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INVITED REVIEW

Chronic kidney disease and bone metabolism

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Abstract Chronic kidney disease-related mineral and bone disease (CKD-MBD) is a syndrome defined as a systemic mineral metabolic disorder associated with CKD, and the term renal osteodystrophy indicates a pathomorphological concept of bone lesions associated with CKD-MBD. Cortical bone thinning, abnormalities in bone turnover and primary/secondary mineralization, elevated levels of circulating sclerostin, increased apoptosis in osteoblasts and osteocytes, disturbance of the coupling phenomenon, iatrogenic factors, accumulated micro-crackles, crystal/collagen disorientation, and chemical modification of collagen crosslinks are all possible candidates found in CKD that could promote osteopenia and/or bone fragility. Some of above factors are the consequences of abnormal systemic mineral metabolism but for others it seem unlikely. We have used the term uremic osteoporosis to describe the uremia-induced bone fragility which is not derived from abnormal systemic mineral metabolism. Interestingly, the disease aspect of uremic osteoporosis appears to be similar to that of senile osteoporosis.

Keywords Chronic kidney disease (CKD) · Chronic kidney disease-related mineral and bone disease (CKD-MBD) · Uremic osteoporosis · Material property

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Introduction

The risk of hip fracture is remarkably high in all patients with chronic kidney disease (CKD), including those undergoing maintenance hemodialysis therapy [1–3]. However, bone metabolism in CKD patients has not been fully elucidated, and systematic understanding has not been achieved. In this brief manuscript, bone metabolic conditions and their pathophysiology in CKD patients are described.

Disease concept of chronic kidney disease-related mineral and bone disease (CKD-MBD)

CKD-MBD is a syndrome defined as a systemic mineral metabolic disorder associated with CKD which can result in disorders of the bone metabolism and/or the cardiovascular system [4]. This disease consists of three components: abnormalities observed in laboratory examinations, including parathyroid gland dysfunction; abnormality in the bone metabolism; and abnormality in the soft tissue calcification including vascular calcification. The term renal osteodystrophy (ROD) is used to refer to the abnormal bone condition found in CKD patients generally. However, today, the term indicates a pathomorphological concept of bone lesions associated with CKD-MBD.

The disease concept of osteoporosis is defined as any bone fragility condition which causes an increased risk of fracture.

The two major functions of the mammalian endoskeleton are maintenance of the mineral concentration in extracellular fluid and maintenance of body firmness. Osteoporosis is a disease that results in dysfunction of the latter, regardless of the cause. In contrast, CKD-MBD is a systemic mineral metabolic disorder associated with renal dysfunction, and the bone lesions are considered to be a consequence of the abnormal mineral metabolism. In other words, the bone lesions in CKD-MBD are defined on the basis of what causes them, although the affected bone function may not always be "maintenance of body firmness". The majority of clinicians/clinical investigators would consider dysfunction in the "maintenance of mineral concentration in extracellular fluid" to be more important in CKD-MBD, as it could cause the development of cardiovascular disorders including vascular calcification [5]. Thus, the disease concept of bone lesions in CKD-MBD is quite different from that of osteoporosis.

Because the fracture risk is remarkably high in CKD patients [2, 3] and most of such fractures are likely to be fragility fractures, it could be assumed that the prevalence of osteoporosis is high among CKD patients. However, it remains unknown whether osteoporosis in CKD patients shares a mechanism similar to that in primary osteoporosis, which is characterized by a remarkable reduction in bone mass, whether the osteoporosis is secondary to CKD-MBD, or whether it is secondary to some clinical condition other than CKD-MBD [6].

Changes in the internal environment, which have an influence on the bone metabolism in CKD patients

Serum fibroblast growth factor 23 (FGF23) [7, 8] concentrations begin to increase prior to changes in circulating phosphate (P), parathyroid hormone (PTH) and 1,25(OH)2 vitamin D (1,25D) concentrations, along with deterioration of the glomerular filtration rate (GFR) [9, 10]. The elevation of serum FGF23 levels derives from the increase in FGF23 production by osteocytes [11]. The amount of single nephron P excretion increases, even in early CKD, and this might stimulate osteocytes via unknown mediators.

At the same time, osteocytic production of sclerostin also increases [12]. In other words, the activation of osteocytes accompanied by increased production of humoral factors might be the initial event that subsequently leads to overt CKD-MBD symptoms. In addition, the serum sclerostin level is high not only in the early stages of CKD but also in the advanced stages [12]. However, so-called empty lacunae are often found in bone samples obtained from CKD patients, indicating that osteocytic apoptosis may be increased in this disease condition.

