Canadian Journal of Cardiology 35 (2019) 1181–1187

Review

Determinants and Prevention of Coronary Disease in Patients With Chronic Kidney Disease

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ABSTRACT

Chronic kidney disease (CKD) is associated with premature cardiovascular morbidity and mortality. Traditional Framingham risk factors contribute partially to the malignant form of cardiovascular disease in CKD. Uremic-specific risk factors including chronic inflammation, retention of uremic toxins, and abnormal bone mineral metabolism have independently been linked to the pathogenesis of premature vascular aging, atherosclerosis, and cardiovascular disease. In this review we explore the mechanisms by which premature aging occurs in CKD through its pathologic effects on cardiovascular health, and the determinants of cardiac disease in patients with CKD. We outline strategies for prevention and therapeutic interventions in this vulnerable population.

RÉSUMÉ

L'insuffisance rénale chronique (IRC) est associée à une morbidité et à une mortalité cardiovasculaires prématurées. Les facteurs de risque classiques définis dans le cadre de l'étude de Framingham contribuent en partie à la forme maligne des maladies cardiovasculaires chez les patients atteints d'IRC. Des facteurs de risque urémiques, notamment l'inflammation chronique, la rétention de toxines urémiques et un métabolisme minéral osseux anormal, ont été liés indépendamment à la pathogenèse du vieillissement vasculaire prématuré, de l'athérosclérose et des maladies cardiovasculaires. Dans le présent article, nous examinons les mécanismes par lesquels le vieillissement prématuré se produit en présence d'IRC à la suite de ses effets pathologiques sur la santé cardiovasculaire. Nous abordons aussi les déterminants des cardiopathies chez les patients atteints d'IRC. Nous exposons les grandes lignes de stratégies de prévention et d'interventions thérapeutiques applicables au sein de cette population vulnérable.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in all patients with chronic kidney disease (CKD).[1] Coronary artery disease (CAD) accounts for at least 50% of all known causes of death in end-stage renal disease (ESRD),[2] whereas another 25% of all deaths among dialysis patients have been caused by sudden cardiac death.[2] CKD is also noted to have poorer clinical outcomes in patients with CAD, including reduced survival after acute myocardial infarction (MI) and were less likely to receive appropriate standard care.[3,4] Indeed, the relative risk of cardiovascular mortality of a 25- to 34-year old patient with ESRD is similar to that of a non-CKD patient older than 75 years.[5] The pathologic processes driving this association include vascular calcification, impaired coronary blood flow, hypertension, left ventricular hypertrophy, heart failure, arrhythmias, and conduction disease. Such vascular, myocardial, and rhythm disturbances are important contributors to the high cardiovascular morbidity and mortality among patients with CKD. However, in this review, we focus mainly on the vascular burden of CKD.

Common CVD Risk Factors

The link between CVD and CKD exists in part because they share common risk factors (Fig. 1). These include hypertension, diabetes, dyslipidemia, obesity, and cigarette smoking.[6] Some of these, such as hypertension, have a bidirectional relationship with CKD—as cause and consequence of CKD. Hypertension and vascular stiffness result in left ventricular hypertrophy, which is observed in 50% of patients with an estimated glomerular filtration rate of < 30 mL/min/m^2, and might result in reduced cardiac reserve, myocardial ischemia, and myocardial dysfunction.[7] To that aim, Kidney Disease Improving Global Outcomes guidelines[8] recommend treating hypertension in all patients with CKD to a target of $< 140/90$ mm Hg, ideally using an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Other recommendations include lifestyle modifications, such as physical exercise, weight loss, and smoking cessation, which are consistent with the

Received for publication March 11, 2019. Accepted May 16, 2019.

