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Cardiovascular risk factors in chronic kidney disease

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Cardiovascular disease is the primary cause of morbidity and premature mortality in chronic kidney disease. While it is well established that patients with kidney failure (chronic kidney disease stage 5) are at high risk of cardiovascular disease morbidity and mortality [1], patients with earlier stages of chronic kidney disease also experience a high rate of fatal and nonfatal cardiovascular events [2]. Recent guidelines and position statements have therefore defined chronic kidney disease as a cardiovascular risk equivalent, and patients in all stages of chronic kidney disease are considered in the "highest risk group" for development of cardiovascular disease [3].

We propose that patients with chronic kidney disease are at increased risk for cardiovascular disease for several reasons (Fig. 1): (*1*) chronic kidney disease is associated with increased prevalence of traditional and nontraditional cardiovascular disease risk factors; (*2*) chronic kidney disease is an independent risk factor for cardiovascular disease; (*3*) many cardiovascular disease risk factors are also risk factors for progression of chronic kidney disease; and (*4*) the presence of cardiovascular disease may be a risk factor for chronic kidney disease. The interrelationship between cardiovascular and chronic kidney disease, with each contributing to the pathogenesis of the other, leads to a cycle of cardiovascular and kidney disease progression.

In the current review we focus on chronic kidney disease stages 1 to 4 and (*1*) present evidence suggesting that markers of chronic kidney disease, including reduced glomerular filtration rate (GFR) and microalbuminuria, are independent risk factors for cardiovascular disease, (*2*) describe the spectrum of cardiovascular disease in chronic kidney disease, and (*3*) discuss the role of traditional and nontraditional risk factors in the development of the different forms of cardiovascular disease. We do not describe management strategies as this is discussed in an accompanying review.

CHRONIC KIDNEY DISEASE AS AN INDEPENDENT RISK FACTOR FOR CARDIOVASCULAR DISEASE

Reduced GFR as risk factor for cardiovascular disease

An abundance of recent data has demonstrated an association between reduced kidney function and cardiovascular disease morbidity and mortality that persists after adjustment for traditional cardiovascular disease risk factors [2, 4]. Possible explanations for this association include that reduced GFR (*1*) is associated with an increased level of non-traditional risk factors that are frequently not adjusted for in analyses, (*2*) may be a marker of the severity of diagnosed vascular disease or of undiagnosed vascular disease, (*3*) may be a measure of residual confounding from traditional risk factors, for example, the severity of hypertension, and (*4*) patients with reduced GFR may not receive the benefits of optimal therapies such as aspirin, beta blockers, angiotensin-converting enzyme (ACE) inhibitors.

Microalbuminuria as a risk factor for cardiovascular disease

Prospective studies have established that albumin excretion, at levels well below the current cutoffs used to define microalbuminuria, is an independent predictor of cardiovascular disease outcomes [5]. Potential reasons for these findings include the following: (*1*) microalbuminuria may be a marker of generalized endothelial dysfunction and vascular permeability, (*2*) microalbuminuria may be associated with other traditional and nontraditional cardiovascular disease risk factors, and (*3*) microalbuminuria may be a precursor for the development of early or incipient kidney disease. In support of the last hypothesis, studies have demonstrated that microalbuminuria is associated with an increased risk for development of albuminuria, an accepted marker of kidney disease [6].

SPECTRUM OF CARDIOVASCULAR DISEASE IN CHRONIC KIDNEY DISEASE

Manifestations of cardiovascular disease in chronic kidney disease can be broadly classified as those affecting

