Willebrand factor, and factor VII. Many of the circulating cytokines elevated in obese states also cause endothelial activation, resulting in low levels of platelet activation, prostaglandin secretion, and plug formation. Thus, when obesity-induced increases in clotting factor levels and platelet activation are combined with the decreased rate of fibrinolysis attributable to increased PAI-1, they represent a hypercoagulable state, which is thought to contribute to atherogenesis via increased deposition of platelets and fibrinous products to developing plaques. This hypothesis has been validated by the demonstration that elevated levels of each of these prothrombotic serum factors are associated with increased cardiovascular risks.
Tumor Necrosis Factor-α
The contribution of TNF-α to vasculopathy is complex and controversial. Obesity-associated TNF-α is primarily secreted from macrophages accumulated in obese adipose tissue, whereas the adipocytes, per se, predominantly produce unsecreted, membrane-bound TNF-α.12,52 The secreted adipose tissue TNF-α is specifically increased in visceral adipose depots.53 The resulting systemic rise in circulating TNF-α has been implicated in causing adipocyte insulin resistance.54,55

Thus, some of the contribution of TNF-α to vasculopathic processes may be mostly through its involvement in the development of insulin-resistant diabetes and the ensuing hyperglycemia.56 Circulating TNF-α may also contribute by its induction of CRP production and general systemic inflammation, which, in turn, impacts on the vasculature. In vitro experiments have also shown that TNF-α increases activation of endothelial and smooth muscle NF-κB, which, in turn, induces vascular adhesion molecules and cytokines, resulting in inflammatory and foam cell accumulation.57

Despite these intriguing in vitro data, the animal studies on TNF-α and development of atherosclerosis have produced mixed results. Although reducing TNF-α levels in apoE-deficient mice resulted in significant decrease of atheromatous lesions,58 in a wild-type background, it produced no improvements.59 Rats treated with anti–TNF-α therapy showed no improvement in their rate of postbypass graft atherosclerosis.60 In fact, mice deficient for the p55 TNF-α receptor exhibited accelerated atherosclerosis.61 Finally, although TNF-α is thought to play a role in the progression of ischemia-related congestive heart failure, anti-TNF therapy has shown no benefits for congestive heart failure progression in patients.62 Despite these conflicting results, there remains a great interest in testing anti–TNF-α therapies for cardioprotective effects.

Interleukin-6
Like TNF-α, the data as to the significance of increased systemic IL-6 levels in obese states are mixed and controversial. Obesity-associated induction of adipose IL-6 production induces CRP secretion, and there are data that suggest IL-6 decreases lipoprotein lipase activity, which results in increased macrophage uptake of lipids. In young atheromatous lesions, macrophage foam cells and smooth muscle cells express IL-6, suggesting a role for this cytokine in the earliest stages of atherosclerosis. Furthermore, circulating IL-6 stimulates the hypothalamic-pituitary-adrenal axis, activation of which is associated with central obesity, hypertension, and insulin resistance.18

Despite the association of increased IL-6 levels with vasculopathic disease states, and data demonstrating possible specific provasculopathic activities by IL-6, there is growing evidence that it also has roles in inducing lipolysis and decreasing appetite and weight gain, thus controlling obesity-associated pathologies.63,64 The current understanding of the roles of IL-6 and TNF-α in the context of obesity and vascular pathology is ambiguous. Although these cytokines may play an important role in the beneficial control of metabolic functions in lean, physically active individuals,65 their overall effects on vasculopathy in obese states is still unknown. It remains highly likely that they contribute to obesity-associated systemic inflammation and its sequelae and remain potentially important targets for prevention of inflammation-induced insulin resistance or vasculopathy.

Angiotensinogen
Angiotensinogen and angiotensin-converting enzymes (ACEs) are secreted from adipose, mostly from visceral depots.66 Correspondingly, elevated levels of angiotensinogen and AT-II are found in obese states.67 AT-II has numerous effects on the endothelium and vascular smooth muscle, including its well-known vasoconstrictive effects and contributions to hypertension. In addition, AT-II may contribute to local vascular inflammation via induction of endothelial expression of VCAM-1, ICAM-1, and MCP-1.68 It has also been demonstrated that AT-II is a potent activator of endothelial proliferation as well. In addition to its direct effects on vascular components, clinical trials of angiotensin blocking regimens in patients after coronary angioplasty have demonstrated that specific inhibition of the renin-angiotensin axis causes significant decreases in systemic inflammation, including IL-6, CRP, TFN, and metalloproteinases.69 Thus, the observed secretion and resulting elevated levels of AT-II in obese states contribute to angiogenesis, hypertension, and atheromatous changes.67,70