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See page 1185 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.05.025

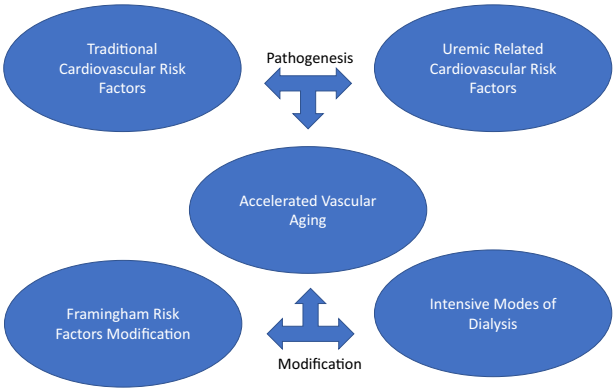

Figure 1. Determinants of accelerated vascular aging in chronic kidney disease.

recommendations to reduce coronary disease risk in the general population. Of note, blood pressure targets in dialysis are not well delineated and remain controversial.

Diabetes is the most common cause of CKD. Appropriate glycemic control to a target hemoglobin A1c (HbA1c) of approximately 7% has been recommended for delaying progression of diabetic nephropathy and reducing the risk of cardiac events for most patients with CKD.[8] The effect of tight glycemic control, targeting an HbA1c level of $< 7\%$, has been shown to reduce the progression of proteinuria in several randomized controlled trials.[9] Although these trials had conflicting outcomes regarding the risk of cardiac events, benefit was shown in subsequent extension trials and meta-analyses.[9] Furthermore, to the best of our knowledge, the effect of such tight glycemic control on renal and cardiovascular outcomes in more advanced stages of CKD and ESRD has not been established in any prospective randomized clinical trials to date. It therefore remains unclear whether targeting the same HbA1c is beneficial for patients with advanced or end-stage kidney disease.

Dyslipidemia is a common comorbidity in CKD and CVD patients.[10,11] In the general population, low-density lipoprotein level is independently associated with the risk of atherosclerotic events and statin-based lipid-lowering therapy have been shown to reduce such coronary risk. On the basis of findings from the **S**tudy of **H**eart **a**nd **R**enal **P**rotection (SHARP) trial,[12] nondialysis CKD patients older than the age of 50 years are recommended to be treated with either a statin or lower dose simvastatin (20 mg/d) with ezetimbe to reduce coronary risk and progression of CKD. However, the relationship between low-density lipoprotein levels and cardiac risk is controversial in ESRD. To date, this population has not been shown to benefit from statin therapy,[11] although most guidelines state that statin therapy is safe in patients who require renal replacement therapy.

CKD: Specific Risk Factors

Traditional Framingham risk factors only account partially for the CVD burden in CKD. As a result, CKD-specific risk factors are implicated including uremic toxins,[13] chronic inflammation-malnutrition,[14] and abnormal bone mineral metabolism and malnutrition.[15] Taken together, the syndrome of uremia has been thought to promote cellular senescence and premature aging.[16,17] Indeed, vascular calcification (usually encountered in aging) that occurs within the smooth muscle cell layer of the vessel media[18,19] is accelerated in CKD. Growing evidence suggests uremia-related toxic alterations (eg, high cyanate levels) in the internal milieu leads to DNA and mitochondrial damage, reactive oxygen species generation, chronic inflammation, Klotho deficiency, stem cell exhaustion, and telomere attrition—each independently leads to premature vascular aging, calcification, and CVD.[20]

Sustained inflammation is associated with cardiovascular aging and CKD. Investigators have explored the pathogenesis of uremia-related inflammation and suggested that chronic inflammation may be caused in part because of retention of proinflammatory cytokines with reduced glomerular filtration rate. Elevated levels of inflammatory cytokines (eg, interleukin 6 and C-reactive protein) are linked to oxidative stress and endothelial dysfunction.[21] The effect of chronic inflammation on CVD is also thought to be mediated through malnutrition and hypoalbuminemia observed in ESRD. Limited data suggest that antioxidant therapy, such as vitamin E, might improve CAD in ESRD. In the **S**tent-Supported **P**ercutaneous **A**ngioplasty of the **C**arotid Artery vs **E**ndarterectomy (SPACE) trial,[22] 196 dialysis patients with known cardiac disease were randomized to receive either vitamin E 800 units per day or placebo; those in the treatment arm had a lower rate of acute coronary syndrome at 1.5 years (16% vs 33%). Similarly, vitamin E-coated dialyzers have been reported to be associated with reduced levels of reactive oxygen species, inflammatory cytokines, and in some cases, regression of carotid intimal thickness.[23-25] However, these studies have been limited by their relative small sample size and poor generalizability, thereby restricting the widespread adoption of these interventions to prevent CVD in patients with CKD.

