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The spectrum of renal osteodystrophy – novel and old paradigms

Violeta Bojinca[1,2], Daria Popescu[1], Cristina Capusa[1,3]

[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2]"Sf. Maria" Clinical Hospital, Bucharest, Romania
[3]"Dr. Carol Davila" Clinical Hospital of Nephrology, Bucharest, Romania

ABSTRACT

"Chronic kidney disease-related mineral and bone disorder" is a newly introduced concept which replaced the former term of "renal osteodystrophy" or "renal bone disease". It highlights the need for understanding the complex relationships among calcium-phosphate axis, bone metabolism, ectopic calcification and cardiovascular morbidity and mortality in patients with chronic kidney disease. It has the merit to shift the focus from monitoring and treating separate biochemical abnormalities at all costs to the greater aim of improvement survival and reducing major cardiovascular events. However, mainly because of the lack of reliable assessment tools, the bone disorders component is discussed to a much lesser extent even it accounts for major physical disabilities and result in significant impairment of the quality of life. Therefore, the current review aimed to briefly remind the older and newer knowledge in the field of bone changes that occur during the course of chronic kidney disease.

Keywords: adynamic bone disease, chronic kidney disease-related mineral and bone disorder, mineral metabolism, osteitis fibrosa cystica, renal osteodystrophy

INTRODUCTION

Chronic kidney disease (CKD) is diagnosed by the presence of at least one marker of kidney damage (mainly increased albuminuria) with or without the decline in the clearance function of kidneys as assessed by glomerular filtration rate, persistent for more than three months (1,2). It is a major public health problem, since it affects up to 8-16% of general population worldwide (3) and it imposes a major socio-economic burden because of both the requirement for renal replacement therapy and the negative influence on many other organs and systems.

Because the kidneys are involved in the homeostasis of calcium, phosphate and vitamin D activation, disturbances in this mineral system are common and occur early in the course of chronic kidney disease. CKD-related mineral metabolism abnormalities evolve silently as the kidney function deteriorates and are difficult to substantiate because the routine biochemical variables remain in normal range until advanced stages. The significant consequent effects on bone structure were recognized long-time ago, but in addition new data linked also calcium-phosphate metabolism abnormalities to vascular and soft tissue calcifications and the increased risk of cardiovascular mortality in CKD patients (2,4).

Furthermore, new understandings of the pathogenesis and types of bone disease associated with the declining glomerular filtration rate have arisen. The aim of the current review is to focus on bone abnormalities associated with CKD.

Chronic kidney disease – related mineral metabolism disorder. A short overview

Chronic kidney disease – related mineral and bone disorder (CKD-MBD) refers to a systemic disorder of mineral and bone metabolism due to CKD in which the kidneys fail to maintain homeostasis of calcium (Ca), phosphate (PO_4) and active vitamin D which leads to maladaptive alterations in related hormones, namely fibroblast growth factor-23 (FGF-23)

Corresponding author:
Cristina Capusa
E-mail: ccalexandr@yahoo.com

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and parathyroid hormone (PTH), and results in defective bone architecture and extraskeletal calcifications (1,2). CKD-MBD occurs from the first stages of CKD (as early as stage 2, when estimated glomerular filtration rate – GFR – decreases below 89mL/min), progresses as kidney function declines and it is manifested by three separate, but interrelated, components that are not necessarily present concurrently in all patients, any combination of these component being possible (2,5) (Figure 1):

- Changes in biochemical profile (calcium, phosphate, vitamin D, parathyroid hormone, FGF-23), which reflect mineral and hormonal abnormalities;
- Bone abnormalities regarding turnover, mineralization, volume, linear growth, or strength;
- Soft tissue (vascular, valvular, and periarticular) calcifications.

The term describes the pathophysiological changes that occur in the vascular and skeletal system in association with chronic kidney disease and underlines the inter-relationships between biochemical changes, bone and ectopic calcifications. The concept of CKD-MBD is justified by the new paradigm in the management of renal bone disease that is to „*think beyond the bones*" and to focus on the improvement of survival, cardiovascular outcomes and quality of life (6). It allows for enhanced communication, increased awareness/diagnosis, and better treatment approaches with the ultimate goal of reducing morbidity and mortality in patients with CKD (7).

