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Cardiovascular disease and its relationship with chronic kidney disease

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Abstract. – Cardiovascular disease (CVD), the leading cause of death, is mostly precipitated by cardiometabolic risk and chronic kidney disease (CKD). CVD and kidney disease are closely interrelated and disease of one organ cause dysfunction of the other, ultimately leading to the failure of both organs. Patients with end-stage renal disease (ESRD) are at much higher risk of mortality due to CVD. Traditional CVD risk factors viz., hypertension, hyperlipidemia, and diabetes do not account for the high cardiovascular risk in CKD patients and also standard clinical interventions for managing CVD that are successful in the general population, are ineffective to lower the death rate in CKD patients. Nontraditional factors, related to disturbed mineral and vitamin D metabolism were able to provide some explanation in terms of vascular calcification, for the increased risk of CVD in CKD. Fibroblast Growth Factor 23, a bone-derived hormone that regulates vitamin D synthesis in renal proximal tubules and renal phosphate reabsorption, has been suggested to be the missing link between CKD and CVD. Acute Kidney Injury (AKI) is strongly related to the progress of CVD and its early diagnosis and treatment has significant positive effect on the outcomes of CVD in the affected patients. Besides this, non-dialysable protein-bound uraemic toxins such as indoxyl sulfate and p-cresyl sulfate, produced by colonic microbes from dietary amino acids, appear to cause renal dysfunction. Thus, therapeutic approaches targeting colonic microbiota, have led to new prospects in early intervention for CKD patients.

Intervention targets for preventing CVD events in CKD patients ideally should include control of blood pressure and dyslipidemia, diabetes mellitus, lowering proteinuria, correction of anemia, management of mineral metabolism abnormalities and life style changes including smoking cessation, decreased consumption of salt, and achievement of normal body mass index. Use of β-blockers, renin-angiotensin blockers, diuretics, statins, and aspirin are helpful in the early stages of CKD. In this review, we will address the biological, pathological and clinical relationship between CVD and CKD and their therapeutic management.

Key Words:
Cardiovascular disease, Chronic kidney disease, End-stage renal disease.

Introduction

Cardiovascular disease (CVD) is the leading cause of death, irrespective of race and ethnicity, and is mostly precipitated by cardiometabolic risk and chronic kidney disease (CKD). CVD and kidney disease are closely interrelated and disease of one organ causes dysfunction of the other, ultimately leading to the failure of both organs and this is often referred as cardiorenal syndrome (CRS). In CKD patients, heart failure (HF) is the major cardiovascular complication and its prevalence increases with declining kidney function[1]. CKD, diagnosed mainly by reduced eGFR (< 60 ml/min/1.73 m^2) and albuminuria/proteinuria (> 30 mg/24 h or albumin/creatinine ratio > 30 mg/g or > 1 on specific dipstick) is considered an independent cardiovascular risk factor and, therefore, diagnosis of CKD implies a very high cardiovascular risk (Figure 1). There are multiple links between the cardiovascular and renal systems that lead to a complex relationship between cardiovascular and renal medicine. The complex association of CKD with CVD is probably due to clustering of several cardiovascular risk factors, including the "traditional factors" (e.g., advanced age, hypertension, diabetes mellitus, and dyslipidemia) and "nontraditional factors" that are specific to CKD (e.g., anemia, volume overload, mineral metabo-

