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Heart failure in chronic kidney disease patients: a summary approach on non-traditional risk factors

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Heart failure in chronic kidney disease patients: a summary approach on non-traditional risk factors

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Aos meus pais.

À minha irmã.

Heart failure in chronic kidney disease patients: a summary approach on non-traditional risk factors

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Abstract

Introduction: Patients with chronic kidney disease are at higher risk for heart failure in comparison to the general population. Such increased risk is multifactorial, being partly due to a higher prevalence of traditional cardiovascular risk factors in this population and to the existence of non-traditional/chronic kidney disease-specific risk factors. Non-traditional risk factors should prompt special considerations in diagnosis and management of heart failure in these patients.

Material and methods: We searched PubMed and Medline during 2017 and 2018, for the terms “Chronic kidney disease” and “Heart failure”. Other search terms were included accordingly to the content found. We mainly focused on publications concerning chronic kidney disease-specific risk factors for heart failure and its pathophysiology. Further publications regarding management of heart failure in chronic kidney disease patients were sought.

Results and discussion: Heart failure is the leading cardiovascular complication in chronic kidney disease. Specific risk factors for heart failure, which are not often found in the general population, include, among others, mineral bone disease, uremic toxins, neuro-hormonal activation, inflammation, oxidative stress, anemia, malnutrition, albuminuria and hyperhomocysteinemia. Management of heart failure in this group of patients is challenging and patients are often undertreated.

Conclusion: Investigation on non-traditional risk factors for heart failure in chronic kidney disease patients is lacking and its pathophysiology is not properly understood. Such understanding is vital to provide proper care, as in the general population. We also question whether some of these specific risk factors could also play a role in heart failure among the general population.

Keywords

Cardiovascular risk factors; chronic renal insufficiency; heart failure.

List of abbreviations

AP-1	Activator protein-1
BNP	B-type natriuretic peptide
CF-PWV	Carotid-femoral pulse wave velocity
CKD	Chronic kidney disease
CTSs	Cardiotonic steroids
EPO	Erythropoietin
ESRD	End-stage renal disease
FGF-23	Fibroblast growth factor-23
GFR	Glomerular filtration rate
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFmrEF	Heart failure with mid-range ejection fraction
IL	Interleukin
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
MIA	Malnutrition-inflammation-atherosclerosis
NF-Kβ	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OSA	Obstructive sleep apnea
PD	Peritoneal dialysis
PEW	Protein-energy wasting
PTH	Parathyroid hormone

RAAS	Renin-angiotensin-aldosterone system
ROS	Reactive oxygen species
RV	Right ventricular
SNS	Sympathetic nervous system
TGF-β	Transforming growth factor-beta
TNF-α	Tumor necrosis factor-alpha
TWEAK	TNF-related weak inducer of apoptosis
UACR	Urine albumin-to-creatinine ratio

Introduction

Chronic kidney disease (CKD) is a major public health problem, affecting more than 10% of the general population in many countries worldwide.[1]

The first report of an association between CKD and cardiovascular abnormalities goes back to 1836.[2] Subsequently, several studies in this area have been performed and the relation between CKD and increased cardiovascular risk is nowadays well established. Cardiovascular disease and kidney disease are closely interrelated and disease of one organ causes dysfunction of the other, ultimately leading to the failure of both organs. This is often referred as cardiorenal syndrome (Table I).[3]

In CKD patients, heart failure (HF) is the leading cardiovascular complication[4] and an important cause of morbidity and mortality.[5] Chronic kidney disease-specific complications contribute to vasculopathy and cardiomyopathy in these patients, ultimately leading to HF through unique pathophysiologic mechanisms, distinct from the ones contributing to HF in patients without CKD. Therefore, HF in CKD patients requires special considerations regarding diagnosis and management, in comparison to HF in patients without CKD. Despite the important impact of HF in CKD patients' prognosis, the predictors of HF as a specific end point have not been satisfactorily characterized in subjects with CKD.[5]

In this review, we address the unique non-traditional/CKD-specific risk factors for HF in CKD patients and their implications in diagnosis and therapy, which should be taken into account when approaching HF in CKD patients.

For this purpose, we searched PubMed and Medline during 2017 and 2018, for the terms "Chronic kidney disease" and "Heart failure". Other search terms were included accordingly to the content found. We mainly focused on publications concerning CKD-specific risk factors for HF and its pathophysiology. Further publications regarding management of HF in CKD patients were sought.

