**REVIEW**

# Cardiovascular Alterations and Structural Changes in the Setting of Chronic Kidney Disease: a Review of Cardiorenal Syndrome Type 4

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## Abstract

Cardiovascular and renal physiology are interrelated. More than a decade ago this was codified in guidelines defining the five subtypes of the cardiorenal syndrome. Morbidity and mortality for those with the cardiorenal syndrome is high compared to demographically matched individuals without cardiorenal disease, acute or chronic. The focus of this review will be the epidemiology, the impact of chronic kidney disease on cardiac structure and function, and associated clinical symptoms, outcomes, and potential treatments for patients with chronic reno-cardiac syndrome, or cardiorenal syndrome type 4. Cardiac structural changes can be profound and are described in detail both at a cellular and physiologic level. Integrating therapies for the treatment of causative or resulting comorbidities may ultimately slow progression of both cardiac and renal disease as well as minimize symptoms and death.

**Keywords** Chronic renal insufficiency · Cardiorenal syndrome · Left ventricular hypertrophy · Fibrosis · Arterial stiffness

## Abbreviations

| | |
|---|---|
| ACR | Albumin creatinine ratio |
| ADQI | Acute dialysis quality initiative |
| AKI | Acute kidney injury |
| AMI | Acute myocardial infarction |
| CKD | Chronic kidney disease |
| CVA | Cerebral vascular accident |
| CVD | Cardiovascular disease |
| eGFR | Estimated glomerular filtration rate |
| ESKD | End-stage kidney disease |
| FGFR | Fibroblast growth factor receptor |
| FGF23 | Fibroblast growth factor-23 |
| HD | Hemodialysis |
| HF | Heart failure |
| HFpEF | Heart failure with preserved ejection fraction |
| HFrEF | Heart failure with reduced ejection fraction |
| IL | Interleukin |
| KDIGO | Kidney disease improving global outcomes |
| LDL | Low-density lipoprotein |
| LVEF | Left ventricular ejection fraction |
| LVH | Left ventricular hypertrophy |
| MI | Myocardial infarction |
| MMP | Matrix metalloproteinases |
| RAAS | Renin-angiotensin-aldosterone system |
| SCD | Sudden cardiac death |
| TGFβ | Transforming growth factor beta |
| TIA | Transient ischemic attack |
| TNFα | Tumor necrosis factor alpha |
| USRDS | United States renal data system |

## Methods

The predominant source of information was obtained through PubMed searching terms including mesh terms (keywords as listed above and here: Chronic renal insufficiency, Cardiorenal syndrome, Left ventricular hypertrophy, Fibrosis, Arterial stiffness. The latter three terms were linked via "and" to the first mesh terms and "renal disease." The citations of individual papers were then reviewed for additional primary source documentation. In addition, for epidemiologic data, we utilized data directly from the United States Renal Data System (https://www.usrds.org/annual-data-report/).

## Introduction

The relationship between the cardiovascular and renal systems has long been recognized. In 2008, the acute dialysis quality initiative (ADQI) released consensus guidelines formally

defining cardiorenal syndrome (CRS) and outlining five subtypes based on chronicity, primary organ of injury, and resultant pathophysiology (Table 1) [1, 2]. Much research interest remains in studying the population with chronic reno-cardiac syndrome, also known as CRS type 4, which is defined as cardiac dysfunction secondary to primary chronic renal disease [2]. Epidemiologic studies suggest that not only do chronic kidney disease (CKD) patients have a ten-fold increase in mortality risk compared to the general population [3, 4], but among this group greater than 50% of deaths are from cardiovascular disease (CVD) causes, including coronary artery disease, valvular dysfunction, arrhythmias, and cardiomyopathies [2, 3, 5–7]. As research aims to better characterize the interface between these two organ systems, understanding the pathophysiologic consequences of renal disease and resultant structural changes within the heart remains an important area of interest.

## Epidemiology

The prevalence of chronic kidney disease in the USA, based on the United States Renal Data System (USRDS) reporting from 2003 to 2018, has remained stable at 14.4%, representing roughly 37 million Americans [8, 9]. This has led to an average annual Medicare cost of $114 billion U.S. dollars to care for these patients. The prevalence of advanced CKD, defined as stages 3–5, decreased from 2003 to 2006 compared to 2015–2018, with the greatest reduction in stage 3 from 6.3 to 5.8%. Within this same period, prevalence of all stages declined the most among individuals greater than age 65, from 43.2 to 36.8%, while remaining constant at 8.6% among those less than age 65. Given an aging population, such trends represent overall improvement, likely as a result of better treatment options and improved management strategies of associated risk factors [10].

