Effects of aging on chronic kidney disease mineral and bone disorder

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Purpose of review
Aging and chronic kidney disease mineral and bone disorder (CKD-MBD) interact to worsen bone health, vascular calcification, and frailty in older patients. The altered FGF23–Klotho axis and disrupted mineral homeostasis emphasize the need for early interventions to mitigate fractures and cardiovascular complications in this vulnerable population. This review provides an updated overview of the current knowledge on CKD-MBD in older patients.

Recent findings
CKD-MBD exacerbates bone fragility and vascular calcification in older populations. Early vascular aging and cognitive decline are associated with increased mortality. Disruptions in calcium, phosphate, and vitamin D homeostasis accelerate bone loss and fracture risk, whereas secondary hyperparathyroidism worsens cardiovascular outcomes. Additionally, polypharmacy, sarcopenia, and cognitive impairment further intensified the clinical burden in aging CKD patients.

Summary
Aging potentially worsens CKD-MBD, vascular calcification, and cardiovascular disease in older patients. This growing field offers promising opportunities for further research to enhance understanding, improve bone health outcomes, and reduce fracture risk.

Keywords
aging, chronic kidney disease, mineral and bone disorder, vascular calcification

INTRODUCTION

Mineral and bone disorder in chronic kidney disease

Focus on older adults

Chronic kidney disease (CKD) is a significant global issue with considerable public health concern due to patient morbidity and mortality, often exacerbated by a delayed diagnosis. Due to improved healthcare and increased access to diagnostic tools, life expectancy is rising, which included individuals with CKD and those 65 years or more [1]. Indeed, patients with CKD experience an accelerated aging process compared to the general population. This process is associated with inflammation and oxidative stress that contributed to vascular disease, persistent low-grade inflammation, sarcopenia, and other health issues. Furthermore, the kidneys are the major source of the antiaging protein Klotho, and CKD reflects a state of deficiency [2].

It is crucial to fully comprehend in older individuals the impact of CKD-associated comorbidities, including diabetes mellitus, hypertension, cardiovascular diseases, metabolic and dietary changes, in addition to the role of uremic toxins, and mineral and bone disorder in chronic kidney disease (CKD-MBD) [3]. In an adenine model-induced CKD in 16-week and 78-week mice evaluated by serum biochemistries and computed tomography imaging, aging mice had parathyroid hormone (PTH) and blood urea nitrogen values higher than all groups and also fourfold higher femoral cortical porosity compared to the young group and more than twofold higher compared to age-matched controls [4]. These results suggest a greater impact on the aging population.

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KEY POINTS

- Chronic kidney disease (CKD) worsens bone, vascular health, and frailty in older patients.
- Aging accelerates kidney failure and bone health deterioration, leading to a higher incidence of complications such as cardiovascular diseases and fractures in older patients with CKD.
- Hyperphosphatemia and vascular calcification increase fractures and cardiovascular disease.
- Elevated FGF23 and reduced Klotho are powerful predictors of adverse outcomes (vascular calcification and progression of chronic kidney disease mineral and bone disorder (CKD-MBD)) in older patients with CKD.
- The intersection of CKD-MBD, aging, and sarcopenia underscores the multifactorial nature of frailty in patients with CKD, a condition associated with higher mortality.

CKD-MBD is a systemic disorder of mineral and bone metabolism that comprises an entirety of some electrolyte imbalances, such as increased fibroblast growth factor 23 (FGF23) concentration, Klotho deficiency, hyperphosphatemia, hyperparathyroidism, and decrease in vitamin D concentration, abnormalities in bone turnover, volume, mineralization, strength, and vascular or other soft tissue calcification [5]. Therefore, CKD-MBD affects the skeletal and cardiovascular systems.

Recently, the KDIGO Controversies Conference reported a unified concept that encompasses CKD-associated cardiovascular disease and CKD-associated osteoporosis as part of a greater risk, driven by traditional risk factors [6]. In this context, older individuals are particularly vulnerable, as they are more likely to have both CKD and age-related traditional risk factors, making them more susceptible to CKD-MBD.

