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Hypertension, left ventricular hypertrophy and chronic kidney disease

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Abstract Left ventricular hypertrophy (LVH) is a cardiovascular complication highly prevalent in patients with chronic kidney disease (CKD) and end-stage renal disease. LVH in CKD patients has generally a negative prognostic value, because it represents an independent risk factor for the development of arrhythmias, sudden death, heart failure and ischemic heart disease. LVH in CKD patients is secondary to both pressure and volume overload. Pressure overload is secondary to preexisting hypertension, but also to a loss of elasticity of the vessels and to vascular calcifications, leading to augmented pulse pressure. Anemia and the retention of sodium and water secondary to decreased renal function are responsible for volume overload, determining a hyperdynamic state. In particular, the correction of anemia with erythropoietin in CKD patients is advantageous, since it determines LVH reduction. Other risk factors for LVH in CKD patients are documented: some are specific to CKD, as mineral metabolism disorders (hypocalcemia, hyperphosphatemia, low serum vitamin D levels and secondary hyperparathyroidism), others are non-traditional, such as increased asymmetric dimethylarginine, oxidative stress, hyperhomocysteinemia and endothelial dysfunction that, in turn, accelerates the process of atherogenesis, triggers the inflammation and pro-thrombotic state of the glomerular and the vascular endothelium and aggravates the process of both CKD and LVH.

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Hypertension and CKD

About 3% of the adult population in the United States have an elevated serum creatinine and 70% of these subjects have hypertension [1]. Among people with ESRD, hypertension is even more prevalent, reaching 86% [2]. Hypertension and CKD are tightly related by a two-way relationship. Hypertension is the second most prevalent cause of renal impairment and ESRD [3]. Although only a small percentage of patients with hypertension will develop CKD [4], this population is expected to increase with the increased prevalence of hypertension in the next decade [5]. Moreover, high blood pressure is a major promoter of the decline in glomerular filtration rate (GFR) in patients with established diabetic and non-diabetic kidney disease [6].

On the other hand, the development of CKD is per se a cause of secondary hypertension and can worsen a preexisting hypertension increasing the incidence of resistant hypertension [7, 8]. Despite a higher treatment rate in comparison with hypertensive people without comorbidities, only a small percentage (23.2–42.2%) of CKD patients have their hypertension controlled [9]. It is now well established that people with CKD are several times more likely to die from cardiovascular causes than those without CKD [10]. A major component of this cause–effect relationship can be safely attributable to development of hypertension and its complications [6]. Therefore, treatment of hypertension is the most important lifesaving intervention in the management of all forms of CKD, and last World Kidney Day 2009 was dedicated to this key issue [11].

Hypertension-induced renal damage

Although progression to ESRD is a quite rare event in the natural history of essential hypertension, mild renal dysfunction frequently occurs. This condition, defined as a GFR <60 ml/min and/or the presence of micro- or macroalbuminuria, even in the presence of serum creatinine in the normal range, has a prevalence varying from 10 to 40% [12–14]. Mild renal dysfunction does not necessarily imply progression toward end-stage renal disease, but it rather contributes to cardiovascular risk, being associated with a 3-times higher incidence of fatal events, regardless of other common risk factors [12]. In the Framingham study, patients with mild renal dysfunction showed an almost 2-times higher prevalence of coronary heart disease, congestive heart failure, ischemic stroke and LVH when compared with control subjects, even if the association of renal dysfunction with cardiovascular events was lost after adjustment for cardiovascular risk factors, including blood pressure [15]. However, in the non-hypertensive, non-diabetic individuals of the Framingham study, a microalbuminuria above the median value was associated with a rate of incident cardiovascular events of 8.8% in 10 years compared with a 2.9% rate in individuals with microalbuminuria below the median value [16].

The pathophysiological mechanisms underlying this association have not yet been fully clarified. Leoncini and coauthors demonstrated that mild renal dysfunction is associated with subclinical end-organ damage, such as LVH and carotid atherosclerosis, in a population of untreated patients with primary hypertension and normal serum creatinine levels [17]. Thus, the presence of target organ damage such as LVH could represent an intermediate link between renal dysfunction and cardiovascular events in all phases of the progression of renal failure, starting from the earliest stages.