Chronic kidney disease

Chronic kidney disease is defined as abnormalities of kidney structure or function, present for > 3 months, with implications in health.[6] Criteria and staging for CKD are presented in Tables II and III, respectively. Chronic kidney disease is frequently associated with progressive decrease in GFR, frequently leading to end-stage renal disease (ESRD).[7]

Prevalence of CKD worldwide is estimated to be 8-16%. Contrary to clinically apparent advanced-stage CKD, precise calculation of the burden of less symptomatic or asymptomatic early-stages CKD is difficult. These account for 80-90% of all cases.[8]

In 1990, CKD was ranked as the 27th cause of total number of global deaths (age-standardised annual death rate of 15.7 per 100 000). In 2010, it rose to 18th (annual death rate of 16.3 per 100 000).[9] These rates are likely underrated. Reported mortality from diabetes-related renal disease is estimated to be four to nine times less than the actual rate.[10]

Diabetes and hypertension are the leading causes of CKD in all developed and many developing countries. In countries of Asia and sub-Saharan Africa, glomerulonephritis and unknown causes are more common. Genetic factors, such as variations in MYH9 and APOL1, are associated with non-diabetic CKD in Africans.[8]

As a result of the loss of endocrine and exocrine functions of the kidney, people with CKD are prone to develop various complications, namely anemia, hypertension, vitamin D deficiency, acidosis, hyperphosphatemia, hypoalbuminemia and hyperparathyroidism, among others.[6] These lead to other complications, including bone disorders and fractures, cognitive decline, and an increase in all-cause and cardiovascular mortality.[8] Patients with CKD should be considered at increased risk for cardiovascular disease.[6] As mentioned, HF is the leading cardiovascular complication.[4]

Heart failure

Heart failure is defined as a clinical syndrome characterized by typical symptoms (breathlessness, ankle swelling and fatigue) that may be accompanied by signs (elevated jugular venous pressure, pulmonary crackles and peripheral edema), caused by structural and/or functional cardiac abnormalities, resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[11]

In developed countries, HF has an estimate prevalence of 1-2% among adults, rising to ≥ 10% in individuals > 70 years of age.[11] This condition shows substantial morbidity and mortality. Indeed, it is the most frequent cause of hospital admission for people over the age of 60 years in the United States.[12] Twelve-month all-cause mortality rates for hospitalized and stable/ambulatory HF patients are 17% and 7%, respectively. Twelve-month hospitalization rates are 44% and 32%, respectively.[13]

Heart failure is caused by a loss of a significant amount of functional myocardial cells after injury to the heart.[14] The aetiology is wide-ranging worldwide and there is no consensual classification system, due to common overlap between categories. Patients often present different pathologies (cardiovascular and non-cardiovascular) underlying HF.[11] The most common aetiologies are ischemic heart disease, hypertension and diabetes, whereas less common causes include cardiomyopathies, infections (viral myocarditis, Chagas' disease), toxins (alcohol, cytotoxic drugs), valvular disease and prolonged arrhythmias.[14] The proposed classification system is divided into diseased myocardium, arrhythmias and abnormal loading conditions. Among the latter, a mechanism that can contribute to HF is CKD.[11]

Heart failure is described according to the measurement of left ventricular ejection fraction (LVEF). Patients with LVEF ≥ 50% present HF with preserved ejection fraction (HFpEF). Patients with LVEF < 40% present HF with reduced ejection fraction (HFrEF). Patients with LVEF between 40-49% are now defined as presenting HF with mid-range ejection fraction (HFmrEF).[11] In the general population, HFpEF currently

accounts for > 50% of all HF cases and its prevalence relative to HFrEF continues to rise at an alarming rate of 1% per year.[15]

Chronic kidney disease and heart failure: an independent association

Heart failure risk is increased among CKD patients. Several studies have shown an independent association between lower glomerular filtration rate (GFR) and HF[16], suggesting the existence of important non-traditional/CKD-specific risk factors for HF in CKD patients.

Beck et al observed a strong association between lower GFR and HF, which remained significant for HF after multivariable adjustment.[1] In the United States, in 2016, the overall prevalence of HF in individuals aged over 66 was 28.8% in CKD patients, as opposed to 6.4% in patients without CKD.[17] In the Atherosclerosis Risk in Communities study, the incidence of HF was 3-fold higher for individuals with GFR <60 mL/min/1.73m^2, versus the reference group (GFR ≥ 90 mL/min/1.73m^2). The overall adjusted relative hazard of developing HF was 1.94 (1.49 to 2.53) for individuals with GFR <60 mL/min/1.73m^2, versus the reference group, and was significantly increased for individuals with and without prevalent coronary heart disease at baseline.[18]