However, older patients present characteristics that make the recognition of CKD-MBD challenging. Biomarkers may differ from those described in the younger population as they can change with age, the risk of fractures is higher, and age-related changes are typical in this population, even in the absence of kidney disease. Additionally, older patients have a higher likelihood of vascular calcification, one of the components of CKD-MBD, and a greater chance of falls and fractures, which are triggered by age-related changes and worsened in the presence of CKD-MBD.

This review will discuss the differences between older and younger individuals regarding the main components of CKD-MBD.

Chronic kidney disease mineral and bone disorder parameters in older individuals

Phosphate and calcium

In the early stages of CKD, levels of FGF23 and PTH progressively increase, while phosphate levels remain stable or may slightly decline. Elevated levels of PTH and FGF23 have been associated to a higher risk of CVD [7].

Hyperphosphatemia is associated with vascular calcification and mortality and triggers the osteogenic transformation and apoptosis of vascular smooth muscle cells. Furthermore, it seems that phosphate is independently associated with frailty in patients with CKD [8▪].

The European Quality (EQUAL) study analyzed data from 1294 patients older than 65 years with eGFR $\leq$20 ml/min/1.73 m^2 from six European countries to assess all-cause, cardiovascular (CV) and non-CV mortality. Both PTH and phosphate were associated with all-cause mortality [9].

Aging and CKD can disrupt calcium homeostasis. The age-related decline in kidney function can decrease Klotho expression, resulting in reduced vitamin D activation via FGF23 signaling and impaired calcium reabsorption in the renal tubules. Combined with aging, CKD can lead to a more pronounced decline in Klotho levels and a further increase in FGF23.

In older patients with CKD, hypocalcemia reduces calcium sensing receptor signaling in the parathyroid glands, resulting in increased PTH synthesis and secretion. In bone, there is an accelerated bone resorption and impaired bone formation and chondrogenesis. Our group has demonstrated that older patients with CKD have higher levels of calcium and, despite this, higher levels of PTH compared to younger individuals with similar renal function [10]. This finding suggests that calcium-PTH sensing may be altered in older patients with CKD. Over the past decade, calcium and calcium signaling have been recognized as essential regulators in the initiation and control of cellular senescence. Several components of calcium signaling, including calcium channels, calcium-binding proteins, calcium-regulated enzymes, and transcription factors, have been identified as key contributors to this process. The age-related decline in Klotho expression and vitamin D activation, along with reduced calcium sensing receptor signaling, may serve as contributing factors to cellular senescence [11].

Fibroblast growth factor 23 and Klotho

FGF23 is a protein primarily expressed in osteoblasts and osteocytes that plays a key role in regulating phosphorus metabolism. Inhibition of renal phosphate reabsorption by FGF23 promotes phosphate

excretion by the kidneys, reducing the surface expression of sodium-dependent phosphate transporters NaPi-IIa and NaPi-IIc located in the proximal tubule. Klotho, a transmembrane protein that acts as a co-receptor for FGF23, enhances its function by facilitating FGF23 signaling and phosphate regulation. The extracellular domain can be cleaved off by proteases, releasing soluble Klotho (sKlotho) into the bloodstream and urine. Serum sKlotho levels decline during the progression of CKD and several factors have been suggested to explain this behavior, including albuminuria, hyperphosphatemia, and epigenetic regulation of the Klotho gene promoter by inflammatory cytokines and uremic toxins. Serum Klotho levels also decline with aging, and therefore older adults with CKD have less klotho than younger individuals.

Elevated FGF23 levels have been associated with increased cardiovascular morbidity and mortality in CKD patients, potentially through mechanisms involving left ventricular hypertrophy and direct effects on vascular smooth muscle cells.

