Coronary Artery Disease in End-Stage Renal Disease: No Longer a Simple Plumbing Problem

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The lifespan of patients with end-stage renal disease (ESRD) is reduced, and cardiovascular disease (CVD) accounts for a premature death in more than 50% of patients from Western Europe and North America undergoing regular dialysis (1). Actually, the risk for CVD in a 30-yr-old ESRD patient is similar to the calculated risk of a 70 to 80-yr-old subject from the nonrenal population. It is notable that the risk of cardiovascular disease seems to be substantially lower in ESRD patients of Asian origin (2). Though the prevalence of traditional Framingham risk factors is very high in ESRD, the extent and severity of cardiovascular complications is clearly disproportionate to the underlying risk factor profile (3). Therefore, much recent interest has focused on nontraditional risk factors, such as inflammation, malnutrition, and oxidative stress, all common phenomena of ESRD that may promote atherosclerosis (4,5). Although non-atherosclerotic CVD may also contribute to the high cardiovascular mortality rate in ESRD, available evidence suggests that ESRD patients are subjected to a process of accelerated atherogenesis (6).

As previously discussed by London and Drüeke (7), the clinical distinction between the two coexisting conditions associated with arterial disease, arteriosclerosis and atherosclerosis, may not be easy to define. Whereas arteriosclerosis is primarily a medial degenerative condition associated with aging that causes stiffening of arteries, atherosclerosis is a disease process that typically results in narrowing or occlusion of arteries (7). Although several clinical methods (such as carotid ultrasonography and coronary angiography) are available to assess the degree of arteriosclerosis and atherosclerosis in ESRD patients, it should be noted that most previous studies on the association between vascular disease and cardiovascular risk factors have used a clinical definition of CVD as a surrogate marker of vascular disease. However, there are at least two distinct but related processes in the progress of atherosclerotic coronary artery disease (CAD), (a) the slow progressive atheroma formation and (b) the instant plaque rupture with formation of an occlusive thrombus (Figure 1); therefore, a clinical definition may fail to predict the overall atherosclerotic burden. Thus the use of a clinical definition of CVD, as used in many previous studies, may be inappropriate and misleading. It should also be noted that a number of functional nonatheromatous factors, such as abnormal vasodilation and increased extravascular resistance, might contribute to CVD in ESRD (8). Therefore, as the use of a clinical definition of CVD may not estimate the true prevalence and incidence of atherosclerosis in ESRD, it should be used with caution. The present review will focus on recent advances in the understanding and treatment of atheroma formation and plaque rupture, particularly in the context of two common features of ESRD: inflammation and oxidative stress. We will discuss new findings regarding these putative associations as documented in the recent nonrenal literature; when possible, we will also try to put these findings into the context of ESRD and its associated state of inflammation and oxidative stress.

Atherosclerosis: No Longer a Simple Plumbing Problem

Not more than 10 to 15 yr ago, cholesterol deposition in atherosclerosis was considered merely a passive and degenerative process of aging. As atherosclerosis was viewed as more of a “plumbing problem,” mechanical means such as bypass surgery and percutaneous interventions were considered to be the most appropriate therapeutic approaches for patients with clinical manifestations. However, recent findings clearly show that the arterial lesions besides deposition and oxidation of lipoprotein components (oxLDL) are also closely related to an inflammatory process (9). In fact, Ridker et al. (10) recently showed that an inflammatory marker, C-reactive protein (CRP), is a stronger predictor of cardiovascular events than LDL-cholesterol and that it adds prognostic information to that conveyed by the Framingham risk score. According to the classic paradigm by Ross (11), a number of disparate risk factors act on a final common pathway that ultimately lead to endothelial dysfunction, which is the initial stimulus for the development of the atherosclerotic plaque. Endothelial damage in humans may represent a balance between the magnitude of injury and the capacity for repair. Indeed, Hill et al. (12) recently showed that there is an inverse relation between Fra-
mingham risk factors and bone marrow-derived endothelial progenitor cells (EPC), which seems to have a pivotal role as “repair” cells in the response to endothelial injury.