Arguments against the concept of CKD-MBD have surfaced as it has been difficult to establish an ideal serological marker that directly correlates with the severity of bone disease (6,8). Routinely, serum phosphate and calcium levels are used to screen for abnormalities of mineral metabolism that may lead to PTH excess, but PTH and FGF-23 levels begin to rise way before there is measurable hyperphosphatemia or hypocalcemia, making detection difficult (8). Likewise, bone alkaline phosphatase levels can monitor bone activity, but specific values of the enzyme that correlate with bone histology have varied in several studies (1,6). In addition, it has not currently been demonstrated that individual components of CKD-MBD, like calcium or bone alkaline phosphatase levels have an additive predictive value for morbidities in CKD (8). Nevertheless, the concept of mineral and bone disorder in the context of CKD is a clinically useful one because it suggests a common underlying mechanism responsible for the pathological manifestations observed (8) and it prompts supervision of serum markers in these patients from early stages.

It is estimated that even below a GFR of 60 mL/min/1.73 m^2 (stage 3a of CKD), the prevalence of abnormalities in bone metabolism is high and 40% to up to 100% of patients with severely decreased kidney function present with histologic and radiologic evidence of bone disease (1). A study by Levin et al., found hyperparathyroidism in 21% of patients with GFR of 60-69 mL/min/1.73 m^2 and 56% of those with a GFR <60 mL/min/1.73 m^2, while 20% of patients with GFR 50-59 mL/min/1.73 m^2 had vitamin D deficiency (<15 ng/mL) (9).

While the current literature focus mainly on the cardiovascular component of CKD-MBD because of its impact on the hard clinical outcomes and the current day-to-day medical practice is still centered on biochemical abnormalities because of the convenience for assessment, less attention is paid to the

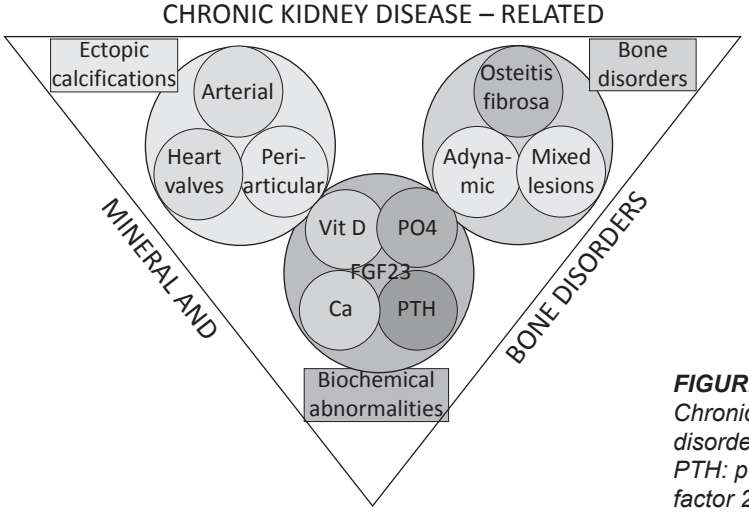

***FIGURE 1**. Schematic representation of the concept of Chronic kidney disease-related mineral and bone disorder. (Ca: calcium; PO4: phosphate; Vit D: vitamin D; PTH: parathyroid hormone; FGF23: fibroblast growth factor 23)*

bone disorders. However, the bone changes account for a significant part of the morbidity in CKD, starting from the growth retardation in the pediatric CKD population, ending with skeletal deformities and fractures, and having in-between a lot of pain.

Bone abnormalities in chronic kidney disease

Multiple factors jointly contribute to bone abnormalities in CKD: PTH, calcitriol, uremic toxins, inflammatory citokines, aging, diabetes mellitus, hormonal deficiencies, and various medications (especially corticosteroids) (7).