Genesis of hypertension in CKD

Genesis of hypertension in chronic kidney disease is multifactorial. The traditional mechanisms relate hypertension to volume overload or to excessive activation of the renin–angiotensin-aldosterone system (RAAS) in relation to the state of sodium/volume balance [8]. Since interventions directed only to normalize body fluid volume and to antagonize RAAS often fail to reduce blood pressure, new mechanisms have been hypothesized.

Multiple mechanisms, for example, renal ischemia or activation of NAD(P)H oxidases by intrarenal RAAS can increase oxidative stress in CKD. Reactive oxygen species are important signaling molecules promoting vascular smooth muscle cell growth and migration, endothelial dysfunction and activation, and modification of the extracellular matrix. Oxidative stress in CKD can also impair dimethylarginine dimethylaminohydrolase activity, leading to accumulation of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthesis that promotes endothelial dysfunction [18]. Furthermore, renal ischemia, via RAAS activation, production of reactive oxygen species or through stimulation of renal afferences from kidneys to central nervous system, is able to increase sympathetic nervous system activity, thus altering blood pressure autonomic regulation and promoting hypertension [19]. Also, ADMA accumulation seems to be related to sympathetic activation in CKD, representing another possible mechanism of blood pressure raising [20].

Endothelin (ET)-1 is a potent systemic and renal vasoconstrictor, capable to induce inflammation, endothelial dysfunction, arterial stiffness, vascular and cardiac hypertrophy [21]. ET-1 concentrations are increased and intrarenal ET system is activated in CKD: thus, ET could be involved in genesis of hypertension and increased cardiovascular risk in CKD [21].

Finally, erythropoietin, a cornerstone in treatment of anemia associated with CKD, can frequently cause hypertension [22]. The effect is largely independent of changes in red blood cell mass or viscosity and possibly related to increased release of ET-1 and increased noradrenergic sensitivity [22].

Reactive oxygen species, endothelium-derived substances, RAAS and sympathetic activation, can induce modifications in large artery function and structure, that seriously affect blood pressure in CKD patients. Moreover, arterial elastic properties are further altered by calcifications of the arterial wall, frequently identified in uremic patients [23, 24]. In this regard, it is generally accepted that vascular calcification in uremic patients is localized predominantly in the tunica media of the artery [25]. However, atherosclerotic plaques tend to be calcified, especially in advanced atherosclerosis [26]. Therefore, arterial calcification in patients with ESRD is the sum of intimal (atherosclerotic) and medial calcification. Vascular calcification in CKD and ESRD patients can worsen aortic stiffness [27], which is the primary cause of increased systolic and pulse pressure in CKD patients, whereas diastolic pressure decreases as arterial stiffness increases. As pulse wave velocity increases, transmission velocity of both forward and backward travelling waves increases, which causes the reflected wave to arrive earlier in the central aorta and augments pressure in late systole [28]. In CKD patients, systolic and pulse blood pressures are stronger predictors of stroke, coronary heart disease, myocardial infarction, heart failure and cardiovascular mortality than diastolic pressure [6, 29]. Furthermore, diastolic pressure is inversely related to coronary heart disease and cardiovascular mortality [6, 29].

LVH in CKD

LVH has a prevalence of approximately 40% in patients with chronic kidney disease (CKD), and it progressively increases with CKD progression until to 75% in ESRD patients [30–32]. LVH is the strongest independent predictor of cardiovascular mortality in CKD patients [33], and several factors including hypertension, hypervolemia, anemia, increased neuro-hormone activation, secondary hyperparathyroidism (SHPT) and mineral metabolism disorders are implicated in the development of LVH [34].