Löfman *et al* found a higher prevalence of CKD in HFpEF than in HFmrEF and HFrEF (56% vs 48% and 45%, respectively, p <0.001). Hypertension, atrial fibrillation and valvular heart disease were more common in HFpEF whereas ischaemic heart disease and revascularization were more common in HFmrEF and HFrEF. All these variables increased with worse kidney function. Patients with worse kidney function more often had HF with longer duration and were in a more severe class, regardless of LVEF. In addition, CKD was strongly associated with mortality in all LVEF groups, in keeping with earlier studies.[19]

Non-traditional risk factors for heart failure in chronic kidney disease patients

Heart failure in CKD has been proposed to be closely related to structural myocardial disease.[5] Among CKD patients, abnormalities related to left ventricular (LV) structure and function are very common.[20] About 40% have left ventricular hypertrophy (LVH), which progressively increases as kidney function declines.[6] Alterations in LV structure and geometry likely precede the development of HF.[21] Patients with CKD can develop HFrEF, HFmrEF, or HFpEF, the latter being more common.[22] Most CKD patients develop concentric myocardial hypertrophy with interstitial fibrosis and CKD-associated cardiomyopathy, contributing to left ventricular stiffness, causing diastolic dysfunction leading to HFpEF.[6]

Heart failure and CKD frequently coexist and share common risk factors (diabetes, hypertension, hyperlipidemia) that interact to worsen prognosis.[11] Multiple mechanisms contribute to the pathophysiology of HF in patients with kidney disease. Traditional HF risk factors (such as age, male sex, hypertension, Diabetes mellitus, smoking, obesity, coronary artery disease, LVH) are more prevalent among CKD patients than in the general population. These patients also show unique non-traditional/kidney-specific risk factors for HF, namely malnutrion, uremic toxins, mineral bone disturbances, anemia, sympathetic hyperactivity, among others.[22]

Next, we address such non-traditional/kidney-specific risk factors for HF in CKD patients.

Mineral bone disease

Mineral and bone homeostasis, maintained through interactions between calcium, phosphorus, parathyroid hormone (PTH), vitamin D and fibroblast growth factor (FGF-23) is commonly disrupted in CKD patients (especially when GFR <45

ml/min/1.73 m^2).[23] Secondary hyperparathyroidism occurs, as a result of decreased serum calcium, increased serum phosphorus, and decreased production of calcitriol.[24]

The most important complications related to mineral bone disease in CKD patients comprise vascular calcification and cardiovascular disease.[24] Hypocalcemia and hyperphosphatemia can precipitate arrhythmias and depress cardiac contractility.[25] Vascular calcification can occur, through two mechanisms. The first involves focal calcification associated with lipid-laden foam cells found in atherosclerotic plaques. The second involves diffuse calcification in the media of vessels - Mönckeberg's sclerosis -, which increases blood vessel stiffness and decreases vessel compliance, leading to cardiovascular disease.[26]

Carotid-femoral pulse wave velocity (CF-PWV) is the gold-standard for assessment of large artery stiffness.[5] As GFR declines, CF-PWV increases. Each 10 ml/min/1.73 m^2 decline in GFR is independently associated with a 0.23 m/s increase in CF-PVW.[27] Chirinos et al demonstrated that CF-PWV is associated with a marked increase in the risk of incident HF in a CKD population. This association persisted after adjustment for blood pressure and other confounders.[5]

Large artery stiffness occurs secondary to arteriosclerosis (degeneration, fibrosis and calcification) of the medial layer of the aorta.[5] Consequently to increased arterial stiffness, a greater reflection of the pulse wave back to the central aorta occurs, which adds extra work to LV contraction.[27] Thus, large artery stiffness has an important impact on LV pulsatile afterload, affecting early aortic systolic pressure rise, the total compliance of the arterial system and the velocity at which pulse waves travel forward in the arteries and reflected waves travel backwards towards the heart.[5] Furthermore, large artery stiffening is associated with lower diastolic pressure, contributing to a decreased coronary perfusion pressure.[5] Such increase in the pulsatile afterload is likely the mechanism responsible for the relation between aorta stiffness and risk of incident HF, leading to increased systolic wall stress, diastolic and systolic dysfunction and LVH.[5]

Uremic toxins

As CKD develops, parenchymal and glomerular sclerosis evolves, eventually leading to uremia.[25] In CKD, uremia itself is associated with the development of LVH, due to accumulation of hypertrophic substances and insulin resistance.[28]

