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CHRONIC KIDNEY DISEASE AND HEALTHY BONE: A REVIEW

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ABSTRACT

Background: Chronic Kidney Disease (CKD) is defined as an abnormality of the renal structure or function, present for more than three months, with implications for health as a whole (OKORIE et al., 2018), with increasing epidemiological importance, health burden public and social and economic implications. Patients with CKD are usually inserted in a systemic context of chronic and severe inflammatory disease, which involves several organs, resulting in a vicious circle oxidative stress, also compromising the osseointegration process. **Objeticve:** Describe the main bone diseases associated with CKD and their pathophysiological principles. **Methods:** Literary review based on articles from Pubmed, CAPES, Scielo and Google Academic platforms, in Portuguese, English and Spanish. **Results:** Description, based on referenced articles of the most prevalent bone diseases in CKD, their pathophysiology, diagnoses and treatment. **Conclusion:** Although very commonand widely discussed, there are unanswered gaps in the link between CKD and bone disease secondary to this disease. It is expected that, with the advancement of research, biological markers and more enlightening tests, these gaps will be filled in order to prevent, attenuate evolution or lead to more appropriate and individualized therapeutic approaches, improving quality of life, survival and decreasing the cardiovascular risk in chronic renal patients.

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INTRODUCTION

Chronic Kidney Disease (CKD) is defined as an abnormality of renal structure or function, present for more than three months, with implications for health as a whole1, with increasing epidemiological importance, public health burden and social and economic implications2.

The CKD patients are usually inserted in a systemic context of chronic and severe inflammatory disease, which involves several organs, resulting in a vicious circle oxidative stress, also compromising the osseointegration process3. The main causes of CKD currently include Diabetes mellitus (DM) and Systemic Arterial Hypertension (SAH) (often concomitant in the same individual), inserted or not in the context of metabolic syndrome, with alcoholism, smoking, use of illicit drugs, sedentary lifestyle, hyperuricemia,

dyslipidemia, among other factors (including hereditary) can accelerate the evolution of the disease, as well as compromise its prognosis, lead to unfavorable outcomes and, ultimately, accelerate mortality4. Thus, the consequences of CKD are many and varied, including sequelae of compromised bone turnover, such as renal osteodystrophy and other osteometabolic diseases5. It is also well established that patients with end-stage CKD have increased fracture rates compared to the general population, usually associated with substantial morbidity and mortality and high cardiovascular risk6,7.

Even though this correlation is well known, when it comes to people's bone health for those with CKD, follow- up, screening methods and therapeutic targets for electrolytes and hormones are not well determined, with most current therapeutic decisions being based on scientific data with a low level of evidence and expert opinion, requiring further studies on the subject8,9.

It is known that the prevalence of CKD changes with age, reaching the highest values among the elderly, ranging from 25.1% in Nicaragua, aged 60 to 70 years, to 30.8% in Canada, among those aged ≥ 65 years10. The reduction in glomerular filtration rate (GFR) to less than 60 ml/min/1.73 m2 can be attributed to the physiological process of aging itself resulting from progressive structural and functional changes, or as a consequence of the presence of comorbidities and exposure to risk factors throughout life, in this case better called Chronic Kidney Failure (CRF)11,12,13. In Brazil, the total estimated number of patients on dialysis was 112,004 14. Estimates national dialysis treatment prevalence and incidence rates were 552 (range: 364 in the North and 672 in the Southeast) and 180 patients per million of the population, respectively14.

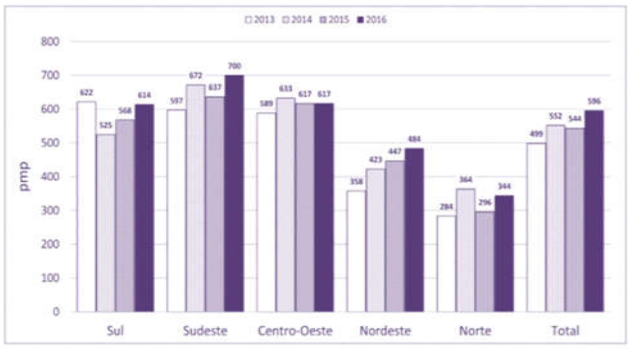


Figure 1. Estimated prevalence of dialysis patients in Brazil, by region, 2013-2016.Extracted from: J Bras. Nefrol, 2017;39(3):261-266, SESSO et al, 2016

It is consensual that the metabolic repercussions in CKD involving bone tissue are directly associated with the chronic inflammatory process of this disease, present since its onset, preceding clinical and even laboratory manifestations15. There are already known biochemical markers associated with inflammation, although some not specific for kidney disease itself or changes in bone metabolism 6, but directly associated with prognosis and cardiovascular risk16. Therefore, knowledge of the best markers or predictors of poor or earlier outcomes would be important for preventive actions and treatments more adequate17.