Overall, bones in patients with CKD have decreased strenght due to both quality (bone architecture) and quantity (bone mass) defects. The former results from changes in bone turnover, mineralization, and collagen structure/organization. While the loss of bone mass can be measured by dual X-ray absorptiometry and computed tomography, the architecture changes are not easily assessed clinically (7).

The spectrum of renal osteodystrophy

Renal osteodystrophy refers exclusively to an alteration in bone morphology in patients with CKD. It represents the skeletal component of the systemic disorder CKD-MBD and it is quantified by histomorphometry of bone biopsy (5). However, the term fails to describe adequately the adverse changes in mineral and hormonal metabolism in CKD that have serious consequences for patient survival (6).

Because biochemical laboratory and imaging tests do not adequately predict the underlying bone histology, current guidelines recommend consideration of bone biopsy in patients for whom the cause of clinical symptoms and biochemical abnormalities is not certain and for whom the effect of treatment on bone needs to be assessed (1). The preferred site for a bone biopsy is 2 cm posterior and 2 cm inferior to the anterior iliac crest. It should be performed using a trocar or a drill to obtain a core of bone of at least 4-5 mm diameter (5). Transiliac bone biopsy and histomorphometry with double-labeled tetracycline or its derivatives is the gold standard for diagnosis of renal osteodystrophy because it provides both static and dynamic data of bone quality and quantity (7). Unfortunately, beyond its invasive nature, the method requires highly specialized personnel, especialy from the part of anatomo-pathologist, and it is not widely available.

The major disorders of bone in the context of CKD-MBD are (5,10) (Table 1):

1. High bone turnover with high PTH levels, namely osteitis fibrosa cystica;

2. Low bone turnover with low or normal PTH such as adynamic bone disease and, less commonly, osteomalacia (some cases due to aluminium toxicity).

TABLE 1. *Classification of bone disorders in chronic kidney disease*

Bone disorder	***Histological characteristics***	***Potential causes***
I. High bone turnover *Osteitis fibrosa cystica*	Increased bone formation rate High activity and number of osteoblast and osteoclast Reduced osteoid volume High peritrabecular fibrosis surface area	Hyperparathyroidism Other factors (BMP-7, cytokines, growth factors)
Mild hyperparathyroid disease	Increased bone formation rate High activity and number of bone cells Reduced osteoid volume Absence of fibrosis	Early hyperparathyroidism
Mixed lesions	Variable degrees of bone formation rate (from high to normal and low) Increased osteoid volume Increased fibrosis surfaces area	Hyperparathyroidism plus vitamin D deficiency or unknown factors
II. Low bone turnover *Adynamic bone disease*	Low bone formation rate Low number and activity of bone cells Reduced osteoid volume Absence of fibrosis	Over-suppression of PTH (excess calcium salts, vitamin D and calcimimetic therapy) Parathyroidectomy Aluminium overload Other factors (aging, diabetes mellitus, malnutrition, cytokines, acidosis etc)
Osteomalacia	Low bone formation rate Increased osteoid volume and thickness Reduced fibrosis	Vitamin D deficiency Aluminium overload Other factors (iron overload, diabetes mellitus)

The prevalence of these various forms of renal osteodystrophy have changed over the years, with a decrease in osteomalacia and aluminum disease and an increased prevalence of adynamic bone disease (37-60% among dialysis patients), and a notably stable proportion of high-bone turnover disease at 40-50% (7).

In the routine medical practice, measurements of serum parathyroid hormone (PTH) and bone-specific alkaline phosphatase (where it is available, or total alkaline phosphatase instead) provide orientation for the assessment of bone disease in patients with CKD stages 3 to 5. Markedly high or low PTH values can be used to predict the underlying bone turnover with a certain degree of approximation (1).

Osteitis fibrosa cystica

It is the hallmark lesion of chronic kidney disease. The bone turnover is high and it is characterized by PTH-driven increase in the activity of osteoblasts (direct) and osteoclasts (indirect) with anarchic bone formation, accelerated resorption and consequent fibrosis (10).