Vascular Endothelial Growth Factor
Along with increased AT-II, obesity is associated with increased levels of the angiogenic factor vascular endothelial growth factor (VEGF), which has been demonstrated to play a part in hypertension and atherosclerosis. In adults, most organ systems have reached their final size and are programmed to be maintained at steady state. However, adipose tissue is unique because of its almost unlimited growth potential. Therefore, it is not surprising that upon differentiation, adipocytes begin to express angiogenic growth factors like VEGF,71 which can increase the vascular bed for the increasing needs of adipose tissue. Elevated insulin levels are an additional signal of caloric excess and continued adipose expansion, and correspondingly, it has been shown that adipocytes express and secrete VEGF in an insulin-dependent manner,72 leading to the observation that obese states are associated with increased adipose tissue VEGF secretion. Furthermore, given the regulation of endothelial VEGF secretion by AT-II and the elevated AT-II levels in obese states, it is easy to see why obesity should be associated with increased systemic VEGF levels.73 Like many of the inflammatory cytokines we reviewed here, VEGF levels are particularly elevated in the context of visceral adipose tissue expansion,10,73 underlining the significance of visceral adipose tissue and VEGF for hypertension, the metabolic syndrome, and vasculopathy (discussed below). Although the angiogenic effects of VEGF are necessary for proper vascular remodeling after angioplasty and for the genesis of collaterals in diabetic peripheral vascular disease, VEGF is also implicated in the initial development of atheromatous change and postcatheterization restenosis.74 Recent data indicate that in addition to its effects on vascular remodeling, the angiogenic growth factor VEGF plays a role in AT-II–induced vascular inflammation and remodeling, specifically increasing aortic subendothelial macrophage accumulation and intimal thickening.75 As illustrated in the results of anti-VEGF treatment
in postcatheterization coronary restenosis, VEGF has already been demonstrated to be an important target in specific cardiac vasculopathies. It remains to be seen just how important the obesity-induced changes in systemic VEGF are and what the role of anti-VEGF therapies may be in the context of obesity and cardiovascular risk states.

**Leptin**

Although leptin is not usually thought of as an inflammatory cytokine, hyperleptinemia has been shown to be induced by inflammatory signals such as endotoxin and has important effects on Th1 immune responses and activates blood monocytes in culture. Furthermore, leptin levels are correlated with the CRP and other inflammatory markers in healthy and morbidly obese subjects. Better known is the role of elevated leptin levels in the obese state. Here, leptin is thought to contribute to insulin resistance and considered to be one of the links between obesity, insulin resistance, and atherosclerosis. However, a recent study looking at type 2 diabetics demonstrated that hyperleptinemia is associated with atherosclerosis independent of insulin resistance. Leptin has also been demonstrated to contribute to vasculopathy via obesity-associated hypertension, not through metabolic actions, but instead via its action on central sympathoregulatory pathways. Finally, leptin plays a role in diet-induced neointimal thickening after vascular injury. These activities, in addition to possible contributions to atheromatous inflammation through monocyte and Th1 activation, may explain the epidemiological association between elevated levels and cardiovascular risk.

**Serum Amyloid A3**

SAA3 is an acute-phase reactant secreted by many tissues of the body, including adipocytes, and there is growing evidence that it may make a significant contribution to atherogenesis. Circulating levels are elevated in obese and diabetic patients because of induction via inflammatory signal transduction pathways, as well as activation by hyperglycemia itself. The proven and hypothesized activities of SAA3 include action as a chemottractant, inducer of remodeling metalloproteinases, and stimulation of T-cell cytokine production. It also acts as an apolipoprotein, binding HDL and possibly targeting the deposition of the transported cholesterol to atheromatous foam cells. These lipoprotein-binding properties of this protein have been suggested to act as a means of absorbing toxic bacterial cell wall lipids. Whatever the purpose for this protein in infection, in the context of obesity-induced inflammation, it is thought to promote local inflammation and inappropriate lipid accumulation.