Moreover, aging results in a gradual decline in physical and cognitive abilities, including memory loss. Recent studies have shown that low serum Klotho levels are connected to poorer cognitive performance [12▪▪], increased physical and psychological frailty [13], greater dependence on others for daily activities, and a higher frequency of falls [14]. Concerning dementia, sKlotho has been found reduced in the cerebrospinal fluid in patients with Alzheimer's disease [15]. Low levels of Klotho have been associated with intracranial vascular calcification in patients with CKD [16].

Parathyroid hormone

Secondary hyperparathyroidism (SHPT) in the context of CKD-MBD in older patients, combined with hyperphosphatemia, plays a significant role in contributing to cardiovascular damage. Patients age $\geq$65 years with CKD have higher risk of SHPT, which has been associated with lower eGFR, low levels of 25(OH) vitamin D and furosemide therapy, while thiazide use was a protector factor [10]. In addition, the Ca/PTH ratio seems to be lower in older than in young patients with CKD, even with similar renal function. Older patients also exhibit a higher prevalence of primary hyperparathyroidism, mainly caused by benign parathyroid adenomas [17].

Among patients on hemodialysis, older individuals more often achieve normal range of PTH than younger ones. For instance, low levels of PTH can be found in malnourished individuals.

Vitamin D

Vitamin D deficiency is highly prevalent among older adults, particularly in high-risk groups such as those who are institutionalized [18]. Aging leads to significant changes in vitamin D metabolism and activity. Intestinal resistance to calcitriol develops, hindering calcium absorption. Simultaneously, the number of vitamin D receptors (VDR) decreases across key organs involved in calcium regulation. Moreover, the decline in renal function with age reduces 1α-hydroxylase activity, further impairing vitamin D activation.

Vitamin D deficiency has been associated with an impaired cognitive function and an increased risk of Alzheimer's disease, potentially due to its role in facilitating the phagocytosis of soluble amyloid-β [19].

Alongside with the reduction in renal production of calcitriol, aging is associated with a decline in the expression of renal VDR, leading to decreased efficiency in renal calcium reabsorption.

A systematic review and meta-analysis, including 16 326 patients with a mean age of 75 years, found that individuals with vitamin D deficiency had a higher likelihood of experiencing orthostatic hypotension compared to those without deficiency [20].

A summary of changes in CKD-MBD parameters in older patients is shown in Table 1 and Fig. 1.

Other parameters of chronic kidney disease mineral and bone disorder – chronic kidney disease-associated osteoporosis and vascular calcification

CKD-associated osteoporosis with skeletal aging – falls and fractures

Osteoporosis, characterized by reduced BMD, compromised bone quality, and decreased bone strength, often occurs alongside CKD-MBD, especially in older adults. Current definitions of osteoporosis, along with the emerging classifications of kidney-induced osteoporosis and CKD-associated osteoporosis, underscore the pivotal role of osteoporosis within the broader context of CKD-MBD [6].

Recent findings from the ERCOS study provide valuable insights into the osteoporosis profile of older patients with CKD. The study included 162 Spanish patients, predominantly postmenopausal women (71.2%) with a median age of 77 years. The mean eGFR was 36 ml/min/1.73 m^2, and 38% of the participants were undergoing dialysis. Notably, the study revealed a high prevalence of fragility fractures, affecting 37.7% of the cohort [21]. A previous study from our group that included 1072 individuals with CKD showed that osteopenia and osteoporosis in at least one site (total hip or spine) were found in 32.7% and 20.0% of patients,

Table 1. Behavior of CKD-MBD biomarkers in older individuals

Parameter	Characteristic in older individuals	Outcome
Calcium	Reduction of calcium-sensing receptor	Hypocalcemia
Phosphorus	Besides hyperphosphatemia, low levels can be found in malnourished patients	Increased risk for mortality and vascular calcification
Vitamin D	Intestinal resistance to calcitriol, reducing absorption Reduction of VDR Diminish 1α-hydroxylase activity with decline in renal function by aging Diminish 1α-hydroxylase and VDR expression (experimental studies)	Hypovitaminosis, increased risk of Alzheimer's disease, orthostatic hypotension
PTH	Lower Ca/PTH ratio Limited tolerance to medical prescription Beneficial effect of cinacalcet against fractures Lower need for phosphate binders	Cardiovascular disease and fractures Higher prevalence of primary hyperparathyroidism than in young patients High mortality
Klotho	Aging decline in renal function decreases klotho, increasing FGF23	Impaired cognitive performance, frailty, falls

Ca, calcium; CKD-MBD, chronic kidney disease mineral and bone disorder; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; VDR, vitamin D receptor.

respectively. Older age and hyperparathyroidism were independent risk factors low BMD at the total hip [22].

