CARDIOVASCULAR REMODELLING IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Left ventricular (LV) structure and function abnormalities are frequent in patients with chronic uraemia; these disorders increase the risk of cardiovascular (CV) and overall morbidity and mortality in the predialysed population, during dialysis treatment, and in renal transplant recipients. Since the first description of the association between chronic kidney disease (CKD) and heart disease, many epidemiological studies have confirmed and extended this finding. The risk of cardiovascular disease (CVD) is notably increased in patients with CKD. When adjusted for traditional CV risk factors, impaired kidney function increases the risk of CVD 2 to 4-fold. CVD is frequently underdiagnosed and undertreated in patients with CKD. This review will attempt to summarise current knowledge of the prevalence and pathophysiological mechanisms of LV disease in chronic uraemia, and to discuss useful medical strategies in this population.

Keywords: Chronic kidney disease, cardiovascular remodelling, risk factors.

INTRODUCTION

Left ventricular hypertrophy (LVH) is the most frequent cardiac complication in patients with chronic kidney disease (CKD), and carries a poor prognosis.[1] Nearly 75% of adult patients have LVH at the time of initiation of dialysis therapy. The development of LVH is associated with decreased survival in patients with CKD. The reason for this is that LVH may cause cardiac arrhythmias, diastolic dysfunction, ischaemic heart disease, and progression to overt heart failure (HF). The high risk of cardiovascular disease (CVD) results from multiple factors, including haemodynamic overload and metabolic and endocrine abnormalities.[2]

PATHOLOGICAL CARDIAC REMODELLING

Cardiac remodelling is frequently identified in patients with CKD. Remodelling can be defined as molecular, cellular, interstitial, and genomic expression changes that manifest as myocyte hypertrophy, intramyocardial cell fibrosis, and decreased capillary density.[3] Cardiac remodelling is clinically manifested by changes in cardiac size, shape, and function in response to cardiac injury or increased cardiac load. The cardiac cells involved in the remodelling process are cardiomyocytes and fibroblasts. Fibroblast stimulation increases collagen synthesis and causes fibrosis of both the infarcted and non-infarcted regions of the ventricle.[3] This leads to a loss of cardiomyocytes by apoptosis or necrosis. Eventually these cardiomyocytes are replaced by fibroblasts and extracellular collagen. Marked remodelling of the heart has also been observed in CKD patients.[3]

There is a high rate of both eccentric (ventricular dilatation owing to volume overload) and concentric (increased ventricular wall thickness secondary to pressure overload) hypertrophy in patients with CKD. Additionally, in the setting of renal insufficiency there are many non-

haemodynamic factors that promote both hypertrophy and fibrosis. Cardiac remodelling can be both adaptive and destructive.[4] Pathologic remodelling develops as a response to prolonged stress on the heart from chronic volume overload, pressure overload, and non-haemodynamic factors. This pathologic remodelling involves diffuse fibrosis and hypertrophy, which lead to increased myocardial stiffness and impaired diastolic relaxation. Remodelling under these conditions is associated with HF progression and poor prognosis.[5]

The prevalence of LVH is strikingly increased in patients with early or advancing CKD. When the estimated glomerular filtration rate (GFR) is <30 mL/min per 1.73 m^2, around 50% of patients develop LVH, of which most is concentric hypertrophy.[6] Both preload and afterload-related processes affect the heart simultaneously and likely affect both patterns of hypertrophy. There appears to be an additive or even synergistic effect in promoting LVH. Additionally, many present in CKD have direct hypertrophic effects that are independent from their haemodynamic effects (e.g. renin-angiotensin-aldosterone system [RAAS] activation, increased sympathetic output, oxidative stress, inflammation, increased endothelin activity, hyperparathyroidism, and fibroblast growth factor 23 [FGF-23]).

Increased CV risk in individuals with CKD is due partly to the high prevalence of traditional risk factors. Also, non-traditional kidney-specific mechanisms make notable contributions to cardiovascular (CV) risk. Clarification of these mechanisms could reveal ways to lessen the CV risk in patients with CKD.[7]

Hypertension is a well-known and strong risk factor for development of CKD. Nevertheless, the cause-effect association can also be in the opposite direction. Even in the early phases CKD can cause hypertension, which is likely to increase CV risk in affected patients. A target blood pressure (BP) of <140/90 mmHg is deemed appropriate to prevent CV events in patients with CKD; a lower target BP of <130/80 mmHg is recommended only in patients with increased albuminuria (>30 mg/g).[8]

The primary structural component of the extracellular matrix (ECM) is fibrillar collagen. There are five types of fibrillar collagen; Type 1 and Type 3 are the predominant isoforms in the heart, accounting for approximately 80% of the myocardial collagen.[9] Collagen forms a structural scaffold that provides both strength and elasticity. This scaffold is important in maintaining structural integrity of the myocardium and actively participates in force generation and transmission across the LV wall. Taken in whole, the ECM is the primary determinant of ventricular stiffness and passive relaxation during diastole. An imbalance between collagen production by myofibroblasts results in a net accumulation of fibrillar collagen and myocardial fibrosis. Oxidative stress, inflammation, and excess hypertrophic growth factors are involved early-on in the course of CKD haemodynamic overload. At the same time, with progressive CKD, chronic anaemia, hyperphosphataemia, and uraemic toxins also play a role in promoting fibrosis.