In the same reasoning, the comparison between the various possible approaches in end- stage renal disease addressing biomarkers, bone health and other demographic and epidemiological data could provide guidance to several open questions, suggest paths and open doors for other possible interventions and scientific research, including med. public health events. When it comes to the pathophysiology of CRF, the end product is severe nephron involvement. Proper early diagnosis and treatment allows reducing cardiovascular complications and mortality18,19. Such goals are challenging where access to health services is limited6.

DISCUSSION

Regardless of etiology, a common denominator is changes in phosphate metabolism ("Trade-off Theory"), a key element for several physiological pathways, such as skeletal development, bone mineralization, membrane composition, nucleotide structure, maintenance of plasma pH and Cell signaling21. Phosphate is stored mainly in bones, but the kidneys play a key role, with two hormones playing important roles in renal phosphate handling: PTH and fibroblast growth factor 23 (FGF23)22. Both hormones have hypophosphataemic effects, decreasing tubular phosphate reabsorption, with opposite effects on the regulation of 1,25-dihydroxyvitamin D (1,25(OH)2D)23. A third major regulator of phosphate metabolism is 1,25(OH) 2D, which increases intestinal phosphate reabsorption and inhibits PTH synthesis24. An overview of phosphate physiology is provided, with intestinal reabsorption, renal excretion, and bone metabolism. From then on, a cascade of events develops, culminating in a chronic inflammatory state and hyperuricemia and, therefore, with a high cardiovascular risk, the main cause of death in this population19. Inflammatory and prothrombotic markers involved in its pathophysiology, as mentioned before, some have been described, some of which are still not fully elucidated or clarified, the target of recent research26,27. As examples, increases in C-reactive protein, pentraxin 3 (PTX3), a serum component of amyloid are described A , procalcitonin (PCT), interleukin 6 (IL-6), alkaline phosphatase (AF), sclerostin, cystatin-C, kidney injury molecule 1 (KIM-1), β-catenin, interleukin 18 (IL- 18), interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), tumor necrosis factor beta (TNF-β), and tubular urinary enzymes such as asymmetric dimethylarginine (ADMA) nitric oxide (NO) and low molecular weight proteins28. Concomitantly, there is a decrease in markers positively related to inflammatory improvement, such as the Klotho gene, sestrins 1 and 2, resistin and adiponectin, among others29. Therefore, understanding the interaction of these markers is essential for more effective and individualized therapeutic measures27. Considering that Chronic Non- Communicable Diseases (NCDs) are affecting increasingly younger populations and considering the aging population, the reduction in the burden on public health and the improvement in the quality of life of patients and their caregivers are of undeniable importance30,31. The harms to bone health, in this context, impairs metabolic and hemodynamic control and compromises quality of life32. Among the main complications related to bone health, the most prevalent are Renal Osteodystrophy (ROD), responsible for important bone changes and trigger for cardiovascular diseases, Osteomalacia, Adynamic Bone Disease (ABD), Mixed Uremic Osteodystrophy (MUO) and Cystic Fibrous Osteitis (CFO) 23,33.

Several factors are involved in bone disease initiated and established in CKD, such as Secondary Hyperparathyroidism (HPTs), plasma and tissue levels of phosphorus, calcium and alterations in PTH and vitamin D, in addition to the influence of FGF-2334. FGF-23 exerts its phosphaturic activity, it is necessary that there are links with the FGF receptor families, having as main cofactor the Klotho protein35. HPTs cause changes in bone remodeling, due to a deficit of 25dihydroxyvitamin D3 (25OHD), increase in serum phosphate, changes in calcium and urinary phosphate36. In CKD, they contribute to HTPs, mainly, hypocalcemia and decrease in calcium-sensitive receptors , resistance and lower synthesis of vitamin D receptors, resistance to the action of PTH and hyperphosphatemia37,38. Knowledge about the pathogenesis of bone disease in CKD is important for early intervention in prevention and effective treatment39. Currently, treatment is mainly aimed at preventing parathyroid hyperplasia and its consequences on bone tissue, using a specific diet (control of phosphorus) and drugs that fix the same, in addition to calcitriol (vitamin D3) and calcimimetics, according to each case40. The physiological mechanism of bone disease in CKD is still not completely understood, which is why the studies should still be continued, providing more answers on the topic41. In ROD there are changes in mineral and bone metabolism, confirmed by changes detected in laboratory tests of calcium, phosphorus, parathormone

