Inflammatory Markers and the Metabolic Syndrome
Insights From Therapeutic Interventions

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Inflammation in the vasculature might be an important pathogenic link between cardiovascular diseases and the metabolic syndrome. Inflammation can be reduced by a variety of approaches including diet, exercise, cardiovascular drugs, and insulin sensitizers. Importantly, these different measures improve vascular function and reduce inflammation by distinct mechanisms. Therefore, combination therapy including lifestyle modifications and multiple drugs from separate classes might produce additive beneficial outcomes. We review plausible mechanisms for effects of combination therapy to reduce inflammation, improve endothelial dysfunction, and decrease insulin resistance in atherosclerosis, coronary heart disease, and hypertension in the context of insulin-resistant states including diabetes, obesity, and the metabolic syndrome. (J Am Coll Cardiol 2005;46:1978–85) © 2005 by the American College of Cardiology Foundation

Hypercholesterolemia (1), hypertension (1), estrogen deficiency (2), and insulin resistance (3) contribute to endothelial dysfunction accompanied by inflammation in the vessel wall, increased lipoprotein oxidation, smooth muscle cell proliferation, extracellular matrix deposition, accumulation of lipid-rich material, activation of platelets, and thrombus formation. These pathogenic features contribute to development of atherosclerosis and coronary heart disease (2–5). Serial angiographic studies performed before and after myocardial infarction indicate that the underlying plaque responsible for unstable angina and myocardial infarction usually produces an arterial narrowing of <50% before the acute event (6). Thus, mechanisms in addition to luminal occlusion are likely to be important determinants of plaque rupture, activation of platelets, and thrombus formation that culminate in acute coronary events. In this review, we discuss the role of inflammatory markers in linking endothelial dysfunction in cardiovascular diseases with metabolic disorders, including diabetes, obesity, and the metabolic syndrome. Particular emphasis is given to insights derived from therapeutic interventions with diet, exercise, cardiovascular drugs, insulin sensitizers, and combination therapies that have important anti-inflammatory actions.

INFLAMMATION AND ATHEROSCLEROSIS

Chronic inflammation is a pathogenic feature of atherosclerosis (Fig. 1) (4). Initiation of vascular inflammation is multifactorial. Direct injury to the vessel wall causes endothelial and smooth muscle cells of large arteries to become transcriptionally active and synthesize pro-inflammatory proteins, including chemokines, cell adhesion molecules (CAMs), and cytokines as well as growth factors and prothrombogenic substances. Cytokine-activated macrophages and smooth muscle cells secrete matrix metalloproteinases, which, when activated, digest connective tissue elements within the vessel wall and thin the fibrous cap overlying vulnerable plaques. This increases the potential for plaque rupture with exposure of thrombogenic plaque contents (7).

Endothelial dysfunction characterized by reduced production of nitric oxide (NO) and increased synthesis and secretion of endothelin-1 enhances vasoconstrictor tone and increases synthesis and release of pro-inflammatory cytokines. Decreased NO production also promotes platelet aggregation and release of growth factors in the vessel wall (2–5). Importantly, elevated levels of free fatty acids associated with insulin resistance, obesity, diabetes, and the metabolic syndrome cause endothelial dysfunction by activating innate immune inflammatory pathways upstream of nuclear transcription factor, nuclear factor (NF)-kappaB (3). Thus, inflammation contributes to endothelial dysfunction while endothelial dysfunction promotes inflammation. The resultant decrease in NO bioactivity is important in initiation and progression of atherosclerosis. Taken together, these findings help to explain why markers of acute inflammation reflect increased cardiovascular risk (8,9) and the transition from stable to unstable angina is associated with a systemic inflammatory response (8).

INFLAMMATION BIOMARKERS AND THERAPEUTIC INTERVENTIONS

Pro-inflammatory states enhancing innate immune signaling results in activation of NF-kappaB that regulates transcription of adhesion molecules vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule...
NF-kappaB also activates transcription of genes encoding chemoattractant factors, including monocyte chemotactic peptide and macrophage stimulatory factor that attract monocytes into vessel walls (Fig. 2). Moreover, NF-kappaB promotes synthesis and release of pro-inflammatory cytokines that enhance attachment of monocytes and macrophages to vessel walls (2).