Biopsies of bones affected by osteitis fibrosa show increased activity of both osteoblasts and osteoclasts (11). The cancellous component of bone is eaten away and dissected centrally along the length of the trabeculae by osteoblasts, creating the appearance of railroad tracks and producing what is known as "dissecting osteitis" (12). The marrow spaces around the affected surfaces are replaced by fibrovascular tissue and cavities of osteoclast resorption, hence the name osteitis fibrosa cystica (11). These lesions lead to a marked increase in fracture rates, and growth failure in children (10). The bone loss predisposes to microfractures and secondary hemorrhages that elicit an influx of macrophages and fibroblasts which create a mass of reactive tissue, known as a brown tumor, named so due to the vascularity, hemorrhage, and hemosiderin deposition and the cystic degeneration commonly encountered in this type of lesion (11).

Overt symptoms are lacking until advanced phases of the disease, when bone pain and deformity, proximal muscle weakness and pruritus secondary to cutaneous mineral deposits occur. Usually, PTH and bone alkaline phosphatase are increased, while serum calcium concentrations are variable (10).

The most characteristic radiological feature of osteitis fibrosa is subperiosteal bone resorption and a pattern of radiolucency in long bones such as the phalanges, humerus and distal epiphysis of the clavicle, indicating the extreme thinness of these bones (12,13). Subchondral resorption is common in the sacroiliac, sternoclavicular and acromioclavicular joints, while subligamentous and subtendinous resorption can occur at the ischial tuberosities, femoral trochanters and insertions of the coraco-clavicular ligaments (13). The bones can be bowed or fractured with lytic lesions that appear as cysts (12).

In a study on end-stage renal disease patients (i.e. undergoing chronic dialysis) with secondary hyperparathyroidism, Lacativa et al. found subperiosteal bone resorption at the phalanges and distal clavicles as the most common abnormality, while brown tumors were present in 37% of the examined subjects (12).

Adynamic bone disease

In contrast to osteitis fibrosa cystica, adynamic bone disease (ABD) represents a state of reduced turnover without osteoid accumulation and is characterized by decreased bone cells activity (6,10). Bone biopsy shows reduced bone volume, formation and mineralization, due to a decline in both the rate of collagen synthesis by osteoblasts and the subsequent mineralization of bone collagen, as measured by tetracycline uptake into bone (14,15). Assessment of bone turnover requires double labeling with tetracycline and reading of the biopsy specimen requires particular expertise and resources (1). In vivo tetracyclines are used because they bind to actively forming bone areas and show fluorescence in ultraviolet light (16). Pre-biopsy in vivo tetracycline labeling as well as amyloid and aluminum stains are required for complete diagnostic work-up for the adynamic bone disease (16). Histologically, there are few or no osteoblasts in samples of ABD and minimal or no peritrabecular fibrosis or marrow fibrosis. The cellular activity is low and the osteoid presents few remodelling sites, resulting in low volume of cancellous bone and low bone formation in general (16). The reduced osteoid volume (below 12-15%) is used to distinguish adynamic bone disease from osteomalacia (the latter having increased values) (17).

Clinical symptoms are often absent, as are the positive radiological findings. There are increased incidence of fractures (which also heal poorly) and vascular calcifications. Adynamic bone disease is suggested by low levels of bone-specific alkaline phosphatase. The typical biochemical findings include increased serum calcium (because the ady-

namic bone has a very low capacity to incorporate calcium in the mineralized matrix) and phosphate, with low or normal PTH and alkaline phosphatase (10).

Although, it remains difficult to assess adynamic bone disease, reported prevalence ranges between 5% to 40% of patients with CKD stages 3 and 4, while in stage 5 dialysis patients, the reported prevalence varies from 10% to 50% (15). The causes of ABD are not clearly defined, but the most commonly involved factors were increased calcium load, excessive treatment with active vitamin D (which both oversuppress PTH synthesis), age, diabetes mellitus, aluminium accumulation and peritoneal dialysis (6).