Presence of CVD (defined as acute myocardial infarction [AMI], cerebral vascular attacks [CVA], and heart failure [HF]), is much greater among the CKD population at 66.6%, compared to 37.5% among individuals without CKD (Fig. 1) [8, 11]. As the degree of CKD worsens, HF becomes more prevalent (Fig. 2), and is the most common cardiac manifestation within this population, with a prevalence in 2018 of 27.7% (11.5% HF with reduced ejection fraction [HFrEF], 9.6% HF with preserved ejection fraction [HFpEF], 6.5% undefined), which is roughly 4 times higher than in similar individuals without CKD [8, 12].

Patients with both CKD and CVD have increased risk of hospitalizations, need for intensive-unit level of care, and death [12]. For these reasons, cardiorenal syndromes remain a significant public health burden, and as such, gaining a comprehensive understanding of pathophysiology is all the more necessary towards developing new management strategies.

## Cardiorenal Syndromes

Cardiac and renal dysfunction results in a nuanced spectrum of disease with several shared risk factors and whose biochemical and hemodynamic pathways still have much to be discerned. As a result of this fine interplay and limited mechanistic understanding, several challenges exist in formulating an accurate definition and classification system. The National Heart, Lung, and Blood Institute attempted to encompass cardiorenal disease with a broad definition, whereby worsening renal function leads to worsening cardiovascular outcomes [13]. This definition, however, failed to encompass all observations seen in clinical practice and describe a clear mechanistic pathway.

The ADQI consensus guidelines established in 2008 remain the principal definitions used in practice today [2]. Cardiorenal disease was classified into five subtypes, defined by primary organ injury, resultant secondary organ insult, and chronicity: either acute or chronic. This definition was appealing in that it encompassed clinical presentations of cardiorenal disease, which better identified affected populations that helped facilitate development of therapeutic strategies [1, 14, 15]. Several mechanistic questions still persist, however as the definitions did not elaborate on the exact underlying pathophysiologic mechanisms of each disease state [1, 14].

## Type 4 Cardiorenal Syndrome

Given the large prevalence of CKD in the general population, and the associated high morbidity and mortality of CVD events described above, it is important to understand