**CAMs.** Serum concentrations of CAMs are higher in patients with coronary artery disease than in healthy control subjects (10). Moreover, men in the Physician’s Health Study with levels of ICAM-1 in the highest quartile are at greater cardiovascular risk than men in the lowest quartile (11). Age-adjusted soluble ICAM-1 and VCAM-1 levels increase in a stepwise fashion across tertiles for common carotid intima-media thickness (12). Thus, systemic inflammation might contribute to development of atherosclerosis.

Ito et al. (13) assessed the effect of weight reduction on soluble ICAM-1 and soluble E-selectin. Their program consisted of lectures on diet, exercise sessions, and behavioral modification. After three months, soluble ICAM-1 and soluble E-selectin, as well as body fat mass, decreased in the intervention group, with no changes in the control subjects. Soluble ICAM-1 and soluble E-selectin were positively correlated with central obesity. In postmenopausal women, a high-fiber, low-fat diet and aerobic exercise significantly reduces glucose, insulin, C-reactive protein (CRP), and soluble ICAM-1 with an increase in insulin sensitivity after two weeks (14).

Simvastatin and candesartan significantly reduce soluble ICAM-1 levels in hypercholesterolemic patients (15,16). Three-month therapy with the peroxisome proliferators-activated receptor (PPAR)-alpha agonist fenofibrate significantly decreases CAMs levels in hypertriglyceridemic patients (17). Interestingly, rosiglitazone treatment for 24 weeks significantly reduces CRP, von Willebrand factor, insulin resistance, and mean low-density lipoprotein (LDL) density without changing flow-mediated dilation or ICAM-1 or VCAM-1 levels in men with coronary artery disease without diabetes mellitus. Rosiglitazone treatment significantly increases LDL and triglyceride levels. Rosiglitazone reduces markers of inflammation and endothelial activation, but this does not translate into an improvement in flow-mediated dilation. Increased LDL and triglyceride levels might be responsible for this finding (18). It is also important to note, however, that several large meta-analyses of studies examining effects of thiazolidinediones on cardiovascular risk factors and dyslipidemias in patients with type 2 diabetes find that pioglitazone significantly lowers triglycerides along with improving insulin sensitivity and increasing high-density lipoprotein cholesterol with a neutral effect on LDL cholesterol (19,20). Rosiglitazone, however, increases both high-density lipoprotein and LDL cholesterol with a neutral effect on triglycerides (19). Nevertheless, head-to-head comparisons between these two different glitazones are necessary to make firm conclusions regarding...
the beneficial effects of pioglitazone versus rosiglitazone on lipid profiles in insulin-resistant states.

**Monocyte chemoattractant protein (MCP)-1.** Patients with angina have significantly elevated levels of MCP-1 when compared with control subjects. Higher levels are seen in unstable angina when compared with stable angina (21). In a large population-based study, plasma levels of MCP-1 were associated with traditional risk factors for atherosclerosis, supporting the hypothesis that MCP-1 mediates atherogenic effects (22).

Yang et al. (23) evaluated effects of a high-cholesterol diet and parallel exercise training on vascular function in rabbit aortas. A high-cholesterol diet causes significant lipid deposition and expression of P-selectin, VCAM-1, MCP-1, and inducible NO synthase. These changes are significantly reduced by exercise training. Troseid et al. (24) recently showed beneficial effects of combining exercise and pravastatin therapy with respect to levels of MCP-1 and IL-8 in subjects with the metabolic syndrome. After 12 weeks of exercise, plasma MCP-1 levels were reduced (p = 0.098). Of interest, combined therapy with exercise and pravastatin therapy significantly reduces MCP-1 levels even further (p = 0.01) when compared with baseline.

Angiotensin II activates NF-kappaB through angiotensin II type 1 and type 2 receptors and induces MCP-1 expression in cell culture (25). In hypertensive patients, candesartan therapy significantly reduces plasma levels of MCP-1 from baseline levels when compared with placebo (26). Combined therapy with simvastatin and losartan or ramipril significantly decreases MCP-1 levels more than monotherapy alone in hypercholesterolemic, hypertensive patients (Fig. 3) (27,28). Distinct biological actions of simvastatin and losartan or ramipril therapies on lipoproteins and the angiotensin system to improve endothelium-dependent vascular function and reduce MCP-1 levels might explain beneficial effects of combination therapy. Fibrates reduce CRP-induced expression of MCP-1 in human umbilical vein endothelial cells (29). Rosiglitazone treatment reduces plasma MCP-1 and CRP in obese patients (30).

