

## Accelerated Atherosclerosis in the Setting of Chronic Kidney Disease

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### Abstract

Between 35% and 50% of deaths among patients with chronic kidney disease (CKD) can be attributed to cardiovascular disease. Even after adjusting for traditional cardiovascular risk factors, cardiovascular mortality risk is substantially increased in a linear fashion with decreasing glomerular filtration rate in CKD. Uremic toxins, oxidative stress and inflammation are critical factors found in CKD that can accelerate the atherosclerotic process. Although the precise mechanistic link(s) between CKD and cardiovascular disease are not yet fully defined, this review will discuss the current state of our knowledge. Lack of effective treatment for cardiovascular disease in CKD is a major unmet clinical need that can only be resolved with greater insight into the unique molecular and cellular mechanisms underlying cardiovascular disease pathogenesis in CKD.

**Keywords:** Atherosclerosis, Ckd, Statin, Inflammation, Oxidative Stress, Microbiome.

### INTRODUCTION

Chronic kidney disease (CKD), the gradual loss of kidney function over time, is associated with reduced life expectancy and affects approximately 1 in 10 people globally (1, 2). Cardiovascular disease is the leading cause of death in patients with kidney disease and degree of renal insufficiency measured as worsening glomerular filtration rate correlates

with risk and severity of atherosclerosis (3, 4). Atherosclerosis demonstrates several properties specific to the population of patients with kidney disease compared to the general population. One major difference is that atherogenesis is accelerated in this population (5, 6). Controlling for traditional atherosclerotic risk factors, the presence of CKD is a major risk factor for and independent predictor of the development of atherosclerosis (7-9) (Table 1).

**Table 1. Cardiovascular Risk in CKD. Aggravating factors.**

Atherosclerotic Risk Factors: CKD	
Traditional	Non-Traditional
Age	Inflammation
Gender	Cytokines
Obesity	Oxidative Stress
Diabetes	Uremic toxins
Smoking	Decreased glomerular filtration rate
Hypertension	Endothelial dysfunction
Hyperlipidemia	Infection
Physical inactivity	Abnormal gut microbiome

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The mechanism by which atherogenesis differs in patients with CKD compared to the general population is incompletely understood and is presently under active investigation. Amongst the abnormalities seen in CKD, enhanced inflammation and accumulation of uremic toxins are regarded as key factors promoting atherosclerosis (10, 11). For example, patients with CKD have been shown to manifest signs of increased oxidative stress (12-14). Hypertension, a known contributor to cardiovascular risk, is common in CKD and likely participates in atherosclerosis in CKD (15,16). Histologically, atherosclerotic lesions in CKD patients are similar in composition to those observed in persons with normal kidney function (17). This brief review will explore how the unique inflammatory environment in CKD affects the atherosclerotic process and discuss strategies for cardiovascular disease prevention and treatment in CKD.

### INFLAMMATION, OXIDATIVE STRESS AND UREMIC TOXINS IN CKD

Inflammation appears to play a role in atherogenesis as supported by several lines of evidence including the observation that premature atherosclerotic cardiovascular disease occurs more frequently in patients with systemic lupus erythematosus and rheumatoid arthritis, both examples of chronic immunologically-mediated diseases characterized by inflammation (18-20). The chronic inflammatory state that occurs in CKD may be attributed to a number of factors including increased production, slowed degradation and compromised clearance of pro-inflammatory cytokines, elevated levels of reactive oxygen species and chronic, recurrent infections (21).

Uremic toxins are solutes excreted by healthy kidneys that are not removed adequately in CKD and cause adverse effects (22). They are pro-atherogenic due to multiple actions such as enhancement of oxidative stress, and promotion of vascular smooth muscle and endothelial dysfunction (23-27). Oxidative stress in CKD results from impaired defenses as well as higher rates of pro-oxidant activity. There is excess formation of reactive oxygen and nitrogen species and increased oxidative burden in the kidney and vasculature with concomitant inflammation and production of oxidatively modified atherogenic lipids (13, 28, 29).