CKD: Bone Mineral Metabolism Dysfunction

Normally, phosphate and calcium are regulated by a complex interaction between kidney, bone, and gut in conjunction with a network of endocrine hormones. Alterations in the metabolism and homeostasis of calcium and phosphate, as well as regulatory hormones, such as parathyroid hormone (PTH) and vitamin D, occur in the context of CKD. The balance of these hormones and minerals is altered even in early stages of CKD.[25] The resulting increase in serum calcium and phosphate levels, systemic inflammation, cellular apoptosis, and depletion of calcium inhibitors stimulates an active calcification process throughout the body.[26] Such alterations have been associated with an increased risk for acute coronary events, CVD, and accelerated vascular calcification. The relationship between vascular calcification and cellular aging was reported in a study that showed that low levels of fetuin A—a serum inhibitor of vascular calcification—were associated with short telomere length in leukocytes.[27,28]

Both hyperphosphatemia and hypercalcemia are associated with mineralization of calcium in vessel walls, thereby promoting the phenotypic aging of the vasculature. In patients with CKD, calcification of blood vessels occurs at intimal and medial layers, which are clinicopathologically correlated with atherosclerosis and arteriosclerosis (or, arterial stiffening), respectively.[29] The intimal calcification of atherosclerosis is commonly observed in the early stages of CKD in association

with concomitant hypertension, dyslipidemia, and diabetes; whereas the medial calcification of arteriosclerosis typically occurs in more advanced stages of renal dysfunction in association with a uremic milieu.[29] It remains unclear whether intimal and medial calcification represent distinct pathophysiological processes and distinguishing them clinically might be difficult.[30] However, both have been implicated in the development of CVD including atherosclerosis, left ventricular hypertrophy, decreased coronary perfusion, and myocardial ischemia.[31]

Hyperphosphatemia might further contribute to premature vascular aging and CVD through its effect on vascular smooth muscle cells. By inducing DNA damage, hyperphosphatemia might hasten the process of senescence in these cells.[19,25] This is consistent with findings in humans and other organisms that phosphate levels are inversely associated with longevity.[32] In fact, recent evidence shows that high serum phosphate levels might accelerate vascular aging in the general population.[15,33] Clinical support for these theories among patients with CKD was shown in a multiethnic study of atherosclerosis,[34] which showed that phosphate concentration correlated with vascular calcification and a greater prevalence of CAD. Similarly, increased serum phosphate levels were reported to predict progression of coronary artery calcium scores,[31] which is independently associated with cardiovascular morbidity and mortality in the general population and those with CKD.[35]

Treatment of hyperphosphatemia with dietary phosphate restriction is often recommended, although the treatment effect is recognized to be small. The greatest benefit of treatment is derived from effective dialysis and noncalcium-based phosphate binders to maintain phosphate levels within normal range.[14] Several important trials have examined the effect of sevelamer—the most commonly prescribed noncalcium-based phosphate binder—on coronary artery calcification in CKD and ESRD patients. Some of these showed a reduction of calcification with use of sevelamer,[36,37] although differing opinions continue to be present. More recently, a meta-analysis of 31 studies on the effect of sevelamer on cardiovascular outcomes showed a significant reduction in coronary artery calcification scores and acute coronary events compared with calcium-based phosphate binders, but no effect on cardiovascular mortality.[38] However, it remains unclear whether the benefit observed with sevelamer in these studies was confounded by possible hypercalcemia caused by the calcium-based binders in the control arm. In clinical practice, the use of sevelamer might also be affected by its relatively high cost and gastrointestinal side effects, which limit its tolerability.