Many factors influence left ventricular geometry in CKD patients. Abnormal arterial stiffness and systolic hypertension opposing left ventricular ejection cause a pressure afterload, with development of concentric LVH. Moreover, arterial stiffness causes an increase in myocardial oxygen consumption and a decrease in myocardial perfusion pressure, which may induce an imbalance in the supply–demand ratio, with secondary coronary reserve reduction (Fig. 1). Additionally, CKD is associated with excess parathyroid hormone and reduced vitamin D levels that are also likely to contribute to concentric myocardial hypertrophy. Conversely, hypervolemia and chronic anemia, causing an excessive volume load, are the principal factors contributing to the development of eccentric LVH [32]. In summary, CKD patients are faced with both pressure- and volume overload states. However, sustained overload in combination with CKD-associated factors such as SHPT, RAAS activation and anemia may result in maladaptive LVH [35] until the final picture of uremic cardiomyopathy, characterized by structural changes in the myocardium, such as collagen accumulation, cardiac cellular apoptosis, fibrosis and calcification, resulting in systolic and diastolic dysfunction [34, 36, 37] (Fig. 2).

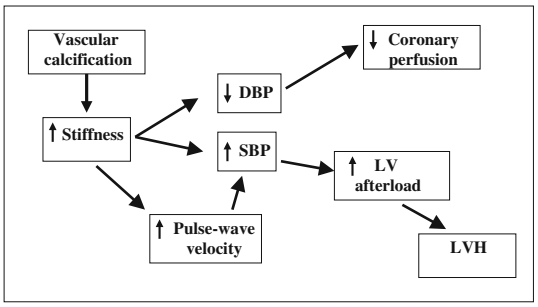

Fig. 1 Relationship between the changes in arterial wall, blood pressure, coronary perfusion and cardiac remodeling in CKD patients. *DBP* diastolic blood pressure; *SBP* systolic blood pressure; *LV* left ventricle; *LVH* left ventricular hypertrophy

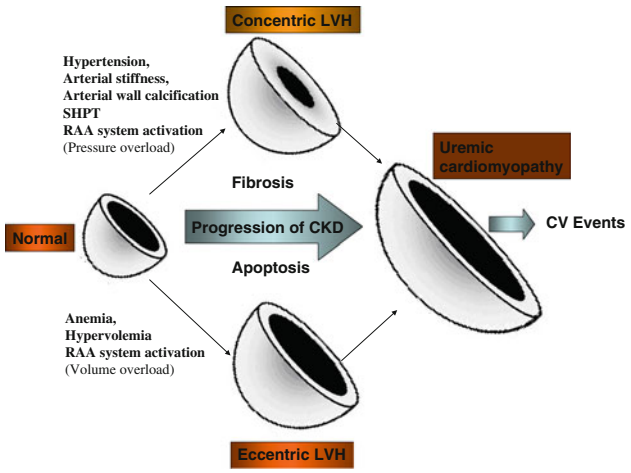

Fig. 2 Concurrent pathogenic factors that contribute to the adaptive LV remodeling process in relation to the progression of CKD, until to the uremic cardiomyopathy. *SHPT* secondary hyperpathyroidism; *RAA* renin-angiotensin-aldosterone; *LVH* left ventricular hypertrophy; *CKD* chronic kidney disease; *CV* cardiovascular

SHPT, mineral metabolism disorders and LVH

SHPT occurs in most patients during the progression of CKD and it is secondary to hypocalcemia, deriving from reduced synthesis of 1,25-dihydroxyvitamin D (1,25OH-D3) in the kidney. Both low 1,25OH-D3 and SHPT with their metabolic consequences—high serum phosphate and calcium x phosphate (Ca x P) product—are associated not only with bone loss but also with cardiovascular complications (vascular calcification and LVH) [38, 39] and events (myocardial infarction and congestive heart failure) [40]. Moreover, a direct mechanism of cardiotoxicity of PTH has been postulated. In fact, PTH in excess, acting as uremic toxin and ionophore agent, facilitates the entry of calcium ions within the vascular and cardiac myocytes. Hence, the intracellular calcium overload, by increasing myocyte contractility, can directly promote, on one hand, an increase in vascular reactivity, with secondary augmented peripheral vascular resistance and hypertension and, on the other hand, can cause cardiac hypertrophy [39] and fibrosis [41] and cardiomyopathy [42]. In hemodialysis patients with SHPT, intravenous calcitriol administration was associated with a significant reduction in PTH concentration, left ventricular mass and wall thickness [43]. However, 1,25OH-D3 seems to play a non-secondary role in the pathogenesis of cardiovascular disease in CKD, independently from its calciotropic effect. Experimental studies showed that active vitamin D regulates cardiomyocyte proliferation and hypertrophy [44], improves cardiac function and induces left ventricular hypertrophy regression in patients with ESRD [45, 46]. Moreover, 1,25OH-D3 is a negative regulator of the renin-angiotensin system [47] and might be involved in the