**CRP.** Pro-inflammatory cytokines including IL-1beta, IL-6, and tumor necrosis factor (TNF)-alpha released from injured arteries initiate hepatic synthesis of acute phase reactants. Some acute phase reactants have effects on the arterial segment and contribute to the inflammatory response. More than 20 prospective epidemiologic studies demonstrate that high-sensitivity CRP is an independent predictor of risk of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death, even in apparently healthy individuals (32).

Esposito et al. (33) investigated effects of weight loss and lifestyle changes on vascular inflammatory markers in obese women. After two years, body mass index decreased more in the intervention group than in control subjects, as did serum concentrations of IL-6, IL-18, and CRP, whereas adiponectin levels increased significantly. Beneficial effects of a Mediterranean-style diet on endothelial function and vascular inflammatory markers were documented in patients with the metabolic syndrome. Compared with
patients consuming the control diet, patients consuming a Mediterranean-style diet had significantly reduced serum concentrations of high-sensitivity CRP, IL-6, IL-7, and IL-18 as well as decreased insulin resistance (34). In addition, two recent studies demonstrate that exercise training with weight reduction lowers CRP levels significantly (35,36). After supervised aerobic exercises, both weight and CRP levels were decreased; however, changes in CRP levels were not proportionally associated with the extent of weight reduction. In quartile analysis of percent weight reduction, the largest weight reduction quartile did not show significant decreases in CRP levels, whereas the middle quartiles showed remarkable CRP decreases. Considering inflammatory status, there might be an optimal pace of exercise combined with weight loss (35). In another study, CRP levels decreased significantly with training, although none of the CRP variants were associated with training-induced CRP changes. C-reactive protein +219G/A and −732A/G genotypes and haplotypes and exercise training appear to modulate CRP levels; however, training-induced CRP reductions are independent of genotype at these loci (36).

Simvastatin or atorvastatin lowers CRP in hyperlipidemic coronary patients (37). After statin therapy, the reduced progression of atherosclerosis is significantly related to greater reductions in CRP levels. Patients with low CRP levels have better clinical outcomes than those with higher levels, regardless of LDL cholesterol level (38,39).

C-reactive protein upregulates AT1 receptors in vascular smooth muscle cells. These effects are attenuated by losartan (40); however, in hypertensive patients, losartan, irbesartan, or candesartan do not significantly lower serum CRP (41). Interestingly, simvastatin combined with ramipril significantly reduces CRP levels more than monotherapy alone in hypercholesterolemic diabetic patients (Fig. 5) (42). Fenofibrate therapy significantly lowers CRP levels in patients with hypertriglyceridemia or combined hyperlipidemia (43,44). Rosiglitazone reduces CRP levels in patients with type 2 diabetes (30,45). In addition, CRP attenuates survival, differentiation, and function of endothelial progenitor cells, in part, by reducing expression of endothelial NO synthase. Rosiglitazone inhibits the negative effects of CRP on endothelial progenitor cells (46).

**TNF-alpha.** Tumor necrosis factor-alpha is a cytokine associated with coronary atheroma that is secreted from endothelial and smooth muscle cells as well as macrophages and adipose cells (Fig. 4). It enhances monocyte recruitment into developing atherosclerotic lesions and might help link obesity with atherosclerosis. Association of LDL accumulation in rat arteries with TNF-alpha expression suggests a role for inflammation in early-stage atherosclerosis (47). Plasma levels of TNF-alpha are persistently elevated among patients at increased risk for recurrent coronary events (48). Weight loss in response to lifestyle modification in obese individuals is accompanied by decreased TNF-alpha levels (49). Simvastatin and fenofibrate treatment in hyperlipidemia significantly lowers plasma levels of TNF-alpha (50,51). Candesartan or rosiglitazone therapy significantly lowers plasma levels of TNF-alpha in hypertensive or obese diabetic subjects (26,30).

**IL.** Interleukin–6 is the principal procoagulant cytokine. It increases plasma concentrations of fibrinogen, plasminogen activator inhibitor type 1, and CRP (52). Elevated levels of IL-6 are associated with increased risk of future myocardial infarction in healthy men (53).