Hypertrophic substances associated with uremia include endothelin-1, PTH, tumor necrosis factor-alpha (TNF-α), leptin, interleukin (IL)-1, IL-6 and cardiotonic steroids. Ouabain and marinobufagenin, two endogenous cardiotonic steroids, interact with the α-subunit of the Na^+/K^+-ATPase transmembrane protein on the surface of cardiomyocytes. They are found in high concentrations in CKD patients, but their role in uremic cardiomyopathy pathogenesis is not well understood.[28]

Uremia is associated with underlying insulin resistance, which plays a role in uremic cardiomyopathy through the Akt pathway. Insulin displays pleiotropic and metabolic actions through intracellular signaling pathways, namely the Akt pathway. Insulin resistance in these patients leads to disruption of this pathway, which is believed to contribute to the development of LVH.[28]

Neuro-hormonal activation: sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS)

The development of CKD is associated with increased activation of the SNS, which has been suggested as an important mechanism for cardiovascular events in this population.[29] Plasma catecholamine concentrations are approximately doubled in CKD patients.[30,31]

The kidneys have both afferent and efferent nerve fibers, which are located in the adventia around the renal artery.[32] The signal that commands the brain to increase sympathetic outflow is generated in the diseased kidneys.[33] Graded stimulation of efferent activity induces renin release and subsequent RAAS activation, followed by an

increase in sodium reabsorption and a decrease in renal blood flow at higher levels of stimulation.[32]

Besides being associated with elevated blood pressure and progression of kidney damage independently of blood pressure in CKD patients, sympathetic hyperactivity is also related to LVH and HF.[33] Excessive SNS activation can cause decreased myocardial beta-adrenergic receptor density (particularly β_1), uncoupling of the receptor from intracellular signaling mechanisms and cardiomyocyte dysfunction and fibrosis, leading to cardiac remodeling.[25] Siddiqui et al showed that left ventricular mass (LVM) in CKD patients is greater than in healthy controls, even though arterial blood pressure in the patients was reasonably well controlled for a long period of time. There was a positive relationship between LVM measurements (LVM index and LV mean wall thickness) and sympathetic activity, independent of blood pressure.[34] Indexes of LVM correlated with plasma norepinephrine levels.[33]

Inflammation

Persistent, low-grade inflammation is frequently present in CKD, and it is linked to cardiovascular disease, protein-energy wasting (PEW), and cardiovascular and all-cause mortality. An inverse correlation between GFR and inflammation has been reported.[35] Patients with CKD produce multiple inflammatory cytokines, which regulate cell survival and death, such as TNF-α, transforming growth factor-beta (TGF-β), IL-1 and IL-6.[25] Multiple factors may cause immune dysregulation and inflammatory activation in CKD.[35]

Chronic kidney disease patients present decreased clearance of pro-inflammatory cytokines. In addition, CKD patients are not able to form $1,25(OH)_2$ vitamin D nor maintain its normal serum levels. Immune dysfunction associated with vitamin D deficiency occurs, as vitamin D plays a role as regulator of the immune system.[35] Uremic milieu produces both oxidative and carbonyl stress, which are highly

pro-inflammatory. Uremic toxins may lead to intestinal dysbiosis and increased translocation of gut bacteria and bacterial components into the circulation, contributing to systemic inflammation.[35] Dialysis patients are prone to inflammatory stimulation caused by catheter-related bloodstream infections, access site infections, thrombosed arteriovenous fistulas and grafts (hemodialysis patients) and episodes of peritonitis (peritoneal dialysis patients).[36] Increased neuro-hormonal activity in CKD patients may also contribute to inflammatory activity. In animal models, angiotensin II upsurges TNF-α and IL-6 expression in cardiomyocytes, possibly through increased activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kβ) and activator protein-1 (AP-1).[37] Also in animal models, chronic stimulation with beta-adrenergic agonist isoproterenol led to increased mRNA synthesis of pro-inflammatory cytokines TNF-α, IL-6 and IL-1β in cardiomyocytes and cardiac blood vessels.[38] Moreover, CKD patients also display raised levels of endotoxin, possibly due to dysbiosis and fluid overload that may occur in these patients. The latter favors mesenteric venous congestion and bowel wall edema, with translocation of gram-negative bacteria trough the endothelium of the intestinal villi.[39]

In animal models, TNF-α mediates progressive LV dilation and dysfunction, as well as increased cardiac mortality.[39] Both TNF-α and IL-1β reduce contraction amplitude, sarcoplasmic reticulum calcium concentration and calcium transient amplitude in rat ventricular myocytes.[40]

TNF-related weak inducer of apoptosis (TWEAK) has also been shown to increase cardiac apoptosis and extracellular matrix degradation, thus contributing to adverse ventricular remodeling in HF.[39]

