Assessment and management of cardiovascular disease in patients with chronic kidney disease

**Abstract**

Cardiovascular disease is the leading cause of death in the set of chronic kidney disease (CKD) patients, whether on renal replacement therapy or conservative treatment. A better understanding of cardiovascular risk factors, diagnostic approach and management are central keys to develop strategies to reduce cardiovascular mortality among those patients. This review article discusses some aspects of pathophysiology, investigation methods and current treatment of cardiovascular disease in CKD patients.

**Keywords:** cardiovascular diseases, uremia, left ventricular hypertrophy.

**Introduction**

Patients with chronic kidney disease (CKD) are at great risk for early death, especially that of cardiovascular cause. Cardiovascular events often manifest before end-stage kidney disease. This review article discusses the risk factors involved in the development of cardiovascular disease (CVD) in CKD, the most frequently used investigation methods, and the therapeutic strategies and targets that may determine a favorable impact for reducing adverse clinical outcome on the CKD population, whether on dialysis or not.

**Risk factors and physiopathology of CVD in CKD**

The identification and clinical application of risk factors for cardiovascular disease are important, because they can indicate peculiar pathological mechanisms, determining better understanding of the disease’s natural history and developing therapeutic strategies to reduce morbidity and mortality. Similarly, CKD-specific cardiovascular risk factors require specific investigation in that group of patients, who develop peculiar arteriopathy and cardiomyopathy.

The pathogenesis of the cardiovascular disease in that population is complex and seems to be determined by a high prevalence of traditional risk factors, such as arterial hypertension, diabetes mellitus, and dyslipidemia, and by the presence of other emerging risk factors and/or risk factors inherent to chronic kidney failure. Of the emerging risk factors and/or risk factors related to uremia, the following stand out: anemia; mineral metabolism disorders; systemic inflammation; and oxidative stress exacerbation.
Anemia is common in several stages of CKD and in its dialysis modalities. It has a multifactorial physiopathology, but basically depends on the reduction in the synthesis of endogenous erythropoietin. Hemoglobin levels lower than 11g/dL are associated with a decrease in the quality of life and an increase in cardiovascular morbidity and mortality.1

Patients with CKD often develop bone and mineral metabolism disorders, especially hyperphosphatemia, hyperparathyroidism, and vitamin D deficit, which are associated with an increase in the risk of cardiovascular calcifications and mortality.2 In past years, special attention has been given to the potential damages caused by the systemic deficit in activation of vitamin D receptors on the cardiovascular system, which seems related to early and late mortality of patients on hemodialysis (HD).3

Chronic kidney dysfunction has been frequently associated with oxidative stress increase4, consequent to the reduction in the antioxidant capacity associated with renal function loss or the increase in the production of oxygen reactive species, with an elevation in metabolic disarrangement markers. Among the multiple factors associated with malnutrition, cardiovascular disease, and mortality in patients with CKD, low-degree chronic inflammatory process stands out, evidenced by high levels of C-reactive protein, and affects 40%-50% of CKD patients.5 That disorder is determined by several causes, some resulting from progressive renal function loss and others associated with systemic low-degree chronic inflammation.

Figure 1. Pathophysiology of cardiovascular disease (CVD) in patients with chronic kidney disease (CKD)

In the initial stages of CKD, the traditional risk factors for CVD act as triggers not only for initiating the deleterious modifications in the cardiovascular system, but also as promoters of CKD progression. In intermediary stages of the disease, the typical CKD phenomena involved in the pathogenesis of CVD, such as anemia, mineral metabolic disorders, and systemic inflammation begin to install. In CKD end stages and dialysis phase, traditional risk factors, those inherent to uremia, and new specific factors related to the ongoing dialysis modality, work jointly. Systemic low-degree chronic inflammation plays a central role in pathophysiology. Several myocardial alterations, especially those associated with fibrosis and vascular calcifications, occur, justifying innumerable events of sudden death (due to cardiac arrhythmias) and congestive heart failure. Atherosclerotic damage in medium and large-caliber arteries account for cerebro-vascular accident, peripheral vascular disease, and abdominal aorta aneurysm.
with dialysis in end-stage renal disease.