Unless particular treatment interventions are applied, hyperparathyroidism, hypocalcemia, hyperphosphatemia and a decreased circulation level of 1,25D appear in advanced CKD stages [13–15]. The abnormal mineral metabolic conditions found in these advanced CKD patients represent the basal onset groundwork of classic CKD-MBD and ROD.

However, such typical abnormalities are not often found in CKD patients today. Nowadays, hypocalcemic CKD patients are rather rare because of the administration of therapeutic exogenous 1,25D. The circulating PTH concentration varies from extremely high levels to physiologically normal levels. Since PTH action is blunted in uremic conditions [16, 17], those CKD patients with physiologically normal PTH levels exhibit clinical features similar to remarkable hypoparathyroidism [18].

It is important to note that bone disorders are not the only clinical manifestation of abnormal mineral metabolism in CKD patients. One major strategy to protect bone mechanical strength would be to maintain high circulating mineral levels. However, the frequent occurrence of vascular calcification is regarded as a more serious problem than bone metabolic disorders in CKD patients; therefore, the amount of exogenous 1,25D administration is often limited to avoid hypercalcemia [19].

In addition to abnormal mineral metabolism, uremia has the potential to affect bone metabolism. For example, advanced CKD strongly induces the production of non-enzymatic crosslinks due to extreme oxidative stress [20, 21]. Experiments on uremic animals have shown that uremic toxins directly modify the properties of bone elastic materials [22, 23]. $A\beta_2M$ amyloidosis, which is sometimes observed in patients undergoing long-term hemodialysis therapy [24], induces local osteolytic lesions that can cause fragility fractures [25, 26]. However, since $A\beta_2M$ amyloidosis does not induce systemic bone metabolic disorder, we will not discuss its further pathophysiology in this manuscript.

Thus, although metabolic bone disorders are still common among CKD patients, the stereotypical parathyroid malfunction-based bone disorder represents only a fraction of them today.

Bone metabolic characteristics in CKD patients

Abnormalities in bone mass

Bone mineral density measured with dual-energy X-ray absorptiometry (DXA) declines markedly in CKD patients before dialysis induction [27, 28] and after kidney

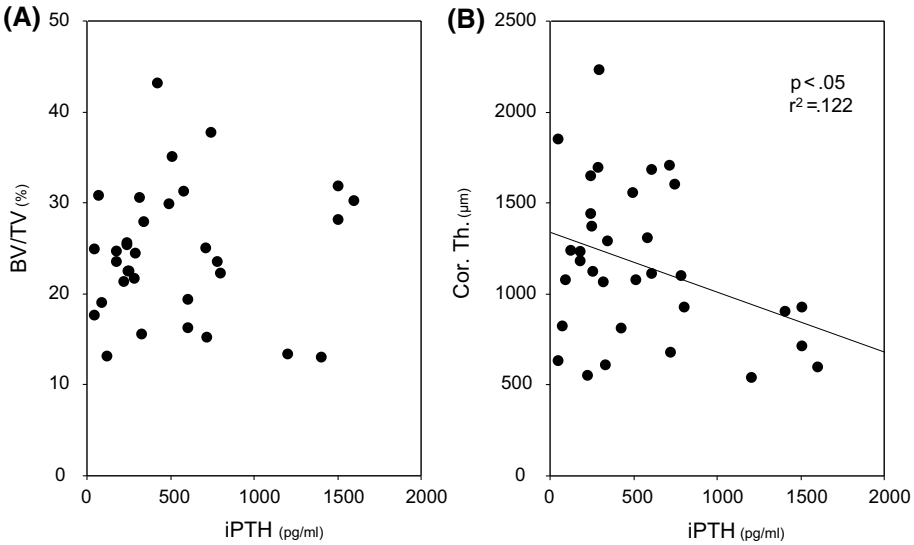

Fig. 1 Parathyroid function and bone mass. Bone histomorphometric data were compared with the circulating intact PTH levels in 33 stable dialysis patients. While cancellous bone volume (BV/TV) showed no specific relationship (**a**), the thickness of cortical bone (Cor. Th.) demonstrated a significant negative correlation (**b**) with intact PTH

transplant [29, 30], although less-evident changes in bone mineral density are observed during maintenance dialysis [31]. The bone mass itself tends to be lower in most dialysis patients who have experienced a predialysis period.

