Chapter 4

Cardiovascular Risk Factors: The Old Ones and a Closer Look to the Mineral Metabolism

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Abstract

Patients with chronic kidney disease (CKD) are particularly susceptible to cardiovascular complications, and cardiovascular disease (CVD) accounts for more than 50% of all deaths in this population. Cardiac diseases are independently associated with a deterioration of renal function and worsening of existing kidney disease. On the other hand, chronic kidney disease is an independent risk factor for increased cardiovascular morbidity and mortality. It has a complex pathogenesis, and traditional risk factors are not able to fully explain its high incidence and prevalence. Several substances have been identified, and they seem to play important roles in different physiological functions. This chapter will review traditional risk factors such as hypertension, diabetes, dyslipidemia, and left ventricular hypertrophy. The most relevant bibliography will be referred, and also interventional studies will be discussed. Other new emerging factors associated with the osteomineral metabolism have been described, mainly in advanced stages of CKD, and frequently are associated with higher cardiovascular risk, which in turn will contribute to the unfavorable prognosis of this population.

Keywords: cardiovascular risk factors, chronic kidney disease, mineral metabolism

1. Introduction

The burden of chronic kidney disease (CKD) throughout the world is steadily increasing. Patients with CKD face a particularly high risk of cardiovascular disease (CVD). Cardiovascular events, regardless of the stage of kidney disease, are the leading cause of premature death in patients with CKD, with the rate of CVD progression being twice as common compared with the general population [1–3]. Over the last 30 years, it has become clear that

the risk of CVD increases early in the course of progressive kidney disease and that the epidemiology, pathophysiology, prevention, and treatment of CVD and CKD are closely related and interdependent [4].

In this chapter, we initially describe the epidemiology of CKD and cardiovascular risk in CKD. We then discuss the common risk factors for CVD (traditional and nontraditional) and key aspects of its pathophysiology.

1.1. CKD epidemiology

Patients with CKD represent an important segment of the population (7–10%) [5], which is projected to grow worldwide at a rate of 8% annually, with the fastest growth expected in developing nations [4, 6]. The National Health and Nutrition Examination Surveys (NHANES III and IV) stated that a moderate degree of renal impairment (glomerular filtration rate (GFR) 15–59ml/min/1.73m^2, as estimated by the Modification of Diet in Renal Disease (MDRD) formula) had 4.2 and 3.7% prevalence, respectively [5, 7]. In the AusDiab study, the prevalence of moderate renal failure (GFR<60, >30 ml/min/m^2) as assessed by the Cockcroft-Gault method was even more alarming, reaching 11% [5, 8]. The PREVEND study showed an incidence rate of moderate renal insufficiency of 4.2% in 4 years [9].

In a retrospective cohort study by the Kaiser Permanente Center, only a minority of patients (about 1%) with mild-to-moderate renal insufficiency developed ESRD over a 5-year follow-up [10]. However, as many as 19 and 24% of patients with mild and moderate renal insufficiency, respectively, died, mostly because of atherosclerotic complications, during the same 5 years. Thus, the true risk of renal insufficiency is cardiovascular rather renal [5, 10].

1.2. Cardiovascular risk in CKD

The prevalence of CVD, including stroke, peripheral vascular disease, sudden death, coronary artery disease (CAD), and congestive heart failure, is about twice of that observed in general population and is increased over the entire span of CKD [4]. Coronary artery disease (CAD) is a leading cause of death among people with advanced CKD [4]. In addition, the onset of CVD frequently is premature when compared to general population [11]. In the last decade, the high frequency of renal impairment as an epiphenomenon of cardiovascular damage and/or cardiac dysfunction has been fully recognized [5]. The Cardiovascular Health Study analysis demonstrated that in every 10 mL/min per 1.73 m^2 decrease in glomerular filtration rate (GFR), the risk of CVD and all-cause mortality increased by 5 and 6%, respectively [11]. It can be estimated that the (fully adjusted) risk associated with moderate renal insufficiency is about 40% higher than normal [10]. The risk increases linearly as renal function deteriorates until the GFR <15ml/min. Cardiovascular risk in patients who reach the end-stage phase of renal disease is staggering, being 5 times higher than normal in 85- to 95-year-old ESRD patients and 65 and 500 times higher than normal in those 45–54 years old and 25–35 years old, respectively [12].

