Cardiorenal syndrome in chronic kidney disease

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Purpose of review
The purpose of this study is to review current perspectives regarding the pathogenesis of cardiorenal syndrome (CRS) in chronic kidney disease (CKD), and current treatment guidelines for this condition.

Recent findings
The pathophysiological mechanisms underlying the development of CRS in CKD include neurohumoral, haemodynamic and CKD-related mechanisms. Recent evidence suggests that sympathetic nerve activity plays a role in CRS, but the SYMPLICITY HTN-3 trial failed to show a reduction of blood pressure after catheter-based renal denervation in patients with resistant hypertension. Kidney injury in patients with heart failure was previously considered to result from arterial underfilling due to low cardiac output, but the role of renal venous hypertension in this process has also recently been investigated. It would be useful to develop a reliable treatment option for CRS due to haemodynamic mechanism other than volume control using diuretics. Fibroblast growth factor 23 (FGF23) is a phosphaturic hormone that has recently been identified as a CKD-related factor affecting CRS. FGF23 treatment has both advantages and disadvantages in terms of CRS progression.

Summary
Multiple disorders underlie the development of CRS. Current treatment options include renin–angiotensin system blockade and volume control, but remain limited. A multidisciplinary approach is required to prevent CRS, including renal sympathetic denervation, treatment of renal venous hypertension and FGF23 treatment.

Keywords
fibroblast growth factor 23, nitric oxide, renal venous hypertension, renin–angiotensin system, sympathetic nerve activity

INTRODUCTION

Chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease (CVD), and there is a high prevalence of CVD among patients with CKD. Mortality due to CVD is 10–30 times higher in dialysis patients than in the general population [1], and patients with CVD often have CKD. This interaction between CKD and CVD is known as cardiorenal syndrome (CRS).

Ronco *et al*. [2,3▪▪] proposed division of CRS into five categories according to the associated etiologic and chronologic factors. Each category is characterized as follows: CRS type 1 – acute worsening of cardiac function [e.g. acutely decompensated congestive heart failure (CHF)] leading to acute kidney injury or dysfunction; CRS type 2 – chronic abnormalities in cardiac function (e.g. chronic CHF) causing progressive and permanent CKD; CRS type 3 – acute worsening of kidney function leading to acute cardiac injury or dysfunction, such as acute myocardial infarction, CHF or arrhythmia; CRS type 4 – primary CKD contributing to decreased cardiac function, cardiac hypertrophy, fibrosis or increased risk of adverse cardiovascular events; and CRS type 5 – acute cardiac and renal injury and dysfunction in the setting of an overwhelming systemic insult.

This classification describes the clinical setting associated with CRS, but is not based on pathophysiological mechanisms. CVD is common in patients with CKD and is associated with substantially increased risk of end-stage renal disease (ESRD) and all-cause mortality before the development of

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KEY POINTS

- The complicated pathophysiological mechanisms underlying the development of CRS in CKD include neurohumoral and haemodynamic disorders as well as CKD-related factors such as anaemia, calcium-phosphate imbalance and inflammation.
- The effects of renal venous hypertension on CRS have recently been investigated; increased tubulointerstitial pressure and decreased arterio-venous gradient can result in the reduction of glomerular filtration pressure and renal blood flow, but the precise mechanisms underlying the worsening of renal function secondary to renal venous hypertension remain unclear.
- Although the results of experimental studies suggest that renal sympathetic nerves play an important role in the pathophysiological mechanisms leading to CRS, it is currently unclear whether catheter-based renal denervation is useful for the treatment of CRS.
- FGF23, a newly identified phosphaturic hormone, may have both advantages and disadvantages, with a protective effect on arterial calcification in nondialyzed CKD patients and promotion of left ventricular hypertrophy in anuric patients; and alteration of FGF23 concentrations may lead to new strategies for the treatment of CRS.

ESRD [4▪]. These findings suggest that cardiac and renal injuries affect each other, and that CRS types 2 and 4 according to the Ronco classification are overlapping and coexistent.

In addition to haemodynamic changes, neurohumoral factors such as renin–angiotensin system (RAS) activation, sympathetic nerve activity (SNA) activation and nitric oxide level play important roles in the interactions between the heart and kidneys in patients with CKD and CVD [5▪,6]. In this review, we describe the interactions among these factors and their impact on the mechanisms underlying the development of CRS, and therapeutic strategies for the management of CRS.