(PTH) and vitamin D42 metabolism, compromising not only remodeling, mineralization and bone volume, but also with the presence of extra-skeletal calcifications, especially vascular and soft tissue18. Diagnosis is performed by evaluating serum markers, non-invasive imaging and bone alterations43. The onset of bone disease is insidious, with progressive evolution over months or years44. Thus, patients are asymptomatic, initially or with complaints of diffuse, vague or nonspecific pain45.

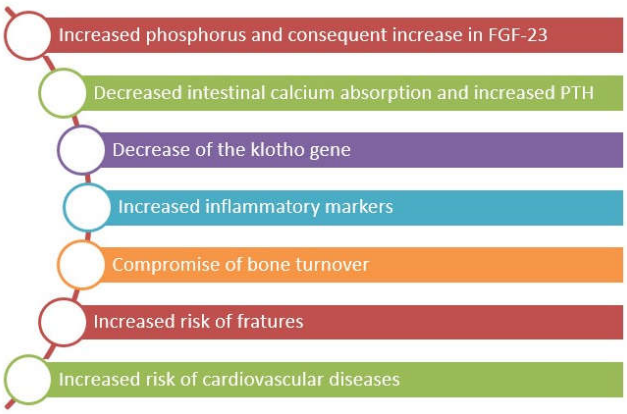
Controlling PTH from the early stages of CKD is considered essential and beneficial for the control of bone and cardiovascular disease46. With the natural evolution of CKD, skeletal deformities may occur, such as Cystic Fibrous Osteitis (OFC) and Mixed Uremic Osteodystrophy (MUO), resulting from the high bone remodeling resulting from HPTs47. OFC is identified as the most common form of ROD, present in up to 50% of patients in the pre-dialysis phase or onset of dialysis, reducing bone thickness, changing cortical porosity and trabecular bone resorption48. In this situation, osteoclast activity, with the mediation of osteoblasts, leads to fibrosis, dissecting trabecular resorption and loss of bone volume49. Low remodeling diseases present in CKD are osteomalacia (associated with aluminum poisoning or vitamin D deficiency) and Adynamic Bone Disease, resulting from excessive parathyroid suppression secondary to metabolic changes, calcium overload, excessive use of calcitriol, intoxication by aluminum, among others)24. Osteomalacia is related to abnormal mineralization (accumulation or excess of non-mineralized osteoid), resulting from bone deposition of aluminum, less common today. dialysis (replaced by new techniques) and prolonged intake of aluminum-containing phosphate fixatives, currently replaced by calcium salts49. Its risk factors are the history of kidney transplantation and rejection, bilateral nephrectomy, DM, uremia and severe deficiency of vitamin D50. Adynamic Bone Disease is characterized by decreased osteoblastic and osteoclastic activity, resulting in low or absent bone formation and is related with low levels of parathormone51,52. More frequent in the elderly and diabetics, it can be an iatrogenesis of parathyroidectomy or excessive consumption of calcium and calcitriol, as well as trabecular aluminum deposition, the latter being more rare53. The MUO presents biochemical evidence of HPTs and also the bone mineralization defect, bringing together characteristics of OFC and osteomalacia54. Less common nowadays, it usually affects patients with OFC who are subject to aluminum-associated bone disease, resulting in lesions with high and low rates. of bone remodeling55. The conditions found are persistent hypocalcemia and/or hypophosphatemia, usually associated with chronic malnutrition and sarcopenia56.