Iatrogenic factors are considered to be one of the main causes of the rapid decline in bone mass in predialysis and posttransplantation CKD patients [32]. For instance, both glucocorticoids [33] and calcineurin inhibitors such as cyclosporine A [34, 35] are commonly used immunosuppressants after kidney transplantation. They are also frequently applied as therapeutic agents for chronic glomerular diseases, although they are known to increase the risk of osteoporosis. Heparin, which is commonly used for patients with chronic kidney disease (CKD), also increases the risk of osteoporosis [36]. It is also true that preserved kidney function could cause mineral loss through urinary excretion in predialysis and posttransplantation patients. Abnormal vitamin D metabolism, abnormal parathyroid function and excess oxidative stress [21] found in this condition could exacerbate osteoporosis, and secondary osteoporosis such as that secondary to diabetes is also often implicated.

The significance of bone mass measurement for predicting fracture among CKD patients has been controversial [37]. Recent clinical studies have demonstrated the association of low bone mass with fracture risk among dialysis patients [38, 39], resulting in a majority of clinical investigators now accepting the potential usefulness of antiosteoporotic agents use.

As mentioned above, the serum sclerostin concentration is high throughout the clinical course of CKD. This fact might in part cause low bone mass through suppressed bone formation in CKD patients. Osteoblastic apoptosis is evident in CKD patients, especially those with hyperparathyroidism, which could be another mechanism for the decline in bone formation [40]. Hyperactivated parathyroid function is associated with cortical bone thinning, whereas it has little effect on cancellous bone volume (Fig. 1).

Practically all of the anti-osteoporotic agents available today are drugs that increase bone mass. Since the relationship between osteopenia and an increased risk of fracture has been recognized, the propriety of administering anti-osteoporotic agents to CKD patients has begun to attract attention. Yet, the safety of some anti-osteoporotic agents has not been confirmed in patients with deteriorated kidney function. Bisphosphonate is eliminated mainly through urinary excretion, and its use in patients with CKD is currently quite limited [41, 42]. The safety of selective estrogen-receptor modulator use in CKD patients is also not fully confirmed [43]. Although the use of vitamin D receptor activator for CKD patients is generally acceptable, its calcemic action sometimes causes acute exacerbation of the kidney injury. In contrast, the hypocalcemic action of denosumab is sometimes enhanced by kidney injury [44, 45]. Odanacatib [46] and romosozumab [47] are promising anti-osteoporotic agents for CKD patients.

Abnormalities in bone turnover

Bone turnover is a vague idea that indicates the frequency of bone remodeling in general. Bone histomorphometric parameters such as the bone formation rate (BFR/BS and/or BFR/BV) or activation frequency (Ac.f) are often used as an index of bone turnover [48]. This concept appears to be a convenient tool for assessing bone lesions in CKD-MBD, and was therefore adopted as one of the three evaluation axes by the new ROD classification criterion known as the turnover mineralization volume (TMV) classification [49] (Fig. 1b).

In CKD patients, the most critical factor determining bone turnover is parathyroid function. Because of increased

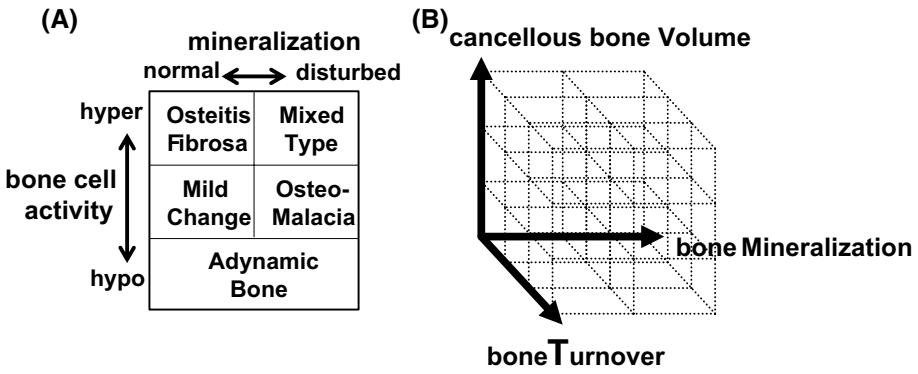

Fig. 2 Histological classification of ROD. ROD is a morphological concept that describes the bone histological changes found in CKD patients. Conventionally, a classification in which bone cell activity and mineralization are used as the two assessing axes has been widely accepted (**a**). Categorical terms that appear in the classification, including osteitis fibrosa, adynamic bone and so on, are still used in clinical practice. A new classification system, in which bone turnover, mineralization and cancellous bone volume are used as the three assessing axes (TMV classification), was adopted in 2006 (**b**). The practical merits of the switch from the conventional classification to the TMV classification have not yet been determined