CVD and CKD coexist in patients with CRS, and conventional risk factors for CVD and CKD, such as hypertension and diabetes mellitus, influence the development of CRS [7]. An understanding of the factors that cause CRS in patients with both CKD and CVD is important for determining optimal therapeutic strategies for these patients.

This study discusses the interactions among three maladaptive cycles that lead to the development of CRS: neurohumoral disorders, haemodynamic alterations and CKD-related factors (Fig. 1).

NEUROHUMORAL DISORDERS

Neurohumoral factors are essential haemodynamic regulators and strongly affect blood pressure and body fluid volume. Each of these factors interacts complicatedly with each other, and also has a direct effect on organ injury in a haemodynamic-independent manner.

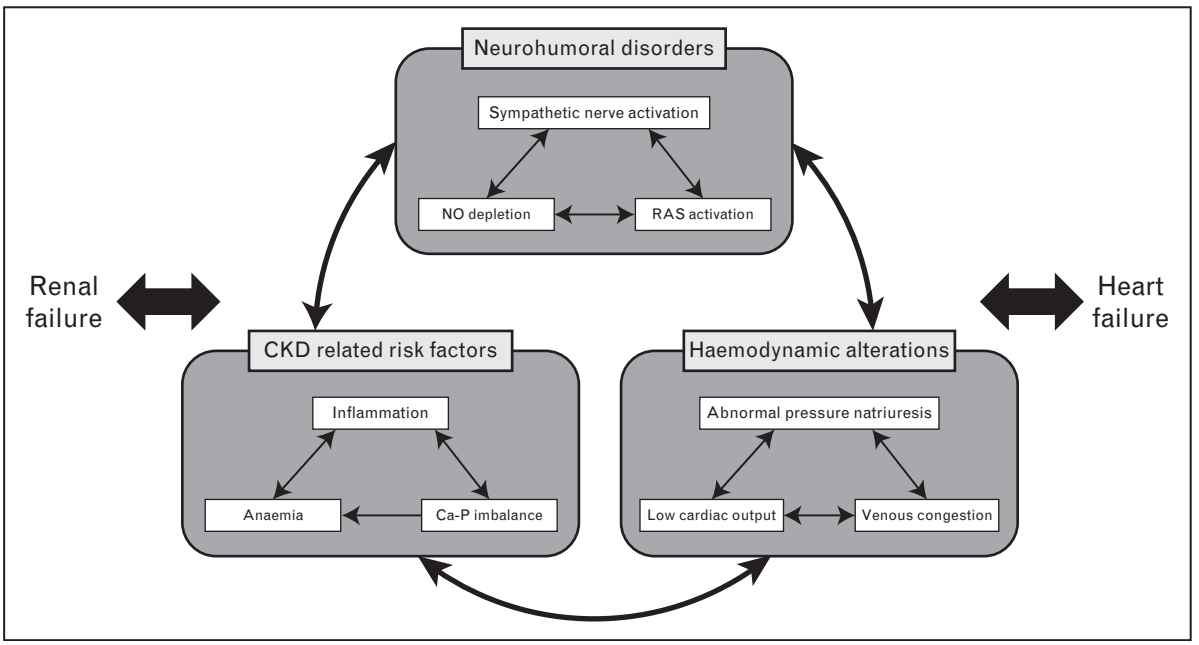

FIGURE 1. Pathophysiology of cardiorenal interactions in chronic kidney disease. The multifactorial cardiorenal interactions in patients with CKD include three positive-feedback cycles: neurohumoral disorders, haemodynamic alterations and CKD-related factors. Ca, calcium; NO, nitric oxide; P, phosphorus; RAS, renin–angiotensin system. This figure is original.

Interactions among renin–angiotensin system, sympathetic nerve activity and nitric oxide

RAS, SNA and nitric oxide interact with each other and have important roles in the neurohumoral maladaptive cycle leading to the development of CRS [6,8,9]. In an animal model, continuous intravenous injection of angiotensin II [10] or intracerebroventricular injection of angiotensin II [11] caused SNA activation, and increased secretion of renin from the juxtaglomerular apparatus after SNA-induced activation of β1 receptors caused RAS activation, resulting in a positive-feedback cycle. The RAS interacts with nitric oxide [12] and lowers the nitric oxide level in the renal cortex of rats injected with angiotensin II [13].