**Table 1** Cardiorenal syndrome definitions. Adapted from Ronco et al. 2010 [2]

| Syndrome | Definition |
| --- | --- |
| Type I (acute cardiorenal) | Sudden decline in heart function leading to acute kidney injury and dysfunction |
| Type II (chronic cardiorenal) | Chronic impairment in heart function leading to chronic kidney disease |
| Type III (acute reno-cardiac) | Sudden decline in kidney function leading to cardiac injury and dysfunction |
| Type IV (chronic reno-cardiac) | Chronic kidney disease leading to heart injury, disease, or dysfunction |
| Type V (secondary Cardiorenal syndrome) | Systemic illness leading to simultaneous cardiac and renal impairment |
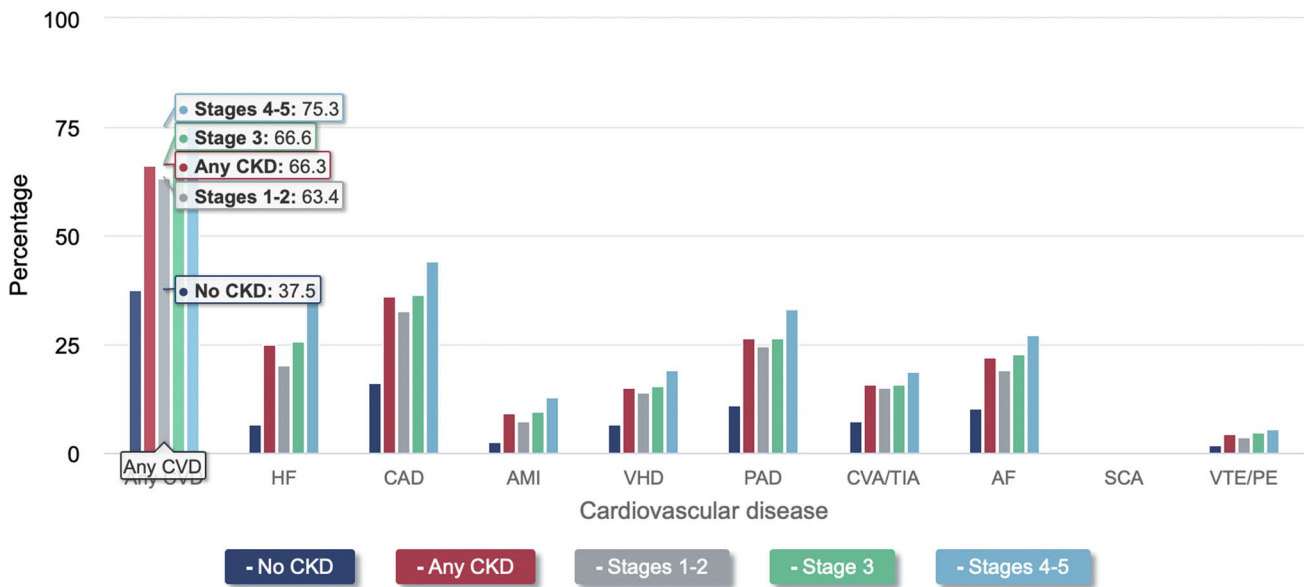
**Fig. 1** Prevalence of various cardiovascular disease in CKD and non-CKD patient populations. Based on 2018 epidemiology data. Graph transcribed from USRDS Annual Data Report. 2020 [8]. Cardiovascular disease (CVD); heart failure (HF); acute myocardial infarction (AMI); valvular heart disease (VHD); peripheral artery disease (PAD); cerebral vascular attack (CVA); transient ischemic attack (TIA); atrial fibrillation (AF); sudden cardiac arrest (SCA); venous thromboembolism (VTE); pulmonary embolism (PE)
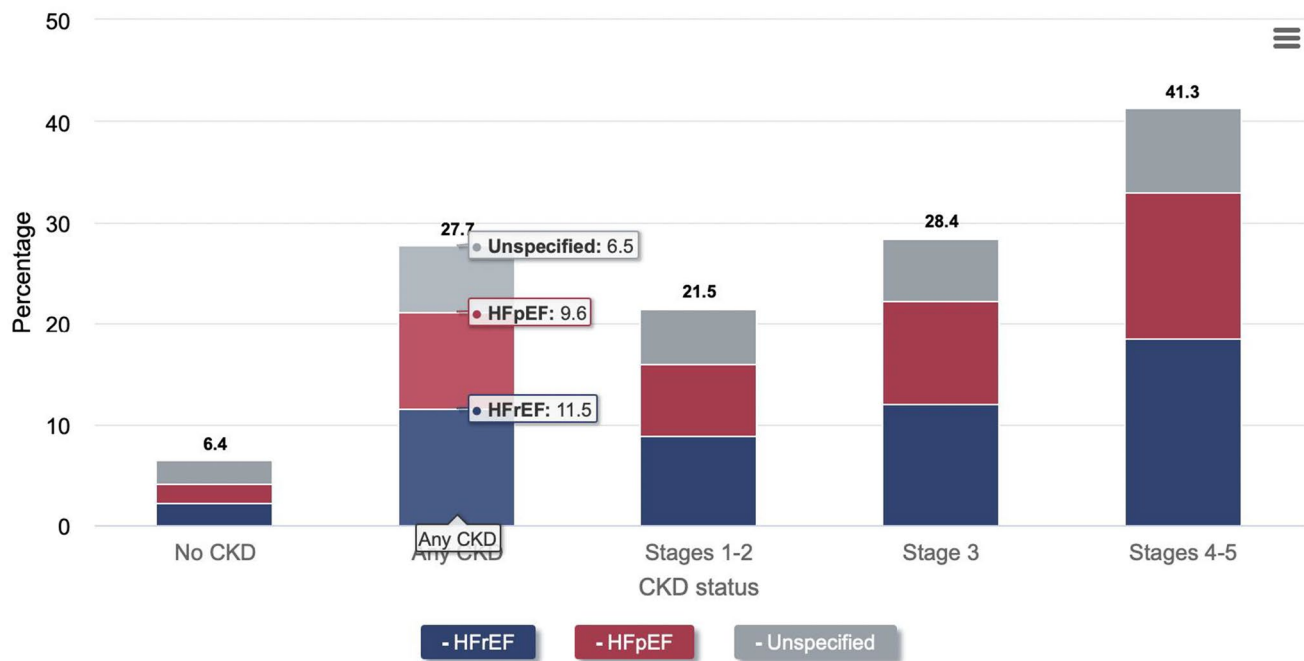


**Fig. 2** Increasing prevalence of heart failure in worsening stages of CKD. Based on 2018 epidemiology data. Graph from USRDS Annual Data Report. 2020 [8]

the features of Type 4 CRS, also known as chronic renocardiac syndrome, with the intent to better establish therapeutic options going forward.