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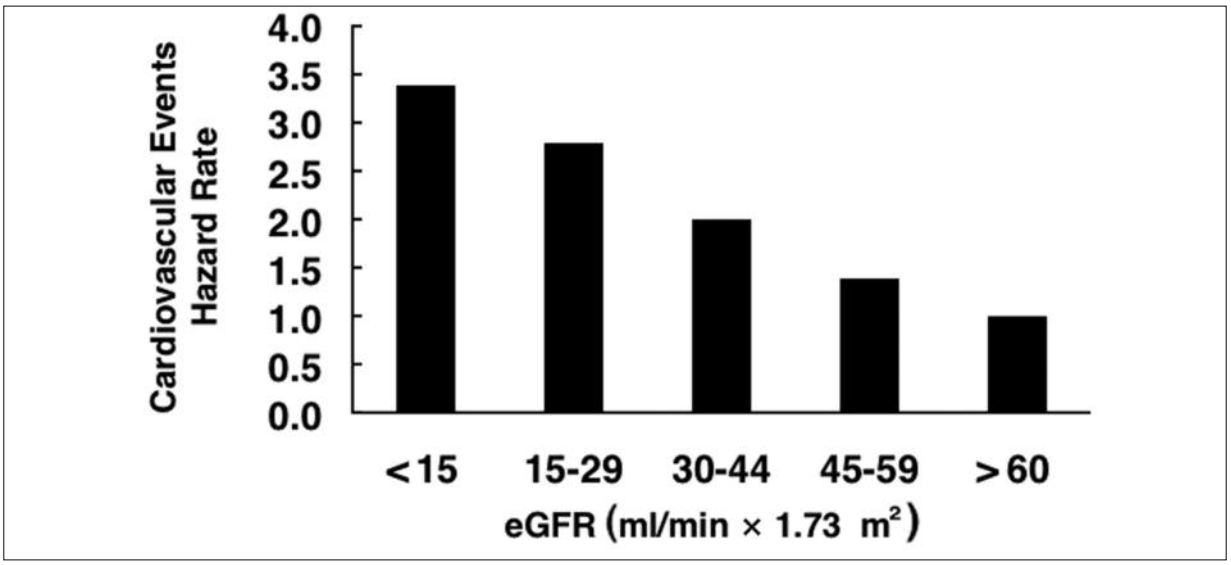

Figure 1. The inverse relationship between estimated glomerular filtration rate (eGFR) and the hazard rate of cardiovascular events. The results are adjusted for Framingham risk factors, like sex, age, etc.

lism abnormalities, proteinuria, malnutrition, oxidative stress, and inflammation), in CKD patients[2]. Traditional CVD risk factors do not account for the high cardiovascular risk in CKD patients and also standard clinical interventions for managing CVD that are successful in the general population, are ineffective in CKD patients. Non-traditional factors were able to provide some explanation in terms of vascular thickening and calcification, for the increased risk of CVD in CKD patients (Figure 1). Acute Kidney Injury (AKI) is strongly related to the progress of CVD and early diagnosis and treatment of AKI has been shown to have significant positive effect on the outcomes of CVD in the affected patients. Pre-clininal studies have shown that haemodynamic derangement in CVD probably activates renal inflammation-fibrosis processes that lead to CVD-associated renal dysfunction

The prevalence of CVD in the CKD Population and its Influence On Mortality

The median prevalence of CKD in the general population in Europe, America, Asia, and Australia was 7.2% (for > 30 years age) and varied between 23.4-35.8% for the older people (> 64 years age), women showing slightly higher prevalence[3]. Across the world the most frequent causes of CKD are diabetes mellitus and hypertension. Epidemiological studies from China revealed that CVD accounts for nearly 44.2- 51.0% of overall mortality among dialysis patients. Overall, there is approximately 50-fold increased CVD mortality rate among dialysis patients (age 25-64 years) as compared with the general population[4]. In the United States, the prevalence of CVD in CKD patients reaches 63%, as compared to just 5.8% in people without CKD (up to 9-times higher than in the general population)[5]. There appears to be direct correlation between the prevalence of CVD and severity of CKD[2]. In end-stage renal disease (ESRD) patients, who are dialysis dependent, the risk of cardiovascular mortality is 10-fold to 20-fold higher than in people without CKD[6,7]. Majority of the ESRD patients who are recently diagnosed with HF do not live more than three years from the time of diagnosis[8]. Dialysis patients with baseline HF have a median survival of ~36 months, as opposed to 62 months of survival for the patients without baseline HF[9]. Chronic kidney disease has become an important public health problem in China, with an overall prevalence of 10·8%, i.e., ~119·5 million people. Geographically, the prevalence of CKD was found to be much higher in northern China (16·9%) and southwestern China (18·3%). Among the other factors independently associated with CKD, hypertension, diabetes and CVD were found to be most important[10]. In fact, hypertension was suggested to be the most common and leading risk factor for premature deaths and it is estimated that ~2.33 million total CVD deaths and 1.27 million premature CVD deaths were attributable to increased hypertension[11].