Conversely, inhibition of nitric oxide by chronic administration of N^{ω}-nitro-L-arginine methyl ester increases RAS activation by reducing the renal circulation [14,15▪▪], although this inhibition of nitric oxide initially lowers RAS activation [16] because of volume overload [8]. Moreover, inhibition of nitric oxide promotes a reduction in the glomerular filtration rate (GFR) by increasing the renal response to angiotensin II [17].

Inhibition of nitric oxide in rats also results in SNA activation by resetting the baroreceptors over time, although there is an initial transient decrease in SNA activation due to the baroreceptor reflex response to increased blood pressure [18]. Blocking of the afferent baroreceptor pathways results in SNA activation immediately after inhibition of nitric oxide [18]. Several studies reported that decreased nitric oxide production in the central nervous system resulted in SNA activation [11,19].

Conversely, activation of SNA inhibits nitric oxide production. Decreased activity of the L-arginine–nitric oxide metabolic pathway is reported in patients with CHF in whom SNA activation is thought to occur [20]. Couto *et al.* [21] found reduced nitric oxide bioavailability in the small vessels of mice that had sympathetic hyperactivity because they lacked α_{2A}/α_{2C}-adrenergic receptors.

Nitric oxide

Accumulation of asymmetric dimethylarginine results in chronic inhibition of nitric oxide [22▪]. RAS and SNA activation result in accelerated progression of CKD, and decreased nitric oxide production due to accumulation of asymmetric dimethylarginine results in further RAS and SNA activation and development of CRS [22▪]. Bongartz *et al.* [23,24] reported on the impact of nitric oxide inhibition on CRS progression using two models of CRS. These models of CRS induced by subtotal nephrectomy as well as coronary ligation, or by transient nitric oxide reduction, can be applied to clinical situations [25], and show that nitric oxide inhibition plays an important role in the development of CRS. Although these findings suggest that retrieval of nitric oxide should be an important therapeutic strategy in CRS, this strategy has not been shown to be clinically effective.

Renin–angiotensin system

RAS activation results in organ damage in patients with CKD and CVD, and RAS inhibitors are used as first-line treatment in hypertensive patients with CRS [5▪]. Albuminuria is an independent risk factor for the progression of CKD and CVD even when renal function is normal [26], and randomized controlled trials of RAS inhibitors found that greater reduction in urinary protein excretion was associated with stronger protective effects against CRS [27,28]. It has also been reported that reduction in proteinuria in the early stage of CKD lowers the risk of progression of CKD [29▪]. Treatment with a RAS inhibitor is therefore required from the early stage of CKD to prevent the progression of CKD and CVD, using the degree of albuminuria as a therapeutic target.

Sympathetic nervous system

SNA activation is observed from the early stage of CKD [30] and during progression to ESRD [31], and is associated with CVD and mortality in these patients [30]. SNA activation was reported in various experimental models of renal injury [15▪▪,32,33]. Ye *et al.* [33] reported SNA activation after a limited renal injury induced by intrarenal injection of phenol.

The mechanisms underlying SNA activation in CKD include increased circulating RAS [10] and brain RAS [11], nitric oxide depletion [18], stimulation of renal baroreceptors, chemoreceptors and sensory receptors [32], reduction in renal mass [33], renal ischemia [34] and other factors [35].

A recent study reported that renal denervation resulted in reduction of albuminuria without affecting the blood pressure in a rat model of CRS induced by hemi-nephrectomy and aortic regurgitation [36]. We then investigated the effects of renal denervation on the interaction between SNA and RAS in a rat model of CRS induced by chronic nitric oxide inhibition, and found that renal denervation had protective effects against cardiac and renal dysfunction [15▪▪]. These effects were associated with decreased RAS activation and were independent of the blood pressure lowering effects (Fig. 2).