Also vascular calcification, another prominent feature of the atherosclerotic process, was previously regarded as a passive degenerative process. However, recent clinical and laboratory findings suggest that this process is also active and related to inflammation (13). Clearly, these apparent paradoxes have shifted the focus from the degree of anatomical stenosis more to the biology and dynamics of the atherosclerotic plaque. In general, acute coronary syndromes such as myocardial infarction are often the result of rupture or ulceration of the fibrous plaque that produces thrombosis (Figure 1). Factors that may contribute to rupture include increased biochemical stress within the fibrous cap and weakening of the fibrous cap matrix by proteolytic enzymes or inflammation (14). Molecular and cellular studies have demonstrated that macrophages are central in atherogenesis because they produce many inflammatory mediators that contribute to the disruption of the vulnerable plaque that trigger thrombosis (14). As reviewed by Libby (9), at least three different types of plaque disruption may occur. It is notable that superficial erosion (or desquamation of endothelial cells), disruption of the microvessels (angiogenesis) that form the atherosclerotic plaque, and a fracture of the fibrous cap of the plaque all seem to involve a process of inflammation (9). In fact, Buffon et al. (15) have shown that there is a widespread activation of neutrophils across the coronary vascular bed regardless of the site of the lesion in patients with unstable angina. Fracture of the fibrous cap (the most common type of plaque disruption) seems to be particularly related to inflammation and increased T-helper 1 (Th1) activity.

Figure 1. (A) Biochemical, functional, and anatomic evaluation of coronary heart disease in end-stage renal disease (ESRD). (B) Schematic view of the atheroma’s development. The normal human coronary artery is composed of three layers of cells: endothelial cells resting on a basement membrane, the intimal layer (containing smooth muscle cells and extracellular matrix), and the underlying tunica media. In early atherogenesis, recruitment of inflammatory cells and the accumulation of lipids (foam cells) lead to formation of a fatty streak. If inflammatory conditions prevail and risk factors such as dyslipidemia persist, the lipid pool can grow, and proteinases secreted by the activated leukocytes can degrade the extracellular matrix and cause cell death while proinflammatory cytokines that stimulate Th1 activity can limit the synthesis of new collagen. These changes may thix the fibrous cap, making it susceptible to rupture. When rupture occurs, blood in the plaque coagulates, leading to thrombus formation and an acute coronary syndrome. Stenotic lesions may restrict flow, particularly under situations of increased cardiac demand, which leads to ischemia and symptoms such as angina pectoris. As stable stenotic plaques may be more fibrous and calcified, they are less susceptible to rupture (higher Th2 activity). (C) Therapeutic measures to be implemented according to the different evolution phases of the atherosclerotic lesion.
because proinflammatory cytokines can inhibit collagen production by smooth muscle cells (9). Moreover, proinflammatory mediators stimulate the expression of specialized enzymes, so-called matrix metalloproteinases (MMP) from the foam cells, which are thought to play a prominent role in destabilization of plaques (9).

Although coronary artery calcification is associated with adverse cardiovascular prognosis, the influence of the calcification process per se on plaque stability is not clear. On the one hand, Huang et al. (16) showed that calcium deposits might prevent plaque disruption because they may strengthen the plaque against circumferential mechanical stress. On the other hand, under mechanical stress induced by balloon angioplasty, calcified plaques may be more likely to rupture than noncalcified (17). Whether or not the extensive vascular calcification process in ESRD patients may confer protection from plaque rupture remains to be determined (Figure 1).

Renal Failure Is Associated with Altered Plaque Composition

Since the first report by Lindner et al. (6) of an accelerated atherosclerotic process in ESRD patients, both autopsy (18) and clinical (19) investigations have documented a higher prevalence of coronary artery plaques in patients with advanced renal dysfunction. Moreover, renal insufficiency has been shown to be a significant and independent risk factor for advanced renal dysfunction. Moreover, renal insufficiency has been shown to be a significant and independent risk factor for coronary artery plaques in patients with ad- 

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superoxide might induce expression of MMP in foam cells, another factor that may contribute to plaque instability (30). Since MMP-9 may not only reflect inflammation and oxidation of LDL but also contribute to weakening of the atherosclerotic plaques and vascular remodeling (Figure 1), it has been suggested that serum MMP-9 levels may be a useful parameter in the evaluation of the severity of CVD. As enhanced expression of MMP-9 mRNA are found in ESRD (31), MMP may be an important mediator of cardiovascular complications in these patients.