It has been observed that as compared to non-CKD patients, where CVD prevalence is about 13.9% in men and 9.3% in women, the prevalence of CVD among stage 1-5 non-dialysis CKD patients is 17.9% and 20.4%, respectively for men and women. This rate rises up to 40% in patients with dialysis and at this stage ~85% of the patients show impaired left ventricular function or structure, on the basis of echocardiographic criteria[12,13]. Cardiovascular mortality is about 40% in the general population in USA and rises to > 50% in non-dialysis CKD patients and even higher (15-times) in ESRD patients than in the general population[5]. Since the prevalence of stage 5 CKD (ESRD) is ~30-times lower than that of stage 3 CKD, any patient diagnosed with stage 3 CKD is at a higher risk of dying of CVD than of starting renal replacement therapy[5]. Various studies showed strong association between the markers of CKD, typically the reduced eGFR and albuminuria/proteinuria, and progression to ESRD, mortality, and CVD. The eGFR is indirectly related to the elevated probability of progression to ESRD, death, or CVD[14,15]. A recent large population study on 7 million participants reported an increased risk of major vascular events and all-cause mortality by 20-30% with a 30% decrease in eGFR[16].

Cardiorenal Syndrome (CRS) and Acute Kidney Injury (AKI)

Considering the primary diseased organ (heart or kidney) and the duration of the diseased state, CRS could be defined as either "acute" or "chronic"[17]. Acute CRS (Type 1) is defined as a rapid deterioration of heart function, leading to acute kidney injury (AKI). Chronic CRS (Type 2) is defined as chronically disturbed cardiac function such as chronic heart failure (HF) leading to progressive CKD. Acute CRS Type 3 is defined as a sudden and primary damage to kidney such as hypoxic–ischemic injury, leading to acute cardiac dysfunction such as acute HF, arrhythmia and ischemia. Chronic CRS Type 4 is defined as primary CKD contributing to reduced heart function, ventricular hypertrophy, diastolic dysfunction, and increased risk of adverse cardiovascular events. A type 5 secondary CRS is defined as the combination of cardiac and renal dysfunction due to acute or chronic systemic disorders such as sepsis[17]. In type 1 CRS, AKI has been found to be highly incident and predictive of poor clinical outcomes in different cardiovascular conditions such as cardiac surgery, acute decompensated heart failure and acute myocardial infarction. On the other hand, in type 4 CRS, CKD has proven to be an important health concern worldwide as its incidence as well as the associated cardiovascular morbidity and mortality were found to be much higher. AKI, which is frequently associated with CVD, is a strong predictor of mortality in patients with either myocardial infarction or with HF[18]. As mentioned above, renal dysfunction, even mild, is strongly associated with elevated risk for long-term mortality[19]. Approximately, 10-20% of hospitalized patients with acute myocardial infarction suffer from AKI[19] and 24-45% of these patients with AKI die during hospitalization, a rate that is 4.4-8.8 times higher than that in patients without AKI[20]. Besides, renal function declines progressively with time, following myocardial infarction[14].