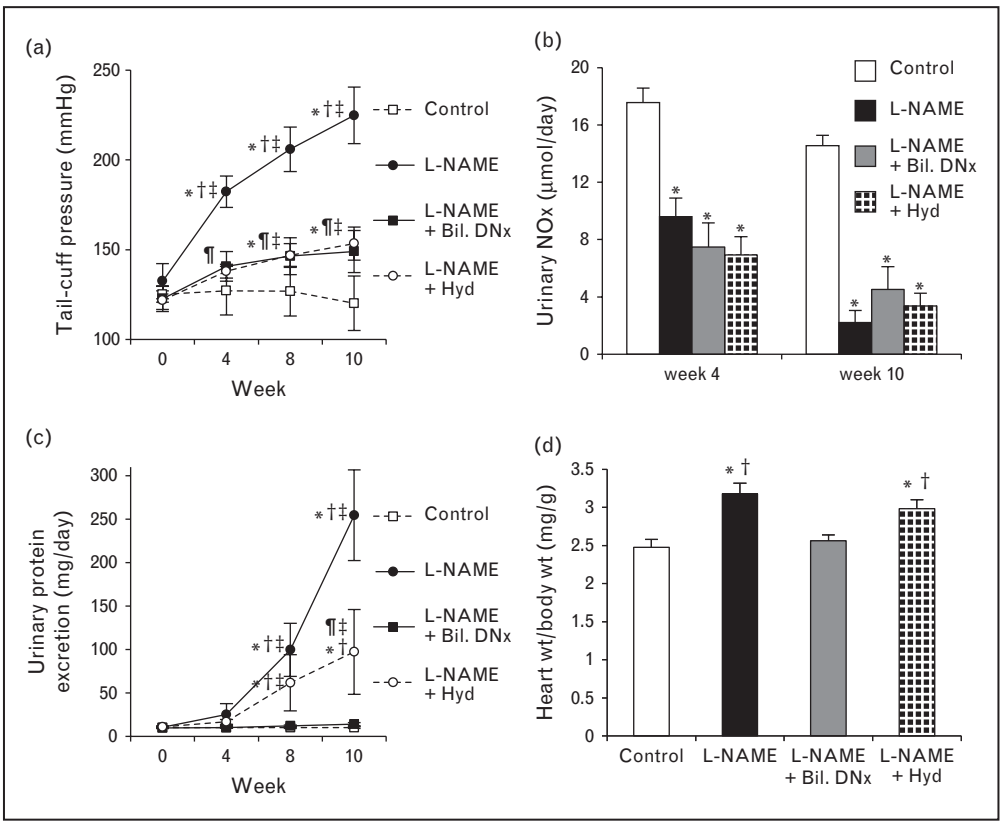

FIGURE 2. Renal denervation in an experimental study. Chronic administration of N^{ω}-nitro-L-arginine methyl ester (L-NAME; a nitric oxide synthase inhibitor) was used to induce proteinuria and cardiac hypertrophy, similar to cardiorenal syndrome, in Wistar rats. These changes were suppressed by bilateral renal sympathetic denervation (Bil. DNx), but not by hydralazine (Hyd) treatment, even though blood pressure and nitric oxide depletion were maintained at the same levels in both groups. SBP (a), urinary nitric oxygen (NOx) (b), urinary protein excretion (c) and heart weight (d) are shown. Values are mean ± standard error of the mean. $^{*}P < 0.05$ vs. control rats, $^{**}P < 0.05$ vs. Bil. DNx rats, $^{***}P < 0.05$ vs. L-NAME rats, $^{\dagger}P < 0.05$ vs. baseline values. This figure is a direct copy of [14].

Renal denervation using catheter devices has been reported to be clinically effective for the prevention of hypertension [37], atherosclerosis [38], left ventricular hypertrophy (LVH) [39], albuminuria [40] and CKD [41], but these studies were not comparative trials. The blinded randomized controlled SYMPLICITY HTN-3 trial [42▪▪], which used a sham-operation group for comparison, did not show a significant difference in the reduction of SBP in patients with resistant hypertension (Fig. 3). As many physicians expect renal denervation to be an attractive therapeutic modality in patients with CRS, it should be determined why this was not shown to be effective in the SYMPLICITY HTN-3 trial [43]. First, it is possible that ablation using the catheter device was incomplete. We found that one-sided denervation did not prevent increase in blood pressure or progression of organ damage [15▪▪]. Second, it is possible that the patient selection process was not appropriate. In a preliminary experiment using a puromycin aminonucleoside-induced model of nephrotic syndrome, we did not find that renal denervation reduced proteinuria or hypertension. It is important to identify clinical markers that can be used to confirm adequate denervation and to ensure appropriate selection of candidates for denervation.