Oxidative stress

Oxidative stress occurs among CKD patients as a consequence of an increase in reactive oxygen species (ROS) production and decrease in antioxidant defenses.[41]

Increased ROS generation in CKD patients may be prompted by inappropriate activation of the RAAS and, later on, diminished nitric oxide (NO) availability (as inactivation of NO by ROS takes place)[25], uremia and impaired mitochondrial respiratory system.[41]

Excessive ROS lead to cellular dysfunction, protein and lipid peroxidation, DNA damage and eventually cell damage and death. Besides having direct cytotoxic effects, ROS, in particular, superoxide ($O_2^{\cdot -}$), can spontaneously combine with NO to form peroxynitrite ($ONOO^-$). This reaction culminates both with the formation of a highly reactive antioxidant and the consumption of cytoprotective NO. Nitric oxide has an important role in normal heart function, as it participates in coronary vasodilatation, inhibition of platelet and neutrophil adhesion and activation and inhibition of oxidative stress.[42]

Oxidative stress has been growing as a pathophysiologic mechanism of cardiac remodeling, contributing to HF development and progression. ROS activate a wide range of hypertrophy signaling pathways, apoptosis inducers, inflammatory mediators and proteolytic enzymes, ultimately contributing to LVH.[42]

Anemia

Anemia is common among CKD patients.[25] There is a relation between decreased GFR and anemia. As kidney function declines and in more advanced CKD stages patients, incidence and prevalence of anemia increase.[43]

In CKD patients, anemia is primarily due to insufficient erythropoietin (EPO) production.[25] Erythropoietin is synthetized in the cortex and outer layer of the renal medulla, by specialized type I interstitial fibroblasts. In healthy individuals, the main stimulus for EPO synthesis is tissue hypoxia. However, pathologic conditions affecting the kidney in CKD may disrupt this feedback, leading to developing anemia which is not satisfactorily compensated by an adequate increase in EPO synthesis. Another

important mechanism underlying renal anemia is iron deficiency. It may occur in dialyzed patients due to excessive blood loss during dialysis. In addition, iron deficiency may occur because of stimulation of hepcidin production by proinflammatory cytokines, particularly IL-6.[43] Chronic kidney disease is associated with chronic inflammation, which can induce hepcidin increase (up to 100-fold).[44] Increased hepcidin levels block iron absorption from food in intestines and its release from iron stores.[43] Furthermore, some degree of dilution anemia due to hypervolemia may also take place in CKD.[45]

Due to anemia-induced tissue ischemia, peripheral vasodilatation and lowering of the blood pressure occur. This leads to SNS activation, causing tachycardia, increased stroke volume and renal vasoconstriction, which can lead to water and salt retention. Reduced renal flow activates the RAAS and antidiuretic hormone, triggering additional renal vasoconstriction and water retention. Increased plasma volume causes ventricular dilation, which increases strain on the previously stressed heart. Ultimately, LVH develops, which can lead to apoptosis and necrosis of cardiomyocytes.[46]

Additionally, anemia can contribute to an anomalous oxidative state, as hemoglobin is an antioxidant[25], causing cardiomyocytes damage.[46] Lack of EPO can directly worsen cardiac function, since it has a direct effect on the contractility of cardiac muscle, prevention of cardiomyocytes apoptosis, stimulation of angiogenesis in the myocardium and improvement endothelial cell function.[46]

Therefore, anemia contributes to increased cardiac output, development of LVH and HF.[43]

Pressure and volume overload

Chronic kidney disease patients tend to present both pressure and volume overload. The first often results from hypertension and arteriosclerosis, and

occasionally from aortic stenosis. The second may be due to arteriovenous fistula - in hemodialysis patients -, anemia and hypervolemia.[28]

Pressure overload results in increased afterload, whereas volume overload results in increased preload. Both contribute to the development of LVH as an adaptive remodeling process. Increased afterload leads to a concentric thickening of the LV wall (concentric hypertrophy), in order to boost the intraventricular systolic pressure. Volume overload leads to LV dilation (eccentric LVH), by accumulation of new sarcomeres in series. Both patterns of LVH, likewise a mixed pattern, are common in CKD patients, since afterload and preload factors often coexist, having an additive or synergistic outcome.[20]