**Adiponectin**

Adiponectin is an adipocyte secretory protein, the circulating levels of which are decreased in obese and diabetic states. This protein has been shown to play a role in liver insulin sensitivity and whole-body metabolism. Adiponectin has been implicated in cardiovascular health as well, at the very least as a highly sensitive serum marker for the prediction of future cardiovascular events. Retrospective case-control studies demonstrate that patients with the highest levels of adiponectin have a dramatically reduced 6-year risk of myocardial infarction compared with case controls with the lowest adiponectin levels, and this relationship persists even when controlling for family history, BMI, alcohol, history of diabetes and hypertension, hemoglobin A1c, CRP, and lipoprotein levels. Animal models also corroborate these observations, showing that adiponectin is particularly important for preventing diet-induced progression of atherosclerosis.

The exact mechanism of the antiatherosclerotic activity of adiponectin has not been completely elucidated. The association between adiponectin levels and cardiovascular risk independent of other variables suggests that adiponectin mediates direct effects on vascular health, as opposed to indirect effects through insulin sensitivity and diabetes. A number of studies have shown direct effects of adiponectin on endothelial and vascular smooth muscle cells. It has also been hypothesized that adiponectin has inflammatory-modulating activities, and clinical studies have demonstrated inverse associations between adiponectin levels and serum markers of inflammation.

An early article using a truncated recombinant form of adiponectin suggested that it activates NF-κB in endothelial cells, whereas subsequent articles have found anti-inflammatory effects on endothelium and macrophages. Unfortunately, all of these studies used a recombinant, bacterially produced, truncated form of the protein. Although this fragment is a form with potential as a pharmacological agent, it differs in its bioactivity from the endogenous post-translationally modified and multimerized hormone. Thus, the conclusions from studies that exclusively rely on the use of this recombinant trimeric ligand must be interpreted with caution.

Although it is not clear how or whether adiponectin itself has anti-inflammatory properties, it is clear that adiponectin production by adipose can be inhibited by systemic inflammation, at least under some circumstances. Adiponectin production by adipocytes has been shown to be inhibited by inflammatory cytokines such as TNF-α in vitro. This inhibition may be mediated in part by NF-κB signaling. In vitro studies on cultured adipocytes, as well as in vivo studies using obese diabetic mice, revealed that inhibition of adipocyte inflammatory NF-κB signaling by an IκB kinase inhibitor resulted not only in decreased cytokine levels but also increased adiponectin levels in plasma. Thus, IκB kinase inhibition is leading to increased plasma adiponectin levels, concomitant with an improvement in systemic insulin sensitivity. If adiponectin does have anti-inflammatory activities, they are likely mediated by its principal signaling target, the AMP-activated protein kinase (AMPK). There is evidence that the truncated bacterial form of adiponectin has anti-inflammatory effects on endothelium via AMPK-mediated modulation of NF-κB and Akt/protein kinase B. Thus, there is preliminary evidence that some of the proven antiatheromatous effects of adiponectin may be mediated by anti-inflammatory activities acting directly on the vasculature.

In addition to its possible anti-inflammatory properties and their implications for CVD, it is important to mention the recent demonstration that adiponectin may also have an important role in protecting against cardiac hypertrophy in cardiac overload states such as hypertension, hypertrophic cardiomyopathy, and ischemic heart disease. Adiponectin was shown in mice to protect against overload-induced and adrenergically induced cardiac myocyte hypertrophy, specifically by inhibiting hyper-
Association Between Visceral Adipose Mass, Secretion of Inflammatory Cytokines, Insulin Resistance, and the Metabolic Syndrome

A growing body of literature demonstrates that body fat distribution, not the absolute amount of adipose tissue, is what leads to the increased risks for CVD observed in many overweight individuals, pinpointing the intra-abdominal visceral fat pads as the major culprits in the process. These observations are best typified by the data regarding the metabolic syndrome. The American Heart Association defines the metabolic syndrome as the combination of abdominal obesity, dyslipidemia, hypertension, and insulin resistance, a constellation of disorders that bestow a cardiovascular risk far greater than any of its individual components. The defining characteristic of this disease is increased visceral adipose tissue mass, but since its description, it has been a mystery exactly how the other defects relate to this fat deposition pattern. More recently, it has been discovered that the second defining characteristic of the metabolic syndrome is increased systemic inflammation. In fact, the association between CRP and the metabolic syndrome is so strong it has been suggested that it become another diagnostic requirement. What role does visceral adipose tissue play in obesity-associated inflammation? And what is the impact of these two players on development of the insulin resistance, hypertension, and dyslipidemia that define the remainder of the syndrome? Visceral fat explants have been shown to secrete far greater amounts of CRP, IL-6, TNF-α, VEGF, angiotensinogen, and PAI-1 compared with dissected subcutaneous adipose. Products released from visceral adipose tissue travel directly to the liver via the portal vein. Thus, the livers of obese subjects are directly downstream of the visceral fat pads that show a dramatic upregulation of inflammatory cytokines. When compared with BMI-matched controls with increased subcutaneous fat deposition, patients with increased amounts of abdominal fat have increased circulating levels of CRP, TNF-α, IL-6, PAI-1, angiotensinogen, increased platelet-activating eicosanoids, and increased numbers of activated platelets.