Longevity may be related to bone health, as aging is an unavoidable biological process. Osteopenia and osteoporosis are signs of skeletal aging. Fragility fractures and the associated medical burden have been described as the most serious outcomes of skeletal aging [23].

Bone tissue experiences cellular senescence, which contributes to age-related diseases such as osteoporosis. Bone aging occurs due to insufficient

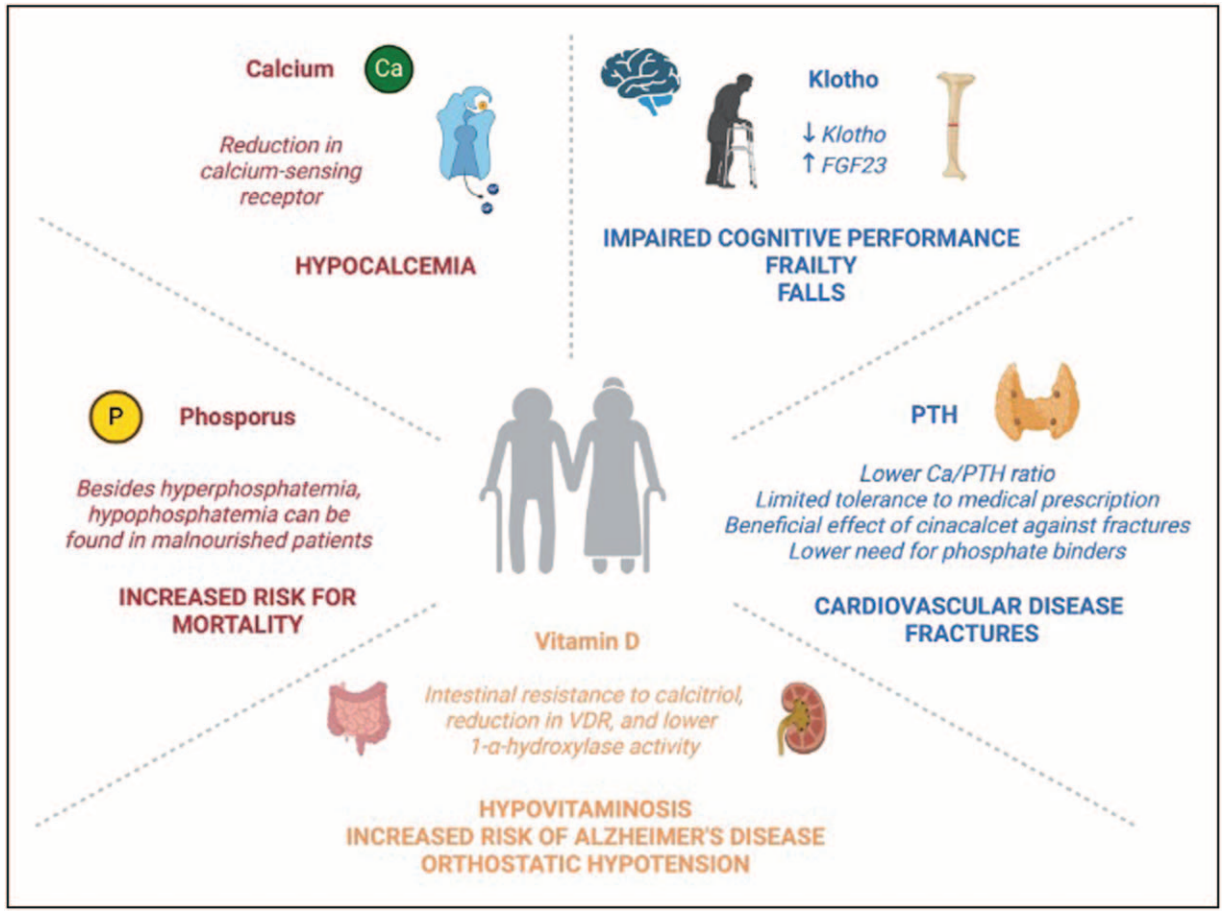

FIGURE 1. CKD-MBD biomarkers in older individuals and outcomes. Ca, calcium; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; VDR, vitamin D receptor. CKD-MBD, chronic kidney disease mineral and bone disorder.

refilling of resorptive osteoclastic lacunae by osteoblasts, leading to a gradual decrease in bone mass over time and an elevated risk of fractures.

CKD-MBD adversely impact bone quality and increase the risk of fractures. Abnormalities in bone turnover, mineralization, and volume are additional factors that affect both bone quality and quantity. These changes raise the susceptibility to fractures in older patients with CKD who are already at higher risk due to skeletal aging.

In the Chronic Renal Insufficiency Cohort (CRIC), which followed approximately 4,000 participants over 11 years, it was found that, in addition to classic risk factors such as diabetes, lower body mass index, and steroid use, CKD-specific risk factors – such as lower eGFR, proteinuria, and elevated PTH – were also associated with an increased risk of fractures, even after adjusting for covariates [24▪].

Fractures pose a significant threat to the health and quality of life of older adults, mainly in the context of aging and CKD. CKD-MBD exacerbates skeletal fragility through disruptions in calcium, phosphate, and PTH homeostasis. These factors, combined with age-related bone loss, contribute to an elevated fracture risk in this population.

A recent systematic review and meta-analysis highlighted a strong link between declining kidney function, indicated by a lower estimated GFR (eGFR), and an increased fracture risk, particularly for hip fractures. This risk becomes significant when eGFR falls below 60 ml/min/1.73 m^2 and intensifies as kidney function worsens [25].