CRS type 4 is defined as longstanding CKD leading to cardiac injury and/or dysfunction [2]. According to the kidney disease improving global outcomes (KDIGO) guidelines in 2012

and 2019, CKD is defined as renal function with persistently reduced estimated glomerular filtration rate (eGFR) of $<60$ ml/min/1.73 m$^2$, or at least one indicator of kidney damage for greater than 3 months, including albuminuria, elevated urine sediment, or histological and structural renal abnormalities (Table 2) [12]. Physiologically, GFR is maintained at approximately 140 ml/min/ 1.73 m$^2$ until age 40 (though epidemiologic cross-sectional analyses suggest decline begins as early as age 20), and gradually declines by 8 ml/min/1.73 m$^2$ per decade afterwards [16, 17]. The presence of albuminuria, measured as a random urine albumin/Cr ratio (ACR) of 30 to 300 mg/g, also indicates CKD regardless of eGFR. Shared risk factors, including diabetes, hypertension, dyslipidemia, physical inactivity, smoking, and relevant family history harm both organ systems [8]. Both eGFR and degree of microalbuminuria have been shown to be independent contributors to risks of acute kidney injury (AKI), AMI, HF, CVA, or death.

Cardiovascular risk factors such as hypertension, volume overload, anemia, iron-deficiency, nutritional deficiencies, bone disease, and uremic toxin buildup begin to develop once eGFR falls below 60 ml/min/1.73 m$^2$ [4, 18]. Such factors trigger myocardial and endothelial dysfunction, resultant inflammation and oxidative stress, leading to vascular microcalcification and myocardial fibrosis. The cascade then manifests on a macrovascular level with reduced myocyte contractility, left ventricular hypertrophy (LVH) and/or dilation, ensuing heart failure (Fig. 3). At the level of the kidneys, glomerular sclerosis and renal parenchymal fibrosis are concomitantly observed [1, 3, 4, 7, 14, 19].

## Microvascular Pathways and Changes

Cardiorenal syndrome can be thought of as a spectrum of disease with several microvascular pathways and mediators which all culminate in the final common denominator of fibrosis. An important aspect to consider is that many of these microvascular mechanisms are closely interlinked; thus, it is difficult to independently define a specific pathophysiologic role to each one individually.

### The Renin–Angiotensin–Aldosterone System and Sympathetic Nervous System

The neurohormonal axis, composed of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (SNS) is one such pathway. Chronic, persistent RAAS activation observed in renal disease patients occurs due to dysregulated renal blood flow. In addition to the net effect of sodium and water retention, elevated levels of aldosterone, and angiotensin II have numerous downstream implications within the inflammatory cascade and cardiac myocytes. Angiotensin II, a powerful vasoconstrictor, reduces coronary blood flow, and ensuing ischemia triggers an inflammatory cascade which then facilitates myocardial injury and necrosis, that then stimulates myocardial fibrosis and causes maladaptive remodeling and hypertrophy on the macrovascular level [21, 22]. Interestingly, in vivo studies on mice also suggested that circulating levels of angiotensin II may be cardioprotective following ischemic reperfusion

**Table 2** CKD Stages one through five categorized according to eGFR and degree of albuminuria, with corresponding estimated percentages among the US general population surveyed between 2015 and 2018. From USRDS Annual Data Report. 2020 [8]