On the other hand, in US Medicare patients admitted to the hospital with myocardial infarction and heart failure, the prevalence of moderate renal failure (creatinine clearance <60 ml/min/1.73 m^2) was very high, 60 and 52%, respectively, and these patients had a high risk of renal disease progression [13].

Traditional risk factors for development of CVD include hypertension, diabetes, dyslipidemia, smoking, increased body mass index, older age, male gender, physical inactivity, stress, and positive family history [11]. The same traditional risk factors can incite renal dysfunction. As renal function deteriorates, nontraditional risk factors play an increasing role both in glomerular filtration rate (GFR) loss and in cardiovascular damage [5]. The higher mortality from CVD persists even after adjusting for most of the traditional risk factors, suggesting the possible contributions of uremia-related, nontraditional risk factors. It seems that CVD and CKD can initiate, enhance, and perpetuate each other, eventually leading to vicious circle and premature death [11]. This has led to the current understanding that the pathophysiology of CVD in CKD involves a complex interplay of both the traditional and nontraditional, uremia-related risk factors [2], sequentially considering traditional risk factors as dominant for triggering initial renal damage and cardiovascular events in the general population, but with nontraditional risk factors becoming increasingly important as renal function worsens [5].

Mineral metabolism disorders are a part of those uremia-related risk factors mentioned, but for their complexity and multiplicity of interplay mechanisms, as for their hidden precocious action on cardiovascular balance makes it obligatory to explore more deeply.

2. Traditional risk factors

2.1. Hypertension

Hypertension is simultaneously a cause and a consequence of chronic kidney disease (CKD), and this strong relationship has been recognized since the nineteenth century. As the renal function declines, the prevalence of hypertension increases, and for that reason, more than 80% of the patients beginning renal replacement therapy have high blood pressure [14]. The physiopathology of hypertension associated with CKD is complex and multifactorial, mainly in the late stages of CKD. In addition to the well-known factors such as increased intravascular volume and excessive activity of the RAS, there are new recognized players such as increased activity of the sympathetic nervous system, endothelial dysfunction, and alterations of several neural and humoral factors that increase the blood pressure [15]. Although hypertension is clearly a risk factor of cardiovascular disease in the general population, when we look to the renal population, this association is less evident due to the reverse epidemiology phenomenon [15, 16]. In CKD patients, hypertension is associated with ischemic heart disease, heart failure, and left ventricular hypertrophy [17–20]. Secondary analysis from randomized controlled trials such as the HOPE, IDNT, and ADVANCE studies demonstrated that hypertension treatment in CKD patients can reduce the risk of cardiovascular events [21–23]. Recently, the SPRINT study [24] showed that treatment of systolic blood pressure to a lower target (120 vs. 140 mmHg) reduced 25% of the composite CV outcome. However, in this study, less than 30% of the patients had CKD, and diabetic patients were excluded. There is a bulk of evidence that treating patients to lower blood pressure levels increases morbidity and mortality, mainly in elderly patients [17, 18, 24, 25]. The real challenge is how far we should go when we treat renal patients. The KDIGO guidelines recommend that the blood pressure

should be less than 140/90 mmHg in CKD nondiabetic patients and less than 130/80 mmHg in CKD diabetic patients and nondiabetic proteinuric patients [26]. Kovesdy et al. proved that the optimal blood pressure in patients with CKD seems to be 130 to 159/70 to 89 mm Hg [18], and Agarwal [17] pointed out that higher levels of systolic and lower levels of diastolic blood pressure are associated with poorer cardiovascular outcomes. We should treat carefully our renal patients, lowering their systolic values but paying attention to the diastolic values. This concern is especially important in the elderly patients [27]. Regarding dialysis patients, there is a suggestion that treating hypertension decreases cardiovascular morbidity and mortality [28, 29], but there are no randomized controlled studies addressing the target of the blood pressure.