The emerging concept that MMP-related genetic variations may contribute to heterogeneity in the presentation and natural history of atherosclerosis (32) motivates further studies on the role of MMP-polymorphisms in the accelerated atherogenic process of ESRD. Considering the major risk of acute coronary events in association with unstable plaques, much recent interest has focused on interventions that stabilize the atheroma; i.e., strengthening the plaques biologically and rendering them less likely to rupture (9). As MMP inhibitors such as doxycycline (33) may promote plaque stabilization, this may be a future therapeutic target in the management of ESRD patients. Moreover, as it has been shown that chronic vitamin C deficiency make plaques more vulnerable to rupture (34), further studies are needed to investigate how oxidative stress is related to plaque stability in ESRD.

**Myeloperoxidase: A Link between Inflammation Oxidative Stress and Atherosclerosis?** MPO, an important enzyme found in neutrophils that are involved in the ROS production, has recently attracted significant attention because it seems also to be involved in a broad range of noninfectious diseases, such as lung cancer, Alzheimer disease, multiple sclerosis, atherosclerosis, and vasculitis (35). In fact, distinct products of MPO, such as 3-chlorotyrosine, are enriched in human atherosclerotic lesions and in LDL recovered from human atheroma (36). Moreover, MPO was linked to the modulation of the vascular signaling and vasodilatory functions of NO during acute inflammation, impairing the endothelium-dependent relaxant response through the catalytic consumption of NO by the free radicals generated by MPO (37). Himmelfarb et al. (38) showed that also the formation of MPO-catalyzed 3-chlorotyrosine is increased in dialysis patients, indicating increased oxidative stress. Also, advanced glycation end products (AGE) can be generated as a consequence of increased ROS production. For example, pentosidine
can be generated as a result of increased MPO activity through the increased production of aldehydes (39). It is suggested that AGE might form in the inflamed foci under experimental conditions and that the generation of N\(^{\text{IV}}\)-(carboxymethyl)-lysine (CML) is driven by the MPO-pathway using \(\alpha\)-amino acids as substrate (40). Indeed, Miyata et al. (41) observed that CML and pentosidine production is accelerated under oxidative stress in ESRD patients and proposed that AGE could be considered markers of oxidative stress damage to proteins (42).

It is notable that an important functional single nucleotide polymorphism has been identified in the promoter region of the MPO gene, consisting of a G to A substitution. Previous studies have demonstrated that the G allele (in contrast to A allele) creates a strong SP1 binding site, which is correlated with a 25-fold transcriptional enhancement of the gene (43). We recently described an association between this MPO genetic variation and the presence of CVD in ESRD (44), confirming results previously described by Nikpoor et al. (45) in a group of patients with CAD.

**Malnutrition and Oxidative Stress.** It has been speculated that patients with signs of malnutrition and a low plasma albumin concentration will have a significantly diminished plasma antioxidant capacity due to the diminished availability of thiol groups (5). It seems plausible that increased inflammation and hypoalbuminemia will have a synergistic effect on the risk for cardiovascular toxicity, because inflammation would result in increased production of oxidants by leukocytes and hypoalbuminemia results in reduced scavenging capacity for these oxidants (5). Malnutrition may also cause decreased concentrations of other important antioxidants as well. Similarly, when hypoalbuminemia occurs due to diminished nutritional intake, from either illness or anorexia, the burden of oxidative injury may be increased by diminished intake of exogenous antioxidants, such as ascorbate and tocopherols. It could be speculated that malnutrition, which is related to chronic inflammation (4), may further contribute to cardiovascular morbidity and mortality by reducing antioxidant defenses due to poor nutritional intake (46). Taken together, these observations may provide one explanation for why hypoalbuminemia and inflammation so strongly correlate with cardiovascular mortality.

**Inflammation and Atherosclerosis**

In a healthy condition inflammation is a local and fine-tuned response to microbial invasion or injury that must be regulated precisely because both deficiencies and excesses to the inflammatory response may cause morbidity and mortality (47). Much recent interest has focused on the role of an excessive inflammatory response in diseases, such as rheumatoid arthritis, diabetes mellitus, Alzheimer disease, and atherosclerosis. Although the concept that inflammation plays a central role in the pathophysiology of atherosclerosis has gained a lot of recent interest, our knowledge of the initiating inflammatory factors remains largely unknown. It is obvious in ESRD patients that a number of both dialysis-related (such as bioincompatibility and quality of dialysis water) and dialysis-unrelated factors (such as infections) may contribute to a state of chronic inflammation (4). Interestingly, recent data suggest that also the reduction of renal function per se may be associated with an inflammatory response. Indeed, as renal function deteriorates during the progression of renal disease, increasing concentration of plasma proinflammatory cytokines and other inflammatory biomarkers are observed in both mild (48) and advanced (49) renal failure. Also, as ESRD is associated with sympathico-activation, the fact that the central nervous system is a significant regulator of the inflammatory response deserves further attention (47). Finally, as the prevalence of inflammation seems to be lower in ESRD patients of Asian origin, factors related to diet and genetics may also influence the inflammatory response in uremia (2).