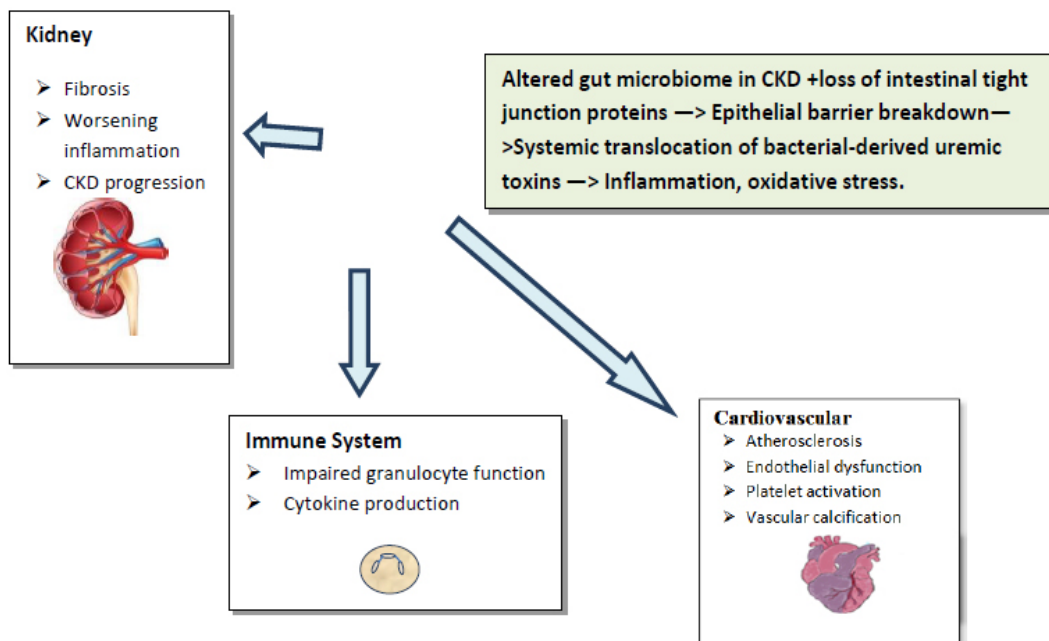
The uremic solute indoxyl sulfate has been shown to induce oxidative stress and inhibit endothelial

cell proliferation and migration in culture (30, 31). Indoxyl sulfate also makes cultured endothelium more adhesive to monocytes by increasing monocyte chemoattractant protein 1, E-selectin and intercellular adhesion molecule 1 (32-34). The inflammatory cytokines interleukin (IL)-1 $\beta$ , IL-18, IL-6 and tumor necrosis factor (TNF) $\alpha$  can be considered uremic toxins that may be atheroma-promoting (35-38). Other uremic toxins involved in atherogenesis are advanced glycation end products (AGEs) and leptin. AGEs, generated nonenzymatically by the Maillard reaction that binds reducing sugars with the free amino groups in proteins, lipids or nucleic acids, cause tissue damage and oxidative stress and are pro-inflammatory (39-41). AGEs inhibit nitric oxide synthase, leading to endothelial damage and dysfunction (42). Leptin, a peptide hormone produced by white adipose tissue, can also induce endothelial dysfunction, oxidative stress and inflammation while also promoting vascular smooth muscle proliferation and platelet activation (43, 44).

CKD is also associated with dysbiosis of the gut microbiome with an increased ratio of pathogenic and pro-inflammatory flora over symbiotic species (45). Pathogens that colonize the intestines enhance protein fermentation, producing waste metabolites such as microbial-derived uremic toxins. Further, a local inflammatory response to endotoxins produced by these microbes can allow breach of the intestinal barrier so that toxins more easily enter the circulation. These toxins are poorly excreted when kidney function is insufficient and can then add to the build up to harmful levels in CKD (46-48) (**Figure 1**).

### TREATMENT OF ATHEROSCLEROSIS IN CKD

In CKD patients, cardiovascular disease is often underdiagnosed and may be undertreated (49). Management of conventional risk factors for atherosclerotic cardiovascular disease that are prevalent in CKD patients is generally by well-established methods including medication to manage dyslipidemia, control blood pressure and reduce hyperglycemia (50) (**Table 2**). However, traditional Framingham risk factors are inaccurate predictors of cardiovascular prognosis in CKD (51). Other non-conventional atherosclerotic risk factors in CKD such as chronic inflammation do not yet have definitive treatments (52).



**Fig 1. Dysbiosis in CKD.** An abnormal gut microbiome may contribute to cardiovascular risk in CKD. Increased permeability of the gut epithelial barrier results in systemic translocation of bacterial-derived uremic toxins. These toxins induce oxidative stress and damage.