These findings underscore the intersection of CKD-MBD, aging, and osteoporosis, highlighting the importance of addressing skeletal health in CKD patients, particularly those at higher risk of fragility fractures due to advanced age.

Vascular calcification

CKD is a significant risk factor for the development of vascular calcification and vascular aging in older patients. Pathophysiology of vascular calcification includes a complex process within vascular smooth muscle cells and the formation of calciprotein particles (CPPs) [26]. Both aging and CKD are closely linked to the onset and progression of soft tissue calcification.

Age has been identified as an independent risk for severe coronary artery calcification (CAC) in a predictive nomogram model in 369 end-stage kidney disease (ESKD) patients [27▪].

Experimental studies aimed to investigate medial vessel calcification and senescence-associated secretory phenotype (SASP), have demonstrated a significant and progressive calcification in the thoracic aorta, abdominal aorta, and the renal artery [28].

The concept of early vascular aging (EVA) is an important risk factor for the development of premature cardiovascular disease (CVD) in older patients with ESKD [29]. Several pathophysiological mechanisms commonly observed in patients with advanced CKD contribute to increased vascular aging and enhanced EVA. These include uremic toxins, inflammation and oxidative stress, Klotho deficiency, and suppressed nuclear factor-erythroid 2-related factor (NRF2) activity.

CVD is the primary cause of death in patients with CKD. Notably, both atherosclerosis and arteriosclerosis progress more rapidly in patients with kidney failure. Traditional risk factors for these conditions such as advanced age, hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking are commonly found in patients with ESKD.

The trabecular bone score (TBS) is a parameter that assesses variations in dual energy X-ray absorptiometry (DXA) images of the lumbar spine. TBS decreases with age and seems to reflect qualitative aspects of bone structure that complement bone mineral density (BMD) [30]. The inverse relationship between TBS and vascular calcification may offer valuable insights into bone–vascular interactions in CKD.