bone resistance to PTH stimuli, actual bone turnover is generally lower than that expected from circulating PTH levels in CKD patients [50]. Therefore, those CKD patients with PTH levels within the normal physiological range exhibit extremely low bone turnover. Since urinary Ca loss is limited, such low bone turnover does not usually result in hypocalcemia in CKD patients. Although some investigators seem to believe that accumulated micro-crackles in CKD-related extremely low-turnover bone could cause fragility, this assumption has not yet been fully proven. On the other hand, bone turnover becomes extremely high in CKD patients with extraordinarily hyperactivated parathyroid function and would be fatal due to hypercalcemia if it appeared in individuals with normal kidney function. Thus, the spectrum of bone turnover in CKD patients is extremely broad [51].

However, strictly speaking, the idea of bone turnover rests on the premise that osteoclastic bone resorption must always be accompanied by both osteoblastic bone formation and proper mineralization, and this premise is often incorrect in CKD patients. A remarkable example of this premise being incorrect is the so-called mixed change type in the classic ROD classification (Fig. 2a). The original disease concept of this type of ROD is evident osteoclastic bone resorption accompanied by osteoid formation while osteoid mineralization is disturbed. Therefore BFR/BS should be remarkably decreased in spite of the fact that the bone cells are hyperactivated. It is difficult to grasp this disease condition using the concept of bone turnover. Moreover, a stable bone surface in a reversal phase is often observed in adynamic bone (Fig. 3a), as is a true quiescent bone surface. Such uncoupling bone should be classified as abnormal bone remodeling and, to be exact, cannot merely be categorized as low bone turnover with a low remodeling frequency. For the handling of these problems, the classic ROD classification is more rational than the TMV classification.

Abnormality in bone mineralization

The primary osteoid mineralization in the calcified front can also show various values in patients with CKD. Although osteoid mineralization can be represented by the mineral apposition rate (MAR) and/or mineralization lag time (Mlt) in general, those parameters alone often fail to discriminate those CKD cases with extremely suppressed osteoid formation. Therefore, osteoid volume (OV/BV) is often used together with the above parameters. This parameter was adopted as a main index of the mineralization in the classic ROD classification; however, it could not precisely screen cases with a mineralization defect by itself.

Although abnormal findings, including unclear expansion and/or crowding, are often found in bone samples obtained from CKD patients, those findings are not readily expressed by numerical bone histomorphometry values. The reason such abnormalities appear in CKD patients has not yet been fully explained. As late as the 1980s, many CKD cases with a primary mineralization defect due to aluminum and/or iron deposition could still be found [52–54]. However, we seldom encounter such cases any more because of dialysis water ultrapurification, the reduction in aluminum gel use, and the reduction in blood transfusions. The number of cases with osteomalacia is declining [55]. However, abnormal mineralization has not yet disappeared. It is unlikely to be simply a consequence of abnormal vitamin D metabolism because exogenous active vitamin D metabolite is usually administered to CKD patients today.