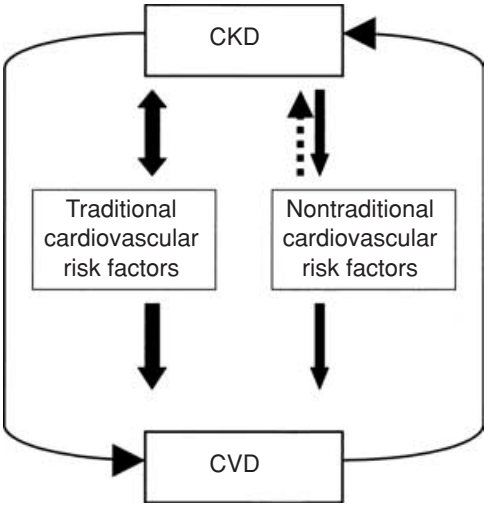

Fig. 1. Chronic kidney disease (CKD) is a risk factor for cardiovascular disease (CVD) and cardiovascular disease may be a risk factor for progression of chronic kidney disease. Traditional cardiovascular disease risk factors promote the development and progression of both chronic kidney disease and cardiovascular disease. Declining kidney function is associated with elevated levels of traditional and nontraditional cardiovascular disease risk factors. It remains unknown whether nontraditional cardiovascular disease risk factors (dotted arrow) are important risk factors for progression of kidney disease. Reproduced with permission from [7].

the myocardium and those affecting the blood vessels although these pathophysiologic processes are not mutually exclusive and are in fact closely interrelated (Fig. 2). As described below, clinical manifestations of myocardial and vascular remodeling include left ventricular hypertrophy (LVH), increased pulse pressure, and ischemic heart disease, all of which are independent risk factors for mortality in patients with kidney failure [8–10].

Myocardium

The pressure and volume overload that are inherent to the abnormalities of homeostasis seen in chronic kidney disease lead to structural alterations of the myocardium [11]. These structural changes include ventricular remodeling that may lead to eccentric or concentric LVH, systolic and diastolic dysfunction, and resultant clinical symptoms of heart failure.

Abnormalities of myocardial structure are common in chronic kidney disease. The prevalence of LVH was 30% in a cohort of patients with chronic kidney disease stages 3 and 4 [12]. In a large cohort derived from a health maintenance organization, the prevalence of heart failure ranged from 5% to 21% among patients with GFR of 15 to 60 mL/min/1.73 m^2 [4]. In a community-based cohort of patients with heart failure, 55% had creatinine clearance <59 mL/min [13].

Blood vessels

The hemodynamic and metabolic milieu evident in chronic kidney disease facilitates arterial remodeling. The resultant structural abnormalities include changes in the arterial lumen as well as components of the vessel wall [14]. Manifestations of intimal disease include atherosclerotic plaque formation and subsequent development of coronary artery disease and ischemic heart disease. Structural changes in the arterial wall such as increased collagen, calcification and extracellular matrix result in arteriosclerosis and arterial stiffening.

There is a high prevalence of both atherosclerosis and arteriosclerosis in chronic kidney disease. A coronary angiographic investigation of predialysis patients with chronic kidney disease stage 5 with no history of heart disease noted that 53% of the cohort had significant coronary artery stenosis defined as >50% stenosis [abstract; Ohtake T et al, *J Am Soc Nephrol* 9:0765, 2005]. In the population-based Atherosclerosis Risk in Communities (ARIC) Study, the prevalence of symptomatic coronary heart disease was 11% among persons with chronic kidney disease versus 4% in those without kidney disease [2]. There was a significant association between arterial stiffness, estimated as pulse wave velocity, and kidney function in a cohort of patients with mean creatinine clearance of 68.5 mL/min/1.73 m^2 [15].

Interrelationships of different forms of cardiovascular disease

The consequences of arteriosclerosis and loss of arterial compliance include increased afterload that in turn causes ventricular hypertrophy thus setting up a cycle of deteriorating myocardial function [13]. In turn, LVH increases myocardial oxygen demand thus further exacerbating ischemic heart disease.

RISK FACTORS FOR CARDIOVASCULAR DISEASE IN CHRONIC KIDNEY DISEASE

Both traditional and nontraditional risk factors have been implicated in the development of cardiovascular disease in chronic kidney disease. Traditional risk factors are those defined in the Framingham Heart Study and used to predict coronary heart disease outcomes in the general population [16]. Nontraditional risk factors are uremia-related factors that increase in prevalence as kidney function declines and may contribute to the excess risk of cardiovascular disease seen in chronic kidney disease [3] (Table 1).