In a recent study, Martin et al.[10] demonstrated early myocardial fibrosis with impaired diastolic function in an experimental model of mild renal insufficiency produced by unilateral nephrectomy. Nephrectomy rats in the investigational group showed a significant increase in myocardial fibrosis compared to the control group after 4 weeks. These findings were independent of any change in BP, sodium retention, activation of aldosterone, GFR, proteinuria, or plasma B-type natriuretic peptide (BNP) level. After 16 weeks these changes progressed to more global remodelling and dysfunction with increases in LV mass, LV end diastolic diameter, and plasma BNP, with a modest decrease in LV ejection fraction (LVEF).

FUNCTIONAL CONSEQUENCES

Diastolic dysfunction is the predominate physiology seen in patients with CKD and is associated with a higher mortality rate than systolic dysfunction.[11] CKD can lead to adverse cardiac remodelling and fibrosis (LV dysfunction, HF, etc.). At this stage, the clinical syndrome is typically progression and is a common cause of hospitalisation and suddenly death. All of the features and complications manifested by low LVEF have been described and found to be increased with progressively lower levels of GFR including increased symptoms, decreased exercise tolerance, reduced peak oxygen consumption, higher risks of arrhythmias, thromboembolism, device failure, and death.[12]

Over the last two decades, with the development of highly sensitive and cost-effective assays, serum biomarkers have become integral tools in all phases of diagnosis, management, and prognosis

of HF.[13] Many commonly used biomarkers are substances released upon damage to or stress on the myocardium (including troponin and BNP); these can be considered to be bystander biomarkers as they are not actively involved in promoting disease progression. It is considered that there are other biomarkers that appear to be helpful in risk stratification of patients with HF, particularly after an acute myocardial infarction (e.g. serum levels of soluble ST2 receptor and interleukin-33 [IL-33]).[14]

Except hypertension, renal anaemia and increased vascular stiffness might play key roles in the development of LVH that leads to reduced coronary reserve.[15] The latter could be aggravated by reduced cardiac capillary density in CKD and impaired coronary dilatory responses, as has been shown in animal studies. Expression of endothelial nitric-oxide (NO) synthase is down-regulated, which suggests a possible mechanism for coronary endothelial dysfunction in the early stages of CKD.[7] The high prevalence of LVH, with its associated risk of cardiac rhythm disturbances, could at least partly explain why the prevalence of sudden cardiac death is increased in people with CKD. In the general population, sudden cardiac death accounts for roughly one death per 1,000 person-years and for 6–13% of all deaths, whereas among individuals with kidney failure, the rates are 59 deaths per 1,000 person-years and 26% of total mortality.[16] Besides the high prevalence of LVH, abnormal electrolyte concentrations and increased prevalence of coronary artery disease (CAD) are predisposing factors for sudden cardiac death in patients with CKD. Electrolyte disturbance, especially hyperkalaemia, may cause severe arrhythmias, including ventricular fibrillation and asystole. Dyslipidaemia and inflammation are also caused by CKD.[17] In patients with impaired kidney function and high albuminuria, lipid profiles become atherogenic. Mechanisms of increased systemic inflammation in CKD are unclear, but the increased production of inflammatory mediators has been attributed to raised oxidative stress and the accumulation of post-synthetically modified proteins and toxins that are cleared with normal renal function.[18]

Other factors that raise CV risk in patients with CKD include increased activity of the renin–angiotensin system and sympathetic nerve activity in CKD. Bioavailability of NO, which is involved in vascular smooth-muscle contraction and growth, platelet aggregation, and leukocyte adhesion to the endothelium, becomes decreased. Albuminuria can be interpreted as a sign of, but also as a consequence/marker of, endothelial dysfunction.[18] Another key factor for endothelial function seems to be asymmetric dimethylarginine (ADMA), the concentration of which is a predictor of mortality and CV complications in patients with CKD.[18] ADMA is an endogenic inhibitor of NO; it reduces cardiac output and raises systemic vascular resistance and BP. Increased concentrations of ADMA and sympathetic overactivity are associated with concentric LVH, which fits with the hypothesis that these factors may be associated with cardiac abnormalities in CKD.[19]