### (a) Percentage by eGFR and ACR, 2015-2018

| eGFR Categories | A1: Normal to mildly increased (ACR <30 mg/g) | A2: Moderately increased (ACR 30-299 mg/g) | A3: Severely increased (ACR ≥300 mg/g) | Total |
|---|---|---|---|---|
| G1: Normal or high (eGFR ≥90ml/min/1.73m²) | 53.5 | 4.1 | 0.58 | 58.3 |
| G2: Mildly decreased (eGFR 60-89 ml/min/1.73m²) | 31.5 | 2.9 | 0.43 | 34.8 |
| G3a: Mildly to moderately decreased (eGFR 45-59 ml/min/1.73m²) | 3.9 | 0.84 | 0.27 | 5.0 |
| G3b: Moderately to severely decreased (eGFR 30-44 ml/min/1.73m²) | 0.88 | 0.40 | 0.17 | 1.5 |
| G4: Severely decreased (eGFR 15-29 ml/min/1.73m²) | 0.11 | 0.09 | 0.17 | 0.37 |
| G5: Kidney failure (eGFR <15 ml/min/1.73m²) | 0.01 | 0.01 | 0.09 | 0.11 |
| Total | 90.0 | 8.3 | 1.7 | 100 |
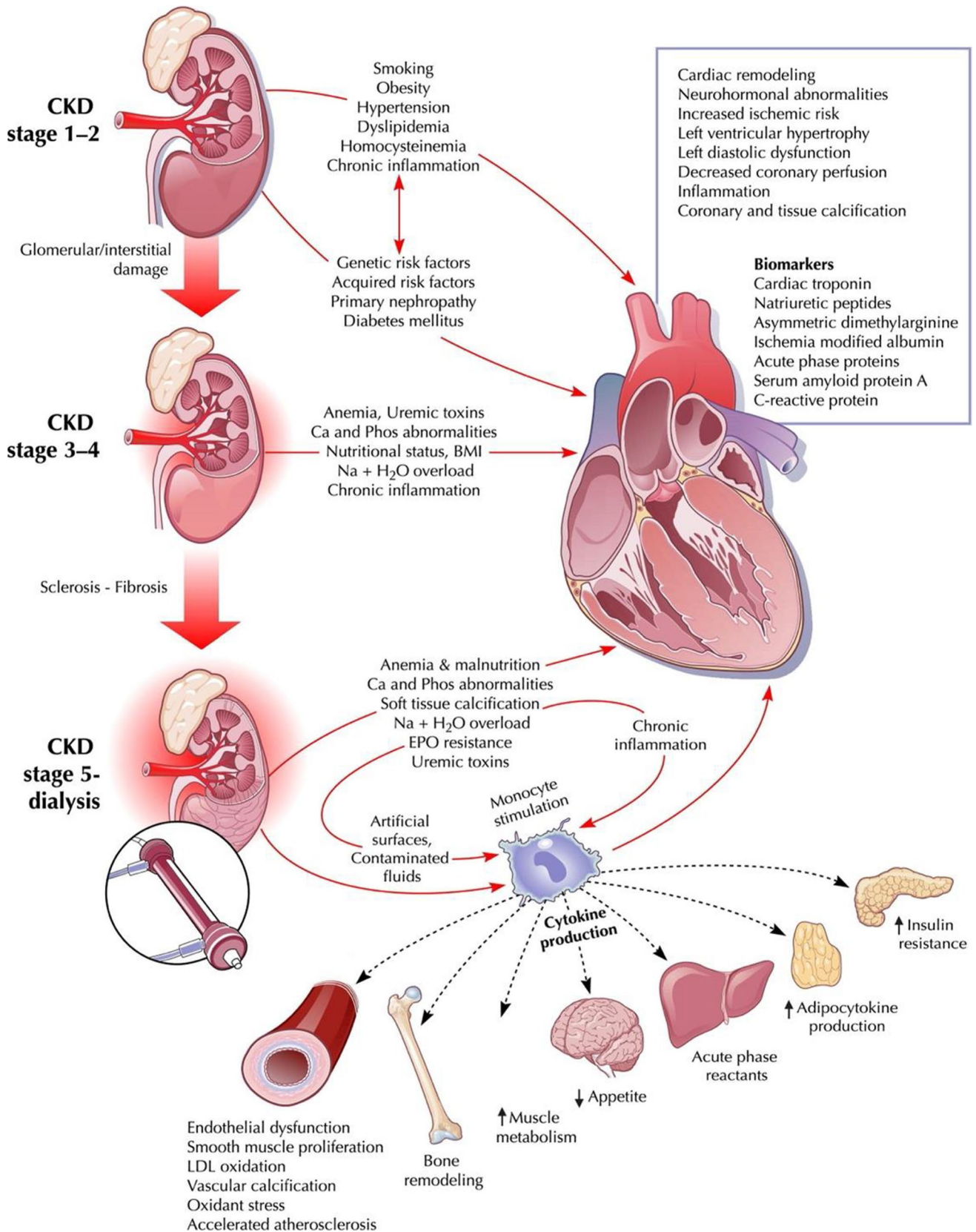
**Fig. 3** Overview of pathophysiologic mechanisms implicated in cardiovascular structural changes in the setting of CKD. Figure from Ronco et al. (2008) [20]

injury [23], with one proposed mechanism stipulating that reduced coronary blood flow reduces the arrival of inflammatory mediators and thus limits inflammation; a hypothesis that will need validation in other models. Furthermore, several smaller peptides believed to be cleaved from angiotensin II, referred to angiotensin 1–7, can have cardioprotective effects [23]. Ongoing research is required to further delineate such mechanisms.