HAEMODYNAMIC ALTERATIONS

Haemodynamic alteration in CRS, which has been explained as the low-flow theory, is an indispensable factor in talking about cardio-renal interaction. We address the recent proposed theory concerning how 'renal venous hypertension' affects the renal perfusion in this section.

Abnormal pressure natriuresis for low cardiac output (low-flow theory)

Regulation of sodium balance according to the pressure natriuresis curve and heart and kidney function is important for the maintenance of appropriate blood pressure and body fluid volume [44].

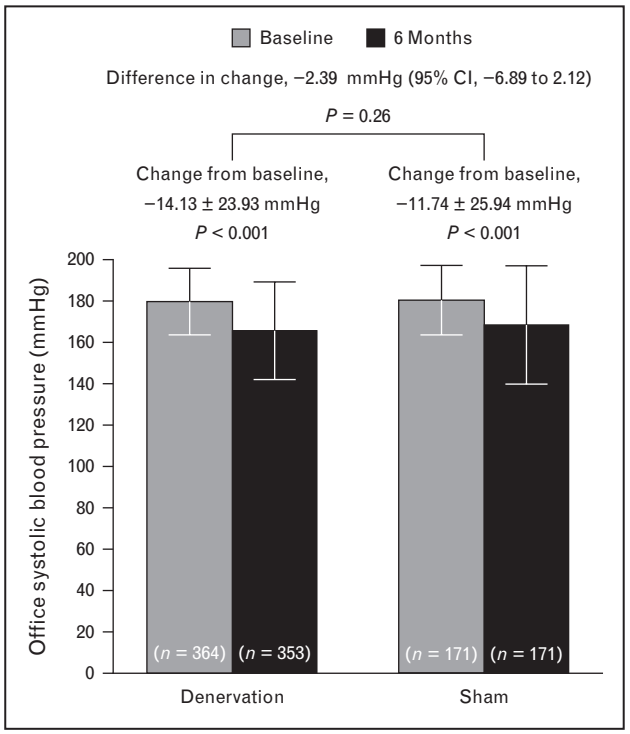

FIGURE 3. Renal denervation in a clinical study. In the SYMPLICITY HTN-3 trial, the difference in change in blood pressure between the two groups was 2.39 mmHg, which was not significant. CI, Confidence interval. This figure is a direct copy of [41].

Increased blood pressure resulting from a normal cardiac response to increased fluid volume, and pressure natriuresis in response to the increased blood pressure, are required for excretion of excess sodium and body fluid. In patients with CKD who have insufficient sodium excretion because of reduced GFR due to reduced numbers of functional nephrons, there is insufficient pressure natriuresis. Pressure natriuresis is also affected by neurohumoral factors, with a shift of the pressure natriuresis curve to the right after RAS and SNA activation [44].

Renal venous hypertension

It was previously thought that impaired pressure natriuresis was caused mainly by reduced renal blood flow due to low cardiac output and by arterial underfilling due to left ventricular contractile dysfunction. However, a study of 1 184 655 patients with heart failure in the ADHERE database did not find an association between left ventricular contractile dysfunction and renal dysfunction, suggesting that renal dysfunction was not attributable only to low cardiac output [45]. This finding suggests that renal venous hypertension due to venous congestion, rather than arterial underfilling, may cause renal dysfunction.

The results of recent clinical trials also suggest that renal dysfunction may be caused by renal venous hypertension due to venous congestion rather than by arterial underfilling [46,47]. A subanalysis of the ESCAPE trial showed the relationship between increase in central venous pressure and decrease in estimated GFR after adjusting cardiac index (Fig. 4) [46]. GFR is considered to decrease in response to reduction in the net filtration pressure caused by increased hydrostatic pressure in Bowman's capsule secondary to increased interstitial pressure (Fig. 5) [48,49]. Other suggested causes of renal dysfunction are neurohumoral factors, myogenic responses, regulation of renal blood flow and