OTHER PARTICULARITIES IN OLDER INDIVIDUALS WITH IMPACT ON CHRONIC KIDNEY DISEASE MINERAL AND BONE DISORDER

Polypharmacy

The appropriateness of polypharmacy, arising from the careful adherence to disease-based clinical guidelines, has been called into question for multimorbid older patients. A prospective cohort study involving 2023 patients (mean age, 69 years) investigated the relationship between polypharmacy, CKD, and the risk of fragility fractures. The prevalence of polypharmacy (≥5 medications) and hyperpolypharmacy (≥10 medications) was 43% and 9% in non-CKD patients, 62% and 23% in nondialysis-dependent CKD patients, and 85% and 34% in dialysis-dependent CKD patients, respectively [31]. A higher number of medications was associated with a greater fracture risk. Compared to participants without polypharmacy, the adjusted HR for fragility fractures was 1.32 for those with polypharmacy and 1.99 for those with hyperpolypharmacy, after adjusting for osteoporosis risk factors, CKD status, and comorbidities [31].

Cognitive impairment

Individuals with CKD face a markedly higher risk of cognitive impairment compared to the general population, affecting critical functions such as memory, learning, concentration, and decision-making [32]. Interestingly, the prevalence of Alzheimer's disease (AD) dementia in CKD patients is comparable to that of individuals without kidney disease who share a similar age and comorbidity burden, suggesting that AD is not the primary contributor to the elevated cognitive impairment risk associated with CKD.

Aging and CKD-MBD contribute significantly to this risk through vascular complications. CKD-MBD is associated with increased vascular calcification and arterial stiffness, which, combined with the age-related decline in vascular health, exacerbate cerebrovascular disease. This vascular component highlights the complex interplay between CKD-MBD, aging, and cognitive health in this population.

In addition, the large number of medications, coupled with the potential for drug interactions and reduced kidney clearance, significantly increases the risk of sedation, delirium, and cognitive impairment.

Frailty and sarcopenia

Frailty is a multidimensional syndrome characterized by the loss of lean body mass (sarcopenia), muscle weakness, decreased exercise capacity, and a reduced ability to adapt to physiological stress. This condition is particularly prevalent in patients with CKD-MBD and the aging process. A considerable number of adult patients on hemodialysis exhibit frailty, with a higher prevalence in older individuals [33]. Sarcopenia and malnutrition play pivotal roles in perpetuating the cycle of frailty in CKD patients.

A prospective cohort study of 450 patients found that 15.3% had coexisting sarcopenia and undernutrition, which was associated with a significantly lower cumulative survival rate. The combination of sarcopenia and undernutrition was strongly linked to increased mortality risk [34▪▪]. Furthermore, the prevalence of CKD-related sarcopenia is substantially higher than sarcopenia attributed to aging alone. Sarcopenia is most common in patients on hemodialysis, compared to those with nondialyzed CKD, patients on peritoneal dialysis, and kidney transplant recipients [35].

The intersection of CKD-MBD, aging, and sarcopenia underscores the multifactorial nature of frailty in CKD patients. Disturbances in calcium-phosphate metabolism, inflammation, and hormonal imbalances contribute to muscle wasting and bone fragility, exacerbating the clinical burden of frailty and increasing the risk of poor outcomes.

CONCLUSION

CKD in older patients is challenging and impacts bone health, vascular function, and overall aging. As CKD advances, mineral and bone disorders exacerbate the aging process, leading to increased fracture risk, cardiovascular complications, and frailty. Aging contributes to the decline in kidney function, modifying phosphate, calcium, and vitamin D homeostasis while worsening bone and vascular health. Altered FGF23 and Klotho regulation plays a central role in this process, underscoring the importance of early intervention, considering issues such as polypharmacy, cognitive impairment, and sarcopenia. Addressing CKD-MBD in this population is crucial to improve quality of life, mitigating the effects of aging.

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Conflicts of interest

There are no conflicts of interest.

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