**Assessment of Atherosclerosis in CKD**

At least in diabetic patients on HD, clinical symptoms and standard risk factors for cardiovascular disease are not valuable predictors of coronary artery disease (CAD). In fact, diagnosing CAD based only on classical symptoms and clinical factors in patients with CKD is extremely difficult. For example, the isolated analysis of the electrocardiogram (ECG) of HD patients has shown that the presence of a ST segment depression during sessions was efficient in diagnosing CAD in symptomatic patients. That exam had sensitivity of 67% and specificity of 52% in patients undergoing renal replacement therapy. In that same study, the author has reported that exercise ECG cannot be performed in most patients, due to their lack of physical fitness and several medicamentous interactions. Another study with that population has shown that 44% of those undergoing exercise ECG did not reach 85% of the predicted heart rate.

The use of pharmacological stress tests in association with echocardiographic images (stress echocardiography) seems to be a valid alternative for assessing the presence of obstructive coronary artery disease in patients with renal dysfunction. Nevertheless, this method has the disadvantage of largely depending on the examiner. More sophisticated tests, such as myocardial scintigraphy and coronary angiotomography, also have limitations. Examples of those limitations are the 85% sensitivity in diabetic patients undergoing the exam with thallium, and the high prevalence of arterial calcifications, that hinder tomographic vascular assessment.

For detecting CAD in dialysis patients, data currently available suggest that vasodilator-induced stress nuclear scintigraphy (adenosine or dipyridamole) is less sensitive than stress echocardiography. Those data, however, derive from studies in diabetic patients being assessed for transplantation, and cannot be extrapolated to the entire dialysis population. Thus, very often, CKD patients on dialysis undergo coronary cineangiography for investigating CAD, since non invasive methods have no significant accuracy. Thus, the ideal way of searching CAD in patients with CKD is yet to be found, and a combination of sequential exams can increase the final accuracy of CAD detection in those patients.

**Assessment of Cardiomyopathy in CKD**

The ECG, classically considered a low-sensitivity and good specificity method, has a very limited overall accuracy for excluding left ventricular hypertrophy (LVH) in patients with CKD. Echocardiography (ECO) is the imaging method with the greatest body of evidence proving its usefulness in clinical practice and research protocols. Traditionally, M-mode, two-dimensional, and Doppler ECO provide a detailed analysis of heart anatomy, diagnose dysfunction (even subclinical), and provide substitutive markers of cardiovascular outcomes for prognosis and intervention studies. Recent advances, such as the introduction of three-dimensional ECO (3DE) in the clinical setting, made the method even more precise for determining left ventricular mass, volumes, and ejection fraction. In comparison with other methods, 3DE accuracy is greater than that of M-mode and two-dimensional ECO, and similar to that of heart magnetic resonance imaging (HMR).

Heart magnetic resonance imaging is the current gold standard method for assessing heart mass, volumes, and function, in addition to detecting the presence and extension of myocardial fibrosis. The HMR precision is less affected by the variations in volume after a HD session as compared with that of ECO. However, the widespread use of HMR is limited in practice by several disadvantages, such as low availability, high cost, formal contraindications (claustrophobia and use of implantable cardiac devises), and risk of progressive nephrogenic fibrosis (secondary to gadolinium) in patients with advanced CKD.

Cardiac tomography has also good accuracy to determine volumes and mass, in addition to quantifying calcium score (prognostic parameter) and coronary stenoses (with contrast medium injection), but involves radiation and has restricted availability.

Finally, a recent alternative is the use of cardiac biomarkers (especially, troponin-T and NT-pro-BNP) as useful adjuvant tools in the diagnosis and prognosis of uremic cardiomyopathy.