Although the association between CVD and inflammation is well documented in ESRD patients (4), we do not know if the acute phase response is merely an epiphenomenon reflecting established atherosclerotic disease or if the acute-phase reactants are actually involved in the initiation and/or progression of atherosclerosis. However, several lines of evidence suggest that the prototypic inflammatory marker CRP, as well as other biomarkers of inflammation, per se may contribute to atherogenesis (4). Indeed, recent publications provide evidence that CRP is part of both the innate immune response within oxidized LDL (50) and decreases eNOS expression and bioactivity in human aortic endothelial cells (51).

**Pro-Atherogenic Effects of IL-6.** Various proinflammatory cytokines might also have atherogenic properties. For example, TNF-\(\alpha\) has been shown to downregulate Apo E secretion, promote in vitro calcification of vascular cells, and cause endothelial dysfunction (4,52). Since injections of recombinant IL-6 exacerbated early atherosclerosis in mice (53), it has been speculated that this proinflammatory cytokine may also have significant pro-atherogenic properties. Indeed, IL-6 may activate the endothelium to produce vasoconstrictor substances and may have procoagulant property (54). Moreover, increased levels of monocyte-related cytokines, such as IL-6, are found in patients with unstable angina, suggesting that activation of monocytes is involved in the vulnerability of the underlying atheromatous plaque (55). Further support for the atherogenicity of IL-6 comes from a clinical study showing that elevated IL-6 predicts myocardial infarction (56) and genetic studies that show that both plasma IL-6 levels and a \(-174\ G/C\) polymorphism is associated with peripheral artery occlusion (57) and the development of cardiovascular disease (58) in nonrenal patients. In ESRD patients, IL-6 is not only a strong predictor of poor outcome (59), it is also independently associated with carotid atherosclerosis in dialysis patients (60,61). Clearly, in view of the strong prognostic impact of IL-6 further studies are needed to elucidate the independent role of genetic predisposition, comorbidity, and renal dysfunction as causes of elevated IL-6 levels in ESRD patients.

**The Balance between Proinflammatory and Antiinflammatory Cytokines.** When discussing the putative proatherogenic effects of IL-6 in ESRD patients, several concerns need to be addressed. First, we do not know yet whether the atherogenic effect of IL-6 is due to the subsequent generation of atherogenic acute phase reactants, to IL-6 itself, or due to an
as yet unidentified mechanism. Although IL-6 may be viewed as a classical marker of Th1 activation, it should also be pointed out that this cytokine may also stimulate the Th2 axis and B cells. Second, as inflammatory cytokines, such as IL-6 and TNF-α, influence contractility and contribute to the remodeling process in the failing myocardium (62), nonatherosclerotic myocardial dysfunction may ultimately enhance the risk of cardiovascular events and death in ESRD. Third, other inflammatory cytokines than IL-6 and TNF-α may also deviate the functional pattern of T cell activation toward Th1 differentiation, thus leading to a reduction of Th2 and B cell function. In fact, a recent study by Blankenberg et al. (63) demonstrated that IL-18, which acts in synergy with IL-12 to promote the development of Th1 responses, is also a strong predictor of cardiovascular death and unstable angina. Moreover, although acute phase reactants and cytokines may promote atherogenesis directly, the association between chronic inflammation and CVD may be indirect. Indeed, as chronic inflammation is associated with several features known to cause atherosclerosis, such as endothelial dysfunction, insulin resistance, and increased oxidative stress, they may all be partners in crime (64). Finally, the activity and expression of various antiinflammatory cytokines, such as IL-10, should be taken into consideration when evaluating the risk of elevated IL-6 levels in ESRD. In fact, an elevation of circulating IL-10 has been shown to be associated with a decreased risk of coronary events in patients with unstable angina (65); in dialysis patients, the antiinflammatory IL-10 genotype seems to be protective for cardiovascular events (66). Thus the balance between proinflammatory and antiinflammatory cytokines, rather than the absolute levels of proinflammatory cytokines, may be more predictive of future risk of cardiovascular events. Since the immune dysfunction in ESRD patients is characterized by both immunodeactivation (reflected by increased levels of proinflammatory cytokines and acute phase reactants) and immunosuppression (reflected by the poor response to vaccination and impaired defense against pathogens), a combination of increased susceptibility to infections and inflammation may contribute to the extremely high cardiovascular mortality in this population. Further studies are clearly needed to elucidate how factors that orchestrate the inflammatory response behave in the uremic milieu.