Vascular calcification is increasingly recognised to be a frequent complication in patients with CKD.[20] In the general population electron beam computed tomography evidence of vascular calcification is a useful index of atherosclerotic burden. It not only predicts adverse coronary events, but it is also associated with a lower event-free survival.[21] The significant correlation observed between valvular calcification and aortic atheroma[22] suggests that valvular calcification may be a manifestation of generalised atherosclerosis.[23] The calcified regions of the cardiac valves not only share common features with arterial atherosclerotic plaque with infiltration of inflammatory cells, lipoproteins, and calcium deposits, but also express 'bone' matrix proteins,[24] suggesting that the process of valvular calcification simulates bone formation. Interstitial cells with osteoblastic characteristics identified in cardiac valves were suggested to be partly responsible for the increased expression of 'bone' matrix proteins. The protein deposition 'bone' matrix in vascular calcification in uraemic patients[25] suggests that valvular and vascular calcification are likely associated syndromes, both involving an active cell-mediated process and not just passive accumulation of minerals.

Atherosclerosis is frequently seen in patients with kidney failure but also occurs in those with early CKD. The key modulators in this field have not been elucidated in intervention trials, but might include calcification inhibitors (e.g. fetuin-A and matrix Gla protein), promotors (e.g. hyperphosphataemia), calcium-phosphate product, parathyroid hormone (PTH), and leptin.[26]

FGF-23 is a recently discovered regulator of phosphate and mineral metabolism.[27] FGF induces phosphaturia by reducing the number of Na-P co-transporters on renal tubular cells, as well as

mitigating the effects of calcitriol on intestinal absorption.[28] The biological effects of FGF-23 are exerted through activation of FGF receptors (FGF-R). Klotho is a transmembrane protein originally described in mice with a phenotype of accelerated aging and atherosclerosis. Klotho directly interacts with FGF-R, allowing it to bind FGF-23 with a higher affinity and increased specificity. The activation of FGF-23 therefore occurs in a Klotho-dependent manner.[29] The main known physiological role of FGF-23 is to regulate urinary phosphate excretion and maintain a stable serum phosphate. An important secondary role is the counter-regulation (against PTH) of vitamin D biosynthesis. The main stimuli for increased expression of FGF-23 are high dietary phosphate, calcitriol, and persistent hyperphosphataemia. In CKD, recently reported clinical studies support a phosphate-centric, FGF-23 mediated pathogenesis of secondary hyperparathyroidism, and findings suggest that FGF-23 plays an active role in CKD. There is also growing evidence of the association between CVD and FGF-23 levels. In an observational study of 833 patients with early CKD and stable CAD, elevated FGF-23 was independently associated with mortality and CV events.[30] Association between arterial stiffness and FGF-23 has also been demonstrated once in a cohort of 967 patients with early CKD, where arterial stiffness was measured with ShygmoCor.[31]

Patients with impaired kidney function frequently develop a deficiency of active vitamin D because of a lack of its precursor, impaired activity of the kidney enzyme 1-α-hydroxylase, which converts this precursor to the active hormone, or both.[33] Observational studies in patients with CKD have shown associations between vitamin D deficiency and increased risk of CV events, and experimental data suggest that the vitamin D pathway is involved in modifying cardiac structure and function.[33]

The complex interaction between the kidneys and the heart has been termed the cardiorenal syndrome (CRS), in which five types have been defined.[34] Type IV CRS is classified as CKD contributing to decreased cardiac function, cardiac hypertrophy, and increased risk of adverse CV events, and is referred to as chronic reno-cardiac syndrome. As CKD progresses and kidney-specific risk factors become more and more relevant the risk of CVD is amplified. However, traditional risk factors remain the major determinants of CV remodelling in CKD.

PREVENTION

CVD can be prevented by lifestyle and pharmacological interventions. In view of the progressive increase in CV risk as kidney function declines, however, prevention of loss of kidney function should be viewed as a target by itself. Treatment strategies that slow or even halt the progressive loss of kidney function might not only postpone the need for dialysis or kidney transplantation, but also attenuate CV risk. Thus, the assignment of strength and grade to recommendations balances CV and renal protective effects.