Osteomalacia

Represents the softening of bones caused by unmineralized bone matrix due to the inability to incorporate calcium into the bone. It is characterized by a very low rate of bone turnover, a mineralization defect and marked accumulation osteoid. Patients with osteomalacia present with low bone density, even when their bone volume is normal (17). Most cases of osteomalacia (OM) were associated with aluminum toxicity, but in the current era, when the use of aluminium-based phosphate binders was drastically restricted, vitamin D deficiency become the most common cause of OM worldwide. Other factors were also considered to increase the risk for osteomalacia in CKD patients: diabetes mellitus, iron accumulation in bone (in the context of widespread use of intravenous iron formulations for the renal anemia treatment), persistently low levels of PTH (after parathyroidectomy or long-term use of calcimimetics), and increased bone content of magnesium (17,18).

Clinical symptoms include: bone and joint pain, myalgias, proximal muscle weakness, fractures (ribs, vertebral bodies, pelvis, hips) and skeletal deformities. Microcytic anemia and encephalopathy may exist in aluminium-induced OM (17).

Bone alkaline phosphatase (BAP) is considered the most useful biochemical parameter to assess bone formation and elevated levels of BAP virtually exclude an adynamic renal bone disease (14). However, elevations of BAP along with total alkaline phosphatase may be seen in cases of severe osteomalacia (16).

Patogenesis of renal bone disease

As kidney function declines, there is progressive deterioration in bone-mineral homeostasis and changes in levels of PTH, 25-hydroxyvitamin D (calcidiol), 1,25-dihydroxyvitamin D (calcitriol), and fibroblast growth factor-23 (FGF-23) (6).The mechanisms accountable for renal bone disease are complex and differ in high- and low-turnover states, but finally have similar clinical consequences (Figure 2).

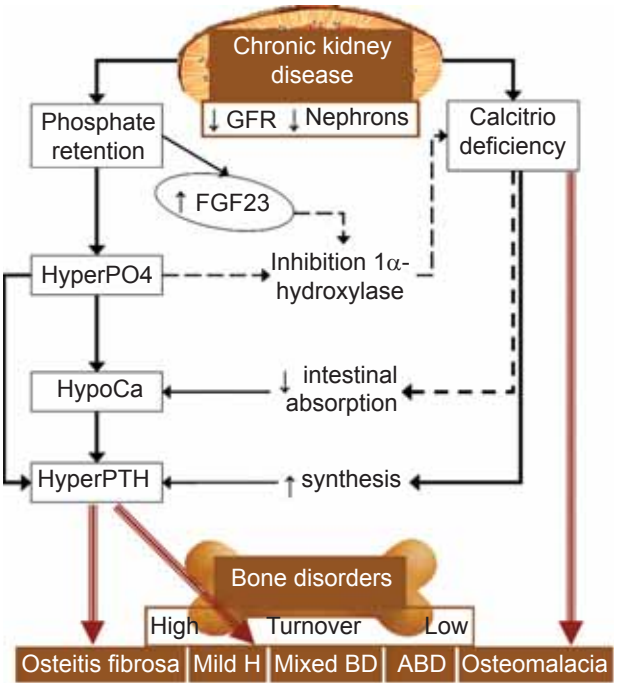

FIGURE 2. *Pathogenesis of Chronic kidney disease-related mineral and bone disorder. (GFR: glomerular filtration rate; FGF23: fibroblast growth factor 23; PO4: phosphate; Ca: calcium; PTH: parathyroid hormone; Mild H: mild hyperparathyroid disease; BD: bone disease; ABD: adynamic bone disease; ↑: increased; ↓: reduced)*

In order to maintain calcium-phosphate equilibrium despite the loss of functional kidney mass, adaptive mechanisms are started from the earliest stages of chronic kidney disease, at glomerular filtration rates (GFR) of 70-80 mL/min, when the serum creatinine levels are still normal or only slightly elevated. In response to nephron loss, the work of each remaining intact nephron is augmented, but also bone cells need to reset their activity in order to substitute some of the kidney's duties with respect to the control of mineral homeostasis. Phosphate retention triggers the increase osteocytes production of FGF-23 (either directly or by increasing the molecule stability thus preventing its cleavage), which acts as a phosphatonin and enhance tubular excretion of phosphate. This rise in FGF-23 simultaneously inhibits calcitriol production and increases its catabolism, an effect which is initially favorable because it reduces dietary phosphate absorption (19).