Angiogenesis, Vascular Remodeling, and Inflammation

Angiogenesis and vascular remodeling are recognized features of the atherosclerotic process and have been described in the context of unstable atherosclerotic lesions, which may occur in response to stimuli, such as hypoxia and increased wall stress. Indeed, a recent study showed a higher microvessel density in unstable atherosclerotic lesions, suggesting associations among plaque vascularity, quantity of intraplaque hemorrhage, and the presence of symptomatic carotid occlusive disease (67). It is hypothesized that microvessel formation in plaques may not only serve as a site for hemorrhage and thrombosis but may also promote growth of the plaque by a nutritional supply (9). Thus, as neovascularization may promote growth of the atherosclerotic plaque, various antiangiogenic therapies have been suggested to prevent restenosis (68). In the context of coronary plaques as dynamic structures reflecting a state of microinflammation (14), it is of immediate interest that neovascularization and excessive angiogenesis seems to be present in many chronic inflammatory disorders in humans (69). In fact, the expression of vascular endothelial growth factor (VEGF), which is the major putative angiogenic growth factor mediating new blood vessel formation (69), is markedly upregulated by both nonenzymatic glycation products and proinflammatory cytokines (70,71). Free plasma VEGF levels are high in chronic renal impairment (72), and increased expression of VEGF in arterial vessels of the heart has been documented after subtotal nephrectomy in rats (73) and may enhance plaque progression (74). However, as Amann and Ritz (8) observed diminished capillarization in the uremic heart, their finding may imply that some type of VEGF resistance and blunted angiogenesis occur in this organ. Indeed, Wagner et al. (75) recently postulated that there might be a posttranscriptional abnormality in the VEGF-mediated pathway to angiogenesis in ESRD, which may explain the reported discrepancy between VEGF expression and the diminished capillarization (8). Alternatively, as uremic toxins may inhibit the activity of stem cells (76), decreased neovascularization may also be the result of an exhaustion of EPC from the uremic bone marrow. In this respect, it is of major interest that Kocher et al. (77) recently showed that increased neovascularization of infarcted myocardium by bone marrow–derived angioblasts improves cardiac function and may have the potential to reduce cardiac morbidity and mortality.

Vascular Calcification Is a Prominent Feature of ESRD

It is clear that vascular calcification in both general and coronary arteries increases with age and is present in most subjects aged over 65 yr, especially in diabetic patients. Also in ESRD patients there seems to be an extensive heterotrophic calcification of the vascular tree. Indeed, Goodman et al. (78) used electron-beam computed tomography to demonstrate that coronary artery calcification is common and progressive, even in young adults undergoing dialysis. Moreover, the prevalence and extent of vascular calcifications and arterial stiffness are strong predictors of cardiovascular and all-cause mortality in HD patients (79). Similarly, a recent study by Wang et al. (80) showed that cardiac valve calcification was an important predictor for all-cause and cardiovascular mortality in PD patients. There may be several reasons why cardiovascular calcification progresses more rapidly in ESRD patients than in the general population. Much recent interest has focused on calcium and phosphate metabolism and its putative associations to vascular calcification, cardiovascular disease, calciphylaxis and poor outcome (81). Indeed, several lines of evidence indicate that abnormalities of calcium and phosphate metabolism may play an important role in cardiovascular morbidity and mortality of ESRD patients. First, Ganesh et al. (82) showed strong relationships among elevated serum phosphate, the Ca × P product, PTH, and cardiac death, especially deaths resulting from CAD and sudden death. The observed increase in CAD sug-
gests a direct role of elevated levels of phosphate (or the Ca × P product) in the natural progression, including rupture, of the uremic plaques. Second, it was recently shown that an elevated serum phosphate level was also associated with increased risk for valvular calcification (83). Finally, the importance of phosphate in the process of vascular calcification is further underscored by the fact that even in nonrenal patients there seems to be a correlation between serum phosphate and coronary calcification (84).