The diagnostic tests and control of bone disease in CKD aim to provide the levels of PTH, alkaline phosphatase and deferoxamine, especially50. The gold standard diagnostic method is bone biopsy of the iliac crest using tetracycline and histomorphometric analysis (reserved for special cases), with simple abdominal radiography, preferably lumbar radiography, or radiographs of the hands and hips and echocardiography being more commonly used for extra-skeletal calcifications57. Bone densitometry is of limited use in end- stage renal disease, as it is not a good predictor of fracture in this population, it does not even point to the type of osteodystrophy, and a better assessment with high Absorption Computed Tomography scans and morphometric analysis of the trabecular bone58 should be expected. However, this test is directly related to the amount of fat-free mass, that is, the greater the bone density, the lower the sarcopenia, and it can also be used for this purpose, in addition to evaluating the composition the body46. Plain radiography can also be used for the diagnosis of other spectra of the disease, but it has a low sensitivity and changes only when the disease is in a more advanced stage58. The treatment aims to normalize the biochemical parameters of mineral and bone metabolism; reduction in serum phosphorus levels, reduction in ROD symptoms and the need for parathyroidectomy59. Thus, it is expected that there will be a reduction in the number of fractures and cardiovascular events, with improvement in quality of life and survival60. The non-pharmacological treatment of CKD recommends a phosphorus-restricted diet, guided by a nutritionist and dialysis, important in the control of calcium and phosphorus61. The recommended pharmacological treatment uses calcium carbonate, sevelamer hydrochloride, calcitriol, paricalcitol as a therapeutic arsenal, cinacalcet and deferoxamine62. Treatment with calcitriol or 25hydroxyvitamin D (25OHD) is also recommended after parathyroidectomy or after successful kidney transplantation3.

Regarding the Klotho protein gene, experimental studies with rodents made it possible to identify it in 1997, showing that its low expression determines negative conditions such as pulmonary emphysema, neurovegetative diseases, atherosclerosis, renal failure, osteoporosis and other conditions that promote aging and decrease of life expectancy63 ,64. The decrease in Klotho protein is also related to aging, early atherosclerosis, osteopenia, thymus atrophy, sterility, skin atrophy, pulmonary emphysema, ataxia, muscle wasting, hyperphosphatemia, hypercalcemia, increased serum calcitriol and decreased survival, among other consequences mentioned16, in addition to being intrinsically associated with vitamin D metabolism, insulin/glucose ratio, oxidative stress and vascular calcifications39.
The worsening of acute kidney disease and the progression of CKD are observed when the expression of Klotho is reduced, and the decrease in this protein is considered an early marker of kidney disease65. On the contrary, in animal research, when administered, it reduces the kidney injury and has a positive effect on healing, protecting against inflammatory processes and oxidative stress17. Later, the Klotho protein was identified as the co-receptor between FGF-23; the binding of Klotho with the receptors increases the affinity for binding with FGF-2316. The relationship between hypocalcemia, hyperparathyroidism and hyperphosphatemia in CKD has long been attributed only to reduced production of vitamin D66. Thus, parathyroid hormone (PTH) and vitamin D were cited as responsible for bone disease in CKD35. In addition to these factors, there is currently the influence of peptides from the family of fibroblast-derived growth factors (FGF) and their receptors, produced by osteocytes and osteoblasts67. In humans, there are already22 FGFs described, four different specific receptors, however, the most potent action of FGF23 is obtained only with binding to the FGFR1c receptor, associated with the cofactor Klotho68. FGF23, whose main producer tissue is bone, is described as a regulator of phosphorus, calcium and PTH during the phase of loss of renal function, and very intensely in the dialysis phase, in addition to being important in bone control over the metabolic alterations of CKD 63. In summary, FGF-23 is produced by osteocytes and, when in excess, it decreases phosphorus and calcitriol synthesis, elevates PTH and impairs bone mineralization69.

When deficient, FGF23 causes an increase in phosphorus and calcitriol, suppression of PTH and soft tissue calcification70. Klotho is expressed in distal renal tubules, parathyroid gland, choroid plexus and sinoatrial nodule, tissues that regulate calcium homeostasis, and participates in the process as FGF23 coreceptor, by binding to the FGF-R1c receptor35. It is observed that FGF23 increases in the early stages of CKD, and phosphorus reabsorption would be the desired effect, called this “Trade-off Theory”39. However, the Klotho protein cofactor is reduced in CKD and impairs the action of FGF23, dependent on the Klotho protein for non-excretion of excess phosphorus and hyperphosphatemia71. The relationship between CKD and osteodystrophy is well established in the literature, as well as the participation of the Klotho protein in these events63. Certainly, more robust and logistical studies are needed to determine the exact mechanisms in this process, contributing to earlier therapeutic strategies in the treatment of bone disease in CKD and with better quality of life16, Figure 2.

“Trade-off” theory: the increase in phosphate, with a consequent increase in FGF-23, leads to a decrease in the Klotho gene, favoring an increase in inflammatory factors directly related to compromised bone health, risk of fractures and increased cardiovascular risk. The evidence that associates the inflammatory process in CKD with bone disease and higher mortality, especially from CVD, is very clear.