Acute Kidney Injury Biomarkers in CVD Patients

Intrinsic AKI is associated with injured renal cells, which abnormally secrete molecules such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule (KIM)-1, interleukin (IL)-18, N-acetyl-β-D-glucodaminidase (NAG) and liver fatty acid-binding protein (LFABP) into urine or lose the capacity to reabsorb filtered molecules such as cystatin C. Therefore, urinary concentrations of these substances reflect the degree of renal parenchymal damage and also are potential biomarkers for early detection of intrinsic AKI. It has been found that NGAL and KIM-1 perform best as an AKI diagnostic marker after cardiac surgery compared to cystatin C, IL-18, NAG and LFABP[21,22]. Unlike the cardiac surgery patients, the use of urinary NGAL in early detection of AKI does not appear to be very promising in patients with acute decompensated heart failure. Early renal dysfunction following myocardial infarction can be reversed at least partly due to transiently lowered systolic blood pressure. While this transient impairment is a reflection of prerenal AKI, inflammatory activation occurs simultaneously with intrinsic renal damage and tends to be persistent and to progress to fibrogenesis. Renal fibrosis progresses over time, finally leading to renal dysfunction. Renal inflammation and fibrosis are likely mediated via the TGF-β-Smad-NF-κB pathway in association with activation of the renin-angiotensin-aldosterone system (RAAS). Thus, interventions with an anti-inflammatory effect or RAAS blockade can potentially prevent progression of renal fibrosis and the late renal dysfunction[18].

Animal Models of CRS

Several animal models have been developed and employed to seek answers in terms of pathogenic mechanism, for the association of CVD with CKD. For example, severe CVD could be triggered in rat models by renal mass ablation[23]. Such intervention was shown to trigger left ventricular hypertrophy, fibrosis, and defective capillarization in the rat[23], as well as severe arterial damage with extensive inflammation, plaque formation, and a propensity to calcified lesions[24,25] in the APO E-/E-mouse. Inasmuch as these pathological changes resemble those noticed in humans, these animal models support the hypothesis that left ventricular hypertrophy, defective myocardial oxygen supply, and severe arterial lesions commonly observed in CKD patients, are the consequence of reduced renal mass. On the other hand, the reverse possibility that heart disease may lead to deterioration of the kidney function as in Type 1 CRS, is also well documented. Thus, in uninephrectomized rats, myocardial infarction triggers a marked rise in albumin excretion rate and a simultaneous increase in focal glomerulosclerosis, and both these changes are related to the myocardial necrosis area[26].

Kidney injury biomarker studies in post myocardial infarction animal models have demonstrated a significant increase in serum and urinary NGAL at day 3 and week 2, but not at weeks 4 and 8, post MI[27]. A significant increase in circulating activated monocytes seen on day 3 post myocardial infarction, as well as an inflammatory reaction in infarcted myocardium, could be the sources of serum NGAL. In another time course myocardial infarction study, renal KIM-1 protein expression was found to be significantly increased at week-1, which later declined at week-4 and then gradually increased by 12 and 16 weeks post myocardial infarction along with the development of renal fibrosis[28]. Elevated urinary NGAL and KIM-1 levels at day 5 post acute myocardial infarction have been demonstrated in a rat model which were found to revert back to the sham level on follow-up day 30[29]. In the same study, high level of both the urinary biomarkers was consistently observed in a rat CKD model until the end of the study endpoint (9 weeks post subtotal nephrectomy), suggesting that urinary NGAL and KIM-1 can be useful in assessing renal damage in the CKD setting.

Pathophysiology of CRS

Predominant cardiac abnormality in CKD and ESRD patients is related to left ventricular (LV) structure and function[2]. Approximately, 73.4% of ESRD patients, who started dialysis, suffer from LV hypertrophy while 35.8% show LV dilatation, and another 14.8% have LV systolic dysfunction[12]. Among other cardiac problems that contribute to ischemia, myocardial cell damage, and fibrosis, the more significant one is coronary artery disease, which is often seen in patients with CKD and ESRD[30]. It has been suggested that myocardial hypertrophy and fibrosis may lead to a reduction in the capillary density and coronary reserve[31,32], which in turn causes imbalanced oxygen supply and demand and, thus, ischemia[33] and considerably increases the risk of ventricular arrhythmias and sudden cardiac death[34]. Ischemia is known to promote cardiomyocyte apoptosis and accumulation of extracellular matrix and collagen, thereby causing interstitial fibrosis, which culminates in LV stiffness, increased LV filling pressure, impaired diastolic filling, and diastolic dysfunction[35].