Left ventricular hypertrophy development is induced by integrins, which initiate intracellular signaling in response to a stretch of the extracellular matrix. Angiotensin II and endothelin-1 are also thought to stimulate cardiomyocytes intracellular signaling pathways in response to stretch.[28] Despite being a beneficial adaptive response at first, myocardial hypertrophy is accompanied by decreased capillary density, causing ischemia. This promotes cardiomyocytes apoptosis, extracellular matrix and collagen accumulation, interstitial fibrosis and LV stiffening.[20] While loss of cardiomyocytes contributes to LV dilation and eventually systolic dysfunction, myocardial fibrosis leads to diminished cardiac compliance and ultimately diastolic dysfunction.[28]

FGF-23

FGF-23 is a bone-derived hormone that regulates vitamin D synthesis in renal proximal tubules and renal phosphate reabsorption.[3]

FGF-23 increases renal phosphate excretion, by reducing the expression of Na/Pi IIa cotransporter, and decreases circulating calcitriol [1,25(OH)2D3] levels. This contributes to increased parathyroid hormone levels, resulting in secondary hyperthyroidism. FGF-23 levels gradually increase with declining renal function,

allowing the body to maintain normal phosphate levels (2.5-4.5 mg/dl) until very advanced CKD stages.[7] Increased FGF-23 levels are associated with an increased risk of all-cause mortality, cardiovascular events and progression of CKD.[47] This has been suggested to be the missing link between CKD and cardiovascular disease.[3]

An independent association between FGF-23 and LVH has been shown. Moreover, *in vitro* and animal model studies demonstrated that FGF-23 directly causes pathological cardiac hypertrophy.[48] FGF receptor-dependent activation of the calcineurin-NFAT-signaling pathway independent of klotho (FGF-23 co-receptor; only expressed in kidney and parathyroid glands) may be the basis of this association.[7] Scialla et al also reported an independent association between higher FGF-23 levels and greater risk of cardiovascular events, particularly HF in CKD stages 2-4 patients.[49] Similarly, in the Cardiovascular Health Study, the risk of HF had a 94% increase among CKD patients with the highest quartile of FGF-23.[50] Scialla et al showed that FGF-23 was not independently associated with coronary artery calcification in patients with CKD stages 2-4.[51] These results suggest that direct effects of FGF-23 on cardiac remodeling, instead of arterial vasculature, may underlie its association with mortality.[7]

Malnutrition

CKD patients frequently present malnutrition, particularly in the form of PEW. PEW occurs in about 30% of patients undergoing dialysis. In this state, there is a multifactorial decrease in body protein mass and body fat.[52]

Suboptimal nutritional intake is a contributive factor for malnutrion in CKD. It is frequent among CKD and ESRD patients, being a direct risk for protein malnutrition.[53] There is a need for careful control of dietary protein intake in CKD patients, as excess dietary protein leads to the accumulation of uremic toxins.[6] However, insufficient protein intake may lead to loss of lean body mass and malnutrition, which is more

common in the elderly.[6] Other factors leading to malnutrition in CKD include the accumulation of uremic toxins, inflammation, oxidative stress, and insulin resistance.[52]

In CKD, malnutrition can occur as part of the malnutrition-inflammation-atherosclerosis (MIA) syndrome. This CKD-related syndrome features closely related malnutrion and chronic inflammation, leading to atherosclerotic damage and increased cardiovascular mortality.[25,52] Pathophysiology comprises chronic inflammation leading to increased proinflammatory cytokine synthesis, activation of protein catabolism, inhibition of albumin production in the liver and decreased muscle mass. Proinflammatory cytokines also play a role by suppressing appetite. Ultimately, these substances cause cardiovascular - and cerebrovascular – complications, by damaging the vascular endothelium.[52]

Despite being acknowledged as a CKD-specif risk factor for HF, further investigation into the role of malnutrion in promoting cardiac disease is lacking.[22]

Albuminuria

Albuminuria is an established biomarker of CKD (Table II). It is also one of the strongest non-traditional cardiovascular risk factors. Mechanisms underlying this association are still unknown.[25]

In HF patients, there is an increased prevalence of albuminuria.[54] Micro- and macroalbuminuria occur in 20-53% and 5-10%, respectively, of HF patients.[55] A higher urinary albumin-to-creatinine ratio (UACR) is associated with increased overall cardiovascular mortality and more recurrent hospitalization for HF and specially predicts progression to HFpEF (in comparison to HFrEF).[54] UACR is a prognosis marker, associated with increased right ventricular (RV) and LV remodeling and longitudinal systolic dysfunction in HFpEF.[54]

Albuminuria is associated with increased LVM, but possible mechanisms linking this biomarker to changes in the heart have not been identified.[54]

Hyperhomocysteinemia

The kidney is a major site of homocysteine metabolism. Its accumulation is a significant contributor to the development and progression of kidney disease. Hyperhomocysteinemia is a serious risk fator for CKD and ESRD.[56] High levels of homocysteine are also an important risk factor for HF.[57]