2.2. Diabetes

Diabetes mellitus is a major cause of CKD, and in most Western countries, the proportion of incident dialysis patients are between 22 and 44% [30].

Diabetes mellitus is a well-known risk factor of cardiovascular disease since the Framingham and other population-based studies. Once the renal population is under an increased risk of cardiovascular disease, not unexpectedly in patients with diabetic nephropathy, this risk increases exponentially. In fact, the NHANES III showed that the standardized mortality of patients with diabetes and CKD was 31.1% compared with a standardized mortality of 11.5% in patients with diabetes and of 7.7% in patients without diabetes or CKD [31]. The mechanisms of how diabetes increases atherogenesis are multiple, associated to hyperglycemia itself (*via* the polyol pathway, protein kinase C, AGEs, hexosamine pathway) and associated to other circumstances such as dyslipidemia, obesity, insulin resistance, and prothrombotic and proinflammatory states [32]. In the early stages of diabetic nephropathy, the presence of microalbuminuria is a harbinger of an increased cardiovascular risk [33], and this risk increases as the nephropathy progresses [34]. Diabetes continues to raise the risk of morbidity and mortality throughout the spectrum of kidney disease. Diabetic patients on dialysis maintain a poorer prognosis when compared with nondiabetic patients [35–37].

The treatment strategy includes the reduction of the progression of diabetic nephropathy with antagonists of the renin-angiotensin system [38, 39], the control of glycemia, and all the complex conditions associated.

2.3. Dyslipidemia

The presence of alterations of the lipid profile is frequent in the early stages of renal disease. Renal patients have, in general, lower levels of HDL, LDL, and total cholesterol and higher levels of triglycerides. There is a clustering of low HDL and elevated Lp(a) and TG-rich apolipoprotein B (ApoB) containing VLDL and LDL [40]. The increased concentration of triglyceride-rich lipoproteins in renal patients is due to delayed catabolism and to the increased hepatic production [41]. The severity of hypercholesterolemia is also associated with the level of proteinuria in CKD predialysis patients. In HD patients, the serum lipid profile is similar of predialysis patients, but PD patients have higher total and LDL cholesterol values and

increased concentrations of small-dense LDL and apolipoprotein B [41]. Although dyslipidemia is clearly a risk factor of cardiovascular disease in the general population in kidney patients, this relationship is not straightforward. Chronic kidney disease is characterized by increased oxidative stress and inflammation, and these are the two major players responsible for the increased atherosclerosis in this group of patients [42–44]. This fact can explain, in part, why there is a solid association between inflammation and cardiovascular disease, and patients with low cholesterol may have poorer outcomes [45–47]. This phenomenon is called reverse epidemiology [45]. However, Koch et al. also found a positive association between cholesterol values and the risk for cardiovascular events in CKD individuals [48].

Regarding therapy, statins improve the lipid profile and exert several pleiotropic effects. Nevertheless, concerning the cardiovascular outcomes, the timing of the initiation of the therapy is critical. The Prospective Pravastatin Pooling Project that included three studies has shown that pravastatin reduced significantly the CV composite outcome only in patients with moderate renal insufficiency [49]. We also found in an observational study that statins plus vitamin D reduced cardiovascular mortality in predialysis patients [50]. The SHARP trial also demonstrated the benefit of simvastatin plus ezetimibe in predialysis but not in patients already on dialysis [51]. This data according with the AURORA and 4D studies had not shown greater survival in patients on dialysis treated with statins when compared with placebo [52, 53]. The lack of benefit of using statins in dialysis patients can have several reasons: high mortality of dialysis patients due to sudden death and cardiomyopathy, existence of other pathways contributing to cardiovascular disease, or just because it is too late to interfere with the natural history of atherosclerosis [54]. Regarding prevention of cardiovascular disease in renal patients, there is a strong evidence of benefit in using statins only in predialysis patients, but their use is not recommended in dialysis patients [55]. The utilization of fibrates is not recommended in patients with advanced renal failure, and other approaches such as niacin, ezetimibe, or Ω-3 polyunsaturated fatty acids need randomized controlled studies to validate their effectiveness.