Nonhemodynamic factors such as hyperphosphatemia, which is associated with high blood pressure[36], increased LV mass[37] and diastolic dysfunction[38] also contribute to the development of LVH and cardiomyopathy in CKD patients[31]. Angiotensin II accumulation in the heart can promote myocyte hypertrophy, interstitial fibrosis and microvascular disease[39]. It has been suggested that elevated levels of serum aldosterone, due to either the activation of renin-angiotensin system or other pathways, can induce myocardial fibrosis, possibly by release of transforming growth factor b[34]. In the CKD patients, HF is the most common cardiac presentation, while LVH is predictive of CV mortality. Atherosclerosis does not seem to be a major contributor to CVD in CKD patients as only 15-25% of cardiac deaths in these patients are attributable to ischemic heart disease, half of which are negative for coronary atherosclerosis[40]. On the other hand, the predominant cardiovascular pathology in CKD patients, i.e., cardiac interstitial fibrosis and non-obstructive vascular diseases are both independent of hypertension[30,41] and yet contribute to the high incidence of sudden cardiac death in the absence of atherosclerosis in the CKD patients.

Mechanisms Underlying the Association of CVD with CKD

Several hypotheses have been proposed for understanding the molecular basis for the link between CKD and CVD. Traditional cardiovascular risk factors are insufficient to explain the high in-

cidence of CVD among CKD patients (Figure 2). Even though CKD-related risk factors viz., anaemia, hypertension and abnormal calcium-phosphorus homeostasis are shown to be closely associated with cardiovascular pathology, correction of these risk factors does not significantly lower the death due to CVD, strongly suggesting that there must be 'missing links' in the disease connection between heart and kidney (Figure 2). Uraemic toxins have been suggested as a potential 'missing link' in this connection[18]. Emerging evidence indicates that protein-bound uraemic toxins (PBUTs), in particular indoxyl sulfate (IS) and p-cresyl sulfate (pCS) are potential factors in the pathogenesis and progression of CRS[42]. Both IS and pCS have been shown to be associated with renal progression and increased cardiovascular mortality[43,44]. These two PBUTSs have been shown to exert their detrimental effects on cardiovascular and renal pathology, including renal inflammation and fibrosis, increased protein and collagen synthesis in heart and endothelial dysfunction[42,45]. Elevated PBUTs, particularly, IS has been implicated in vascular calcification[46], which is commonly found in advanced-stage CKD patients and associated with poor cardiovascular outcomes[47]. Besides this, IS also accelerates renal[48] and cardiac oxidative stress[49]. In fact, it has been suggested that IS induces cardiorenal fibrosis via the ROS-NF-κB-TGF-β1 pathway[42].

Patients with CKD, from the early stages of disease, display abnormal mineral and bone metabolism, the so-called CKD-mineral and bone disorder (MBD), which presents a strong cardiovascular risk for CKD patients. Discovery of fibroblast growth factor 23 (FGF23) has added another dimension to the complex endocrine feedback loops between the kidney, parathyroid gland, intestines, and bone. FGF23 has been reported to be closely associated with cardiovascu-