**Table 2. Strategies to Reduce Cardiovascular Risk in CKD.** Standard and innovative approaches.

Prevention and Treatment of Atherosclerotic Cardiovascular Disease in CKD	
Standard	Non-standard
Control blood pressure	Reduce inflammation
Control blood sugar	Reduce oxidative Stress
Manage lipids	MicroRNA targeting
Program of physical activity	Change gut microbiome - probiotics
Smoking cessation	Cytokine neutralization: monoclonal antibodies

Atherogenic dyslipidemia, characterized by increased triglycerides and decreased HDL levels, is commonly documented in persons with reduced renal function (53, 54). High triglycerides are likely a consequence of impaired clearance and reduced activity of lipoprotein lipase and hepatic triglyceride lipase (55, 56). Statin drugs are mainstay therapy for dyslipidemia with demonstrated impact on atherosclerosis in various populations who are at risk for cardiovascular disease. They are effective in decreasing the incidence of major atherosclerotic events in patients with moderate-to-severe CKD when combined with fibrates (57). Unfortunately, statins and especially statins combined with fibrates, may precipitate development of myopathy and rhabdomyolysis, which are already more likely to occur in CKD (58).

Another problem with statins is that they primarily target low density lipoprotein (LDL) cholesterol which is not as strongly associated with cardiovascular risk in CKD patients as in the general population (59, 60). Statins show even less efficacy in the end stage renal disease population treated by dialysis. In this group, statin therapy does not appear to measurably impact development of atherosclerotic complications and may not be recommended for them.

Another class of lipid lowering drugs, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, work by slowing LDL receptor degradation and it has been suggested that they may be useful in CKD due to their effects on distribution of HDL and LDL particle size, skewing toward larger, possibly less atherogenic particles (61, 62).

Elevated blood pressure among populations with CKD is a major modifiable cardiovascular risk factor with estimated prevalence of 67–86% (63). In their 2017 guidelines, the American College of Cardiology recommends that adults with CKD should be treated to a target blood pressure less than 130/80 mmHg (64, 65). Guidelines recommend blockade of the renin–angiotensin system (RAS) by using an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin-receptor blocker (ARB) because they provide additional blood pressure-independent renoprotection (66–68). ACEi, ARB, beta-blockers and calcium channel blockers are among the drugs commonly used to control blood pressure because lifestyle changes alone are rarely sufficient (69). Diuretics are often added as part of combination drug therapy in CKD and offer antihypertensive and cardioprotective benefits (70, 71).

Dietary and lifestyle modifications are also key components in cardioprotection in CKD (72–74). Smoking may interfere with effectiveness of some drug treatments (75). Diet is important and impacts blood sugar, lipid profile and the microbiome (76, 77). Newer approaches to reduce inflammation and uremic toxins and change the gut microbiome are being explored (78, 79). Resistant starch, a soluble fiber and prebiotic, has been proposed as a dietary supplement that may target the gut microbiome in a way that reduces uremic toxins (80). Anti-oxidants such as N-acetylcysteine are also in early stages of consideration for their ability to improve endothelial function (52,81).

Methotrexate, a powerful anti-inflammatory drug that reduces cardiovascular risk in rheumatoid arthritis, was tried unsuccessfully in non-auto immune populations (82–84). The Cardiovascular Inflammation Reduction Trial (CIRT, HL101422) was a randomized, double blind, placebo-controlled clinical trial designed to determine whether low dose methotrexate would reduce recurrent cardiovascular events in 7,000 patients with cardiovascular disease and type 2 diabetes or metabolic syndrome. The study was halted early due to lack of efficacy (85). However, methotrexate anti-inflammatory and anti-atherogenic effects are largely exerted via increased adenosine levels activating the adenosine A<sub>2A</sub> receptor and the concept of targeting specifically this receptor may still have merit in cardiovascular disease treatment in CKD and other populations (86–89).

## CONCLUSIONS

CKD is a chronic multisystemic disorder associated with accelerated atherosclerosis and enhanced cardiovascular risk (90). Traditional risk factors alone cannot explain the cardiovascular mortality in CKD. It is likely that the uremic environment amplifies pathological atherosclerotic processes through production of uremic toxins, exacerbation of inflammation and increased oxidative stress. Oxidized lipid accumulation and endothelial dysfunction contribute to initiation and progression of atheroma formation. Treatments include diet and lifestyle modifications, encouraging physical activity and smoking cessation. Medications are used to control blood pressure, blood sugar and dyslipidemia. Newer approaches that are still experimental include efforts to optimize the gut microbiome and to limit oxidative stress and inflammation. In the future, targeting of specific microRNAs, small non-coding RNAs that post-transcriptionally regulate gene expression, may be applied to restore functions related to endothelial integrity and other processes adversely impacted by the CKD milieu. Such studies are already underway in murine models (91, 92). Therapy with monoclonal antibodies to reduce cytokine activity is another intriguing possibility since these drugs, including anti-TNF and anti-IL-1 $\beta$  biologics, are already in use for autoimmune disorders (93). An early study of IL-1 $\beta$  inhibition looks promising (94). Unfortunately, cardiovascular disease in CKD remains a persistent and urgent problem with no major breakthroughs on the horizon at this time.

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