Although the idea of linking the ingestion of calcium salts to vascular calcification seems to be appealing, there are several issues that need to be interpreted with caution before advocating the discontinuation of the use of calcium as a phosphate binder. The important role of elevated Ca × P product in the process of vascular calcification is a consistent finding in different studies, but the impact of isolated calcium load on vascular calcification is not that clear. Although patients with vascular calcification have shown to have twice the daily calcium intake from calcium-based phosphate binders than patients without calcification (78), the associations between calcium intake and vascular calcification are inconsistent (85). Therefore, further studies are necessary to analyze the benefits of calcium-free phosphate binders, such as sevelamer (86), in reducing cardiac risk in dialysis patients. Other potential strategies to prevent calcification that need to be evaluated may include the use of a low diyalysate concentration of calcium and D-vitamin analogues that do not promote hypercalcemia.

**Relationships between Vascular Calcification and Inflammation in ESRD**

Although mismanagement of the abnormal calcium and phosphate metabolism in uremia may be one major factor in the development of cardiovascular calcifications in ESRD, several lines of recent evidence suggest that inflammation may also contribute to vascular calcification. First, in a cross-sectional study of PD patients, Wang et al. (87) showed that cardiac valve calcification is not only a passive degenerative process but also involves active inflammation. Second, coronary artery calcification in young adults was associated not only with a calcium-phosphate overload and hyperparathyroidism, but also with inflammation (88). Finally, Stompor et al. (89) used multi-row spiral computed tomography to show an association between coronary artery calcification and markers of chronic inflammation in PD patients.

**Linking Inflammation with Vascular Calcification.**

There may be several reasons why chronic a chronic inflammatory response promotes vascular calcification. First, α-2-Heremans Schmid glycoprotein (fetuin), an important inhibitor of vascular calcification, is downregulated during inflammation. Interestingly, Ketteler et al. (90) have recently shown an independent relation between low fetuin levels and all-cause mortality in HD patients, a finding that may link inflammation and the calcification process. Second, as vascular calcification involves infiltration of monocytes and accumulation of macrophages, it is of immediate interest that Tintut et al. (91) demonstrated that activation of monocytes and macrophages enhance in vitro vascular calcification via two independent mechanisms: cell-cell interaction and production of soluble factors, such as TNF-α. In fact, TNF-α may be an important promoter of vascular calcification by promoting osteoblastic differentiation of vascular cells through the c-AMP pathway (52). Third, it should be noted that also the ob gene product leptin, which may be related to the presence of inflammation in ESRD (92), has been shown to regulate osteoblastic differentiation and enhance calcification of vascular cells (93). Finally, Moe et al. (94) have demonstrated that osteopontin, which is secreted by macrophages and an important regulator of inflammation and biomineralization, was strongly correlated with medial calcification and a history of CAD in patients undergoing renal transplantation. Taken together, these findings may suggest that vascular calcification is, indeed, a part of an active cell-mediated inflammatory process and raise the hope that in the future targeted antiinflammatory interventions might arrest it. More research is also needed to elucidate the independent role of autonomic neuropathy in the uremic calcification process.

**Inflammation and Oxidative Stress as Potential Therapeutic Targets**

Although the process of atherosclerosis seems to be very closely associated to inflammation, there is not yet any recognized treatment for ESRD patients with signs of chronic inflammation. However, a number of various treatment strategies, both related and unrelated to dialysis treatment, have been proposed (4). Recently, the concept of atheroprotection has evoked much interest because it is evident that not only some regions of the arterial tree are more protected from atherosclerosis than others but also that the atherosclerotic process may be very slow in genetically protected individuals and races. Although differences in regional blood flow and shear stress might partially explain the observed differences, much recent interest has been devoted to atheroprotective genes that may modulate the inflammatory response. As discussed by Libby (9), a number of shear stress–regulated genes, such as eNOS, may affect the inflammatory response involving the transcription factor NF-κB. In this respect, it is of interest that recent results by de Nigris et al. (95) show that there is therapeutic possibility to modulate shear stress response genes by cotreatment with antioxidants and L-arginine. Indeed, these findings may have important future clinical implications for the prevention of accelerated atherosclerosis in susceptible individuals with renal disease.