2.4. Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is an established risk factor of cardiovascular morbidity and mortality in the general and also in the renal population. Its prevalence increases as the renal function deteriorates. It is estimated to be around 25% in the early stages of CKD and rises to 75 to 90% at the initiation of renal replacement therapy [56]. There are several factors associated to LVH in CKD. As it happens in the general population [57], age, hypertension, and existence of previous heart disease increase the risk of LVH in renal patients [58]. In these patients, other specific factors related to their condition also influence the left ventricular mass, such as anemia, disturbances of the mineral metabolism, inflammation, and oxidative stress [59, 60]. Concerning the mineral metabolism, recent studies revealed associations between vitamin D, FGF23, and Klotho with LVH [56, 59, 61]. In dialysis patients, the volume status, the presence of arteriovenous fistula, and the time on renal replacement therapy are also relevant aspects [56, 58, 62]. LVH contributes to a greater prevalence of ventricular arrhythmias and ischemic heart disease [63], as was demonstrated in the 4D study [52].

Therefore, it is vital to reduce the left ventricular mass, to control as far as possible the modifiable risk factors, such as the anemia, the mineral metabolism, the blood pressure, and the hypervolemia as was shown in quite a few studies [64, 65]. This reduction of the LVH is associated with diminution of the cardiac events and death [66].

3. Chronic kidney disease: mineral metabolism and cardiovascular risk

3.1. Phosphorus

In recent years, numerous epidemiological studies have shown a link between high phosphorus (P*i*) levels and cardiovascular outcomes, in both the chronic renal failure population and the population as a whole.

The link between P*i* and morbidity and mortality was demonstrated some years ago, initially in the CKD population on dialysis in the classic study conducted by Block et al. [67], and was later confirmed by several other cohort studies both in individuals with CKD and in individuals with normal renal function [68–71]. Analysis of the Dialysis Outcomes and Practice Patterns Study (DOPPS) showed that serum P*i* levels higher than 6.1 mg/dl at the start of the study were associated with an increased risk of death from any cause and from cardiovascular disease compared to P*i* levels within the normal reference range [68]. Very low P*i* levels were also associated with increased mortality, perhaps reflecting the poor nutritional status of these patients [68]. It is also known that high concentrations of P*i* are associated with the presence of vascular, valvular, and soft tissue calcifications in this population [72] even at earlier stages of CKD [73]. These observations were later extended to the general population, and, surprisingly, even P*i* levels at the upper limits of normal were found to be associated with greater cardiovascular disease (CARE post hoc analysis) [69]. This analysis showed that, after 5 years of follow-up, there was a positive, gradual association between baseline serum P*i* levels and mortality due to any cause, conferring a 27% increase in the risk of death for each 1 mg/dL increase in serum P*i*. The Framingham Heart Study cohort [74] and the Atherosclerosis Risk in Communities Study (ARIC) also showed an increased cardiovascular mortality in patients with higher levels of P*i* [71]. These last two studies draw attention to the fact that the serum P*i* levels were still within the normal range. At least two studies showed a correlation between P*i* and the severity of coronary lesions on angiography [75, 76]. This information emphasizes the possibly important role of P*i* in the processes of calcification and atherogenesis [76]. It is interesting to observe that the authors also demonstrated that P*i* was a predictor for atherosclerosis in other sites, such as the carotid arteries, [77, 78] as well as the left ventricular hypertrophy (LVH) in the general population [79]. The mechanisms by which P*i* increases mortality and the incidence of cardiovascular events have not yet been established, but it seems likely that it contributes directly, as a result of its participation in the pathogenesis of vascular calcification and in the atherosclerosis process, [80] and indirectly, by raising FGF23 levels [81]. Hyperphosphatemia, by raising parathyroid hormone (PTH) levels, can also have, indirectly, a harmful effect on cardiomyocytes [82, 83] and interfere with the mechanisms that regulate vascular calcification [84]. This mechanism would also explain