In conjunction with the RAAS, dysregulated and persistent SNS activation, a sequala of CKD, furthers maladaptive cardiac remodeling and dysfunction. Catecholamine release induces vasoconstriction within the kidneys, heart, and peripheral vasculature. Renal vasoconstriction triggers renin release and RAAS activation. Coronary vasoconstriction leads to myocyte ischemia. Catecholamines, in conjunction with angiotensin II and renin, stimulate tumor necrosis factors and interleukins, which in turn trigger endothelial dysfunction, myocyte apoptosis and necrosis, and fibroblast activation [23].

## Inflammation and Cellular Mediators of Remodeling

The inflammatory cascade is important to consider as one of the principal drivers of structural heart changes observed in the setting of CKD. As previously discussed, reduction in eGFR below 60 ml/min/1.73$m^2$ correlates with onset of a chronic inflammatory state [4, 7]. Neurohormonal activation, angiotensin II, catecholamines, uremic toxins activate pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF$\alpha$), interleukin-1 (IL-1), interleukin-6 (IL-6), and transforming growth factor beta (TGF$\beta$) [1, 15, 21, 24, 25]. Renal impairment causes a systemic imbalance of superoxide and reactive oxygen species, which also contributes [22]. Such molecules trigger endothelial dysfunction and disrupt the delicate homeostasis of cellular membranes and mitochondria, leading to premature apoptosis and necrosis. Excessive endothelin-1 production within cardiomyocytes, for example, has been implicated in onset of LVH, as has persistent oxidative stress [1, 21, 24, 26, 27]. In particular, IL-6, a pro-inflammatory cytokine that has received significant attention as a result of its deleterious effects associated with severe COVID-19 infection, is also involved in regulating gene transcription among inflammatory, metabolic, and cell death pathways, and can have such deleterious effects on cardiac myocytes if left unregulated. Decreased nitric oxide availability due to endothelial dysfunction further propagates the above changes [15, 22].

Immune cells including macrophages, mast cells, neutrophils, and fibroblasts subsequently infiltrate the area of injured myocardium, remove the debris, and activate anti-inflammatory cytokines and fibroblasts, which, in mechanisms mediated by toll-like receptors (TLRs), damage-associated molecular patterns (DAMPs) among others, deposit collagen matrix, leading to fibrosis, reduced contractility, and hypertrophy [22]. While several molecules and mechanisms have been identified, the nuanced complexity carried among these systems remains an active area of research and must be further delineated before being effectively carried over to clinical treatments.

Fibroblast growth factor-23 (FGF23) is another mediator that has garnered interest, and, along with the transmembrane protein Klotho, are regarded as potentially having key roles in cardiac remodeling in the presence of CKD [28, 29]. Elevated levels of FGF23 have been implicated in the increased prevalence of LVH and mortality in CKD patients [30]. While the fibroblast growth factor proteins are involved in cellular development, proliferation, and differentiation, FGF23 works within the kidney to regulate phosphorus homeostasis by increasing phosphorus excretion within the proximal convoluted tubule and decreasing concentration of active vitamin D. CKD patients have impaired phosphorus excretion, thus elevated levels of FGF23 [30]. These pathologically elevated levels, in a dose-dependent manner, have been linked to greater risk of cardiovascular events and increased mortality. The study conducted by Faul et al. [30] sought to explain the pathophysiologic link associated with increased circulating FGF23 and CVD. In their proposed model, FGF23 acts upon the FGF receptor (FGFR) signaling cascade within cardiac myocytes, activating a host of tyrosine kinases implicated in signaling pathways that act upon the nucleus to upregulate gene transcription relating to growth and differentiation [30]. Similarly, there is research into the role of micro-RNA and myocyte development. In a model proposed by Bao et al. [31], FGF23, in addition to uremic toxins and TGF$\beta$ suppress cardiac micro-RNA 30 (miR-30) expression, a molecule abundant within cardiac myocytes that is implicated in regulation of cell hypertrophy [32–34]. Loss of miR-30 results in unregulated hypertrophy.

Klotho, a transmembrane protein principally expressed in the kidney and parathyroid glands, has been postulated as an important mediator of protective mechanisms against LVH. Klotho acts as a co-receptor which increases binding affinity of FGF23 to FGFR [30]. Though it was originally believed that Klotho and FGF23 acted in conjunction, Faul et al. demonstrated induction of LVH in mice where FGF23 levels were abnormally elevated, but Klotho was absent. Therefore, the role of Klotho ultimately remains to be further delineated for this reason [28]. However, longitudinal cohort studies among dialysis and pre-dialysis patients also did not detect a significant relationship between levels of circulating klotho and cardiovascular outcomes [35].