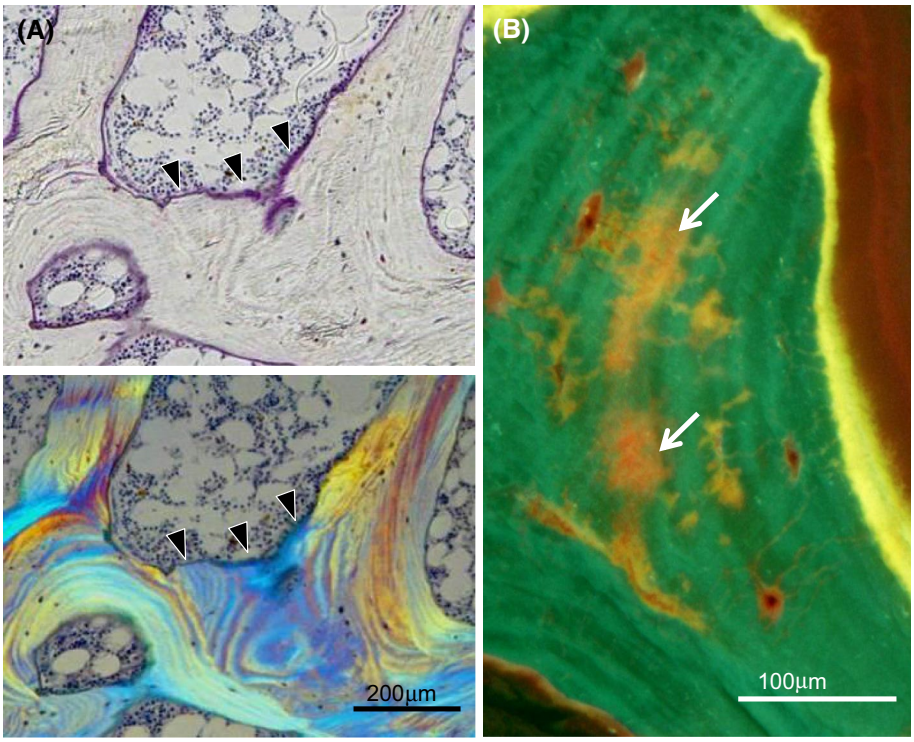

Fig. 3 **a** Reversal phase found in a bone sample obtained from a CKD patient. A rugged bone surface preserved after oeteoclastic bone resorption, but not a true quiescent surface (*arrow heads*), is sometimes found in ROD samples, especially those with the adynamic bone type disease. Strictly speaking, such lesions are not formed by decreased bone turnover, but by disturbed osteoblastic recruitment, namely disturbed bone remodeling. **b** Island-like low-mineralized area found in a bone sample obtained from a CKD patient. Island-like low-mineralized bone lesions (*arrows*) are often found in CKD patients. The cause of such lesions remains obscure. Aggregation of these lesions may be one of the causes of the reduced mechanical bone strength in CKD patients

Yet, abnormal serum Ca/P concentrations may be one of the precipitants of the mineralization disorder.

In addition, islet-like hypomineralized regions sometimes appear inside calcified bone in CKD patients (Fig. 3b). This finding indicates disturbed secondary mineralization; however, it cannot be expressed as a numerical value determined by ordinal bone histomorphometric study.

Abnormality in bone material properties

The extracellular matrix is the primary framework for supporting bone firmness. Various abnormalities were found in the material properties of this extracellular matrix in experimental uremic animals. Interestingly, these changes in the material properties were accompanied by the deterioration of the elastic mechanical properties in bone, and moreover these changes were partially reversed by the administration of AST-120, an oral adsorbent of uremic toxins [23]. AST-120 does not affect the mineral metabolism. These results strongly suggest that uremia modifies bone material properties directly, not indirectly through changes in systemic mineral metabolism. This modification causes the deterioration of the mechanical properties of bone. Therefore, the uremic condition modifies the material characteristics of bones without mineral metabolic disorders; these results suggest that the bone intensity decreases as a result.

Whether a similar phenomenon is reproduced in humans has not yet been confirmed. However, CKD involves a harsh oxidative stress environment [21]. An increased amount of nonenzymatic collagen crosslinking was found in the experimental uremic animals mentioned above [22, 23]. Recently, chemical modification of collagen crosslinking has attracted attention in the field of primary osteoporosis [56–58], and a similar crosslinking modification was also confirmed in CKD condition [59].

There are other candidates besides non-enzymatic collagen crosslinks that could modify the bone material properties under CKD conditions, and further studies, including studies of bone mechanical properties, are needed. If a deterioration of bone mechanical strength that is dependent on uremia toxins but independent of systemic mineral metabolism, as found in experimental uremia animals, is reproduced in CKD patients, this disease condition cannot be considered a part of CKD-MBD, according to the disease concept. Instead, it should be regarded as a new form of osteoporosis specific to uremic conditions. We would like to term this disease "uremic osteoporosis" [6] (Fig. 4). The reasons why we suspect that uremic toxins, but not abnormal mineral metabolism, are responsible for the main pathogenesis of fragility fractures among dialysis patients today are as follows. First, the fracture risk in dialysis patients remains several times higher than that in the general population [60–62]. Second, the management of mineral metabolism has greatly improved but the indicators of mineral metabolism do not predict the fracture risk in dialysis patients. Third, in experimental uremic animals, the adsorption of protein-bound uremic toxins rescued the deterioration of bone elastic mechanical properties. And