**Morphofunctional Alterations**

Left ventricular hypertrophy (LVH) affects 70%-90% of patients on regular dialysis (Barberato et al, Arq Bras Cardiol 2009, in press) and is associated with an unfavorable prognosis (more than two thirds of dialysis patients with LVH die of congestive heart failure or sudden death). Mass monitoring by use of serial echocardiogram is a highly important tool for assessing prognosis and success of interventions aiming at LVH regression.

Left ventricular systolic dysfunction (with or without associated dilation) is found in 15% to 18% of
uremic patients, and is a powerful indicator of unfavorable prognosis for patients on HD20 and after renal transplantation. The adverse effect of systolic dysfunction does not depend on left ventricular mass, but both alterations interact in predicting cardiovascular outcomes, and reach maximum risk in patients with an association of both.

Diastolic dysfunction is present in most individuals on renal replacement therapy. Recent data emphasize the importance of estimating the severity of diastolic dysfunction in a non invasive way, identifying patients evolving with an elevation in filling pressures (advanced diastolic dysfunction, that is, grades II and III). By using integrated echocardiographic approach in patients initiating HD, advanced diastolic dysfunction was identified in approximately one forth of that population, which determined a prognostic impact independent from traditional clinical and echocardiographic data (Barberato et al., Arq Bras Cardiol 2009, in press).

Left atrial (LA) enlargement, estimated through the calculation of LA volume, has shown a great clinical value for stratifying cardiovascular risk in HD patients. The increase in LA volume was an accurate parameter for detecting advanced diastolic dysfunction, was associated with predisposition to intradialytic hypotension, and achieved predictive power independent from overall mortality in patients on renal replacement therapy.

Valvar calcifications, especially of the mitral ring and aortic valve, are often seen in patients on chronic dialysis. In addition to being able to have clinical repercussion, determining reflow and/or valvar stenosis, their importance lies in the suggested association between valvar calcification and greater risk for mortality and cardiovascular events in uremic patients.

Clinical management of CVD in CKD

The management of CVD in CKD is widely influenced by data obtained from observational studies and expert opinions, due to lack of large prospective and randomized studies with outcomes adequate for assessment. Independently from those observations, some interventionalal studies have been carried out and will be here reviewed. Table 1 summarizes the major cardiovascular risk factors in the population with CKD and their respective therapeutic targets.

Regarding HD patients, consensus about ideal blood pressure values lacks, and pre-dialysis values < 140/80 might not be adequate for most patients. In a study conducted in a large cohort of HD patients, lower pre- and postdialysis blood pressure values were associated with higher mortality, which probably reflects associated cardiovascular comorbidities in those patients. Among the classes of anti-hypertensives, the most beneficial for the dialysis population were angiotensin receptor blockers, ACE inhibitors, and beta-blockers. Despite the small number of participants in those studies, a recently published meta-analysis based on those and other randomized studies has suggested that anti-hypertensive therapy in dialysis patients is usually responsible for reducing cardiovascular events, which, however, still requires confirmation with randomized studies involving a larger number of participants.

Although in the population with no CKD a strict control of diabetes is associated with a reduction in chronic complications, in the HD population, a stricter control of glycemia protected patients against death due to infectious processes, but not against those due to cardiovascular events.

Dyslipidemia in CKD and its association with CVD has been extensively discussed, and several mechanisms relating that abnormality to systemic inflammation and to atherosclerosis triggers have been shown. In patients with non-dialytic CKD, the reduction in cholesterol levels with statins has been associated with a reduction in coronary events, but had no influence on cardiovascular mortality. Similarly, in recent studies with dialysis patients, the use of statins has not shown the expected cardiovascular benefits. Other studies are still required to assess the actual role played by statins in reducing cardiovascular events in the dialysis population, but, until then, patients with CKD should be approached as being at high coronary risk.