## Fibrosis as the Final Common Pathway

While the initial cardiorenal syndrome classifications defined the different clinical presentations of disease, many questions remained about the underlying pathophysiology.

Rather than think of each presentation as a distinct phenotype, cardiorenal syndrome is better described as a spectrum of disease, with tightly woven and interconnected pathways and mediators which ultimately result in tissue fibrosis on the microvascular level [14]. While the main intent of these mechanisms is to preserve cellular function and organ structure, the end result manifests as myocyte hypertrophy, increased stiffness with impaired contractility, chamber dilation, and subsequent HF symptoms. In the kidney, similar fibrotic pathophysiology occurs mediated by many of the same processes [14].

## Macrovascular Pathways and Changes

### Left Ventricular Hypertrophy and Increased Left Ventricular Mass

In conjunction with microvascular mechanisms, macrovascular changes also contribute to structural changes within the heart, kidneys, and peripheral vasculature. Post-mortem autopsies of CKD patients have identified LVH, diffuse coronary, valvular, and aortic calcifications, in addition to thickened, calcified pericardia [3]. In a study of 120 post-mortem evaluations of end-stage kidney disease (ESKD) patients, treated with hemodialysis (HD) with more than 1 year, 51% had dilated ventricles [36]. Similar findings have been observed using echocardiography. In a retrospective study of 567 ESKD patients initiating hemodialysis, the most common structural abnormality found at baseline was an increased left atrial volume index (81%), followed by grade 2 diastolic dysfunction (78%) and LVH (49%) [37]. Cardiac structural changes begin early during CKD. Individuals with stage 2 or 3 CKD, without prior cardiovascular heart disease, have subtle left ventricular dysfunction with reduced ventricular global systolic strain and higher left ventricular mass index, though overall LVEF remained preserved [38, 39]. Interestingly, the changes in cardiac structure and function with CKD is beyond the hemodynamic effects of concomitant disorders such as hypertension. In a study comparing 293 individuals with stages 2–5 CKD and hypertension to 289 individuals with hypertension without CKD. The CKD cohort had a significantly higher prevalence of echocardiography determined LVH and diastolic dysfunction of 62.8% versus 51.9% in those with only hypertension [40]. Finally, a cross-sectional study with cardiac magnetic resonance imaging of 134 non-diabetic, pre-dialysis patients with CKD stages 2–5 revealed increased myocardial T1 time, suggestive of increased interstitial fibrosis, with decreasing renal function, all in the setting of increased serum biomarker levels of fibrosis [41].

These studies underscore the observations that morphologic changes to the left ventricle begin to manifest in early stages of CKD, though LVEF remains preserved. Those progressing to ESKD carry a high prevalence of increased left ventricular mass, diastolic dysfunction, and impaired contractility by the time dialysis is initiated [21].

### Hemodynamic Pathway

In terms of a mechanistic explanation of the abovementioned morphologic changes, several hemodynamic factors come into play [7, 21, 42–45]. As the RAAS system remains activated among CKD patients, this leads to a net retention of sodium and water, causing intravascular volume expansion. Resultant increase in central venous pressure causes elevated renal venous pressure, which reduces renal perfusion and further stimulates renin secretion and SNS activation. Interestingly, the right ventricle may play a greater role than previously thought, though the exact mechanism is unclear due to lack of studies highlighting presence of CRS in isolated right heart disease and absent left heart failure [46]. One proposed hypothesis is that increased RV afterload leads to a reduction in RV filling, thus reducing LV filling and output. Persistent RV pressure overload leads to RV wall dilation, which, within the confines of the pericardial sac can cause septal mechanical dyssynchrony with septal bowing into the LV, further reducing LV filling and stroke volume [1, 46]. Presence of RV dysfunction carries an independent association with increased mortality among a cohort of ESKD patients about to initiate hemodialysis [37], therefore further research is necessary on RV mechanistic properties.

At the microvascular level, peripheral venous congestion stresses vascular endothelium, causing phenotypic conversion of these cells into a pro-inflammatory state, accelerating calcification and fibrosis [1, 47]. Anemia of CKD is another contributor to hemodynamic imbalance, whereby reduced oxygen delivery to the endocardium perpetuates myocardial ischemia and triggers fibrosis, increased ventricular mass, and eventual reduced systolic function [48].