Firgure 2. Klotho schema summary| FGF23 in chronic Kidney Disease (made by the authors)

The chronic inflammatory state increases hepcidin secretion, which induces ferroportin degradation, leading to less iron absorption in the intestine; iron deficiency, in turn, stimulates the production of FGF-23 and other inflammatory factors that feed back this process and affect bone turnover (Figure 3).

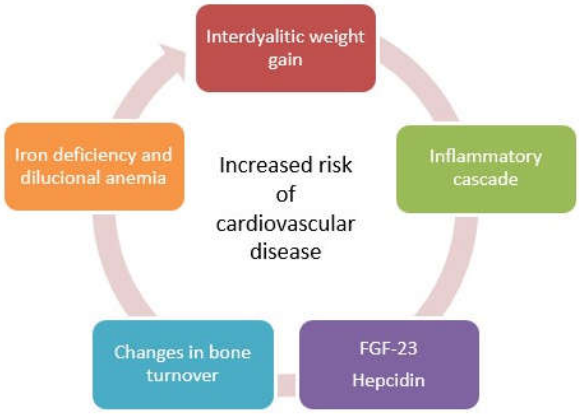


Figure 3. vicious circle between inflammatory cascade, anemia and bone turnover

Interdyalitic weightgain Iron deficiency anddilucional anemia

Dysregulation in bone turnover, both higher and lower, caused by uremic toxemia and secondary hyperparathyroidism, hinders bone formation and resorption, resulting in hyperphosphatemia23. When electrolyte levels are more regulated, and when vitamin D is supplemented, PTH tends to decrease, with an improvement in this turnover, disfavoring bone loss, especially in long bones, reducing fractures, improving chronic inflammation, also impacting CVD and immunity as a whole44. Thus, a better BMD is of extreme importance and must always be evaluated in the CKD15. Sarcopenia, recently redefined as a syndrome characterized both by the loss of muscle mass as well as its function and loss of strength72, is considered an independent cardiovascular risk factor56. In CKD it takes on special importance because it is more common, the difference being significant when compared with people of the same sex and age, and can be explained by chronic inflammation, lack of physical activity, low protein intake and vitamin D deficiency56. More recent works also point out that alterations in phosphorus metabolism, as they happen in CKD, can worsen sarcopenia, favoring the deposition of phospholipids in the muscle and reducing phosphocreatine and increasing the risk of falls and fractures73.

CONCLUSION

The work aimed at describing the inflammatory pattern of CKD, biochemical markers, bone health and potential treatments have been the object of study by several researchers and, increasingly, new possible biomarkers of the disease are being discovered, leading to the clarification of until then gray spots in the its pathophysiology, leading to searches for prevention and alternative treatments. The definition of these concepts, as well as better diagnostic tests and treatment goals are essential for a better understanding of the pathophysiology of bone disease inCKD, favoring both the prevention and evolution of the disease itself, as well as more relevant and individualized therapeutic approaches.

Conflict of Interest: The authors deny any conflicts of interest in this work.

Abbreviations

ADMA
Asymmetric dimethylarginine
CVD Cardiovascular diseases
DM Diabetes mellitus
ABD Adynamic Bone Disease
CKD Chonic Kidney Disease
AF Alkaline Phosphatase
FGF Fibroblastic Growth Factor
FGF-23 Fator de Crescimento de Fibroblastos-23
SAH Systemic Arterial Hypertension
HPTs Secondary hyperparathyroidism
IL-1 Interleukin 1
IL-6 Interleukin 6
IL-10 Interleukin 10
IL-17 Interleukin 17
IL-18 Interleukin 18
IRC Chronic Kidney Insuficience
KDIGO Kidney Disease: Improving Global Outcomes
KIM-1 Kidney Injury Molecule 1
NO Nitric Oxid
ROD Renal Osteodystrophy
OFC Cystic Fibrous Osteitis
MUO Mixed Uremic Osteodystrophy
BP Blood Pressure
DBP Diastolic Blood Pressure
PAS Pressão Arterial Sistólica
PCT Procalcitonin
PTH Parathormone
PTX-3 Pentraxin 3
RAAS Renin Angiotensin Aldosterone System
TNF-α Tumor Necrosis Factor Alfa
TNF-β Tumor Necrosis Factor Beta

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