An adaptive increase in PTH is also induced by phosphate retention and by the reduced active vitamin D (6). Overtime, even the serum levels of phosphate and calcium are maintained in normal ranges until advanced stages (GFR below 20 mL/min), the escalating abnormalities of FGF-23, calcitriol, phosphate, and calcium result in gradually increase of parathyroid hormone (secondary hyperparathyroidism) and parathyroid gland hyperplasia. Subsequently, bone metabolism abnormalities and ectopic calcifications develop.

Osteitis fibrosa cystica

The pathogenesis is mainly driven by the elevated levels of PTH but also involves several other interrelated mechanisms (6). Secondary hyperparathyroidism (resulted from hypocalcemia, reduced calcitriol, hyperphosphatemia and increased skeletal resistance to PTH) is intended to bring calcium and phosphate levels back to normal (20) by activating bone osteoclasts to commence bone resorption with resultant mobilization of large amounts of calcium and phosphate that are normally stored in bone (11). However, because bone resorption and formation are coupled processes, osteoblast activity is also increased in hyperparathyroidism (11). High PTH causes high bone turnover, with both bone resorption and bone formation. Because of the bone resistance to calcemic action of PTH, the serum calcium level remains low despite hyperparathyroidism and continuously stimulates PTH syntesis. In addition, the phosphate release from bone is increased by high levels of PTH, thus exacerbating the hyperphosphatemia and setting off a vicious cycle (6).

Studies on rat models infused with high levels of PTH show poorly mineralized extracellular matrix on bone surfaces and extensive peritrabecular fibrosis which is reversed within one week of PTH cessation (21).

Besides PTH excess, the peritrabecular fibrosis seen in osteitis fibrosa cystica seems to be explained by change in a protein expressed by the kidneys, called bone morphogenic protein-7 (BMP-7), that induces osteoblast differentiation. Low BMP-7 levels (due to renal mass loss in CKD) could explain the abnormal development of osteoblasts into fibroblast-like cells (20). Moreover, because the osteoblast PTH receptors are up-regulated by BMP-7, its reduced levels will lead to decreased specific receptors which will further contribute to compensatory increase in PTH (19).

Another proposed mechanism is the early increase in sclerostin gene expression which inhibits Wnt signaling and, consequently, reduces the osteoprotegerin to the receptor activator of nuclear factor κB-ligand ratio (OPG/RANKL). Thus, the RANKL-mediated activation of osteoclasts is released and a predisposition to osteitis fibrosa is created (19).

Adynamic bone disease

Parathyroid hormone levels are normal or even low. PTH receptors on the bone are down-regulated causing increased resistance to the calcemic action of PTH, a condition unique to CKD patients. The cause for this is multifactorial and includes vitamin D deficiency, high serum phosphate, metabolic acidosis, reduced BMP-7, low estrogen and testosterone levels (17).

It was postulated that PTH receptors are down-regulated due to persistently elevated PTH and low calcitriol levels that are typical of CKD later stages (15). Low bone formation and skeletal remodeling, emblematic for adynamic bone disease, are related to reduced activation of vitamin D and consequent down-regulation of vitamin D receptors (VDR) on osteoblasts (15). VDR is vital for osteoblast proliferation and maintenance of bone formation by modulating de novo production of the bone matrix proteins osteocalcin and osteopontin, at the genomic level (22). In addition, calcitriol-produced stimulation of VDR prevents osteoblast apoptosis (22), but because phosphate retention and rising FGF-23 directly suppress 1 alpha-hydroxylase, further exacerbating vitamin D deficiency, this anti-apoptotic action is diminished (15,23). In a study by Gutierrez et al., FGF-23 emerged as the strongest determinant of calcitriol levels, independent of renal function, serum PO_4, and vitamin D stores, supporting the hypothesis that inhibition of renal 1α-hydroxylase activity by FGF-23 may be more important than loss of renal mass, especially in early-stage CKD (24). Furthermore, secondary hyperparathyroidism and elevated FGF-23 lead to degradation of vitamin D by promoting the enzyme 24-hydroxylase (19,25).