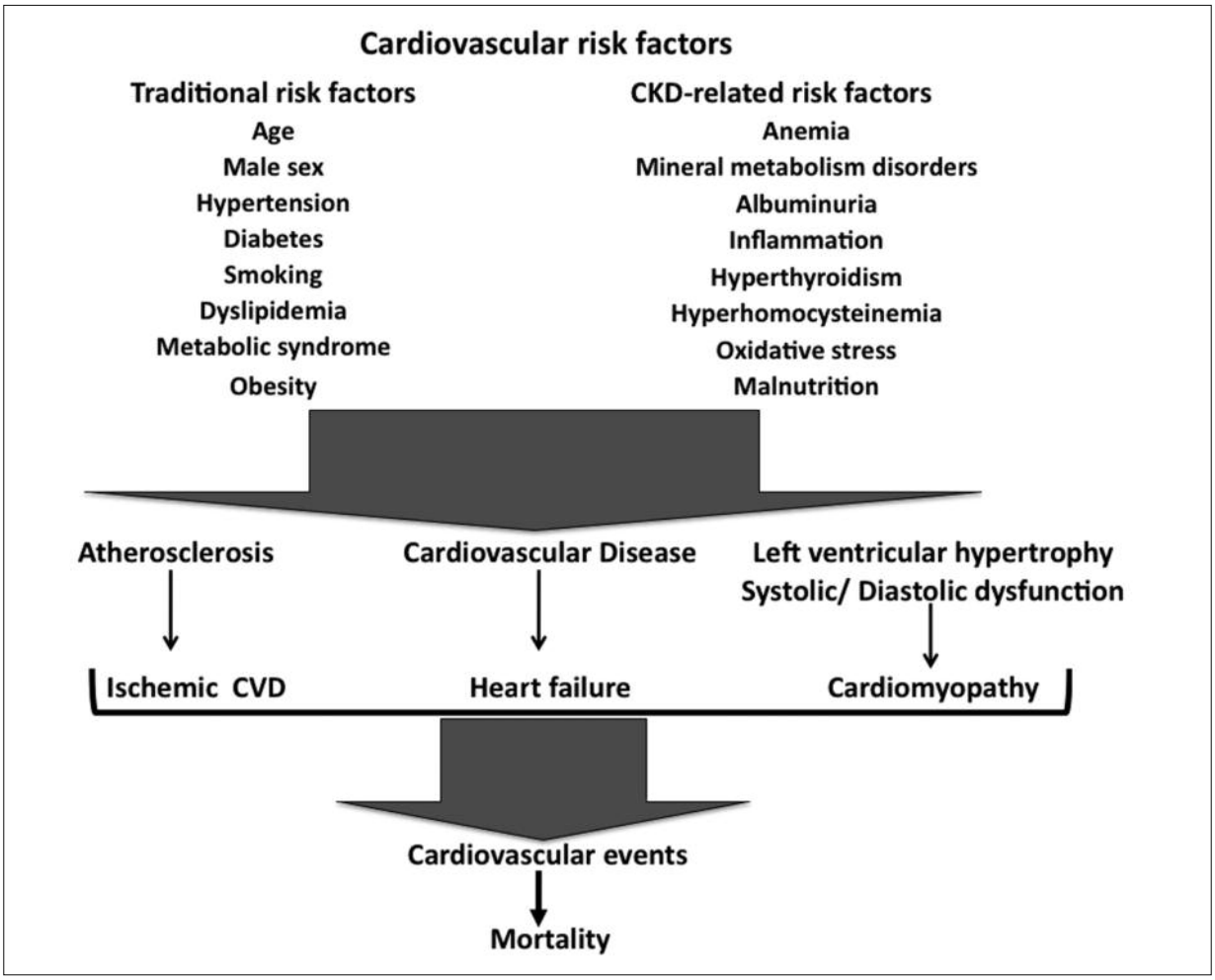

Figure 2. Interrelationship between cardiovascular disease (CVD) risk factors and chronic kidney disease (CKD).

lar risks, left ventricular hypertrophy, and vascular calcification and FGF23-Klotho axis has been shown to exist in the vasculature[50]. Circulating levels of FGF23 are elevated in CKD patients. FGF23 acts on the kidney and parathyroid gland by binding to FGF receptors in the presence of Klotho co-receptors and enhances phosphaturia, and inhibits renal 1-α hydroxylase, leading to reduced vitamin D production. Interestingly, PBUTs have been recently implicated in Klotho deficiency. However, further work is needed to ascertain whether IS and FGF23 are mechanistically interrelated in the pathophysiology of CRS. Klotho might also be involved in PBUT-induced renal fibrosis mediated via the ROS-NF-κB-TGF-β1 pathway. In addition, renal fibrosis induced by IS or pCS is associated with activation of the renal RAAS and epithelial-to-mesenchymal transition of renal tubular cells[18]. Activation of the sympathetic and RAAS, changes in nitric oxide bioavailability, inflammation and excessive formation of ROS are established common pathophysiological pathways that mediate CVD and CKD clinical outcomes. Therapeutic targeting of these pathways offers definitive benefit in patients with CKD or CVD[51,52].