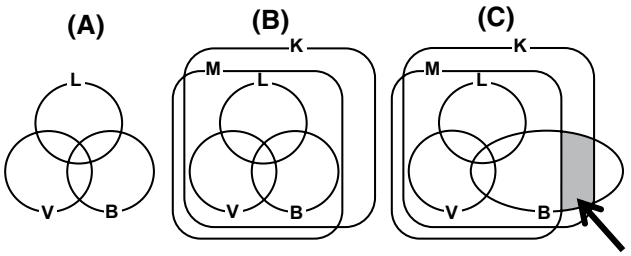

Fig. 4 Concept figure of CKD-MBD and uremic osteoporosis: CKD-MBD is defined as a systemic mineral metabolic disorder associated with chronic kidney disease, which consists of three components: abnormalities observed in laboratory examinations, abnormalities in bone metabolism, and vascular calcification. **a** The widely accepted concept figure. **b** However, the concept should be expressed as here according to the strict disease concept. **c** Not all of the bone metabolic abnormalities found in CKD patients are specific to the CKD condition. Even CKD-specific abnormalities are not always derived from disturbed systemic mineral metabolism. We termed such CKD-specific bone disease that is not caused by abnormalities in the systemic bone mineral metabolism *uremic osteoporosis* (*arrow* and *shadow*). *L* abnormalities observed in laboratory examinations, *B* abnormality in the bone metabolism, *V* abnormality in the soft tissue calcification including vascular calcification, *K* specific disease condition associated with CKD, *M* abnormalities in systemic mineral metabolism

finally, it is still technically difficult to remove protein-bound uremic toxins by blood purification therapy [63]. However, the measurement of these serum uremic toxin levels is not yet generally performed in clinical practice, and therefore we currently have no clinical data regarding the relationship between fractures and uremic toxins.

Conclusions

Two different sets of characteristics were found among the bone metabolic disorders observed in CKD patients (Table 1).

One type of disorder was associated with abnormalities in circulating mineral levels, vitamin D metabolism and parathyroid function, and thus could be considered a bone lesion in CKD-MBD. Because these bone lesions looked so impressive, nephrologists have paid attention only to abnormal parathyroid/mineral metabolism to assess bone metabolism in CKD patients.

However, such abnormal mineral metabolism-related changes are not the only characteristics of bone disorders in CKD patients. Increased apoptosis of osteoblastic lineages [36], increased production of osteocyte-derived humoral factors, and changes in the material properties of bone are also characteristic of CKD, although they do not fit within the general concept of conventional ROD. In other words, they represent a pathological condition causing uremic

Table 1 Two major categories of bone metabolic abnormalities found in CKD patients

Consequence of abnormal systemic mineral/parathyroid metabolism (CKD-MBD)	Cortical thinning*
	Abnormalities in bone turnover*
	Abnormalities in primary mineralization*
	Abnormalities in secondary mineralization
?	Accumulated micro-crackles
	Increased secretion of sclerostin*
	Increased osteoblastic apoptosis*
	Increased osteocytic apoptosis
	Contamination of crystal components
Factors independent of systemic mineral/parathyroid metabolism (uremic osteoporosis)	Disturbed maturation of physiological crosslinks
	Increased amount of non-enzymatic crosslinks
	Disorientation of collagen/crystal
	Disturbed coupling phenomenon*

Bone metabolic abnormalities in CKD patients were divided into two categories. One is related to abnormalities in the systemic mineral metabolism, which is regarded as a part of CKD-MBD. The other involves recently recognized symptoms that are unlikely to have a strong association with systemic mineral metabolism. The former category largely shares a disease concept with the stereotypical classic ROD, whereas the latter appears to be quite similar to senile bone change. All the factors listed could cause bone fragility, and factors indicated by * have the potential to induce osteopenia

osteoporosis. Quite interestingly, these findings are surprisingly similar to the senile bone changes observed in individuals with normal kidney function [64]. The CKD condition is sometimes classed as a progeroid model [65, 66], and uremic osteoporosis is a typical example.

The aging-bone-like changes have not been noticed before because they are hidden behind the obvious bone changes due to abnormal mineral metabolism, namely the bone lesion in CKD-MBD. Recent progress in the treatment of mineral metabolism has successfully ameliorated the bone lesion of CKD-MBD in dialysis patients. The fact that their fracture risk still remains extremely high indicates that we are finally coming up against the CKD-specific aging-bone-like change, in other words uremic osteoporosis.

It is still uncertain whether these two disorders, namely systemic mineral metabolic-disturbance-related bone disorder and senile-change-like bone disorder, should be regarded as two symptoms correlated with each other in a single syndrome or as two different diseases that happen to coexist in CKD. Further studies of bone disorders in CKD patients may provide a novel approach to understanding the pathophysiology of primary osteoporosis as well as contributing to fracture prevention among CKD patients.

Conflict of interest All authors have no conflicts of interest.

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