Hyperhomocysteinemia is common in CKD patients and contributes to adverse cardiac remodeling and HF.[58] Homocysteine levels are inversely correlated with diastolic function. An association between hyperhomocysteinemia and diastolic dysfunction has also been established.[58]

Obstructive sleep apnea

Obstructive sleep apnea (OSA) comprises repeated upper airway obstruction, resulting in hypoxaemia and sleep fragmentation. Studies have shown increased incidence of CKD among OSA patients in comparison to controls. On the other hand, renal failure could promote OSA though increased chemoresponsiveness or fluid retention, causing upper airway to collapse in the recumbent position.[59]

In OSA, repetitive cycles of apneas and hypopnoeas contribute to greater swings in negative intrathoracic pressure, increasing preload and afterload. This leads to RV distention and consequent limited LV filling, due to diastolic shift of the interventricular septum. Obtructive sleep apnea also appears to affect cardiac structure and function through increased sympathetic tone, while parasympathetic tone is significantly reduced.[60]

Diagnosis of heart failure in chronic kidney disease patients

Heart failure can result from any structural or functional cardiac abnormality, compromising the heart ability to function as a pump that maintains a physiological circulation.[20] It is a clinical diagnosis, based on a typical history and physical exam revealing of insufficient cardiac output or cardiac filling to meet systemic demands.[22] Diagnosis is often completed with cardiac imaging studies, assessment of fluid status and natriuretic peptides levels.[20]

In the CKD population, diagnosis of HF can be challenging, contributing to underdiagnosis and undertreatment of this condition.[22]

Cardiac imaging studies

Echocardiography is an important tool for HF diagnosis, providing accurate measurements for ventricular diameters and volumes, wall thickness, chamber geometry and ejection fraction.[3] However, it may be difficult to interpret in CKD patients, as LVH is highly prevalent among this population.[22] In the Chronic Renal Insufficiency Cohort study, LVH prevalence in patients without a HF diagnosis and eGFR ≥60, 45-59, 30-44 and <30 ml/min/1.73 m^2 was 32%, 49%, 57% and 75%, respectively.[61] The relation between GFR and LVH remained statistically significant after fully adjusted multivariable models. This emphasizes the prominence of cardiac abnormalities in CKD patients, even in the absence of a HF diagnosis.[21] Therefore, structural abnormalities in LVM and geometry may not necessarily aid HF diagnosis among CKD patients.[22]

Assessment of fluid status

A precise diagnosis of HF is based on signs and symptoms of volume overload (shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, and edema) and signs

of increased cardiac filling pressure (jugular venous distension, displaced apical impulse).[22] CKD patients may present symptoms and signs of volume overload in the absence of HF, due to systemic volume overload, contributing to a challenging HF diagnosis in this population.[22]

In ESRD/hemodialysis patients, assessment of fluid status is done through dry weight evaluation. In most centers, it is clinically determined, based on the lowest body weight a patient can tolerate without developing intra- or interdialytic hypotension or other symptoms of dehydration.[20] This method lacks specificity, sensitivity and objectivity, so others have been proposed, namely echocardiographic measurement of inferior vena cava diameter and collapsibility, relative plasma monitoring, bioelectrical impedance analysis and ecographic evaluation of pulmonary congestion.[20]

B-Type natriuretic peptide (BNP) and its amino-terminal fragment (NT-proBNP)

Together with atrial natriuretic peptide and C-type natriuretic peptide, BNP is part of the major natriuretic peptides, a group of hormones with an important role in sodium and body volume homeostasis.[62]

The main stimulus for BNP and NT-proBNP secretion is hemodynamic overload leading to myocardial strecht.[7] Consequently to ventricular myocyte stretch, preproBNP is enzymatically cleaved to proBNP and released as BNP (the active hormone form) or NT-proBNP (an inactive fragment). Both are released in a 1:1 ratio.[7]

In patients with normal renal function, BNP and NT-proBNP are associated with HF severity and LV function, being useful for HF diagnosis, management and prognosis.[62] In CKD patients, BNP and NT-proBNP values are influenced by decreased clearance and cardiac damage/stress secondary to renal dysfunction. Reduced eGFR may have an independent inverse correlation with increased BNP levels.[7] Therefore, there is a likely need to raise the cut point for HF diagnosis when eGFR is <60 ml/min/1.73 m^2.[62] In such patients, BNP/NT-proBNP serum concentrations should be

thoughtfully interpreted and in relation to GFR, regarding HF diagnosis and assessment of volume status.[6]