Diagnosis and Prevention of CRS

Echocardiography has proven to be important in obtaining correct diagnosis as it can provide reliable measurements for ventricular diameters and volumes, wall thickness, chamber geometry, and ejection fraction (EF) and an echocardiogram is considered essential in the diagnosis of any patient presenting with new cardiac symptoms or events[53], suffering from CKD. For ESRD patients, echocardiograms are recommended within 1-3 months after the start of dialysis by the guidelines of kidney disease outcomes quality initiative (KDOQI). An evaluation for the occurrence of coronary artery disease either by noninvasive imaging (stress echocardiography, nuclear imaging, or computed tomographic angiography) or by invasive imaging tests (coronary angiography), must be undertaken in CKD patients with significant LV systolic dysfunction[2]. Since volume overload may be both a result and a precipitating factor of HF, assessment of fluid status is very important in all CKD, particularly in ESRD patients.

Blood and urinary biomarkers are also quite helpful in the diagnosis of CVD in CKD. Plasma levels of BNP and NT-pro-BNP, which are produced by atrial and ventricular myocytes in response to an increase in atrial or ventricular diastolic filling pressure and wall distension[54], reflect LV wall stress[54]. Levels of these peptides are significantly increased in patients with HF and correlate strongly with the severity of LV systolic and diastolic dysfunction[54], and also with HF severity. Even though impaired renal clearance in CKD and ESRD patients can also influence the plasma levels of the natriuretic peptides[55], these peptides still maintain a strong relation with LV end-diastolic wall stress. Significant associations between circulating natriuretic peptides in dialysis patients with LVH[56], LV systolic and diastolic dysfunction, and LA dilatation[55] have been noted. Importantly, it has been shown that BNP and NT-pro-BNP can successfully predict the risk of HF in nondialysis CKD[56].

Treatment Goals

It is well recognized that the general guidelines followed for the management of HF in the normal population cannot be applied entirely to patients with CKD. Prevention of CVD in CKD patients, even though a difficult task, is the best option for increasing the chances of patient survival. The main objectives of HF therapy in CKD patients are (1) to lower the preload and after load and to reduce LVH, (2) to treat myocardial ischemia, and (3) to inhibit neurohumoral hyperactivity, especially the sympathetic nervous system and the RAAS[57,58]. Vitamin D deficiency has been found to be associated with LV dysfunction and risk of CV events, including HF[59] in CKD patients. Thus, intravenous calcitriol administration in patients with secondary hyperparathyroidism led to partial regression of LVH and decrease in plasma renin activity and angiotensin II levels[60]. Similar results showing significant LV mass reduction were noticed with cholecalciferol supplementation to patients with reduced vitamin D and parathyroid hormone levels[61]. American College of Cardiology Foundation/American Heart Association guidelines indicate that a beta-blocker should be prescribed to patients with stable HF due to systolic dysfunction, unless contraindicated or not tolerated[62] inasmuch as three beta-blockers, viz., bisoprolol, metoprolol (selective to b-1-receptors) and carvedilol (selective to a-1-, b-1-, and b-2-receptors), have been found to reduce mortality in patients with HF. The use of beta-blockers in CKD patients with systolic heart failure was shown to lead to a relative risk reduction of 28% in all-cause mortality and of 34% in cardiovascular mortality compared to placebo[63].

Angiotensin converting enzyme inhibitors (ACEI) by inhibiting cardiac RAAS and by blocking the breakdown of bradykinins, prevent LV hypertrophy and dysfunction, via stimulating the synthesis of prostaglandins and nitric oxide, which potentially prevent LVH. ACEIs also reduce sympathetic activity, improve endothelial function, decrease proinflammatory cytokines and prothrombotic factors, and stimulate fibrinolytic factors. All these mechanisms potentially contribute to the improvement of pulmonary, right ventricular and skeletal muscle function[64]. Lifestyle changes, particularly, smoking cessation, exercise, weight loss, and low salt diet, have been proposed to be instituted in CKD patients to prevent/reduce the risk of HF[31,65]. Similarly, glycaemic control is strongly advised in diabetic CKD patients, both for cardiovascular and renal protection.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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