Lifestyle modifications including Mediterranean-style diet and weight loss reduce serum concentrations of IL-6, IL-7, and IL-18 in obese women (33,34). Simvastatin significantly lowers serum IL-6 levels (54). Exercise, either alone or in combination with pravastatin, reduces IL-8 levels after 12 weeks in subjects with the metabolic syndrome (when compared with pravastatin alone or non-exercise control group). This suggests a protective role of exercise to reduce inflammation (24). In human aortic smooth muscle cells, PPAR-alpha activators inhibit expression of IL-6. In patients with mild hyperlipidemia, fenofibrate therapy decreases circulating levels of IL-6 (55). Rosiglitazone does not reduce IL-6 levels in patients with type 2 diabetes compared with placebo (45). Interestingly, rosiglitazone and troglitazone significantly potentiate TNF-alpha–induced production of IL-6 and/or IL-8 in epithelial cells. Thus, thiazolidinediones might enhance the inflammatory response in epithelial cells, a previously unappreciated effect (56).

Interleukin–1 is the prototypical inflammatory cytokine and a critical early mediator of inflammation. Patients with coronary artery disease have markedly elevated levels of IL-1 (57). Levels are particularly elevated in unstable disease. Statin therapy causes marked reduction in IL-1 in peripheral blood mononuclear cells. Enalapril and losartan therapy in patients with stable angina pectoris decreases release of IL-1 and IL-6 (58). In combined hyperlipidemia, fenofibrate therapy reduces IL-1beta levels (44).

Figure 5. Percent change in high-sensitivity C-reactive protein (hsCRP) levels from respective pretreatment values after treatment with simvastatin alone, combined therapy, and ramipril alone (p = 0.004 by analysis of variance [ANOVA]) (42). Median values are provided.
**CD40 ligand.** The pro-inflammatory mediator CD40 ligand (CD40L) is expressed on CD4+ T cells and activated platelets. Both membrane-bound and soluble CD40L (sCD40L) interact with CD40L expressed on vascular cells. CD40 ligand plays an important role in a cascade of inflammatory and proatherothrombotic functions (59).

Patients with unstable angina have higher concentrations of sCD40L than those with stable angina or healthy volunteers, perhaps due to release from activated platelets or T lymphocytes (60). Elevated plasma levels of sCD40L identify patients with acute coronary syndromes at heightened risk of death and recurrent myocardial infarction, independent of other predictive variables (61).

Statin administration reduces elevated plasma levels of sCD40L in patients with hypercholesterolemia (62). Beneficial effects of statin therapy on CD40/CD40L dyad might be due to the fact that lowering lipids and lipoprotein oxidation reduces expression of stimulators of CD40 and/or CD40L. In addition, reduction of cytokine-induced CD40/CD40L expression likely requires lipid-independent anti-inflammatory functions of statins, such as reduced signaling via NF-kappaB (63). Candesartan therapy reduces sCD40L, independent of blood pressure lowering effects (64). Fibrate and rosiglitazone treatment also reduce sCD40L levels (44,65).

**Adiponectin.** Adiponectin is one of a number of proteins secreted by adipose cells that might couple regulation of insulin sensitivity with energy metabolism and serve to link obesity with insulin resistance. Adiponectin stimulates production of NO (66), reduces expression of adhesion molecules in endothelial cells, and decreases cytokine production from macrophages by inhibiting NF-kappaB signaling through cyclic adenosine monophosphate (cAMP)-dependent pathways (Fig. 6) (67,68). Interleukin-6 inhibits adiponectin expression and secretion in 3T3-L1 adipocytes (69). Adiponectin and TNF-alpha reciprocally inhibit production of each other in adipose tissue. In particular, physiological concentrations of adiponectin inhibit TNF-alpha–induced monocyte adhesion to human aortic endothelial cells as well as expression of various adhesion molecules (Fig. 6) (67). Thus, adiponectin might indirectly inhibit CRP and IL-6 expression through its ability to inhibit production of TNF-alpha.

Plasma levels of adiponectin are negatively correlated with adiposity, and decreased plasma adiponectin levels are observed in patients with obesity and type II diabetes (70). Decreased levels of adiponectin might play a key role in the development of both insulin resistance and atherosclerosis.

Lifestyle modification significantly increases adiponectin levels in diabetic or obese subjects (33,49). Treatment with temocapril and candesartan significantly increases adiponec- tin and insulin sensitivity without affecting degree of adiposity (71). Decreased levels of adiponectin might play a key role in the development of both insulin resistance and atherosclerosis.