Therapeutic considerations

The care of patients with coexisting HF and kidney diease is a major medical challenge.[63] The majority of CKD-HF patients have HFpEF. For this type of HF, there are no evidence-based recommendations for therapies that improve outcomes (both in the general population and in CKD patients).[22] Regarding CKD-HF patients in particular, treatment remains unclear, as there is very little strong evidence to support any recommendations.[20]

The level of care for HF offered to people with CKD should be the same as the one offered to those without CKD. However, medications to improve outcome of HF patients are underused in CKD patients.[6]

The main goals for HF therapy in CKD consist of decrease of preload and afterload and reduction of LVH, treatment of myocardial ischemia and inhibition of neurohumoral hyperactivity.[20] Therapy goals should contemplate control of fluid volume, treatment of anemia, management of mineral and bone disorders[20] and vitamin D deficiency.[3] Treatment can include the use of beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, aldosterone antagonists, digitalis glycosides, cardiac resynchronization therapy and optimization of dialysis.[20]

Decreasing PTH levels substantially attenuates the association between eGFR and LV diastolic dysfunction.[64] A small number of studies also showed encouraging changes in LV mass after the correction of anemia, administration of a loop diuretic, the implementation of frequent hemodialysis (six times vs three times per week) and kidney transplantation, which appears to point towards the role of volume overload and uremic toxins in LVH.[23]

In patients with CKD and HF, any escalation in therapy and/or clinical deterioration should prompt monitoring of GFR and serum potassium concentration. Special concerns regarding the risk of hyperkalemia should be encouraged by the use

of aldosterone antagonists in addition to an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blockers, particularly in patients with lower GFRs.[6]

Conclusion

Heart failure is common among patients with CKD and greatly influences prognosis in this population. Regardless of its prevalence, there are substantial challenges to HF diagnosis and therapy in the CKD population, leading to underdiagnosis and undertreatment. The pathophysiology underlying HF in CKD patients is not yet well understood, being distinct from the one that occurs in the general population. Indeed, the existence of non-traditional/CKD-specific risk factors for HF in CKD patients has been acknowledged.

A lot remains to be learnt about the physiopathology behind non-traditional/CKD-specific risk factors for HF in CKD patients and its impact in the development of different HF subtypes. Better understanding of such mechanisms could be the key to find appropriate diagnosis and treatment. There is an urgent need for studies in this area, which should take into account the non-traditional risk factors for HF for maximum benefit and proper care for these patients.

Furthermore, the epidemiology of the different HF phenotypes in CKD versus in patients without CKD has not been properly investigated. In both populations, HFpEF is the most prevalent subtype of HF, which we find surprising, given the existence of unique risk factors in CKD patients. Could it be that some of the presumed CKD-specific risk factors play a role in HF development in patients without CKD?

Conflicts of interests

The authors have no conflicts of interest to declare.

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Tables

Table I

Definitions of the 5 subtypes of cardiorenal syndrome.

Cardiorenal subtype	Definition
Acute cardiorenal syndrome (type 1)	Acute worsening of heart function leading to kidney injury and/or dysfunction.
Chronic cardiorenal syndrome (type 2)	Chronic abnormalities in heart function leading to kidney injury or dysfunction.
Acute reno-cardiac syndrome (type 3)	Acute worsening of kidney function leading to heart injury and/or dysfunction.
Chronic reno-cardiac syndrome (type 4)	Chronic kidney disease leading to heart injury, disease and/or dysfunction.
Secondary cardiorenal syndromes (type 5)	Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney.

Adapted from Iwanaga et al.[62]

Table II

Criteria for CKD (either of the following present for > 3 months)	
Markers of kidney damage (one or more)	Albuminuria (AER ≥ 30 mg/24 hours; ACR ≥ 30 mg/g [≥ 3 mg/mmol])
	Urine sediment abnormalities
	Electrolyte and other abnormalities due to tubular disorders
	Structural abnormalities detected by imaging
	History of kidney transplantation
Decreased GFR	GFR < 60 ml/min/1.73 m^2 (GFR categories G3a-G5)

CKD: chronic kidney disease; AER: albumin excretion rate; ACR: albumin-to-creatinine ratio; GFR: glomerular filtration rate.

Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group.[6]

Table III

GFR categories in CKD		
GFR category	**GFR (ml/min/1.73 m^2)**	**Terms**
G1	≥ 90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	< 15	Kidney failure

CKD: chronic kidney disease; GFR: glomerular filtration rate. *Relative to young adult level. In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group.[6]

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