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REVIEW

Mixed uremic osteodystrophy: an ill-described common bone pathology in patients with chronic kidney disease

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Abstract

Renal osteodystrophy (ROD) starts early and progresses with further loss of kidney function in patients with chronic kidney disease (CKD). There are four distinct types of ROD based on undecalcified bone biopsy results. Adynamic bone disease and osteomalacia are the predominant forms of low bone turnover, while hyperparathyroid bone disease and mixed uremic osteodystrophy (MUO) are typically associated with high bone turnover. MUO is a prevalent but poorly described pathology that demonstrates evidence of osteomalacia on top of the high bone formation/resorption. The prevalence of MUO ranges from 5 to 63% among different studies. The pathogenesis of MUO is multi-factorial. Altered phosphate homeostasis, hypocalcemia, vitamin D deficiency, increased FGF-23, interleukins 1 and 6, TNF-α, amyloid, and heavy metal accumulation are the main inducers of MUO. The clinical findings of MUO are usually non-specific. The use of non-invasive testing such as bone turnover markers and imaging techniques might help to suspect MUO. However, it is usually impossible to precisely diagnose this condition without performing bone biopsy. The principal management of MUO is to control the maladaptive hyperparathyroidism along with correcting any nutritional mineral deficiencies that may induce mineralization defect. MUO is a common but still poorly understood bone pathology category; it demonstrates the complexity and difficulty in understanding ROD. A large prospective bone biopsy-based studies are needed for better identification as proper diagnosis and management would improve the outcome of patients with MUO.

Keywords Mixed uremic osteodystrophy · CKD-MBD · Bone pathology · renal osteodystrophy · management

Introduction

Chronic kidney disease (CKD) is a substantial public health problem. It affects more than 10% of the world's population [1]. Mineral and bone disorders (MBD) are complications of CKD that happen in early CKD stages and deteriorate with progressive loss of kidney function [1, 2]. The syndrome of CKD-MBD was first defined in 2006 by the Kidney Disease Improving Global Outcomes (KDIGO) group, unfolding a complex systemic disorder that involving any of the following: (a) bone and mineral laboratory abnormalities such as calcium, phosphorus, parathyroid hormone (PTH), and/or vitamin D alterations; (b) renal osteodystrophy that includes bone turnover (T), mineralization (M), volume (V), or strength abnormalities; and (c) soft tissue and cardiovascular calcification [3]. The severity of the CKD-MBD dictates the risk of fractures and cardiovascular morbidity and mortality [1].

Renal osteodystrophy (ROD) describes the bone changes seen in patients with chronic kidney disease (CKD). Its pathophysiology is complex, involving disturbances in the metabolism of calcium, phosphate, PTH, and vitamin D, among others, resulting from the loss of renal function; and this complexity is reflected in the bone tissue [3]. Histomorphometric analysis of undecalcified bone is the gold

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standard diagnostic method [4]. It helps in classification of ROD and to guide therapeutic decisions, since, until now, both biochemical markers of bone metabolism and imaging exams are not considered ideal substitutes for the diagnosis of these changes [5, 6].

The results of the histomorphometric analysis are generally expressed following the nomenclature proposed by the Histomorphometry Nomenclature Committee of the American Society of Bone and Mineral Research. The histomorphometric analysis enables the evaluation of structural, formation, resorption, and bone mineralization parameters [7]. Classically, bone diseases in patients with CKD have been classified into one of the following patterns: osteitis fibrosa, MUO, adynamic bone disease, and osteomalacia [8]. However, the diagnostic criteria for each of them have not been homogenous. Studies have used different histomorphometric parameters and cut-off levels to define the same pattern of ROD [9, 10]. In 2006, the KDIGO guidelines proposed using the TMV classification (turnover, mineralization, and volume) as an attempt to standardize histomorphometric analysis in the context of ROD [3]. Although the TMV classification spotted the importance of speaking a universal language in the field of ROD, some pitfalls remained. For instance, it was not clearly established which cut-off values should be used to characterize high or low turnover, normal or abnormal mineralization, and abnormal bone volume. Up to date, only a few studies have gathered biopsy results in normal individuals [11–13]. Therefore, most studies have used the reference values obtained from populations whose ethnicity is different from the study population, which may affect the reliability and the generalizability of the results.

The implementation of the TMV classification highlighted the difficulty in separating patients with osteitis fibrosa from those with MUO. Indeed, based on the TMV classification, in both ROD types, the bone volume can be variable, the turnover is high, being the mineralization, which is abnormal in MUO, the only difference between them [3].

Epidemiology

The prevalence of ROD has changed over the last decades for reasons not completely clear. This could be related to using new medications in MBD management, the improvement of dialysis technology and increased patients' survival. The KDIGO guidelines, published in 2009, pooled the prevalence data of the different types of ROD, from 1983 to 2006, in pre-dialysis, peritoneal dialysis, and hemodialysis patients. The prevalence of MUO was 20%, 5%, and 32%, respectively [14]. Table 1 describes the prevalence of different types of ROD after 2006. For MUO, it ranged from 5 to 50% [15–20]. This wide range could be connected to various epidemiological and clinical differences among patients with different stages of CKD. Moreover, differences between healthcare systems might affect the therapeutic strategies, because of the availability and affordability of various medications used in treatment of ROD.

Pathogenesis

Renal osteodystrophy is consistently seen in patients with CKD. Histologically, ROD is classified into high and low bone turnover states. Low bone turnover includes adynamic bone disease and osteomalacia while high bone turnover states include osteitis fibrosa and MUO [21].

High bone turnover and defective mineralization, with accumulation of the osteoid seams, are the main features of MUO [22]. Secondary hyperparathyroidism is the main inducer of high bone turnover, leading to increased rates of bone formation and resorption. There are different factors involved in the development of secondary hyperparathyroidism [23]. Firstly, phosphate retention, high serum phosphate levels can stimulate PTH secretion, directly by increasing PTH mRNA levels or indirectly through decreasing the serum calcium and calcitriol levels [24]. Secondly, hypocalcemia, low extracellular calcium concentration is the main stimulator of PTH synthesis and secretion [25]. Thirdly, vitamin D deficiency, calcitriol has a direct inhibitory effect on PTH; moreover, its deficiency in patients with CKD leads to decreased calcium intestinal absorption and indirectly stimulation of PTH release [26]. Last but not least, fibroblast growth factor-23 (FGF-23) increases early in the course of CKD progression as an adaptive mechanism to avoid hyperphosphatemia. However, it inhibits PTH release, but at the same time, it decreases activation of 25- to 1,25-dihydroxy vitamin D [27].

Other co-players in the development of MUO include interleukins 1 and 6 and TNF-alpha [28]. Also, heavy metal intoxication, mainly aluminum, can lead to osteoblasts and osteoclasts dysfunction. A defect in bone mineralization due to inactive osteoblasts leads to excessive accumulation of bone matrix. However, recently, Carbonara et al. did not find an association between bone aluminum accumulation and osteomalacia [29]. Other metals implicated include iron and cadmium [30]. The most important reason for defective mineralization in a study performed in dialysis Slovenian patients with MUO was the amyloid deposits on the mineralization front [31] (Fig. 1). Amyloidosis is a well-known cause of CKD and metabolic bone disorders as well. Amyloid bone disease represents a diagnostic challenge and sometimes needs bone biopsy along with bone marrow aspiration and biopsy [32]. Local amyloid production even in patients with systemic amyloidosis can induce lytic myeloma bone disease. The diffuse amyloid protein deposition might

Table 1 Prevalence of ROD according to the most recent bone biopsy-based studies in CKD patients

Study	Authors	Journal	Year	*N*	Study population	Type of bone disease
Bone histomorphometry and indicators of bone and mineral metabolism in wait-listed dialysis patients.	Keronen S et al. [15]	Clin Nephrol.	2016	52	54% hemodialysis	31% MUO 21% ABD 17% osteitis fibrosa 4% osteomalacia
Bone histo-morphology in chronic kidney disease mineral bone disorder.	Bembem K et al. [16]	Indian J Hematol Blood Transfus	2017	32	6 hemodialysis 26 pre-dialysus	50% MUO 44% osteitis fibrosa
Quantitative histomorphometric analysis of halved iliac crest bone biopsies yield comparable ROD diagnosis as full 7.5 mm wide samples.	Novel-Catin et al. [17]	Bone	2020	68	End stage kidney disease	45% osteitis fibrosa 21% MUO 12% ABD 10% osteomalacia
Bone turnover markers predict type of bone histomorphometry and bone mineral density in Asian chronic hemodialysis patients.	Laowalert S et al. [18]	Nephrology (Carlton)	2020	22	All patients in hemodialysis	50% osteitis fibrosa 45% ABD 5% MUO
Iliac crest bone biopsy by interventional radiologists to improve access to bone biopsy in chronic kidney disease populations: technical note and a case series.	Lavigne et al. [19]	J Nephrol.	2021	11	8 hemodialysis 2 CKD stage 5 1 CKD with hypophosphatemia	45.4% ABD 18.1% osteitis fibrosa 18.1% MUO 9.1% osteomalacia 9.1% not defined
Overview of renal osteodystrophy in Brazil: a cross-sectional study	Carbonara C et al. [20]	J Bras Nefrol.	2023	386	315 hemodialysis 31peritoneal dialysis 40 pre-dialysis	51% osteítis fibrosa 42% ABD 25% MUO

ABD adynamic bone disease, *CKD* chronic kidney disease, *HD* hemodialysis, *MUO* mixed uremic osteodystrophy

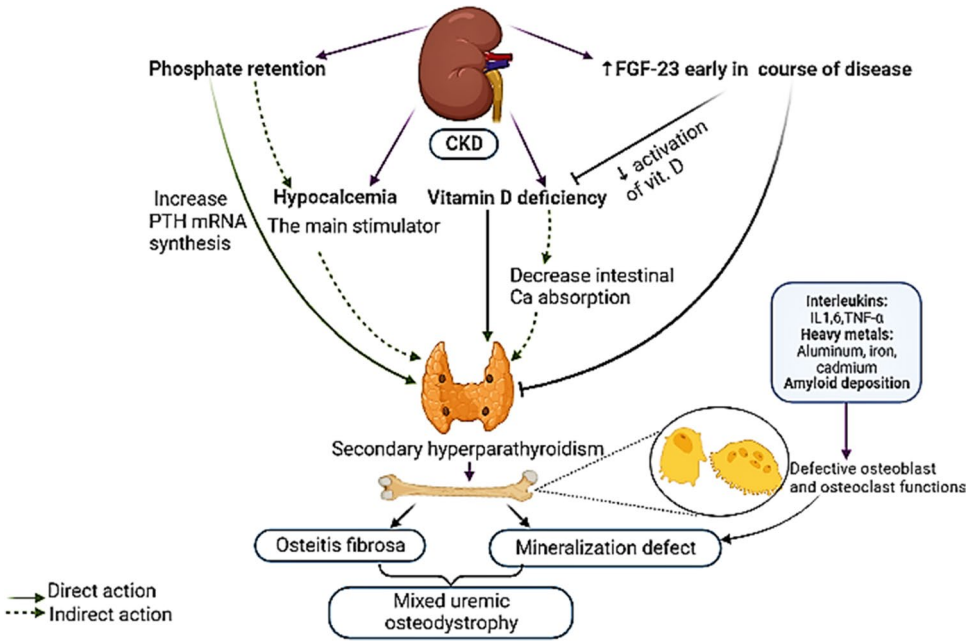

Fig. 1 Pathogenesis of mixed uremic osteodystrophy. Secondary hyperparathyroidism is the main inducer of high bone turnover. Different factors are involved in the development of secondary hyperparathyroidism. Phosphate retention, hypocalcemia, vitamin D deficiency. FGF-23 increases early during CKD progression as an adaptive mechanism to avoid hyperphosphatemia. Other co-players include interleukins 1, 6, and TNF-α. Also, heavy metal intoxication, mainly aluminum, iron & cadmium can lead to osteoblasts and osteoclasts dysfunction. Other factors implicated include amyloid deposits on the mineralization front. Abbreviations: PTH: parathyroid hormone; CKD: chronic kidney disease; FGF-23: fibroblast growth factor-23; TNF-α: tumor necrosis factor-α

replace the normal bone structures leading to skeletal destruction and secondary osteoporosis. Amyloid bone disease must be considered in patients with a monoclonal gammopathy as preventive measures may improve the bone health and decrease fracture risk.

Clinical presentation

Few studies have examined the possible relationship between osteo-muscular symptoms and CKD-MBD. Importantly, the criteria used to perform the bone biopsy, as well as if this procedure was part of a clinical trial, may directly affect this evaluation. According to the KDIGO, 85% of patients had clinical symptoms that could be related to bone disease, of which 32% presented MUO. However, there does not seem to be differences in symptomatology among the histological type of ROD [14]. More recently, a cross-sectional analysis of 396 bone biopsies data from the Brazilian Registry of Bone Biopsy (REBRABO) has reported a significantly higher prevalence of clinical symptoms, such as weakness, bone pain, and myalgia, among patients with high turnover bone disease in comparison to those with low turnover bone disease. However, it was not investigated if there was any difference among various histological patterns of ROD [20].

As MUO is characterized by high bone turnover and defective mineralization [33], it might have clinical characteristics from both osteitis fibrosa and osteomalacia. Thus, clinical features of hyperparathyroidism, along with hypocalcemia, hypophosphatemia, and or vitamin D deficiency might co-exist [34]. Moreover, manifestations of heavy metals intoxications (e.g., aluminum and iron) and/or β2 microglobulin accumulation could be present [31, 35]. Lehmann et al. found that in kidney transplant recipients, patients with MUO were older, had longer dialysis vintage, and received lower doses of corticosteroid compared to other patients with different ROD pathologies [36]. Moreover, Chaer et al. found that compared to osteitis fibrosa, MUO dialysis patients were also older and had lower serum phosphate levels (Table 2) [37].

Diagnosis

Laboratory investigations

Even though it is impossible to discriminate MUO from other ROD subtypes based on non-invasive testing, laboratory evidence of a combination of hyperparathyroid bone disease along with osteomalacia is the key to suspect MUO [38].

Table 2 Clinical and biochemical characteristics of patients with MUO and osteitis fibrosa

	MUO ($n = 18$)	OF ($n = 24$)	P
Age (years)	54.7 ± 11.8	44.8 ± 11.6	0.009
Sex (male/female)	13/5	16/8	0.75
Length on hemodialysis (months)	48 (30; 113)	78 (28; 156)	0.35
Race (White/non-White)	11/7	13/11	0.76
Etiology of CKD			0.48
Arterial hypertension	4 (22%)	6 (25%)	
Diabetes mellitus	5 (27%)	2 (8%)	
Chronic glomerulonephritis	3 (17%)	4 (17%)	
Hereditary kidney disease	3 (17%)	4 (17%)	
Other causes	3 (17%)	8 (33%)	
Total calcium (mg/dl)	9.4 ± 0.7	9.4 ± 0.7	0.77
Phosphate (mg/dl)	5.0 ± 1.7	6.9 ± 1.6	0.001
Alkaline phosphatase (U/l)	166.5 (119.8; 237.5)	152.5 (130.5; 262)	0.83
Intact PTH (pg/ml)	536 (296; 1178)	1073 (402; 1426)	0.21
Vitamin D (ng/ml)	26.1 (21.6; 37.2)	27 (20.5; 31.6)	0.83

Data are expressed as mean SD or median (25^{th}–75^{th}) median

In hyperparathyroid bone disease, high iPTH and alkaline phosphatases (either total or bone specific) are typically found [4]. Furthermore, the unproportionate higher alkaline phosphatase/iPTH ratio may in favor MUO [16]. However, Lehmann et al. did not establish a significant correlation between the pathological ROD forms and serum PTH or the alkaline phosphatase levels [36]. The presence of hypocalcemia, hypophosphatemia, and/ or severe degree of vitamin D deficiency may also suggest MUO in presence of elevated iPTH and bone turnover biomarkers [39]. A potential diagnostic role of serum FGF-23 as a bone turnover and mineralization biomarker has been suggested [40]. Lima et al. reported that abnormal mineralization was only found in patients with FGF-23 levels less than 2000 pg/ml while very high levels of FGF-23 were associated with normal mineralization [27].

Radiological investigations

Bone imaging techniques (e.g., X-rays and DEXA) cannot differentiate between the subtypes of ROD. However, they are useful in some circumstances, such as determination of the severity of the bone disorder and estimation of the fracture risk probability [41]. Radiologically, patients with MUO might show combined features of osteitis fibrosa and osteomalacia. DEXA scan may reveal decreased bone volume (osteopenia/osteoporosis). Moreover, trabecular bone score (TBS) captured from the DEXA image can help in evaluating the bone microarchitecture [42]. High-resolution peripheral quantitative computed tomography (HRpQCT) assesses the bone quality and discriminates the cortical from the trabecular bone abnormalities [43]. X-rays might show features of osteitis fibrosa such as subperiosteal bone erosions, rugger jersey spine, which appears as alternating bands of sclerosis and lucency of the lumbar spines, brown tumor, which appears as a cystic bone lesion, pepper pot skull, or salt and pepper sign, which is diagnosed by showing multiple tiny, well-defined lucencies and a ground glass appearance in the skull. Chondrocalcinosis and fractures or pseudo-fractures may also exist [44]. Similar to osteomalacia, looser-Milkman zones that typically appear as fissures, pseudo-fractures, or radiolucent lines with sclerotic margins in the long bones in a bilateral symmetrical manner can be seen in the plain X-ray films [45]. The presence of multiple trabecular fractures with a variable appearance of different sequences in the MRI images might also suggest osteomalacia [46]. 18F-NaF positron emission tomography (18F-NaF PET) enables the measurement of regional bone turnover by evaluating the bone fluoride activities [47–49]. Aaltonen et al. reported a clear association between the bone histomorphometric measurements and the PET scan bone fluoride activity in hemodialysis patients. In addition, they demonstrated that the performance of the receiver operating characteristic (ROC) curve of the PET scan to discriminate low from non-low bone turnover was better than that of iPTH [50].

Bone histomorphometric analysis

Bone histomorphometric analysis with double tetracycline labeling is the gold standard diagnostic tool of MUO and other forms of ROD. Because of the unavailability of bone biopsies in all centers, the diagnosis of MUO may be delayed or never established. The histological alterations observed in MUO comprise findings similar to those observed in osteitis fibrosa, that is characteristics of high turnover, but with compromised mineralization [51]. The

implementation of the TMV classification highlighted the difficulty in separating patients with osteitis fibrosa from those with MUO. Indeed, based on the TMV classification, in both ROD types, the bone volume can be variable, the turnover is high, being the mineralization, which is abnormal in MUO, the only difference between them [14] (Fig. 2). Table 3 shows unpublished bone histomorphometric parameters of Brazilian CKD patients with MUO compared to osteitis fibrosa (37). There was no significant difference regarding the structural and resorption parameters between patients with MUO and osteitis fibrosa. Otherwise, patients with MUO presented significantly greater osteoid surface and thickness and were quite different in terms of mineralization parameters, which denotes the presence of abnormal mineralization.

Consequences of MUO

Bone fractures

There is scarcity of results about relationship between fractures and the ROD types. A large study that analyzed 2507 bone biopsies over 16 years in Brazil and Uruguay, in which the prevalence of MUO was 20%, did not find any differences in the frequency of fractures among adynamic bone disease, high bone turnover, or MUO [14, 52]. Similarly, in a recent analysis of the REBRABO, the prevalence of bone fractures was not significantly different between high- and low-turnover bone diseases. The relation between the type of ROD and bone fractures was not examined, though [20]. On the other hand, Gerakis et al. found higher prevalence of fractures in patients with adynamic bone disease when compared with other types of ROD [53]. Interestingly, a study that compared the bone histomorphometric analysis of hemodialysis patients who suffered long bone fractures with those without fractures, paired for age, gender, and dialysis vintage found a greater mineralization defect, together with more impaired bone microarchitecture and lower bone formation, in the former group [51]. Although one cannot assign the risk of fracture to a sole bone metabolism abnormality, particularly in CKD patients, this finding highlights the importance of bone mineralization to bone strength and, consequently, might indicate that patients with osteitis fibrosa and MUO may behave differently in terms of fracture risk. This hypothesis warrants further investigation on future bone biopsy-based studies.

Due to the difficulties (e.g., invasive procedure and few specialized centers) to perform bone biopsy followed by histomorphometric analysis, there is a lack of large prospective studies that have investigated the association between risk of fractures and bone histological abnormalities in CKD-MBD [54]. One possible strategy to overcome this hurdle would be to use DEXA as a surrogate marker of bone quantity in the CKD setting. Indeed, recent studies have reported that low bone mineral density (BMD) may be helpful to predict fracture risk in all CKD stages [55, 56]. Nevertheless, it is important to recall some limitations of

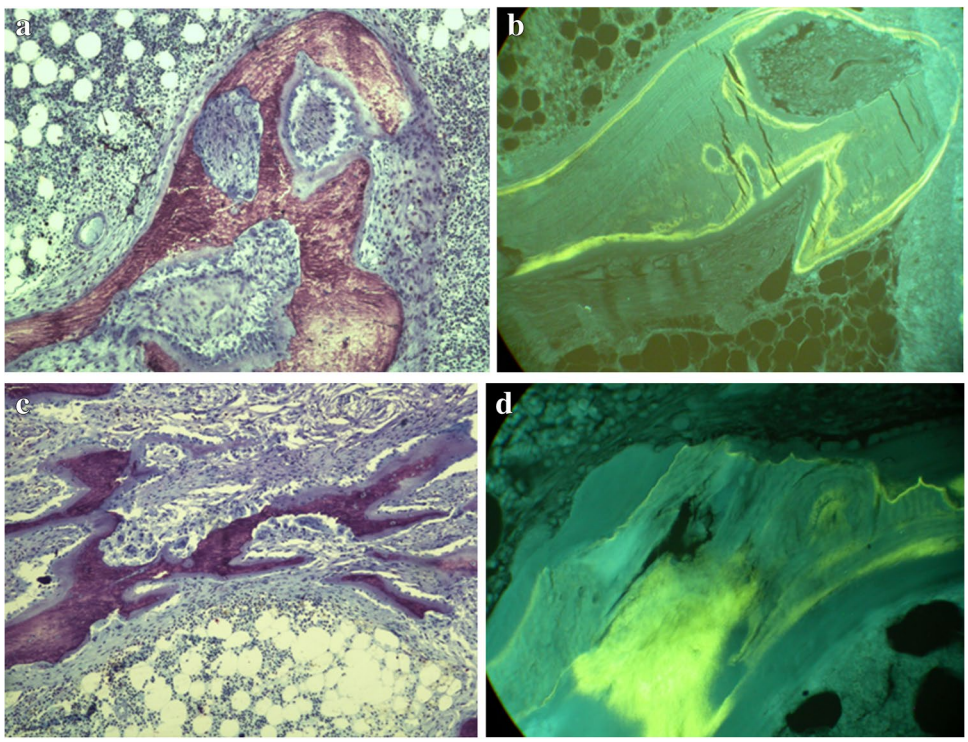

Fig. 2 **a–d** Histological characteristics of osteitis fibrosa and mixed uremic osteodystrophy

Table 3 Comparison of bone histomorphometric parameters between patients with MUO and osteitis fibrosa

	MUO ($n = 18$)	Osteitis fibrosa ($n = 24$)	P	Reference values	
				Males	Females
Structural parameters					
BV/TV (%)	21.6 ± 7.4	23.8 ± 8.4	0.39	24.0 ± 6.1	21.8 ± 7.2
Tb.Th (µm)	138.5 (112.1; 140.4)	117.2 (106.6; 129.4)	0.10	127.9 ± 29.7	126.0 ± 28.8
Tb.Sp (µm)	466.2 ± 200.5	408.8 ± 145.4	0.30	420.6 ±1 24.1	498.3 ± 195.9
Tb.N (mm)	1.6 (1.2; 2.1)	1.8 (1.5; 2.4)	0.17	1.89 ± 0.42	1.76 ± 0.52
Formation parameters					
OV/BV (%)	11.7 (7.6; 16.6)	7.3 (5.2; 11.4)	0.06	2.9 ± 2.7	1.55 ± 1.9
O.Th (µm)	**13.2 ± 2.9**	**10.9 ± 2.9**	**0.016**	11.7 ± 3.5	10.8 ± 3.2
OS/BS (%)	**56.4 ± 12.5**	**44.4 ± 15.8**	**0.011**	16.1 ± 12.6	9.2 ± 8.4
Ob.S/BS (%)	16.4 (11.2; 25.2)	16.1 (12.4; 19.8)	0.77	1.2 ± 1.4	1.2 ± 3.2
Resorption parameters					
ES/BS (%)	11.2 ± 6.8	14.8 ± 6.1	0.078	1.75 ± 1.21	2.3 ± 2.4
Oc.S/BS (%)	2.0 ± 1.2	2.5 ± 1.2	0.24	0.03 ± 0.11	0.03 ± 0.06
Fibrosis					
Fb.V/TV (%)	0.34 (0.08; 1.02)	0.74 (0.37; 2.46)	0.064	0	0
Mineralization parameters					
BFR/BS ($\mu m^3/\mu m^2$/day)	**0.063 ± 0.044**	**0.153 ± 0.072**	**0.0001**	0.13 ± 0.07	0.07 ± 0.03
MS/BS (%)	**7.0 ± 3.4**	**11.9 ± 3.7**	**0.0001**	18.3 ± 7.5	11.5 ± 4.5
MLT (days)	**137.8 (70.6; 197.3)**	**37.1 (21.6; 55.4)**	**< 0.0001**	21.3 ± 2.3	23.7 ± 2.7

Data are expressed as mean SD or median (25^{th}–75^{th}) median

BV/TV trabecular bone volume, *BFR/BS* bone formation rate/bone surface, *MS* mineralizing surface, *ES* eroded surface, *Fb.V/TV* fibrosis volume/tissue volume, *MLT* mineralization lag time, *Ob.S* osteoblastic surface, *Oc.S* osteoclastic surface, *OS* osteoid surface, *O.Th* osteoid thickness, *OV/BV* osteoid volume/bone volume, *Tb.N* trabecular number, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation

this method: (i) DEXA cannot evaluate bone quality, which is as important as bone quantity for skeletal health; (ii) it does not detect the type of ROD; and (iii) its accuracy to predict the risk of fracture is lower in CKD than in non-CKD individuals [53]. It has been demonstrated similar BMD by DEXA in the different types of ROD [57–60]. Otherwise, in a study that examined 73 patients on dialysis by bone biopsy and DEXA, