Kidney in Early Atherosclerosis

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Abstract—Atherosclerosis represents one of the major causes of premature death in the United States today, and it is frequently associated with, exacerbates, and is aggravated by chronic kidney disease (CKD). Atherosclerosis integrates the response to a number of insults, and consequently, the accelerated atherosclerosis found in CKD patients is associated with activation of a variety of humoral and tissue mechanisms. Hypertension, diabetes, dyslipidemia, obesity, metabolic syndrome, and additional nontraditional risk factors can damage the kidney directly and by promoting intrarenal atherogenesis, even in the absence of obstructive lesions in the renal artery. Evidence indicates that increased oxidative stress and inflammation may mediate a large part of the effects of risk factors on the kidney. In turn, progressive deterioration of renal function in CKD may lead to dyslipidemia or accumulation of uremic toxins, which can induce production of free radicals and activate proinflammatory and fibrogenic factors, leading to vascular endothelial cell dysfunction and injury, and favoring development of atherosclerosis. Therefore, the kidney can be a villain or a victim during atherogenesis. The purpose of this review is to provide new insights into the mechanisms by which atherogenic factors may instigate early renal injury. (Hypertension. 2005;45:1042-1049.)

Key Words: kidney ■ atherosclerosis ■ oxidative stress ■ fibrosis

During the past decade, the patient population with end-stage renal disease (ESRD) more than doubled. Arresting its progression mandates recognition of risk factors and the earlier stages of chronic kidney disease (CKD), a worldwide public health problem that affects 11% of individuals >65 years of age. The past few years have also increased the recognition of its frequent association with cardiovascular disease (CVD), especially atherosclerosis, which constitutes one of the major causes of morbidity and mortality in CKD.

Atherosclerosis is a generalized and inflammatory vascular disease frequently associated with renal disease and dysfunction and one of the major causes of premature death in the United States today. Diverse renal vascular diseases, including atherosclerotic renal disease (ARVD), account for more than one third of all cases of ESRD. Atherosclerotic plaques are present in up to 30% of patients with CKD, and ARVD is among the common causes of CKD in Western societies. Atherosclerotic changes in the renal artery are evident in 50% of patients with atherosclerotic disease previously and in 6.8% of adults >65 years or age, they induce significant renal artery stenosis.

However, overt atherosclerotic plaques likely represent an advanced stage of the atherosclerotic process. In fact, a growing body of evidence suggests that atherosclerosis has direct effects on the kidney, largely because of intrarenal microvascular and glomerular disease that precedes the onset and represents the silent phase of ischemic renal disease. Renal function abnormalities may exist at the early stages of atherogenesis and in patients with evidence of only extrarenal atherosclerosis and may precede the onset of overt ischemic nephropathy. Notably, severity of proximal renal artery lesions is often unrelated to the severity of renal dysfunction in patients with ARVD. Furthermore, the direct deleterious effect of atherosclerosis on the kidney is underscored by the observation that ARVD accompanied by significant renal artery stenosis is associated with poorer outcomes compared with fibromuscular dysplasia. Indeed, as the SMART (Second Manifestations of ARTerial disease) study indicated, nonobstructive atherosclerosis accelerates the decrease of renal size and the increase of serum creatinine with age, implying that deterioration of renal function is likely the result of direct parenchymal compromise, likely provoked by atherogenic factors.

Atherosclerosis results from a series of cellular and molecular responses to endogenous and exogenous insults, and cellular events involved early in atherogenesis resemble those triggered in other forms of CKD. Perhaps because glomerular cells mimic some of the characteristics of cells in the vessel wall, atherosclerosis and glomerulosclerosis are postulated as comparable processes. Atherogenic lipoproteins such as oxidized (ox)-LDL can induce endothelial and epithelial cell dysfunction and injury, infiltrate the mesangium and blood vessels, and subsequently induce secretion of growth factors that lead to glomerular and vascular hypercellularity and proliferation of extracellular matrix (ECM), major char-

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characteristic pathological features of both processes. Thus, atherosclerosis superimposed on pre-existing or concurrent renal injury may exacerbate progression of CKD by sharing similar pathophysiological mechanisms. Many of them are likely activated by a number of cardiovascular risk factors (CVRFs) as well, promoting renovascular injury directly or by favoring atherogenesis.

The purpose of this brief review is to summarize the triggers and mechanisms of atherosclerosis-induced renal injury and to provide new insights regarding the potential interaction among them.

**CVRFs in CKD**

CVD is up to 20× more common in ESRD patients and accounts for 40% to 50% of all deaths; accelerated atherosclerosis has been consistently implicated, partly because of a higher prevalence of established CVRFs, such as diabetes, hypertension, and dyslipidemia. Established CVRFs are associated with the development of new-onset kidney disease. Therefore, it is important to assess conventional CVRFs in patients with kidney disease to allow early intervention. In turn, CKD is a marker for elevated CVD risk in elderly adults. In addition to conventional CVRFs, novel CVRFs (Figure 1) such as inflammation, oxidative stress, and hyperhomocysteinemia, among others, are associated with cardiovascular risk. However, establishing the role of individual CVRFs in CKD may be difficult because they may coexist, share similar mechanisms, and possibly interact synergistically.

**Traditional Risk Factors and ARVD**

**Hypertension**

The 2 leading causes of ESRD in the United States are diabetes and hypertension (>65% of all cases). In many patients, both diseases are associated with small- and large-vessel disease and nephrosclerosis, commonly attributed to hypertension or accelerated atherosclerosis. Approximately 70% to 80% of individuals with CKD have hypertension, and its prevalence increases as glomerular filtration rate declines. In fact, even mild-to-moderate hypertension is an important risk factor for progression of CKD toward irreversible renal failure. Furthermore, the prehypertensive state is already associated with increased presence of inflammatory markers linked to atherosclerosis.

Typically, significant hypertension initially affects the renal vasculature, resulting in hyaline thickening of small arteries and arterioles (Table). At an earlier stage, hypertension and atherosclerosis may be intimately linked through their effects on endothelial function. A dysfunctional endothelium allows adhesion of lipid-filled macrophages and consequent chemotaxis and aggregation of inflammatory cells. In large vessels, hypertension favors atherosclerosis progression primarily by accelerating the conversion of fatty streaks to raised lesions. Eventually, the vascular lesions can progress to vessel wall necrosis (fibroid necrosis, necrotizing arteriolitis, and hyperplastic arteriolosclerosis), which may extend to the glomerulus as well (necrotizing glomerulitis).

Upregulation of angiotensin-converting enzyme and angiotensin II in the walls of atherosclerotic arteries underscores the role of the renin-angiotensin system in the pathogenesis of atherosclerosis in hypertension. Angiotensin II may accelerate atherosclerosis through activation of factors such as nuclear factor-κB (NF-κB), adhesion molecules, transforming growth factor-β (TGF-β), or endothelin-1, thereby inducing vascular growth, cell migration, and inflammation. Furthermore, angiotensin II is a potent stimulus for pro-oxidant enzymes such as the nicotinamide adenine dinucleotide phosphate (NAD(P)H oxidase), leading to an increase in reactive oxygen species (ROS) production (eg, superoxide anion) and consequently increased oxidative stress. ROS can induce vasoconstriction directly and by decreasing NO bioavailability, resulting in endothelial dysfunction. In addition, hypertension can also downregulate endothelial NO synthase activity. The decreased bioavailability of NO and increased ROS in hypertension can also activate other mechanisms (eg, LDL oxidation, monocyte and macrophage chemotaxis, smooth muscle cell proliferation) that can further contribute to the pathogenesis of atherosclerosis. Furthermore, elevated
blood pressure transmitted to the arterial walls induces mechanical cellular stretch, which stimulates production of angiotensin II, ROS formation, growth factor activation, and ECM proliferation, key components of the vascular remodeling process and atherogenesis.

**Diabetes**

Diabetes mellitus has become the single most important cause of ESRD. Approximately 30% to 40% of all patients with diabetes will develop nephropathy, and many will progress to ESRD. Experimental studies have shown that glucose can directly stimulate growth factors (eg, angiotensin II and TGF-β) in tubular and glomerular cells, likely via increased oxidative stress. Kidneys of diabetic subjects typically show early enlargement (Table) and basement membrane abnormalities in glomeruli and intrarenal small vessels. At later stages, a gradual progression of renal pathological changes in the kidney often occurs, which may or may not be associated with clinical renal disease, and some of which are relatively nonspecific. Typical renal diabetic lesions include arteriolar hyalinization (similar to hypertension) and sclerosis, focal-segmental and diffuse glomerulosclerosis, tubular vacuolization and atrophy, interstitial inflammation, and fibrosis.

Atherosclerosis, the most common complication of diabetes, develops faster and earlier in diabetic patients and affects the systemic and renal large and microvessels. Advanced glycation end products (AGEs), generated through long-term exposure of proteins to glucose or species derived from glucose, play a key role in dyslipidemia and accelerated atherosclerosis in diabetes. Their cellular effects are largely mediated by interactions with specific receptors. AGE formation and receptor upregulation are accelerated in CKD. AGEs can induce modification of LDL, accumulation of cholesterol and cholesteryl esters within macrophages, and formation of foam cells. Hence, this can exacerbate endothelial dysfunction, LDL oxidation and deposition, and inflammation, and thereby accelerate atherosclerosis. Furthermore, increased lipoprotein formation, oxidation and aggregation, and blunted antioxidant defense mechanisms also contribute to development and progression of atherosclerosis in diabetic patients.

The relationship between renal function and atherosclerosis in diabetes seems to be mutual: as much as diabetes is a strong risk factor for the progression of atherosclerosis and CKD, decreased renal function in turn accelerates atherosclerosis in patients with diabetes, implying CKD as a significant, independent risk factor for atherosclerosis in these patients.

**Hypercholesterolemia**

Hypercholesterolemia is present in ≈50% of the middle-aged adult US population. Lipid abnormalities often accompany and aggravate renal disease, favoring accelerated atherosclerosis and progression of CVD. Proatherogenic ox-LDL can promote glomerulosclerosis, whereas CKD patients develop secondary abnormalities in lipid metabolism (eg, increased triglycerides and ox-LDL, decreased HDL and apolipoprotein A-1) that promote atherosclerosis and increase cardiovascular morbidity and mortality.

Dyslipidemia may trigger renal injury at an early stage. Experimental studies demonstrated that diet-induced hypercholesterolemia resulted in renal endothelial dysfunction, intrarenal inflammation and fibrosis, vascular damage, microvascular remodeling, and ultimately glomerulosclerosis, and that oxidative stress mediated many of these effects. Glomerular mesangial, endothelial, and vascular smooth muscle cells can uptake native and ox-LDL, leading to glomerular injury by inducing formation of foam cells that are associated with later glomerulosclerosis and interstitial injury (Table). Interestingly, foam cell formation can also be induced by diabetes and hypertension. Glomerular adhesion and infiltration of macrophages and monocytes and production of ECM proteins then resemble atherosclerosis and lead to endothelial, tubular, and vascular injury, which may be reflected in proteinuria.

Although its interaction with other CVRFs to exacerbate CKD is prominent, evidence from human studies to establish isolated dyslipidemia as a primary and independent risk factor for renal disease is still incomplete. The risk of loss of renal function with hypercholesterolemia seems to be highest in those patients with moderate to severe CKD and coexistence of other CVRFs. Notably, a synergistic interaction among hypertension, diabetes, elevated ox-LDL, and low HDL has been suggested to accelerate progression of CKD to ESRD.

**Obesity**

The prevalence of obesity and overweight status exceeds 60% among US adults, who become exposed to obesity-related comorbidities and a number of CVRFs. Obesity is a risk factor for progressive renal function loss in patients with known renal disease and may damage the kidneys in otherwise healthy subjects. Obesity can produce renal injury by early upregulation of numerous proinflammatory (eg, leptin, interleukins, adiponectin, tumor-necrosis factor-α) and growth-promoting (eg, angiotensin II, TGF-β, leptin) factors, leading to mesangial matrix production and thickening of the glomerular and tubular basement membranes, lesions that may precede glomerulosclerosis. Furthermore, obese individuals have increased morbidity and mortality from nearly all of the common CVDs, as well as CKDs. Obesity can lead to hypertension by increasing renal tubular sodium reabsorption, impairing pressure natriuresis, inducing volume expansion, and by physical compression of the kidneys. In addition, development of diabetes and lipid abnormalities (decreased HDL, increased triglycerides and LDL) are frequent features in obesity and may favor development of atherosclerosis, adding a burden to renal damage in obese patients.