Risk factors for LVH

Systolic blood pressure and anemia appear to be important determinants of left ventricular remodeling in patients with kidney disease [17]. In addition, several traditional and nontraditional cardiovascular disease factors

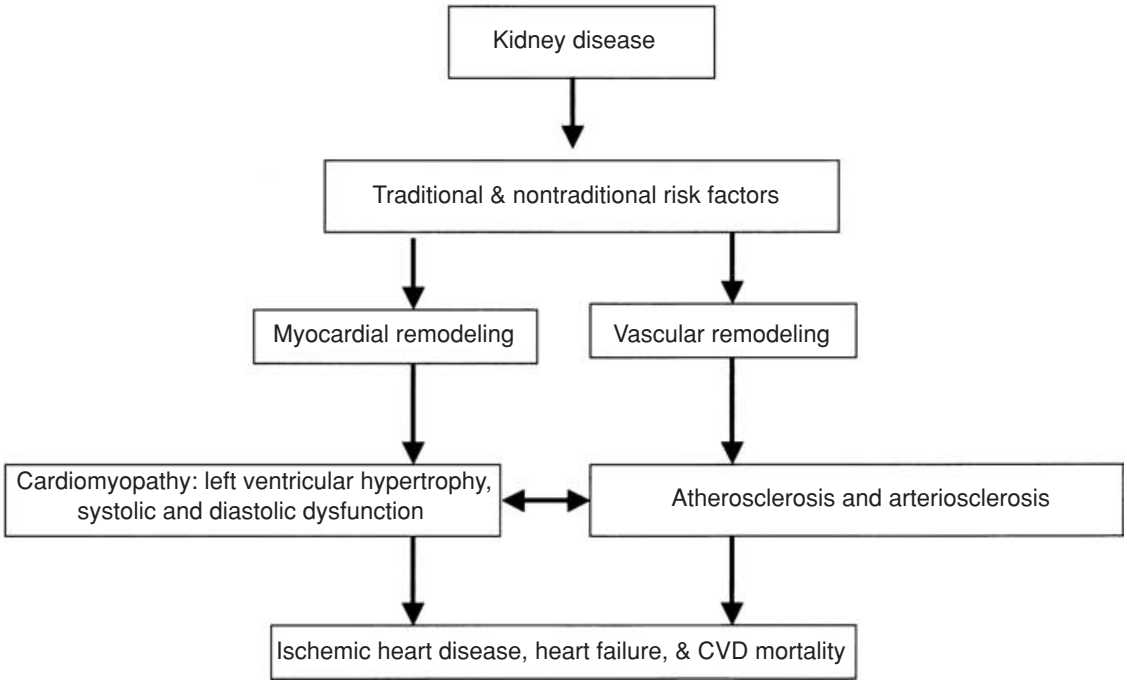

Fig. 2. Traditional and nontraditional risk factors associated with chronic kidney disease may promote myocardial and blood vessel remodeling resulting in different manifestations of cardiovascular disease (CVD), including cardiomyopathy, atherosclerosis, and arteriosclerosis. The latter subsequently lead to clinical manifestations of cardiovascular disease, including heart failure and ischemic heart disease.

are implicated in the pathogenesis of LVH in chronic kidney disease. In a cohort of incident dialysis patients from Dialysis Morbidity and Mortality Study (DMMS) Wave 2, age, hypertension, diabetes, smoking, and serum calcium and parathyroid hormone (PTH) levels were correlates of LVH [18].

Limited data exists on determinants of LVH in patients in the earlier stages of chronic kidney disease. In a nested analysis of data from the Australian Predialysis (SLIM-HEART) Study, LVH was a product of both increased chamber size as well as wall thickness [11]. In a cross-sectional study of patients with mean creatinine clearance of 25 mL/min, older age, higher systolic blood pressure, lower hemoglobin, and decreased level of kidney function were independent predictors of LVH [19]. Similarly, in the ARIC Study, among African Americans with chronic kidney disease stage 3, lower GFR and lower hemoglobin were associated with LVH [20].

More recent data suggest that additional nontraditional factors may be implicated in the development of LVH in kidney disease. In a cross-sectional study of hemodialysis patients, coronary artery calcification score and pulse pressure were independent correlates of LVH [21]. Markers of oxidative stress, discussed later, were also associated with LVH independent of carotid intima media thickness and number of plaques in a cohort of chronic hemodialysis patients [22].