Hyperparathyroidism and vitamin D deficiency are common among patients with CKD and are correlated with vascular calcification. However, it is difficult to assess the independent contribution of elevated levels of PTH on CVD risk, because they are typically accompanied by confounding hyperphosphatemia. At present, insufficient evidence exists to determine whether vitamin D supplementation can be used to slow the progression of CKD or prevent CAD.[15]

Aberrant Klotho/Fibroblast Growth Factor 23 Axis

In recent years, the relationship between serum phosphate levels, bone mineral metabolism, and cardiovascular aging in patients with CKD has been considered in light of the Klotho/fibroblast growth factor (FGF) 23 (FGF23) axis. FGF23 is produced mainly by osteocytes and osteoblasts in bone and participates in the maintenance of mineral homeostasis. Specifically, FGF23 is regulated and produced by the interaction of serum phosphate, iron, and mineral hormones, such as 1,25-$(OH)_2$ vitamin D_3, PTH, and Klotho.[39,40]

The discovery of the Klotho gene occurred serendipitously in 1997 when unrelated transgenic mice developed a phenotypic premature aging syndrome that included atherosclerosis, osteoporosis, and shortened lifespan.[32] Upon further investigation, this silenced gene, later termed Klotho, was shown to encode a transmembrane protein highly expressed in kidneys, mainly in the distal convoluted tubules. The insoluble transmembrane Klotho functions as a coreceptor for FGF receptors to activate the FGF23 signal pathway. Secretases cleave the extracellular domain of membrane-bound Klotho to produce and release soluble Klotho—the main functional form of this protein—into the circulation.[36] Soluble Klotho functions as a phosphaturic and hypocalciuric hormone that can activate FGF receptors to transduce the FGF23 signalling pathway. This has a variety of biological functions including induction of phosphate excretion into urine. FGF23 exerts its phosphaturic and other biologic effects through Klotho-dependent activation of FGF receptors. At very high levels, FGF23 might also exert pathologic effects in a Klotho-independent manner.[36,41]

Levels of soluble Klotho are significantly decreased and those of FGF23 are markedly increased in patients with CKD and ESRD.[42] At present, CKD is considered to be a disorder of pan-Klotho deficiency and accelerated aging.[43] A growing number of animal studies have shown that Klotho deficiency alters nitric oxide synthesis[44] and promotes vascular calcification[45] and cardiac fibrosis and hypertrophy in CKD.[46] It has also been shown to accelerate the transition from acute to chronic uremic cardiomyopathy[47] and exacerbate this condition.[46] The protective effect of soluble Klotho against cardiomyopathy and hypertrophy is thought to be due to the maintenance of normal calcium signalling in the heart and normal serum phosphate levels.[48]

Studies in human subjects with CKD showed an independent association of serum Klotho levels with arterial stiffness, measured according to ankle-brachial pulse wave velocity.[49] Further evidence shows that hypertensive patients with mild CKD have significantly reduced Klotho levels compared with healthy subjects after controlling for estimated glomerular filtration rate.[50] Despite the promise of this new evidence, clinical data on Klotho are mainly derived from small observational studies and still require external validation in larger cohorts.

FGF23 functions primarily to promote phosphaturia and acts as a counter-regulatory hormone for vitamin D through inhibition of renal 1-alpha-hydroxylase and 24-hydroxylase enzymes. FGF23 has recently been reported to predict fast progression from CKD to ESRD and be associated with increased cardiovascular morbidity and mortality.[42] This has included increased risk of coronary disease, heart failure, and left ventricular hypertrophy. Patients with CKD and elevated FGF23 levels also have increased aortic and coronary calcification scores compared with those with low levels of FGF23.[51,52]

High FGF23 levels have been clinically correlated with endothelial dysfunction and arterial stiffness among patients with CKD. The effects of FGF23 on endothelial function are thought to occur via increased superoxide levels, reduced nitric oxide levels, and elimination of acetylcholine-mediated endothelial relaxation, all of which contribute to CVD.[52] Another proposed mechanism through which FGF23 mediates CVD is through atherosclerosis, which is increased in CKD patients with higher FGF23 levels.[53] Similar findings have been observed in the general population, among whom higher FGF23 levels are independently associated with a greater risk of major cardiovascular events. Nevertheless, a direct causal link between FGF23 and CVD has yet to be fully established in humans on the basis of the limited experimental data that currently exist.