Several studies have assessed the cardiovascular impact of correcting anemia with erythropoietin (EPO) on patients with CKD undergoing conservative treatment or dialysis. Such studies have reported a greater cardiovascular risk when higher target levels of hemoglobin are stipulated, suggesting that, up to the present time, values around 11-12 g/dL should be respected in those patients.

In past years, the association of mineral (hyperphosphatemia, hypercalcemia, and hyperparathyroidism) and bone metabolic disorders with increased mortality has become evident, especially in dialysis patients, resulting mainly from cardiovascular calcifications. In that scenario, the use of non-calcium-based phosphate binders could determine, through a reduction in the calcification process, better survival rates. That hypothesis was tested in two randomized clinical trials. The first trial involved more than...
2,000 HD patients and compared patients receiving sevelamer with a group receiving calcium-based binders for three years. Despite the large case series, no significant difference was found in the risk for cardiovascular death between the groups. However, analyses in subgroups of patients in that study have shown that, among those over the age of 65 years, a 23%-reduction in CV mortality was found in patients receiving sevelamer. The second study has assessed cardiovascular mortality and coronary calcification progression in incident HD patients, and has reported that sevelamer significantly reduces those events.

The literature shows increasing evidence that the use of activated vitamin D provides cardiovascular protection to CKD patients. Studies on animal models have provided more detailed information on that issue, suggesting that vitamin D has several beneficial effects on myocardium and endothelium, participating in blood pressure control, attenuating LVH, and regulating the maturation and expression of collagen in heart tissue. Because a great part of the process involving the increase in LV mass in CKD derives from the accumulation of collagen (fibrosis) among cardiomyocytes, the use of activated vitamin D, and especially of its less hypercalcemia-inducing analogues (paricalcitol), is highly attractive and has been the focus of intensive research in recent years.

Another class of drugs currently studied and used for treating hyperparathyroidism associated with CKD is that of the calcimimetic agents, whose great appeal lies on the fact of reducing hypercalcemia events associated with vitamin D treatment, and, in parallel, contributing to the reduction in vascular calcification. Ongoing clinical studies with analysis of cardiovascular outcomes will help in answering questions about the effective reduction in cardiovascular morbidity and mortality with that class of drugs.

Left ventricular hypertrophy in CKD and in dialysis patients is often related to myocardial fibrosis mechanisms, which not necessarily involve preload and afterload (excessive volume) phenomena. In experimental models and in renal transplanted patients, the use of sirolimus (and not of calcineurin inhibitors) has determined a significant reduction in LV mass. The potential toxicity of the drug, however, has not yet allowed the conduction of clinical trials in the dialysis population.

In CKD, interesting connections between elevation in aldosterone levels and magnitude of LVH have already been reported. Solid evidence linking aldosterone and uremic cardiomyopathy, however, is not yet available. Although widely used as cardioprotective in the population with heart failure and no advanced kidney disease (GFR > 60 mL/min), there are few studies on advanced dialytic and nondialytic CKD assessing the efficacy and safety of the drug, because of the preoccupation with episodes of potentially fatal hyperpotassemia.
Thus, the safety of using that type of drug in advanced CKD is still controversial. A recent review about the issue has indicated the need for new studies assessing outcomes focused on the progression of renal disease and cardiovascular death.

Finally, more frequent HD sessions (short daily sessions) or prolonged nocturnal sessions have been compared with traditional sessions three times a week and with peritoneal dialysis, and important outcomes, such as better pressure control, reduction in LVH, and mortality, have been assessed. Long-term actual cardiovascular benefit for those more frequent or prolonged therapies is being evaluated in an ongoing multicenter randomized study, predicted to end in 2010.

**Conclusions**

The mechanisms of CVD in the presence of CKD begin to be better understood. A wider view of the problem including coronary and peripheral arteriopathy and cardiomyopathy is required for identifying patients at risk, more effective investigation, and development of more efficient interventions. Therapeutic targets and ways to achieve them are being identified and should guide clinical management aiming at reducing morbidity and mortality of the association between CVD and CKD.

**References**