Afterload-related factors, such as chronic hypertension and decreased peripheral vascular compliance increase systemic vascular resistance. Arterio-venous fistula creation for hemodialysis can serve as high volume circulatory shunts, worsening intravascular volume overload and right ventricular workload [3, 12, 21]. Maladaptive myocardial cell thickening and concentric LVH in response to these factors may preserve LVEF during early course of CKD, but ultimately can lead to systolic failure [14, 21].

### Peripheral Arterial Stiffness

Reduced peripheral vascular compliance also plays an important role in progressive left ventricular dysfunction in patients with CKD. It has been independently associated with increased cardiovascular risk, whereas reduced stiffness is associated with improved survival [25]. Arterial fibrosis occurs via similar

microvascular pathways described above for the myocardium, leading to inflammation, calcification, and fibrosis of the artery vessel wall. In a mechanism set forth by Zanoli et al., elevated levels of circulating TNFα and decreased endothelial nitric oxide synthase (eNOS) expression allows for the local increase in oxygen radicals that trigger endothelial injury [25]. TNFα also upregulates low-density lipoprotein receptors, increases alkaline phosphatase expression, and reduces α-smooth muscle actin protein expression, ultimately stimulating inflammation and microcalcifications within vessel walls [25, 49]. Studies involving patients with inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease showed that anti-TNF agents may lead to reversal of inflammation-dependent aortic stiffening, and thus may represent a class of therapies to investigate in CKD patients as well [25].

## Hemodialysis and Renal Transplant Implications on Cardiac Structure

Currently, medical options for ESKD patients aimed at reducing cardiovascular complications are limited. Evidence does exist that increasing the number of dialysis sessions reduces ventricular mass and lowers risk of cardiovascular-related hospitalizations and death [21, 50]. However, this potential benefit must be weighed against the risk of vascular access issues, complications, and infection [12]. Renal transplantation can also provide some degree of reversal in cardiac dysfunction, though this reversal is less prominent in those who have been undergoing hemodialysis for a longer period [51–54].

## Arrhythmogenicity and Sudden Cardiac Death

Compared to the general population, patients with CKD have increased risk of atrial fibrillation, ventricular arrhythmias, and a 4–20 times greater risk of sudden cardiac death (SCD), with risk increasing as renal function declines [55, 56]. The mechanism is thought to be due to cardiac fibrosis, which causes high-resistance pathways within the electrical conduction system that delay the physiologic action potential, favors re-entry pathways and induces arrhythmogenicity [21].

To date, no therapy has been shown to decrease the risk of SCD. In a recent prospective, randomized controlled trial 200 ESRD patients on hemodialysis with an LVEF of ≥ 35% underwent implantable cardioverter-defibrillator (ICD) insertion with the intent to prevent SCD; however, the study was stopped due to futility as both arms experienced similar rates of SCD and 5-year survival [19]. Prophylactic implantable cardioverter-defibrillator therapy did not reduce the rate of SCD suggesting that terminal tachy- or bradyarrhythmia's may be more related to systemic processes than immediately reversible cardiac etiologies [19].

Atrial fibrillation is the most pervasive arrhythmia within the CKD population and stage progression. Although no distinct causative relationship has been demonstrated between CKD and atrial fibrillation, the association is strong as both diseases share several risk factors including inflammation, oxidative stress, and fibrosis [56]. With regard to treatment strategies, the risk of stroke must be weighed carefully against the risk of bleeding, particularly in ESKD, as the overall benefit in this population is offset due to a greater risk of bleeding. Currently, there are no proven approaches to guide clinical decision making within this population, further compounded by a lack of randomized controlled trials [57]. Though apixaban has been approved for use in end-stage renal disease, it has never been studied in randomized control trials with respect to efficacy [56].

## Conclusion

Cardiorenal syndromes are a spectrum of diseases with many clinical phenotypes. Though fibrosis represents a common final mechanistic pathway resulting in symptoms of HF, arrhythmias, and death, preceding fibrosis are several microvascular mechanisms are at play. These can be finely interwoven with renal pathophysiology such that it is challenging to isolate a particular point to develop a therapeutic strategy. The RAAS system is perhaps the best understood, and pharmacologic control of this system via ACE or ARB blockade has been used to attenuate the maladaptive remodeling responses within the heart and kidneys and improve outcomes in HF patients as well as attenuate CKD progression. Finally, the recent successes with sodium-glucose cotransporter-2 (SGLT2) Inhibitors in diabetic patients with early stages of CKD to prevent both CVD and reduce CKD progression is an exciting development and with increased mechanistic insights may open the door to additional effective treatment paradigms for patients with type 4 cardiorenal syndrome [58, 59].

## Declarations

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