the relationship between vascular calcification and serum P*i* in the presence of hyperphosphatemia, as seen in the CKD population. Vascular calcification is one of the mechanisms proposed for P*i*-related cardiovascular risk. In vitro studies show that P*i* participates actively in the vascular calcification process. Smooth muscle cells grown in a P*i*-rich medium transdifferentiate into osteoblast-like cells. P*i* is able to enter the smooth muscle cell via the type III sodium-phosphate cotransporter (PiT-1), activate a nuclear transcription factor called Cbfa-1/RUNX-2, and stimulate cell transdifferentiation [85, 86]. The smooth muscle cells acquire phenotypical characteristics similar to osteoblasts and begin to express osteopontin, osteocalcin, alkaline phosphatase, and type I collagen, promoting an authentic "ossification" of the vascular tissue [87]. P*i* overload is also associated with increased production of reactive oxygen species [88], changes in angiogenesis, epithelial migration, and survival of endothelial cells [89].

One of the biggest difficulties in interpreting the harmful effects of P*i* in vivo is to determine if they are the result of their direct action or indirect mechanisms, e.g., via an increase in FGF23 and PTH. However, there is quite a few data demonstrating that the reduction of P*i* levels was associated with improvement in endothelial dysfunction, aortic stiffness, and left ventricular hypertrophy [90] and slowing of the progression of vascular calcification [91]. Furthermore, it was also shown that controlling P*i* through dietary restriction or with the use of sevelamer was effective in reducing mortality in uremic mice with established vascular calcification [92].

Although experimental studies suggest that a better control of P*i* levels is associated with a beneficial effect on the cardiovascular system, including mortality, interpretation of these findings is still controversial. Nevertheless, such findings are considered a strong evidence implicating P*i* as a cardiovascular disease-promoting agent and, as such, an important therapeutic target.

3.2. Vitamin D and PTH

The role played by vitamin D and PTH in cardiovascular function appears to be much more important than was originally thought. The discovery of a protein that binds to calcium, which is calcitriol-dependent and which is present in the myocardium, the vascular smooth muscle, and the endothelium, offered a clearer view on this subject [93–98].

In an experimental context of vitamin D deficiency, it was observed that calcitriol normalizes the contractility of disorganized myocardial areas, promoting regulation of myocyte proliferation and hypertrophy [94]. It also stimulates the production of prostacyclin in the vascular smooth muscle tissue, which prevents thrombus formation, cell adhesion, and proliferation of smooth muscle tissue [97]. Calcitriol is also known to suppress the synthesis and secretion of atrial natriuretic peptide and increase production of the matrix protein carboxyglutamic acid, which has a protective effect against arterial calcification [98, 99].

The recent discovery of the 25(OH)D-1 hydroxylase enzyme—whose activity is regulated by the action of PTH and by estrogenic compounds—in the vascular smooth muscle cell has also contributed to the growing importance of vitamin D in vascular function [93, 96]. Cardiac tissue cells have receptors for both PTH and PTH-related peptides, which affect the physiology of the cardiovascular cell in a different way from the action they exert on classic bone tissue

[100]. PTH-related peptide is produced by the vascular smooth muscle cells, which regulate the arterial smooth muscle tissue proliferation rate, producing positive chronotropic and inotropic effects, not attributable to PTH, in isolated cardiomyocytes [96]. PTH is responsible for the expression of fetal proteins in the cardiomyocytes and, if present in excess, may be related to hypertrophic growth of the myocytes [100]. In animal studies, a relation between PTH levels and a permissive role in fibroblast activation and cardiac fibrosis has been observed, possibly via transformation of growth factor 1, a promoter of cardiac fibrosis [82, 101, 102].

Zittermann et al. [100] proposed various mechanisms to explain the relation between vitamin D deficiency and cardiovascular disease. One of these suggests that the matrix Gla protein—synthesized by the chondrocytes and the vascular smooth muscle and stimulated by calcitriol—is an important inhibitor of vascular calcification. They also mention the important role that inflammatory processes play in the development of adverse cardiovascular effects and the fact that interleukin 6 and tumor necrosis factor (TNF), which are stimulators of C-reactive protein, are suppressed by calcitriol, unlike interleukin 10, whose production is stimulated. The renin-angiotensin-aldosterone system, which is responsible for regulating blood pressure, electrolytes, and volemic status, is regulated by calcitriol via reduction of plasma renin activity and the angiotensin II concentration [99, 103].