Hyperphosphatemia, hypogonadism and metabolic acidosis may also contribute to down-regulation of PTH receptors in adynamic bone disease (15).

Metabolic acidosis, hyperuricemia and uremic toxins retention, some of the most common metabolic complications of CKD, are also involved in the pathogenesis of bone disease (25). Metabolic acidosis impairs collagen synthesis, promotes osteoclast

activity and bone dissolution (15). Uremic intoxication impairs 1 alpha-hydroxylase activity and osteoblast proliferation and decreases vitamin D receptor reactivity along with the intestinal absorption of dietary or supplemental vitamin D (6,15,25). CKD patients with severe proteinuria demonstrate urinary losses of vitamin D binding protein, leading to increased renal loss of vitamin D metabolites (25) and vitamin D resistance due to progressive loss of VDR in the parathyroid gland (26).

Osteomalacia

It results from a delay in the rate of bone mineralization that leads to accumulation of excess osteoid. The underlying pathophysiologic mechanism can result from the use of calcium-based or aluminum-based phosphate binders often prescribed in the treatment of CKD (17). Calcium loading leads to increased degradation of calcitriol, while aluminum overload mainly impairs osteoblast activity (15). In addition, aluminum causes defective mineralization and increased matrix synthesis by existing osteoblasts and inhibits osteoclast function (17). Currently, nutritional or active vitamin D deficiency, as well as resistance to their actions are the most common causes, Vitamin D deficiency may act directly because it was associated with abnormalities in collagen formation and maturation, but also indirectly by decreasing intestinal calcium and phosphorus absorption, both effects leading to a reduced bone mineralization (17).

The ultimate result is a demineralized subperiosteal bone matrix which becomes overhydrated and swollen, pushing out on the periosteum (27).

Osteoarticular morbidity

An increasing body of evidence confirms CKD is an important risk factor for osteoporosis and subsequent falls and fractures (14). Dual-energy photon absorptiometry (DEXA) is used in general population to measure bone mineral density (BMD) and establish a T score, defined as the number of standard deviations of a person's BMD below the mean BMD of the young healthy population. Osteoporosis is diagnosed when the T score is -2.5 or lower, and other causes of bone fragility have been excluded (14,17). The osteoporosis observed in CKD-MBD is actually quite different than post-menopausal or age-related osteoporosis, because it involves a different pathophysiological mechanism and it often coexists with other specific bone disorder (17,28). Whereas in ordinary osteoporosis, cortical as well as cancellous bone is lost, in CKD-MBD induced osteoporosis, bone density is lost mainly from cortical sites, while cancellous areas may remain unaffected. This is due to the long-term effects of secondary hyperparathyroidism on the cortical bone, which result in bone porosity, reduced cortical thickness, increased friability of cortical bone and a predisposition to non-vertebral fractures (28). For these reasons, KDIGO guidelines suggest not to routinely test BMD by DEXA because it does not predict either the fracture risk as it does in the general population or the type of renal osteodystrophy (5).

Clinical consequences of osteoporosis include reduced bone mass, impaired bone strength and bone fragility fractures, also called osteoporotic fractures (14,28). By definition, an osteoporotic fracture occurs with very little trauma to the skeleton, usualy at the vertebrae, hip and wrist (14).

It is important to distinguish between osteoporosis and adynamic bone disease for management strategies, especially in patients with CKD stages 4-5 who present with fractures (14). Overall, the clinical consequences of low bone turnover observed in adynamic bone are similar to those observed in osteoporosis, but with a higher prevalence of bone fractures and higher mortality risk in the former (29). More important, the treatment strategies could also be different (5).