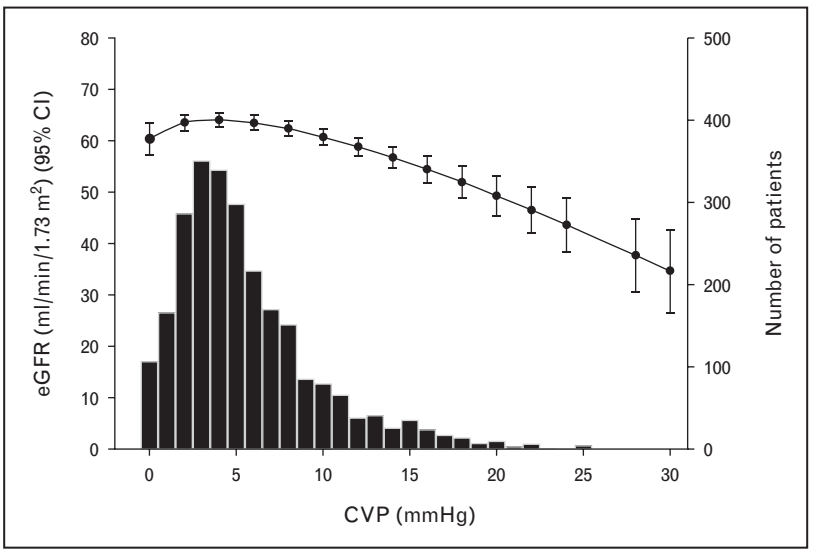

FIGURE 4. Haemodynamic impact of cardiorenal syndrome. The relationship between central venous pressure (CVP) and estimated GFR (eGFR) adjusted for age, sex and cardiac index. CI, confidence interval. This figure is a direct copy of [45].

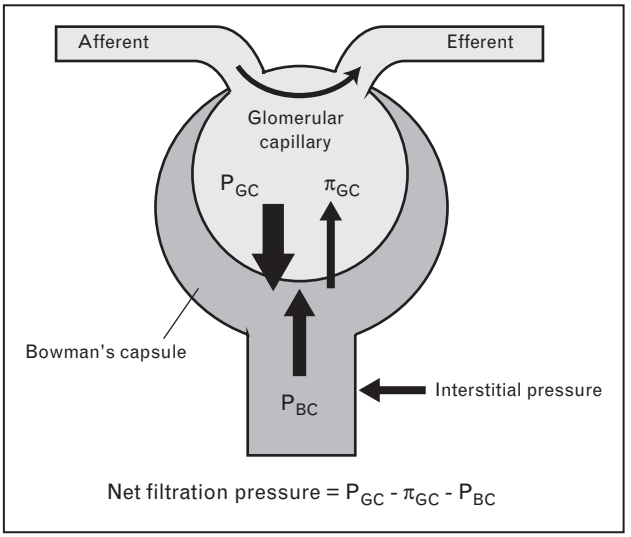

FIGURE 5. Haemodynamic impact of renal venous hypertension on glomerular capillary. Renal venous hypertension is associated with increased efferent pressure (decreased afferent–efferent gradient) and interstitial pressure (P_{BC} elevation), resulting in reduced glomerular flow and net filtration pressure. P_{BC}, hydrostatic pressure in Bowman's capsule; P_{GC}, glomerular capillary hydrostatic pressure; π_{GC}, oncotic pressure in the glomerular capillaries. This figure is original.

GFR by tubuloglomerular feedback [8], and hypoxia and inflammation of the renal parenchyma. These factors suggest that abnormal pressure natriuresis due to decreased GFR, exacerbation of venous congestion and worsening of heart failure due to low cardiac output create a positive-feedback cycle (Fig. 1).

CHRONIC KIDNEY DISEASE RELATED RISK FACTORS

In the past decade, two novel pathogenic mechanisms have been proposed for the development of CVD in patients with CKD: the cardiorenal anaemia (CRA) syndrome proposed by Silverberg *et al.* [50] and the malnutrition–inflammation–atherosclerosis (MIA) syndrome proposed by Stenvinkel *et al.* [51]. In addition, it was also recently reported that disturbances in mineral and bone metabolism are involved in the pathogenesis of CVD in patients with CKD. This mechanism has been termed CKD-related mineral and bone disorder (CKD-MBD), and includes abnormalities in bone and mineral metabolism and vascular calcification [52]. CRA syndrome, MIA syndrome and CKD-MBD are considered to interact with each other in the pathogenesis of CRS (Fig. 6).