In addition to these mechanisms, PTH and vitamin D are significantly involved in the osteoprotegerin/RANKL/RANK pathway, a fact that could make it the connecting link between bone tissue and cardiovascular diseases [104, 105]. Calcitriol, on the other hand, reduces expression of osteoprotegerin [106, 107].

A link between vitamin D deficiency and cardiovascular disease can be found in a number of studies, which demonstrated a 30–50% higher cardiovascular morbidity and mortality associated with reduced sun exposure caused by changes in season or latitude [108–110]. One fact that supports this thesis is that cardiovascular mortality rates are lower in the European countries with greater sun exposure and higher during the winter months [110].

Despite the negative association between vitamin D deficiency and cardiovascular disease described in multiple studies [111–114], clinical trials have failed to convincingly demonstrate a benefit of vitamin D supplements on cardiovascular (CV) health. One such study was the PRIMO trial, which showed no improvement in ventricular mass index or any other remodeling parameters by administering paricalcitol, a selective activator of vitamin D receptors, to patients with chronic renal failure [115]. However, experiments performed in vitro and in several animal models of LV pressure overload show that vitamin D supplements attenuate LV hypertrophy, reduce cardiac fibrosis, and decrease the expression of collagen, fibronectin, and transforming growth factor-β, along with an improvement of the systolic and diastolic function [116, 117].

3.3. FGF23

Fibroblast growth factor 23 (FGF23) is a phosphaturic protein and an inhibitor of 1α-hydroxylase, the enzyme responsible for calcitriol synthesis. Its discovery has enabled a better understanding of chronic kidney disease-related mineral and bone disorders (CKD-MBD) [118, 119].

Recent experimental and clinical studies have confirmed the role of FGF23 in the physiology of MBD and CV disease [120]. FGF23 is produced by osteocytes and osteoblasts, and it acts on the kidneys in the proximal tubular cells, increasing renal excretion of phosphorus and decreasing 1,25-dihydroxivitamin D [1,25(OH)D] [118, 121, 122].

Elevated FGF23 is observed after dietary ingestion due to a resulting increase in intestinal absorption of phosphorus after administration of PTH in experimental work with CKD [123, 124]. The rise in FGF23 associated with the resulting decrease in intestinal absorption of phosphorus, mediated by the decrease in calcitriol, contributes to maintaining adequate blood phosphate levels in the initial stages of kidney disease [125]. In CKD, there are concomitant increases in the levels of phosphorus, PTH, and FGF23, which reflects an increased production and decreased degradation, leading to their accumulation to levels much higher than those in the general population [126].

The action of FGF23 is obtained only when it is bound to the FGFR1c receptor associated with the Klotho cofactor. The Klotho protein is specifically expressed in the distal tubule of the normal kidney, but it is produced in many other tissues and organs [118, 127, 128]. The main targets of FGF23 are defined by the expression of the FGFR1c-Klotho complex. However, important actions of FGF23 on cardiomyocytes occur even in the absence of Klotho, via intracellular mechanisms that are not yet fully understood [129]. Elevated FGF23 levels imply an increase in the mortality rate adjusted for classic CV-KD factors and other traditional CKD markers [71–73].

This link between elevated serum levels of FGF23 and the occurrence of relevant clinical events was initially established in patients with kidney disease who were on hemodialysis [130, 131]. Faul et al. in a cohort study of 3000 patients demonstrated that, in the early stages of kidney disease, FGF23 is an independent risk factor for LVH [132]. The cardiac hypertrophic effects of FGF23 are mediated by FGFR-dependent activation of the calcineurin nuclear factor of the activated T-cell (NFAT) signaling cascade, but do not require Klotho as a co-receptor [133].

The available studies that evaluated FGF23 and cardiovascular changes or events in the general population have a limitation, because their samples included individuals with CKD. Keeping this fact in mind, links were found between FGF23 and LVH, endothelial dysfunction, and total body atherosclerosis as assessed by magnetic resonance imaging in the community [134]. Recently, an analysis of the cohort participating in the Heart and Soul Study, which included 833 patients with coronary artery disease, established FGF23 as a predictor of events in this population [135]. This study included patients with CKD, but the results remained the same after adjusting for this variable.