Potential mechanisms for losartan to increase adiponectin levels include direct effects of losartan on insulin-stimulated glucose uptake, promotion of adipogenesis (72), and induction of PPAR-alpha activity that promotes adipocyte differentiation (73). Recent clinical trials suggest that renin-angiotensin system blockade lowers risk of development of type II diabetes. One mechanism underlying this effect might be an increase in adiponectin levels (27,42). Fenofibrate therapy significantly increases plasma adiponectin levels and insulin sensitivity in patients with primary hypertriglyceridemia (43). Administration of thia-zolidinediones significantly increases plasma adiponectin

![Figure 6. Adiponectin, a cytokine secreted by adipose cells, plays a key role in opposing insulin resistance. Adiponectin has novel vascular actions to directly stimulate production of NO in endothelial cells using phosphatidylinositol (PI) 3-kinase-dependent pathways involving phosphorylation of endothelial nitric oxide synthase (eNOS) by adenosine-monophosphate–activated protein kinase (AMPK) (66). Others report that adiponectin reduces expression of adhesion molecules in endothelial cells and decreases cytokine production from macrophage by inhibiting nuclear transcription factor NF-kappaB signaling through cyclic adenosine monophosphate (cAMP)-dependent pathway (67,68).](image)
concentrations in insulin-resistant humans and rodents without affecting body weight. Adiponectin messenger-RNA expression is normalized or increased by thiazolidinediones in the adipose tissues of obese mice (74). In cultured 3T3-L1 adipocytes, thiazolidinediones enhance expression and secretion of adiponectin in a dose- and time-dependent manner. Rosiglitazone or pioglitazone therapy significantly increases adiponectin levels in diabetic subjects (70,75).

CLINICAL IMPLICATIONS

Randomized clinical trials demonstrate that statins, fibric acids, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II type I receptor blockers improve endothelium-dependent dilation and reduce vascular inflammation resulting in reduced cardiovascular events (Fig. 2). Patients with the metabolic syndrome are increasing in number and comprise one of the largest groups of individuals with obesity, hyperlipidemia, hypertension, and insulin resistance. Distinct biological actions of statin and ACE inhibitors or angiotensin II type I receptor blockers therapies on lipoproteins and the angiotensin system improve endothelium-dependent vascular function by distinct mechanisms (Fig. 2) (76). Indeed, combination therapy has beneficial additive effects on endothelial function and inflammatory markers that might explain positive outcomes of recent clinical trials (77–80). This might be due to combined effects of respective monotherapies to improve endothelial function and reduce inflammation. Thus, additive beneficial effects of combined therapy are predicted to reduce cardiovascular events more than monotherapy with either drug alone, particularly in patients with the metabolic syndrome.

In the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial, addition of trandolapril to the regimen of lipid-lowering drugs did not provide any further benefit in terms of preventing death from cardiovascular events (81). By contrast, perindopril significantly reduced relative risk of this primary end point by 20% in a patient cohort in which 58% were also receiving lipid-lowering therapy (80). The Heart Outcomes Prevention Evaluation (HOPE) trial showed that ramipril significantly reduces the relative risk of major vascular outcomes by 25% in patients also receiving lipid-lowering drugs (79). Potential explanations for the negative results of the PEACE trial include: an underpowered trial—only 8,290 of a planned 14,100 patients were enrolled; the primary outcome was changed to include revascularization; and failure to reach maximal dose because of adverse effects (82,83). Indeed, a meta-analysis of the HOPE, PEACE, and EUROPA data shows significant reductions in mortality, reinfarction, and stroke (82). Thus, there are clear benefits of adding ACE inhibitors (particularly high-dose) in patients with vascular disease without left ventricular dysfunction.

FUTURE PROSPECTS

Inflammation is an important pathogenic factor in atherosclerosis and coronary heart disease, particularly in the context of diabetes, obesity, and the metabolic syndrome. Diet, exercise, cardiovascular drugs, and insulin sensitizers improve endothelium-dependent vascular function and reduce inflammation by distinct mechanisms. This might help explain beneficial effects of combination therapies in recent clinical trials. Thus, there is a scientific rationale for recommending a combination of lifestyle modifications and multiple drugs from separate classes to prevent atherosclerosis and coronary heart disease. Recent evidence suggests that cross-talk between inflammatory-signaling pathways and insulin-signaling pathways causes both metabolic insulin resistance and endothelial dysfunction that synergize to predispose to cardiovascular disorders in the metabolic syndrome (84). Prospective studies are needed to examine the relationships between reductions in inflammatory biomarkers such as CRP, improved insulin sensitivity, and primary end points including outcomes of cardiovascular events and the incidence of diabetes.

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