Inflammation

Inflammation in CKD is induced by increased levels of inflammatory cytokines due to increased production of uremic toxins [53] and reduced clearance due to renal dysfunction [54]. Inflammation is a predictor of cardiovascular and total mortality in CKD [55], and is also a predictor of mortality and disease severity in patients with heart failure [56].

Venous congestion and volume overload have increasingly recognized roles in the development of inflammation in patients with CRS [57]. Oedematous bowels, veins and peripheral tissues can be important sources of inflammatory mediators when exposed to high intravascular and interstitial pressures.

We recently reported that inflammation and malnutrition play important roles in the development of vascular calcification in rats with adenine-induced chronic renal failure [58▪▪], and that vascular calcification in these rats was ameliorated by antioxidant treatment [59].

Inflammation is considered to be one of the important factors regulating CRS. However, recently conducted randomized controlled trials of immune-selective anti-inflammatory derivatives such as etanercept [60] and infliximab [61] did not show any effects on the risk of death from any cause or hospitalization for heart failure. The ACCLAIM trial investigated the effects of nonspecific immunomodulation in patients with heart failure and showed no significant effects in the group overall, but was associated with reduced risk of death from any cause and first hospitalization for CVD in patients with no history of myocardial infarction and patients with New York Heart Association (NYHA) class II heart failure [62].

Anaemia

Patients with heart failure may have anaemia even though they have a high plasma erythropoietin (EPO) concentration. This EPO-resistant anaemia is considered to be caused by inflammation [63]. In patients with CRS, anaemia is attributed to both EPO deficiency and inflammation-induced EPO resistance. Appropriate management of anaemia is important, because it influences mortality and renal survival in patients with CRS.

Calcium-phosphate imbalance

CRS has been reported to be associated with CKD-MBD. Activation of vitamin D exerts various effects such as reduction of RAS activation, reduction of inflammation, reduction of apoptosis, inhibition of cell proliferation and immune modulation, in addition to regulation of bone and

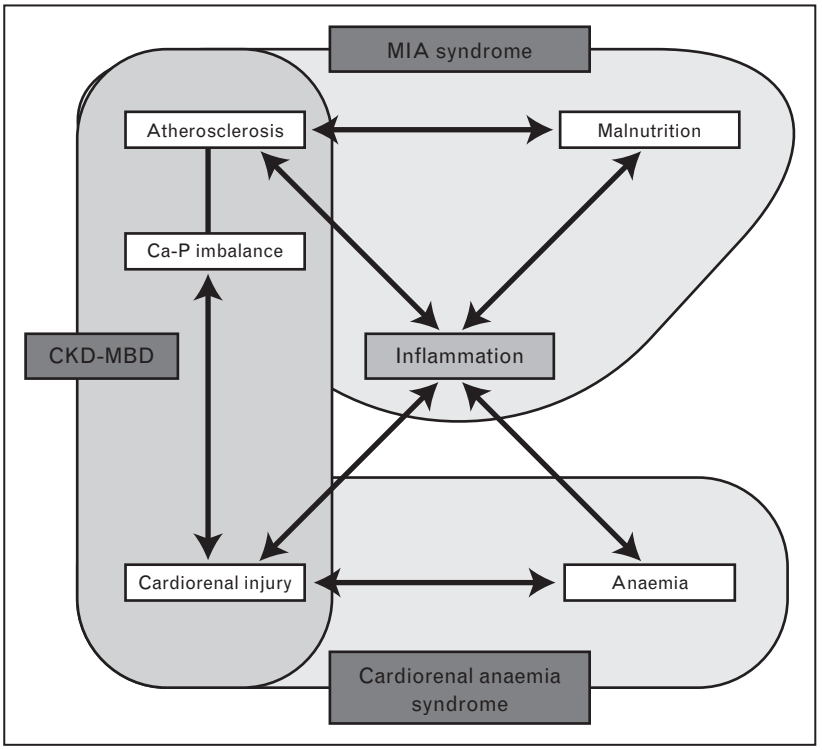

FIGURE 6. Schematic diagram of interactions among chronic kidney disease related factors. Malnutrition–inflammation–atherosclerosis (MIA) syndrome, cardiorenal–anemia (CRA) syndrome and CKD-related related mineral and bone disorder (CKD-MBD) interact with each other. Inflammation plays a central role in all three mechanisms. Ca, calcium; P, phosphorus. This figure is original.