Risk factors for atherosclerosis

There are limited data on traditional atherosclerotic cardiovascular disease factors in chronic kidney disease stages 1 to 4. Much of the existing information is extrapolated from studies in the general population. However, this extrapolation for the most part seems reasonable, as there is no a priori reason to assume that these risk relationships will widely differ in patients in the earlier stages of chronic kidney disease.

A few studies have confirmed the importance of traditional cardiovascular disease risk factors, such as diabetes, higher total cholesterol, lower high-density lipoprotein (HDL) cholesterol, smoking, and higher systolic blood pressure, in the development of atherosclerotic cardiovascular disease in chronic kidney disease stages 1 to 4 [23, 24].

Recent studies have suggested that the Framingham risk equation may be inadequate to attribute risk of coronary heart disease in a person with chronic kidney disease [25, 26], although this remains to be evaluated in large prospective studies. A potential explanation for the Framingham equation being inadequate in chronic kidney disease is the presence of nontraditional factors that are not accounted for by this equation.

There are few prospective studies or randomized controlled trials evaluating nontraditional factors as risk factors for the development of cardiovascular disease in

Table 1. Manifestations of cardiovascular disease in chronic kidney disease and associated putative risk factors

Pathology	Traditional risk factors	Nontraditional risk factors
Cardiomyopathy	Older age	Albuminuria
	Hypertension	Reduced glomerular filtration rate
	Valvular disease	Anemia
	Dyslipidemia	Inflammation
	Smoking	Arteriosclerosis
	Diabetes	Extracellular fluid volume overload
		Abnormal calcium/phosphate metabolism
Atherosclerosis	Older age	Albuminuria
	Male gender	Reduced glomerular filtration rate
	Hypertension	Anemia
	Diabetes	Inflammation
	Dyslipidemia	Oxidative stress
	Smoking	Endothelial dysfunction
	Physical inactivity	Homocysteine
	Left ventricular hypertrophy	Lipoprotein(a)
		Malnutrition
		Thrombogenic factors
		Sympathetic activity
		Insulin resistance/metabolic syndrome
Arteriosclerosis	Older age	Albuminuria
	Male gender	Reduced glomerular filtration rate
	Smoking	Endothelial dysfunction
	Hypertension	Abnormal calcium/phosphate metabolism
	Diabetes	Metabolic syndrome
	Dyslipidemia	

chronic kidney disease. Available evidence for some of these risk factors is briefly summarized below. We do not discuss anemia, as this is the topic of an accompanying review.

Inflammation

Inflammation appears to play an integral part in the pathogenesis of atherosclerosis. The most widely studied marker of inflammation is C-reactive protein (CRP). CRP may not be merely a marker of inflammation but may in fact mediate several key processes in the development of atherosclerosis including plaque initiation, formation, and rupture. In longitudinal analysis, CRP measured at baseline in the Modification of Diet in Renal Disease (MDRD) Study was an independent predictor of all-cause and cardiovascular disease mortality [27]. In the Nurses Health Study, higher levels of CRP, interleukin-6 (IL-6), and tumor necrosis factor (TNF) receptors I and II were associated with increased odds of coronary events in women with creatinine clearance <74 mL/min [28]. Other pro- and anti-inflammatory cytokines, including IL-10, and TNF-α may also play a role in the development of cardiovascular disease in chronic kidney disease [29].

Oxidative stress

Oxidative stress has been postulated as a common pathway via which other cellular processes such as inflammation and insulin resistance culminate in the pathogenesis of atherosclerosis [30]. There are, however, very limited data examining oxidative stress markers as cardiovascular disease risk factors in patients with chronic kidney disease. Post hoc analysis of patients with elevated creatinine in the Heart Outcomes and Protection (HOPE) Study did not find a benefit of Vitamin E on cardiovascular disease outcomes [31]; however, the Secondary Prevention with Antioxidants of Cardiovascular Disease in End-Stage Renal Disease (SPACE) trial demonstrated a reduction in cardiovascular disease events with vitamin E [32]. Similarly, Tepel et al [33] were able to achieve cardiovascular disease event reduction in patients with kidney failure by administration of acetylcysteine, a putative antioxidant agent [33].