PHARMACOLOGICAL INTERVENTIONS

Treatment of high BP in patients with any stage of CKD is of paramount importance to slow or prevent disease progression, and is the mainstay of CV protection.[35] In such patients, drugs to control BP, especially RAAS inhibitors, should be titrated until the target BP is reached and baseline albuminuria is reduced by at least 50%.[35] Lipid-lowering therapies have undoubtedly contributed to a reduced incidence of CV events in the general population.[36] A meta-analysis of all statin trials in individuals with CKD showed that the CV protective effect of these drugs is attenuated in those with low estimated GFR values and limited in patients undergoing dialysis.[37]

Diabetes is an important cause of CKD and significantly increases CV risk in these patients. Optimum glycaemic control slows the progression of microvascular complications, but the evidence for CV or mortality outcomes is of much lower quality.[38] New oral glucose-lowering drugs have become available for clinical use (e.g. GLP-1 analogues), but their long-term effects on CV and kidney outcomes are not yet established so they are not approved for use in dialysis patients or advanced CKD. Targeting future therapies at the underlying cellular mechanisms of CV remodelling, such as the insulin resistance (IR) pathway, may begin to reduce the burden of this disease. Thioglitazones, some of which are currently used to treat diabetes, are thought to be able to manipulate the IR pathway and to have the potential to be an effective therapy for cardiomyopathy in CKD. It should be noted, however, that some thioglitazones have been associated with increased risk of congestive HF, which might complicate their role in the treatment of this disease.[39]

CV protection with antiplatelet and anticoagulant therapy has been documented in secondary prevention trials. Because patients with CKD are at increased CV risk they might benefit from antiplatelet therapy, but they also have abnormal platelet function that raises the risk of haemorrhagic events when treated with anticoagulants, including antiplatelet therapies.[40]

Much attention has been paid to the targeted treatment of specific kidney-related CV risk factors to improve renal and CV health, but results have been mixed. For instance, on the basis of the observation that low haemoglobin concentrations were associated with CV outcomes, erythropoiesis stimulating agents were assessed. Unfortunately, no benefit was seen with the correction of haemoglobin concentrations to >120 g/L, and an increased risk of stroke has been proven.[41]

Vitamin D deficiency can activate the intracardiac renin-angiotensin system (RAS), and active vitamin D supplementation can cause regression of LVH and/or cardiac fibrosis. Lowering greatly elevated PTH levels seen in experimental uraemia by calcimimetics (cinacalcet) decreases cardiac fibrosis but does not affect LV mass. Calcitriol also reduces cardiac fibrosis and microvascular remodelling in experimental models of renal failure.[42]

The identification of clinical manifestations of CVD is challenging in patients with CKD, especially identification of ischaemic heart disease. Some patients with CKD present with classic symptoms, but many are asymptomatic, with no pain or adrenergic manifestations, or develop atypical manifestations despite a major acute ischaemic event.[43] People with diabetes might be particularly prone to asymptomatic ischaemic heart disease because of visceral neuropathy.

Clinicians must be fully aware of the atypical presentations of acute coronary syndromes in patients with CKD to avoid under-diagnosis of potentially life-threatening CV events. This consideration is particularly relevant because patients with Stage 3–5 CKD have notably higher rates of and worse prognoses from comorbidities, conduction abnormalities, and anterior infarctions than do individuals without CKD.[44]

In our opinion there are at least two approaches to prevent CV events in patients with CKD. First, treatment should be started in early stages of CKD. Screening for albuminuria and treatment with angiotensin-converting enzyme inhibitors in patients who have increased albuminuria might be a cost-effective approach to prevent CV events and renal failure, especially in patients at high risk of developing CKD, such as those with diabetes, hypertension, or old age.[45] Such an approach should be formally investigated. Second, in late-stage CKD, intensified, multifactorial interventions may be mandatory. Gaede and colleagues[46] showed benefits with multimodal treatment that included strict glucose management, statins, angiotensin-converting enzyme inhibitors, etc.

Antihypertensive agents and lifestyle interventions (smoking cessation, increased physical activity, and dietary changes) compared with standard care according to national guidelines. The rate of macrovascular complications was halved after 8 years of follow-up, as was CV mortality after 13 years. A similar multimodal strategy was safely and effectively applied to normalise albuminuria and prevent loss of kidney function in patients otherwise predicted to rapidly progress to renal failure.[47]

Rapamycin, targeting mammalian target of rapamycin (mTOR) downstream of protein kinase B (Akt), has been shown to reduce LVH and fibrosis in uraemic mice. It has the potential to be an effective and simple therapy for uraemic cardiomyopathy.[48]

CONCLUSIONS

Identification of the pathophysiological mechanisms underlying CV remodelling will allow for a better understanding of the clinical consequences of these diseases. Mechanisms specific to CKD promote vascular disease and, therefore, substantially increase the burden of CVD in patients with CKD. Experimental and interventional studies designed to test whether biomarkers are not only markers but also aetiological risk factors may provide further information that could lead to novel treatment options. Patients with CKD have a high risk of CVD that requires special attention and monitoring.

Finally, further research into the specific derangements will open the door for development of novel therapeutic targets aimed at treating the underlying disease aetiology and, thus, preventing initiation of the disease. Targeting future therapies at the underlying cellular mechanisms of CV remodelling may finally start to reduce the burden of CV changes in the CKD population.

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