On the basis of the evidence, Klotho repletion and FGF23 antagonism have both been considered as novel therapeutic strategies for CKD and the prevention of CVD in this population. Repletion of Klotho by exogenous administration of this protein would be preferred among patients with CKD and ESRD, who might lack the necessary renal function to upregulate endogenous Klotho production. Phase I animal studies have already shown that bolus administration of soluble Klotho protein is safe and effective in inducing phosphaturia and preventing progression of kidney injury.[45,47] Further, a study of Klotho-deficient CKD mice showed that intravenous delivery of a transgene encoding soluble Klotho improved uremic cardiac hypertrophy. However, the bioavailability, safety, and efficacy of such treatments have yet to be established in humans.

Reduction of FGF23 levels, which in turn causes lower serum phosphate levels, has presented another novel strategy for CVD risk reduction in patients with CKD and ESRD. Antibodies to FGF23 have been developed for this purpose and have been shown to successfully hinder the development and progression of secondary hyperparathyroidism in rats with CKD.[54,55] This antibody-mediated antagonism of FGF23 resulted in undetectable FGF23 levels and effectively produced FGF23 knockout mice. However, this complete or "knock out" depletion of FGF23 resulted in early death of the animals. The results of this experiment suggest that optimal future treatment strategies targeting FGF23 should require dose titration of FGF23. At present, there are no FGF23 blocking agents that have yet achieved this balanced effect.

Biomarkers for CKD and CVD

The development of clinical biomarkers might help to identify patients at high risk of cardiovascular events and might help with primary and secondary prevention among patients with CKD. This approach is on the basis of the assumption that early and accurate assessment of cardiovascular risk would help to facilitate diagnosis and more aggressive or targeted treatments for those most likely to benefit from them. In the general population, markers such as natriuretic peptides (eg, atrial natriuretic peptide, B-type natriuretic peptide [BNP], and C-type natriuretic peptide) and cardiac troponins (TNs; eg, TNT, I, and C) are already widely used for this purpose. These and other novel biomarkers are currently being investigated for application among patients with CKD and ESRD.

Cardiac TNT

TNs are contractile components of cardiac myocytes that are released after myocardial cell injury. TN levels increase 3-12 hours after myocardial insult in proportion to the degree of injury and then normalize over 1-2 weeks. However, patients with CKD commonly have increased levels of cardiac TNT (cTNT) in the absence of acute MI. Nevertheless, some studies suggest that increased TN levels in these patients are still associated with increased risk of CAD and death.[56,57]

In a cohort of 847 Dutch dialysis patients, those with cTNT levels between 0.05 and 0.10 μg/L at 2 years had a hazard ratio of 2.2 for all-cause death (95% confidence interval [CI], 1.7-2.8) compared with patients with levels < 0.05 μg/L; there was a further increase in the hazard ratio, up to 3.3 (95% CI, 2.5-4.5), among patients with cTNT levels > 0.10 μg/L.[58] This association remained significant when isolated for cardiovascular mortality, with hazard ratios of 1.9 (95% CI, 1.2-3.1) and 3.4 (95% CI, 2.1-5.7) for corresponding cTNT levels of 0.05-0.10 μg/L and > 0.1 μg/L, respectively. However, the specific cause of cardiovascular death, such as acute MI or sudden cardiac death, was not reported in this study.

cTNT levels have also been successfully used to identify patients with asymptomatic obstructive CAD. In a study of 142 patients at the time of renal replacement therapy initiation, stepwise regression analyses were used to determine that cTNT was an independent predictor of obstructive, asymptomatic, multivessel CAD among the 27 patients shown to have this condition (sensitivity 92.6% and sensitivity 63.6%).[59] cTNT might therefore be helpful in detecting asymptomatic CAD, which is more common among CKD and ESRD patients, but the lack of day-to-day reliability of the test and the variability between laboratories might limit its widespread use in this population. Technological innovation in test reliability and further experimental studies might aid this process and applicability of cTNT in ESRD patients.