Metabolic syndrome

There is a close correlation between components of the metabolic syndrome and kidney disease; and in fact it has been proposed that albuminuria be considered a component of the metabolic syndrome [34]. Metabolic syndrome has been linked to increased risk of cardiovascular disease mortality in the general population [35] but data are lacking in chronic kidney disease. Hyperinsulinemia and insulin resistance are also prevalent in kidney disease and a prospective study of nondiabetic hemodialysis patients demonstrated an association between insulin resistance and cardiovascular disease mortality [36]. A novel risk factor that has been the focus of recent investigation in kidney disease is adiponectin. Adiponectin, an adipocyte hormone, is inversely related to several metabolic parameters such as body mass index, glucose, and insulin and has been postulated to be a biomarker for the metabolic syndrome. Decreased plasma levels

of adiponectin were associated with increased risk of cardiovascular disease mortality in a cohort of chronic hemodialysis patients [37].

Hyperhomocysteinemia

High homocysteine (tHcy) appears to be associated with increased cardiovascular disease risk in the general population [38]. Similarly, elevated levels of tHcy may be associated with increased morbidity and mortality from cardiovascular disease in patients with kidney failure [39]. In contrast, low tHcy levels were associated with hospitalization and mortality in other studies in hemodialysis patients [40]. Data are lacking on the relationship between homocysteine and cardiovascular disease risk in patients in the earlier stages of chronic kidney disease, and whether decreasing homocysteine levels can reduce cardiovascular disease risk in this patient population.

Abnormal calcium and phosphate metabolism

As described in a subsequent section, abnormal mineral metabolism can promote arterial calcification, and arterial stiffness, which may lead to LVH and thereby potentiation of atherogenesis.

Endothelial cell dysfunction and injury

Abnormal endothelium-dependent vasodilation, manifested as impaired brachial artery reactivity, is a predictor of cardiovascular disease events and mortality in patients with kidney failure and this association is independent of arterial stiffness and LVH [41]. Endothelium-dependent vasodilation appears to be impaired in patients with chronic kidney disease [42], although its association with outcomes has not been studied in this population.

Endothelial cell apoptosis facilitates atherosclerotic plaque formation in several different ways, including increased vascular permeability, proliferation of smooth muscle cells and macrophages, and platelet activation and aggregation. A prospective study in chronic hemodialysis patients noted that levels of sFas, a marker of apoptosis, were independent predictors of future risk of fatal and nonfatal cardiovascular events [43].

RISK FACTORS FOR ARTERIOSCLEROSIS

Endothelial dysfunction

Impaired endothelium-dependent vasodilation is related to carotid wall distensibility in patients with kidney failure, suggesting that endothelial dysfunction may contribute to arterial structural alterations in patients with kidney disease [44].

Abnormal calcium and phosphate metabolism

A growing body of evidence implicates hyperphosphatemia and elevated calcium phosphate product as contributors to the excess cardiovascular disease risk in kidney failure [45]. Potential pathways include increased large vessel calcification with its associated effects on arterial stiffening, increased pulse pressure, decreased coronary perfusion, and LVH. There are limited data evaluating the relationships of serum levels of phosphorus and calcium phosphate product with cardiovascular disease in earlier stages of chronic kidney disease. A recent analysis of a cohort of United States veterans with chronic kidney disease stage 3 demonstrated that serum phosphorus levels>3.5 mg/dL were independent predictors of all-cause mortality [46].

CONCLUSION

Patients in all stages of chronic kidney disease are at high risk of cardiovascular disease. We have briefly presented available data from studies exploring the mechanisms underlying this excess risk. We acknowledge that this is not an exhaustive review of all the potential risk factors involved in the development of cardiovascular disease in chronic kidney disease. Rather, we have focused on a few with some degree of evidence available and that are potentially modifiable. It needs to be emphasized that causal relationships are yet to be established for many of the risk factors discussed. The implications of our present state of knowledge is that a high suspicion for cardiovascular disease is warranted and that aggressive treatment of traditional risk factors should be instituted in the earlier stages of chronic kidney disease. Additional basic science research, observational studies, and clinical trials, are, however, urgently needed to understand the pathophysiology of cardiovascular disease and to evaluate potential interventions to reduce the burden of cardiovascular disease in chronic kidney disease stages 1 to 4.

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