**New Opportunities for Prevention of Atherosclerotic Inflammation.** Considering our new understanding of the central role of inflammation, endothelial dysfunction, and oxidative stress in the pathogenesis of atherosclerosis and plaque instability, exciting new opportunities have emerged for the prevention and therapy of the uremic atherosclerotic disease. As of today, especially four different classes of drugs, HMGC-CoA reductase inhibitors (statins), angiotensin-converting enzyme (ACE) inhibitors, peroxisome proliferator-activated receptor (PPAR) agonists, and antioxidative agents, such as α- and γ-tocopherol, seem to be of particular interest. It is fascinating that, despite their different pharmacologic composition...
and modes of action, all these drugs seem to have beneficial effects not only on the inflammatory process, but also on its partners in crime: endothelial dysfunction and oxidative stress (Table 1). As these drugs pertain processes driven by NF-κB (the central transcriptional control point in vascular inflammation), this observation suggests that inflammation, endothelial dysfunction, and oxidative stress are interrelated and share common proximate pathogenetic pathways (64). In this context, it is of interest to note that statins and ACE inhibitors also reduce cardiovascular events, a finding that may be attributable to their plaque-stabilizing effects (96,97). In fact, as NF-κB is required for cytokine upregulation of MMP in vascular smooth muscle cells, this suggests that drugs that inhibit NF-κB may also promote plaque stabilization (98).

**HMG-CoA-Reductase Inhibitors.** Recently, a large body of evidence demonstrates that statins reduce the risk for coronary events and restore vascular cells to more normal functions in large nonrenal patient populations (9). It is now evident that statins not only inhibit cholesterol synthesis and lipid oxidation but also have antiinflammatory actions (Table 1), such as reduction in leukocyte adhesion and antagonizing macrophage activation (9,96). Intriguing new data also suggest that statins may mobilize EPC from stem cells (99), which may be one reason why statins improve endothelial function (Table 1). Moreover, as statins increases the content of tissue inhibitors of MMP, they may also have a plaque-stabilizing effect (96). As of today, we do not know if the indisputable clinical benefit of statins in the nonrenal patient population is derived mainly from its salutary effects on cholesterol metabolism or its anti-inflammatory effects. As statins seems to have an antiinflammatory effect (100) and are associated with a lower mortality also in ESRD patients (101), there is a need of randomized prospective studies to determine the appropriate use of statins in the ESRD patient population.

**Angiotensin-Converting Enzyme Inhibitors.** Considerable recent evidence supports the notion that the potent vasoconstrictor angiotensin II (AngII) is also an important proinflammatory mediator that can elicit the endothelial and smooth muscle cell expression of both VCAM-1 and IL-6 and augment the production of ROS (9). Within the vascular wall, AngII contributes to the instability of the plaque by stimulating growth factors, adhesion molecules, chemotactic proteins, cytokines, oxidized LDL, and MMP (102). Clearly, the renin-angiotensin system may contribute to inflammatory processes within the vascular wall and contribute to the development of plaque instability and acute coronary syndromes (Figure 1). By inhibiting the formation of AngII, ACE inhibitors (and ALL-blockers) may reduce the damaging effects on endothelial function, vascular smooth muscle cells and inflammatory vascular processes (Table 2). Thus, it is not surprising that treatment with ACE inhibitors not only improve the prognosis of renal patients (103) but also decreases inflammatory biomarkers (104).

**Peroxisome Proliferator-Activated Receptor Agonists.** The fact that fibric acid derivatives, such as gemfibrozil, may reduce clinical complications of atherosclerosis in diabetic and insulin-resistant patient populations has stimulated the research of the PPAR-pathway. As transcription factors, PPAR regulate the expression of numerous genes and affect glycemic control, lipid metabolism, vascular tone, and inflammation. Indeed, modulation of the nuclear receptor and transcription factor PPAR may not only regulate apolipoprotein expression and adipocyte differentiation, but in vitro studies show that stimulation of PPAR-γ may also have anti-inflammatory effects and suppress the generation of ROS (Table 1), probably by targeting NF-κB. Moreover, as a PPAR-γ agonist, troglitazone, reduces osteopontin gene expression (105), it could be hypothesized that PPAR-γ agonists also inhibit plaque formation (106). Thus, as a recent clinical study shows that a PPAR-γ agonist, rosiglitazone, reduces serum levels of both MMP-9 and CRP in patients with type 2 diabetes mellitus (107), it is evident that the use of this new class of insulin-sensitizing drugs may be a novel therapeutic strategy for reducing inflammation and atherosclerosis in ESRD patients.