mineral metabolism. Two studies reported that the anti-inflammatory effects of activated vitamin D provided cardiorenal protection. One study found improvements in proteinuria and renal dysfunction in a murine model of adriamycin-induced nephropathy [64], and another found improvement in LVH in rats with CKD induced by subtotal nephrectomy [65▪]. Two recent randomized controlled trials investigated the cardiorenal protection provided by paricalcitol therapy. Paricalcitol therapy reduced albuminuria in the VITAL study [66], but did not improve LVH in patients with CKD in the PRIMO trial [67]. Further accumulation of evidence of beneficial effects of vitamin D receptor activator (VDRA) on CRS is required in the clinical setting.

Recent studies found that an increase in the serum FGF23 level, which causes reduction of the serum phosphate level by inhibition of proximal tubular phosphate reabsorption through its own suppressive effect on the expression of type 2a and 2c sodium-phosphate cotransporter in the brush border membrane of proximal tubules, and by inhibition of intestinal phosphate absorption secondary to reduction of the 1,25-dihydroxyvitamin D level, is associated with CVD [68▪]. It is currently unclear whether FGF23 is a biomarker or a pathogenic factor in this process. Faul *et al.* [69] reported that intramyocardial or intravenous injection of FGF23 in wild-type mice resulted in LVH. However, Shalhoub *et al.* [70] reported that administration of anti-FGF23 neutralizing antibodies increased vascular calcification and mortality in a rat model of CKD. FGF23 has a preventive effect on arterial calcification because it controls the serum phosphate level via its phosphaturic action in patients with nondialyzed CKD and induces LVH by reducing the activation of vitamin D in patients with ESRD without phosphaturia. FGF23 may therefore have different effects in different patients with CRS, depending on the stage of CKD. It is expected that further elucidation of the pathophysiological impact of FGF23 will lead to the development of new strategies for the treatment of CRS.

More recently, a new phosphate-centric paradigm for pathophysiology and therapy of CKD has been proposed that extracellular phosphate exerts its cytotoxicity when it forms insoluble nanoparticles with calcium and fetuin-A, referred to as calciprotein particles (CPPs) [71▪▪]. These observations

have raised the possibility that CPPs may promote progression of CKD and vascular calcification, resulting in development and progression of CRS.

CONCLUSION

Although many pathogenic factors leading to CRS have been identified, it is possible that an important underlying mechanism remains unclear. Further elucidation of the mechanisms underlying the development of CRS may lead to clinically feasible strategies for the treatment of this condition.

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Conflicts of interest

None.

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In 2008, Ronco *et al.* [2] proposed five distinct CRSs according to the temporal sequence of organ injury and failure as well as the clinical context. Later in 2008, a consensus conference was organized under the auspices of the Acute Dialysis Quality Initiative (ADQI) bringing to Venice, Italy, key opinion leaders and experts in the fields of nephrology, critical care, cardiac surgery and cardiology. In a series of papers and an executive summary, this group presented the definition and classification system for the CRS, epidemiology and diagnostic criteria, prevention and therapeutic approaches, as a result of the consensus process. This study reviews and summarizes key findings from the 11th ADQI consensus conference on the spectrum of pathophysiologic mechanisms at work in the CRS.

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This paper reviews the mechanism of cytotoxicity of hyperphosphataemia in CKD. The author describes how extracellular phosphate exerts its cytotoxicity when it forms insoluble nanoparticles with calcium and fetuin-A, referred to as calciprotein particles (CPPs), which are detected in the blood of animal models and patients with CKD. CPPs are highly bioactive ligands that can induce various cellular responses, including osteogenic transformation of vascular smooth muscle cells and cell death in vascular endothelium and renal tubular epithelium, and associated with adaptation of the endocrine axes mediated by fibroblast growth factor-23 (FGF23) and Klotho that regulate mineral metabolism and aging. These observations have raised the possibility that CPPs may contribute to the pathophysiology of CKD.