At the other end of the spectrum of renal osteodystrophy, osteitis fibrosa is clinically manifested through bone pain, fractures and deformities as a result of decreased bone mass, quality and strength (21). T-scores of affected patients are usually in the osteoporotic range resulting in collapsed vertebral bodies. Other complications are related to compression syndromes caused by brown tumors.

In contrast, patients with osteomalacia present with fractures of the ribs, vertebrae, pelvis or hip, isolated or generalized skeletal pain and proximal muscle weakness (16,30). Osteomalacia may be diagnosed when moderate pressure, such as pressing a finger on the sternum or anterior tibia elicits strong pain (16).

Increased risk of fractures

The prevalence of fragility fractures in CKD patients is greater than in the general population (18). Women with decreased eGFR compared to the general population, are at increased risk of trochanteric fractures (31) and patients treated for osteoporosis

who have creatinine clearance values below 65 mL/min have significantly higher incidence of falls, vertebral and femoral fractures compared to osteoporotic patients with GFR >65 mL/min (32). In elderly patients with CKD stage 3, hip fractures are twice as common as in those with normal renal function, while in patients with CKD stages 3-5, non-vertebral fragility fractures are 2 to 6 times more frequent than in the general population. Furthermore, the one-year mortality after a hip fracture is more than three times higher in dialysis patient as compared to general population (33). On the other hand, non-vertebral fractures involve the peripheral long bones and are associated with significant more pain and disability.

Taken together, these findings suggest that patients with impaired renal function experience increased osteoarticular morbidity, beginning as early as stage 3 of chronic kidney disease (14).

Clinically, stages 4 and 5 CKD pose the highest risk of fractures, suggesting that abnormalities in bone metabolism which are already developed at these stages, namely excess PTH and vitamin D deficiency, are involved in CKD-related osteoporosis and subsequent fractures (14).

Skeletal deformities

Recently, a severe condition resulting from long-standing, untreated secondary hyperparathyroidism in CKD, has been described and named Sagliker syndrome (32). X-rays, CT-scans and histopathological examinations of these patients reveal extremely severe changes in the head and body skeleton. Clinical features of Sagliker syndrome include uglifying of facial features, short stature, extreme changes and defects of the maxilla, mandible, teeth and soft tissues in the mouth, deformities of fingers, knees and scapulae, hearing abnormalities, and neurological and psychological problems, which may become irreversible over time and without prompt and adequate intervention (32,34). Changes, particularly in children and teens, become irreversible and disastrous for appearance and psychological health. An international study conducted in Turkey, India, Romania, Egypt, Malaysia, Tunis, and China identified 40 cases of Sagliker syndrome, concluding that in order to correct these changes and to avoid aesthetic and psychological impairment of these patients, appropriate treatment must begin early (34).

Renal osteodystrophy in pediatric patients results in significant growth deficit, compared to healthy children. Secondary hyperparathyroidism affects the normal architecture of bone growth plates, resulting in disabling bone deformities and growth retardation (35). The North American Pediatric Renal Transplant Cooperative Study estimates that the height of children with kidney failure is 1.5 below the mean standard deviation score of matched controls (36), despite elevations in serum growth hormone (GH) levels in these children, suggesting a possible end-organ GH resistance in children with kidney failure.

CONCLUSIONS

Chronic kidney disease triggers, by multiple mechanisms, compensatory adjustments in bone and mineral metabolism, which eventually result in end-organ damage involving not only the bones, but also bone marrow, joints and vascular system. Thus, it exerts a huge impact on patients' health status and imposes a multidisciplinary approach, including nephrologists, rheumatologists, endocrinologists and cardiologists all together.

Even the current review did not address other mineral metabolism and bone disorders besides those with high and low turnover (like dialysis-related amyloidosis and calcific uremic arteriolopathy), the complexity of interactions among kidneys, skeleton, parathyroid glands and other systems obviously arise. In addition, it should be emphasized that the molecular mechanisms of the disorders are still incompletely elucidated and many doubts regarding the pathogenesis, similarity or disparity with age-related bone disease, and therapeutical strategies hamper the efficient mangement of these patients. However, understanding the new advances in the field is a good point to start.

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