**α-Tocopherol and γ-Tocopherol.** Although there is now a large body of experimental evidence in animal models and epidemiologic data in humans to support the oxidation hypothesis, at least three large epidemiologic studies (GISSI, SELECT, HOPE) have failed to show that vitamin E supplementation improves cardiovascular outcomes in nonrenal patient groups (108). Moreover, a recent study showed that, whereas vitamin E supplementation did reduce circulating oxidized LDL, it did not reduce the progression of atherosclerosis (109). On the other hand, other studies have shown positive results of vitamin E supplementation on outcome (110) and that the combination of vitamins E and C slowed the progression of carotid artery lesions (111). As discussed by Steinberg et al. (108), there may be a number of reasons why vitamin E

| Table 1. Studies that suggest beneficial effects of statins, ACEI, PPAR-γ agonists, and vitamin E on risk factors for coronary artery disease in various patient cohorts |
|-----------------|-----------------|-----------------|------------------|
|                  | Statins         | ACEI            | PPAR-γ Agonists  | Vitamin E        |
| Inflammation    | ESRD (100)      | ESRD (104)      | DM (107)         | DM (118)         |
| Oxidative stress| Dyslipidemia    | ESRD (120)      | Obesity (121)    | ESRD (122)       |
| Endothelial dysfunction | Nephrosis (123) | DM (124)      | Obesity (121)    | CAD (125)        |
| Plaque stability | Carotid stenosis (96) | CAD (97)  | —                | —                |
| Outcome         | ESRD (101)      | CRF (103)       | —                | ESRD (116)       |

*ESRD, end-stage renal disease; DM, diabetes mellitus; CAD, coronary artery disease; CRF, chronic renal failure.*
supplementation failed to improve survival in various nonrenal cohorts. First, it should be emphasized that oxidative stress may contribute to atherogenesis also by mechanisms not linked to LDL oxidation, such as inactivation of NO by ROS (108). Clearly, as vitamin E reacts very slowly with superoxide, it would be an inappropriate antioxidant in such conditions (112). Second, in normally nourished subjects additional vitamin E would not necessarily confer any additional antioxidant protection (113). Moreover, in the absence of other antioxidants, such as vitamin C, vitamin E can paradoxically act as a pro-oxidant (114). Finally, as γ-tocopherol (but not α-tocopherol) and its major metabolite may possess significant antiinflammatory activity (115), it could be speculated that the inclusion of both α-tocopherol and γ-tocopherol in vitamin E supplementation may be more effective in preventing human disease. From these findings, it would be reasonable to speculate that populations under high oxidative stress, such as malnourished and inflamed ESRD patients, would benefit the most from antioxidant intervention. Indeed, in the ESRD population, the SPACE study (116) demonstrated a reduction in myocardial infarction and other cardiovascular events in the vitamin E-treated (800 IU/d) group compared with patients receiving placebo, but with no effect on overall mortality. Moreover, a recent study by Tepel et al. (117) showed that acetylcysteine (a thiol-containing antioxidant), reduced composite cardiovascular end points in HD patients. Clearly, further studies are needed to confirm these findings and to evaluate whether or not the combination of α-tocopherol and γ-tocopherol may be more beneficial than α-tocopherol alone in the setting of chronic inflammation.

Conclusions

End-stage renal disease is characterized by an exceptionally high mortality rate, much of which results from cardiovascular disease. Available evidence suggests the presence of an accelerated atherosclerotic process in renal patients that involves two interrelated processes: vascular calcification and inflammation. Among a number of factors involved in the plaque growth and vulnerability, much recent interest has focused on the role of inflammation, vascular remodeling and oxidative stress. It is evident that the explosion of new knowledge on the pivotal roles of inflammation and oxidative stress in the pathogenesis of atherosclerosis may open new exciting opportunities in the way we should manage and prevent cardiovascular disease in ESRD. It is recognized that many existing drugs, such as statins, ACE inhibitors, glitazones, vitamin E, and aspirin have antiinflammatory effects, which might add to their clinical effectiveness in preventing events. Future potential targets to interrupt the vicious circle of inflammation and oxidative stress and atherogenesis in renal disease include such factors as NF-κB, vascular adhesion molecules, AGE, endothelial progenitor cells, proinflammatory cytokines, and metalloproteinases. There is no doubt that atherosclerosis research entered a new era as we go into the new millennium, and clearly we no longer regard the atherosclerotic process as a simple inert plumbing problem but rather a complex dynamic inflammatory process that can be modulated and prevented.

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Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/