Not surprisingly, when a number of studies that originally focused on overall obesity were re-evaluated specifically for the effects of central obesity, a dramatic and previously unnoticed association between intra-abdominal fat accumulation, its resulting inflammatory signals, and the other correlates of the metabolic syndrome emerged. Compared with BMI-matched controls, obese patients with visceral adiposity display particularly recalcitrant insulin resistance, dyslipidemia, hypercoagulability with increased thrombotic risks, and increased hypertension. Instead of indicting all types of overweight, it may be better presented that obesity, per se, is simply a risk factor for the development of central obesity, and it is central obesity that directly underlies insulin resistance and subclinical inflammation, which, in turn, leads to the metabolic syndrome and CVD.

Effects of Cardioprotective Therapies on Systemic Inflammation

In addition to the epidemiological evidence reviewed above for the role of inflammation in obesity-associated cardiac and cardiovascular risk, clinical studies of patients on cardioprotective drug regimens have revealed that many of the pharmacotherapies mediate their benefits, at least in part, through adipose-specific anti-inflammatory activities. This is the case most strikingly for one class of drugs that improves adipose tissue physiology and insulin sensitivity, the peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists (thiazolidinediones). PPAR-γ agonists, which primarily act on adipocytes through their defining transcription factor target PPAR-γ, not only increase peripheral and liver insulin sensitivity but also cause dramatic decreases in indicators of systemic inflammation. In obese diabetic patients, rosiglitazone has been shown to decrease circulating CRP, IL-6, matrix metalloproteinase-9 (MMP-9) activity, white blood cell count, and platelet activation, effects that are independent of improvements in insulin sensitivity. In patients with angiographic evidence of coronary artery disease, glitazone drugs decrease circulating levels of E-selectin, von Willebrand factor, CRP, fibrinogen, TNF-α, and PAI-1, and inhibit progression of intimal thickening. Finally, in patients with hypertension or non-diabetic metabolic syndrome, glitazones have been shown to decrease CRP, TNF-α, fibrinogen, and PAI-1. Glitazones are thought to mediate their anti-diabetic and anti-inflammatory effects via actions on the PPAR-γ transcription factor expressed in adipocytes and macrophages. The anti-inflammatory effects of glitazones are felt to be mediated partly by their beneficial effects on dyslipidemia, but there is also evidence that glitazones may directly modulate inflammation via transcription factors such as NF-κB.

Similar to their γ-agonist cousins, PPAR-α agonists, like the fibrates, have also demonstrated anti-inflammatory properties in addition to their other beneficial effects on metabolism. Fibrates are used to treat hyperlipidemias because of their effects on the liver, and the cardioprotective effects of these compounds in obese patients have been attributed to this aspect of their bioactivity. However, more recently, it was shown that fibrates lower circulating systemic inflammatory mediators such as endothelin-1, IL-6, CRP, TNF-α, and IFN-γ. Their effects may be mediated through activities on inflammatory signal transduction proteins cyclooxygenase-2 (COX-2), NF-κB, and activator protein-1.

The proinflammatory effects of AT-II were briefly reviewed above, and thus, it is not surprising that the antihypertensive ACE inhibitors and AT-II receptor blockers also have significant anti-inflammatory effects in patients with high cardiovascular risk. In hypertensive patients with and without demonstrable CVD, ACE inhibitors and angiotensin receptor blockers caused dramatic decreases in CRP, IL-6, MMP-9, and platelet aggregation. As mentioned earlier, the proposed mechanisms for the anti-inflammatory effects of either drug involve blockade of the effects of angiotensin on vascular permeability, regulation of adhesion molecules and chemokines, and direct activation of invading inflammatory cells. Clinical trials with hypertensive patients also re-
vealed surprising antidiabetic properties. In hypertensive diabetic patients, AT-II blockade improved patients’ glycemic control and reduced the relative risk of developing diabetes in the nondiabetic patients, and these changes were also associated with decreases in systemic inflammation. Perhaps the most intriguing implication of these clinical trials was that AT-II-mediated increases in vascular and systemic inflammation may mediate part of the progression from high insulin resistance to overt hyperglycemia, and thus, they indirectly recruited yet another powerful vasculopathic mechanism.