pathogenesis of hypertension and hypertension-associated cardiac and arterial disorders [48]. Low 1,25OH-D3 serum levels are independently associated with endothelial dysfunction, arterial stiffness and vascular calcifications in hemodialysis patients [49]. Vascular calcification is a strong prognostic marker of cardiovascular disease mortality in CKD patients. Vascular calcification has long been considered to be a passive, degenerative, and end-stage process of atherosclerosis and inflammation. However, recent evidence indicates that bone matrix proteins such as osteopontin, matrix Gla protein (MGP) and osteocalcin are expressed in calcified atherosclerotic lesions, and that calcium-regulating hormones such as vitamin D3 and parathyroid hormone-related protein regulate vascular calcification in vitro. These findings suggest that vascular calcification is an actively regulated process similar to osteogenesis, and that bone-associated proteins may be involved in the development of vascular calcification. The pathogenesis of vascular calcification in CKD is not well understood and is almost multifactorial. In CKD patients, several studies have found associations of both traditional risk factors, such as hypertension, hyperlipidemia and diabetes, and uremic-specific risk factors with vascular calcification. Most patients with progressive CKD develop hyperphosphatemia. An elevated phosphate level is an important risk factor for the development of calcification and cardiovascular mortality in CKD patients. Thus, it is hypothesized that an important regulator of vascular calcification is the level of inorganic phosphate that directly regulates human smooth muscle cell calcification through a sodium-dependent phosphate transporter mechanism. After treatment with elevated phosphate, there is a loss of smooth muscle lineage markers, such as alpha-actin and SM-22 alpha, and a simultaneous gain of osteogenic markers such as cbfa-1 and osteocalcin, and synthesis of matrix vesicles and collagen-rich extracellular matrix [50] (Fig. 3). Elevated phosphate may directly stimulate smooth muscle cells to undergo phenotypic changes that predispose to calcification and offer a novel explanation of the phenomenon of vascular calcification under hyperphosphatemic conditions, such as in CKD patients.

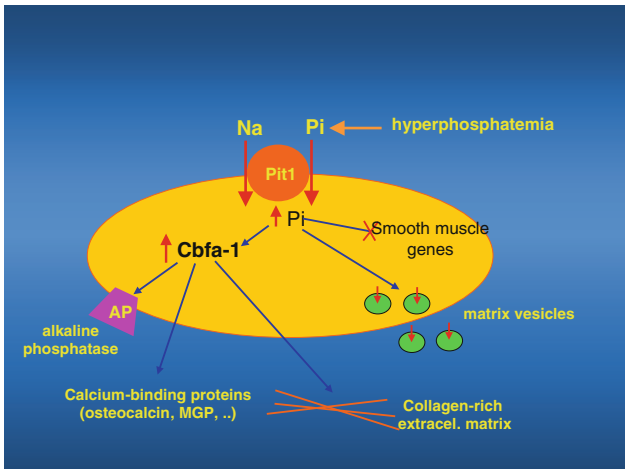

Fig. 3 Effects of hyperphosphatemia in human smooth muscle cells on the synthesis of osteogenic markers and calcium-binding proteins involved in the vascular calcification. (Pit1: Na + -phosphate (Pi) cotransporter; *Cbfa*-1 Core-binding factor alpha 1; *AP* alkaline phosphatase; *MGP* matrix GLA protein