Natriuretic peptides

Natriuretic peptides are involved in sodium and water balance by controlling natriuresis, vasodilation, and diuresis. BNP is released by the myocardium in response to ventricular stretch, often caused by increased preload volume and wall stress, and is commonly used as a biomarker for congestive heart failure. Several studies have also shown their utility as markers of CVD risk in patients with CKD, correlating with the severity of heart failure and left ventricular dysfunction. In a Japanese study, the risk of cardiovascular events in patients with CKD was significantly higher among the participants with the highest serum BNP levels.[60] Similarly, prospective studies have shown that N-terminal prohormone of brain natriuretic peptide (NT-proBNP)—the inactive fragment of BNP—is an independent marker of risk for congestive heart failure or adverse cardiovascular events among chronic peritoneal dialysis patients (odds ratio ranges, 4.25-9.1 for the fourth compared with the first quartile of NT-proBNP) level.[61] This evidence suggests that there might be some prognostic benefit to BNP and NT-proBNP measurement in CKD and ESRD patients.

Dialysis Modality

The process of renal replacement therapy itself is associated with many risk factors for CVD. In conventional hemodialysis, patients receive intermittent sessions, often in approximately 4-hour sessions 3 times per week. This limited duration of each session might result in more aggressive ultrafiltration to remove excess fluid. It might also result in a prolonged interdialytic gap, such as the 72-hour period between Friday and Monday sessions or between Saturday and Tuesday sessions that occur in a typical 3 sessions per week scheduling. This prolonged interdialytic interval results in greater interdialytic weight gain and potentially more aggressive ultrafiltration responses.[62] It therefore engenders a greater risk of rapid changes in fluid and solutes, which is associated with myocardial stunning and higher mortality in patients who undergo 3 times a week hemodialysis.[63] Indeed, McIntyre and colleagues showed that the severity of myocardial stunning documented as regional wall motion abnormality (measured using intradialytic echocardiography and positron emission tomography scans) is directly associated with mortality rates in patients who undergo hemodialysis.[64]

The process of dialysis (hemodialysis and peritoneal dialysis) is associated with increased oxidative stress, and producing more complement fragments, cytokines, and adhesive molecules in endothelial cells that might contribute to the development of accelerated atherosclerosis and coronary artery calcification.[65] At present, the unadjusted mortality rate from cardiovascular events is nearly 30 times higher than that of the general population in the United States. Modifications to dialysis modality might provide a useful avenue to address this increased cardiovascular risk of morbidity and mortality.[1]

Converting to intensive home hemodialysis with longer and more frequent sessions has recently been shown to have a series of cardiovascular advantages including lowering of blood pressure and vasoactive medication need, correction of left ventricular hypertrophy, sleep apnea, augmentation of brachial artery reactivity, restoration of heart rate variability and baroreflex sensitivity, and reduction of cardiovascular-related hospitalization.[66-68] Similarly, a large population-based cohort study in Taiwan showed that patients who underwent conventional hemodialysis had a significantly higher incidence of CAD compared with patients who underwent peritoneal dialysis.[69] However, a recent meta-analysis suggested that insufficient evidence exists at present to compare the effect of renal replacement modality on progression of coronary artery calcification.[70]

Conclusion

CKD is associated with an accelerated burden of CVD. To date, general CKD and dialysis-related determinants and risk factors have been identified. There is an emerging literature that suggests that accelerated aging might be a unifying theory to explain the observed phenotype in patients with CKD. Future strategies in mitigating these pathogenetic risk factors might redress the overall burden of CVD in CKD.

Disclosures

Christopher T. Chan holds the R. Fraser Elliot Chair in Home Dialysis and has consulted for Baxter Inc, NxStage Inc, and Medtronic Inc. Rebecca Rodin has no conflicts of interest to disclose.

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