In addition to the beneficial effects of anti-diabetic and antihypertensive drugs on the subclinical inflammation, the hypolipidemic statins have also demonstrated anti-inflammatory properties. Inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) have been shown to decrease CRP levels in subjects with high cardiovascular risks, and they accelerated the decline of CRP and SAA3 levels after myocardial infarction. It is likely that statins mediate their anti-inflammatory actions by ameliorating the proinflammatory effects of atherogenic lipoproteins. However, newer data suggest that inhibition of HMG-CoA may also modulate intracellular inflammatory signaling directly. In endothelial cells, polymorphonuclear cells, monocytes, and vascular smooth muscle, numerous in vitro studies have demonstrated that inhibition of HMG-CoA reductase inhibits inflammatory signaling via modulation of protein prenylation. Decreased protein prenylation has been shown to modulate activity of Ras, Rho, Rac, and Rab signaling proteins and through these proteins, has effects on adhesion, migration, proliferation, apoptosis, matrix degradation, and coagulation. In the context of obesity and adipose tissue–derived inflammation, it was discovered recently that the statin class of drugs may have direct anti-inflammatory actions on adipocytes themselves. Treatment of cultured adipocytes with cerivastatin decreased expression and secretion of IL-6. The data by these authors further suggested that the prenylating intermediate geranylgeranyl pyrophosphate was stimulating NF-κB p65 activation, and that the statin inhibition of this prenylation pathway was responsible for these anti-inflammatory effects. Finally, in addition to their beneficial effects on cytokine levels, it was shown recently in clinical trials that statins also marginally raise circulating levels of serum total adiponectin. Other studies fail to see a significant effect of statins on circulating levels of adiponectin. In light of these conflicting reports, it will be interesting to see whether future studies find changes in the distribution of adiponectin complexes, similar to the effects reported for PPARγ agonists.

With accumulating evidence for active roles of inflammation in atherosclerotic progression, as well as data suggesting that commonly prescribed therapies mediate cardioprotective activities through their intended mechanisms as well as via anti-inflammatory effects, two issues arise. First, how much of obesity-associated cardiac risk is mediated by the observed systemic inflammation? Second, how can anti-inflammatory processes specifically be targeted toward adipose tissue? Aspirin and COX-2 inhibitors are anti-inflammatory and both lower CRP levels, but aspirin dramatically reduces cardiovascular risk, whereas the accumulating data on COX-2 inhibitors suggest an increase in myocardial infarction risk. An explanation for this dichotomy may be their differential effects on platelets. Aspirin inhibits COX-1 and COX-2 and platelet-activating thromboxane production, whereas the COX-2 inhibitors tend to have platelet-aggregating and vasoactive activities. In addition, aspirin may exert some of its systemic effects by targeting adipocytes with its anti-inflammatory properties, whereas there is very little evidence to suggest a direct effect of COX-2 inhibitors in adipocytes.

Summary

In the search for mechanisms of obesity-mediated vascular pathology, mounting evidence has implicated adipocytes and adipose tissue in the development of a systemic inflammatory state. Numerous studies demonstrate that circulating mediators of inflammation participate in the mechanisms of vascular insult and atheromatous change. Many of these inflammatory proteins are secreted from adipocytes and adipose tissue, with dramatically increased amounts of inflammatory proteins and decreased amount of cardioprotective adiponectin secreted from obese adipose. Secretion of inflammatory factors from visceral adipose tissue into the portal system and resulting effects on the liver and systemic inflammation may be the cause of the tight correlation between increased truncal obesity and vasculopathic phenomena and the metabolic syndrome. Studies on antiobesity and anti-inflammatory therapeutic interventions corroborate these casual relationships. Weight loss correlates with decreased inflammation, the cardioprotective effects of many of the most popular drug regimens are correlated with improvements in systemic inflammation, and in a few cases, it has been demonstrated that the improvements in systemic inflammation may be attributable to decreased inflammatory signaling within adipocytes or adipose tissue macrophages. These observations have provided great insight into the central role of adipose tissue toward the metabolic syndrome. At the same time, recent clinical trials have unexpectedly found that intervening in such a complex and central physiologic process without comprehensive understanding can carry unexpected and potentially devastating risks. These discoveries also beg the question of whether anti-inflammatory therapies directed specifically toward the adipocyte offer an effective and safe approach to prevent CVD.

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