Anemia and LVH

Anemia is highly prevalent in CKD and may potentiate the adverse effects of LVH on cardiovascular outcomes. In fact, in the presence of anemia, volume overload occurs as a physiological adaptation to the reduced oxygen delivery. The heart attempts to compensate volume overload, increasing left ventricular mass and assuming an eccentric geometry. However, as cardiac hypertrophy progresses, capillary density decreases, so may result a maladaptive remodeling with reduced subendocardial perfusion and myocardial fibrosis [32, 51]. Therefore, further subendocardial ischemia increases the susceptibility to cardiac events and to uremic cardiomyopathy. Anemia can lead to progressive cardiac damage as well as progressive renal damage. Correction of the anemia with erythropoietin and, as necessary, intravenous iron may prevent the deterioration of both the heart and the kidneys. There is a triangular relationship, a vicious circle, between heart failure, CKD and anemia where each of these three can be both cause and caused by the other [52]. In this regard, it has been found in a group of CKD patients a significant negative correlation between the drop in hemoglobin and increase in LVMI, in the sense that, for any loss of 1 g/100 ml of hemoglobin, an increase of 20 g/m^2 of left ventricular mass index (LVMI) is expected. Moreover, there appears to be an amplification effect of decline in hemoglobin and GFR on LVMI growth. In fact, when the loss of 1 g/100 ml of hemoglobin is associated with a reduction in GFR of 10 ml/min, an increase of 30 g/m^2 of LVMI is expected [53]. Furthermore, the combination of anemia and LVH in CKD identifies a population at greater risk for myocardial infarction, stroke and death [54]. Indeed, the unfavorable outcome in patients with both CKD and LVH, whose survival is reduced and incidence of fatal and non-fatal CV events increased, can be reversed if LVH is regressed by therapy. Interventional studies have shown that partial correction of anemia through erythropoietin, together with an arterial hypertension successful therapy through RAAS blockers such as ACE-inhibitors or sartans, was able to induce LVH regression in CKD [55].

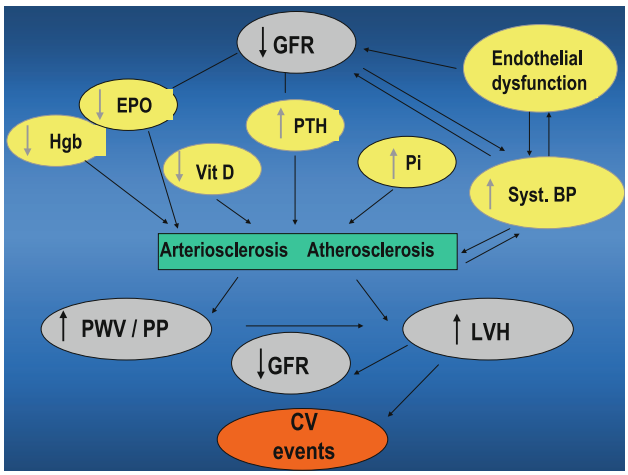

Fig. 4 Effects of hemodynamic and non-hemodynamic factors on the pathogenesis of LVH and the impairment of renal function in CKD patients. *Hgb* hemoglobin; *EPO* erythropoietin; *Vit D* vitamin D; *PTH* parathyroid hormone; *Pi* inorganic phosphate; *syst BP* systolic BP; *PWV* pulse wave velocity; *PP* pulse pressure; *GFR* glomerular filtration rate; *LVH* left ventricular hypertrophy; *CV* cardiovascular

Conclusions

CKD is associated with increased cardiovascular risk. LVH, together with coronary artery disease, has been considered the main target of intervention. LVH is highly prevalent in CKD even in early stages, when compared to general non-selected population. This is mainly due to the multifactorial pathogenesis of LVH in renal patients where both hemodynamic and non-hemodynamic stimuli synergically act inducing either an increase in left ventricular mass, according to a concentric or eccentric pattern, until to the final scene of uremic cardiomyopathy (Fig. 4). Arterial hypertension and anemia, associated with mineral metabolism abnormalities, seem to be the most important factors. The most promising strategy in CKD seems to be LVH early diagnosis, the correct screening of risk factors, as well as starting treatment in the early stages renal failure, with the aim of improving general and cardiovascular prognosis for CKD patients.

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