FGF23 is also being linked to severe aortic and coronary artery calcifications and is considered a marker of CV disease in patients with CKD [136, 137]. One of the mechanisms may be related to a decrease in fetuin-A. Fetuin-A is synthesized by the hepatocytes, is secreted into the blood, and accumulates in the skeleton during bone mineralization due to its high affinity for hydroxyapatite. It is considered an inhibitor of CV disease and represents the most important inhibitor of the formation of circulating hydroxyapatite [138, 139]. Another mechanism that would explain the vascular calcifications associated with FGF23 would be through hyperphosphatemia.

Scialla et al. studied the link between FGF23, P, and coronary calcification as measured by CT scan of the aorta in 1501 subjects with CKD. They concluded that FGF23 was not directly associated with calcification of the aorta and coronary arteries, but rather with phosphorus levels. This group found a link between the severity of the calcification and FGF23 and concluded that FGF23 may be a marker of surveillance and not of the genesis of vascular calcification [140].

3.4. Klotho

The Klotho protein is a potential marker for vascular events. Suppression of the Klotho gene in animal models causes extensive aging-like phenotypes, including atherosclerosis, ectopic calcification, infertility, skin atrophy, and severe hypoglycemia [141], while its overexpression increases life span by 20–30%, in animal models [142]. The Klotho protein is present mainly in the distal tubules of the kidney and in the cerebral choroid plexus, but it can be posttranslationally processed and released into the bloodstream, with the free extracellular domain functioning as a hormone [143, 144]. Its presence in vascular tissue is still a topic of debate [145].

An important physiological property attributed to circulating Klotho is the start of a pathway that inhibits insulin and IGF1 signaling, which contributes to the integrity of the microcirculation and of a healthy endothelium [146, 147].

In chronic kidney disease, serum levels of Klotho are decreased, contributing to increased cardiovascular risk in this population. Tests have been carried out in wild-type and transgenic mice, where it was observed that KL-/- mice with chronic kidney disease (CKD) showed early calcification of the soft tissues compared to wild-type mice (KL+/+) that also had CKD. Mice with CKD that overexpress Klotho (preserved levels of Klotho) showed greater phosphaturia and, consequently, better renal function and less calcification of tissues compared to wild-type mice with CKD [148].

The role of Klotho in uremic myocardiopathy is not yet fully understood. However, in animal models, we know that ventricular hypertrophy is associated with increased expression of transient receptor potential canonical (TRPC6) channels, whose expression is regulated by different mechanisms. Recently, Xie et al. demonstrated that Klotho can inhibit the cardiac TRPC6 channels, thereby protecting the myocardium against excessive/pathological remodeling [149, 150].

The cardioprotective mechanisms of Klotho and the role of FGF23 in the cardiac fibrosis of CKD are not yet fully explained. However, some studies have demonstrated that there are several factors responsible for this complex process: (1) cardiac fibrosis and hypertrophy are associated with primary genetic Klotho deficiency or secondary deficiency associated with aging and CKD; (2) cardiac hypertrophy precedes cardiac fibrosis and is associated with left ventricular dysfunction; (3) high levels of phosphate and low serum levels of Klotho correlate with more cardiac hypertrophy and fibrosis in all the studied models; (4) even in the absence of Klotho, important actions of FGF23 on the cardiomyocytes occur by an intracellular route that is not clarified, promoting cardiac hypertrophy [151, 152].

The role of emerging factors like FGF23 and Klotho in cardiovascular risk in both the early and late stages of chronic kidney disease is not entirely perceptible. The entire process involves direct and indirect mechanisms that contribute to this high cardiovascular risk.

4. Conclusions

Chronic kidney disease is an independent risk factor for increased cardiovascular morbidity and mortality. It has a complex pathogenesis, and traditional risk factors are not able to fully explain its high incidence and prevalence. Several substances have been identified, and they seem to play important roles in different physiological functions.

The CKD mineral disease is another player in this complex puzzle and is one of the factors responsible for this high cardiovascular risk of this population in the early or late stages of the CKD.

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