Obesity is considered the phenotypic hallmark of the metabolic syndrome, which affects 25% of adult Americans, and its prevalence worldwide is increasing. Metabolic syndrome contributes to the development of diabetes, hypertension, and CVD. Notably, the current epidemic of obesity and metabolic syndrome coincides with the growing CKD population and susceptibility to CKD increases with the number of metabolic syndrome traits. Patients with metabolic syndrome have a high prevalence of microalbuminuria,
which is considered an early marker for renal endothelial dysfunction and CKD, as well as for generalized endothelial dysfunction, atherosclerosis, and increased CVD risk. In addition, macrovascular and microvascular derangements of several vascular beds are frequent in this disease and may potentially lead to renal ischemia. Thus, aggressive obesity-lowering therapies are needed to ameliorate renal disease progression in the setting of metabolic syndrome.

Nontraditional Risk Factors
Established CVRFs may lead to renal injury, either directly or indirectly, by promoting atherogenesis (Figure 1). Traditional CVRFs have not fully accounted for the high risk of atherosclerosis, CVD, and total mortality in patients with CKD, and growing evidence supports the contribution of “nontraditional CVRFs” (Figure 1) to the accelerated atherogenesis in CKD. A number of nontraditional CVRFs have been suggested to contribute to CKD. Detailed description of each one is beyond the scope of this review. The most prominent among them (eg, asymmetrical dimethylarginine, homocysteine, and C-reactive protein) often share similar pathogenic mechanisms, including a decrease in NO availability, endothelial dysfunction or injury, and inflammation.

Cellular and Humoral Mechanisms of Atherosclerosis in CKD
Endothelial dysfunction, decreased NO bioavailability, and inflammation have been established as pivotal and common components of the injury cascade that results in accelerated atherogenesis in CKD (Figure 2). In addition, increased oxidative stress, immune responses, and fibrogenic pathways are emerging as key mechanisms.

Oxidative Stress
Studies from other laboratories and our laboratories (Figure 3) have consistently demonstrated the role of oxidative and nitrosative stress in experimental and clinical renal injury. This mechanism appears to be involved in every phase of atherosclerosis, from endothelial dysfunction to plaque formation and rupture. ROS can impair endothelial function and increase systemic and intrarenal proinflammatory and fibrogenic factors, possibly triggering a complex sequence of mechanisms involved in atherosclerosis and renal injury in CKD.

Normally, ROS are curtailed by a wide array of endogenous and exogenous antioxidant defenses. Increased generation of ROS and blunted or overwhelmed antioxidant defenses result in a shift toward a pro-oxidant state. This oxidative burden leads to increased oxidation of protein, lipids, and carbohydrates, escalates as CKD progresses, and is rather extensive by the time ESRD develops. The increased production of ROS and other radicals by endothelial, vascular smooth muscle, and adventitial cells can thereby induce endothelial dysfunction and favor atherogenesis. ROS inactivate NO and oxidize LDL (key events in atherogenesis), whereas ox-LDL, in turn, stimulates ROS production, instigating a pro-oxidant feed-forward mechanism. Furthermore, ROS regulate gene expression of a large number of transcription factors linked to inflammation, cell proliferation, differentiation, death, and tissue remodeling.
Inflammation

Inflammation is recognized in up to 50% of CKD predialysis and dialysis patients. Inflammation can induce and be elicited by endothelial injury, leading to endothelial dysfunction and eventual atherosclerotic plaque formation. Alternatively, inflammation may also be secondary to atherosclerosis (Figure 3), for example, intravascular plaques or ox-LDL. Like ROS, ox-LDL modulates inflammatory cytokines such as interleukins, tumor necrosis factor-α, interferon, and NF-κB. Inflammation is a primary systemic disturbance that may also link the presence and severity of atherosclerosis in different vascular beds. Therefore, its role as a trigger or consequence of atherosclerosis is still debated and is likely dual. Nevertheless, its correlation with increased oxidative stress underscores inflammation and oxidative stress as primary mediators of atherogenesis in CKD.

Notably, systemic inflammation and oxidative stress are considered to be nontraditional risk factors for CKD but may also represent the common downstream pathways by which CVRFs interact to amplify renal injury. For example, uremic toxins accumulated in CKD can induce free radical production in renal cells and therefore activate proinflammatory factors. In turn, inflammatory stimuli may stimulate intrarenal phagocytic cells to generate ROS and other radicals. Moreover, oxidative stress and inflammation may induce and result from endothelial cell dysfunction and injury because the endothelium is a source and a target of oxidants and participates in inflammation. Therefore, this dynamic interaction reflects a latent feed-forward mechanism by which inflammation and oxidative stress promote progression of atherogenesis and renal injury.

Immune Responses

Immune responses are predominant processes in the pathogenesis of atherosclerosis and are often mediated by ox-LDL. Lipid accumulation in intimal macrophages facilitates arterial inflammation, which can trigger and mediate specific immune responses directed against autoantigens or pathogen-derived antigens presented in the vascular wall. Indeed, atheromatous lesions are active sites of immune responses, where innate and adaptive immunity are necessary for the initiation, development, and progression of atherosclerosis.

The complement system, a powerful plasmatic effector cascade involved in the regulation of inflammation and tissue remodeling, can also be produced locally by tubular and glomerular cells as well in response to injury, acting in a paracrine and autocrine fashion. The complement cascade is mainly involved in innate immunity, its products can stimulate leukocyte chemotaxis and promote growth factor release, and its activation can precede and be modulated by the development of atherosclerotic lesions.

Fibrogenic Mechanisms

Either directly or by virtue of oxidation-sensitive pathways, atherosclerosis also modulates cell proliferation, differentiation, and death, culminating in renal structural injury and fibrosis. Oxidized or glycoxidized lipoproteins may promote dysfunction, glomerular injury, and interstitial fibrosis in the atherosclerotic kidney. Moreover, oxidative stress increases the propensity for renal damage in atherosclerosis by modulating transcription of growth factors.

We observed previously that diet-induced hypercholesterolemia may increase circulating levels and renal uptake of ox-LDL and thereby upregulate NF-κB, a transcription factor involved in modulation of genes implicated in inflammation and cell proliferation. Ox-LDL can also stimulate the synthesis and expression of the profibrotic TGF-β, which, in turn, may stimulate ox-LDL receptor expression, thereby perpetuating a vicious circle of oxidation, renal inflammation, and fibrosis. Profibrogenic factors such as the renin-angiotensin system, NAD(P)H oxidase, TGF-β, plasminogen activator inhibitor-1, and others may promote matrix deposition, whereas in parallel, systems involved in renal ECM degradation have been suggested to be blunted in early atherosclerosis. Renal fibrosis (Figure 3) may subsequently invoke microvascular changes, such as tortuosity and increased spatial density (Figure 4), possibly a compensatory mechanism to sustain renal perfusion. Therefore, structural injury in atherosclerosis
likely reflects the culmination of a concomitant increase in tissue production and blunted degradation, overall favoring renal scarring.

Conclusion

Despite recent advances in renal revascularization techniques and stenting, it remains unclear why the kidney affected by atherosclerosis often does not improve or continues to deteriorate after revascularization. This observation led to the speculation that atherogenic factors induce direct renal injury. Indeed, growing clinical and experimental evidence has demonstrated that several deleterious intrarenal pathways are activated during atherogenesis. Before development of plaques, atherosclerosis elicits microvascular and macrovascular dysfunction and tissue structural modifications, favored by traditional and nontraditional CVRFs, which likely activate similar mechanisms, interact, and often exacerbate renal injury. Their pathophysiological mechanisms include oxidative stress and inflammation, with several downstream sequences of feed-forward interactions, activating transcription factors that lead to vascular, tubulointerstitial, and glomerular injury. Moreover, atherosclerosis may blunt intrinsic defense mechanisms designed to preserve renal structural integrity, and thereby facilitate renal scarring (Figure 5). This hierarchical sequence triggers and likely perpetuates downstream mediators that are involved in the progressive renal compromise in atherosclerosis. Therefore, controlling oxidative stress and inflammation in CKD may interrupt this cycle of atherosclerosis-induced renal injury. Future research efforts are needed to uncover additional deleterious interactions in the atherosclerotic kidney and to design effective interventions to slow this process.

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References


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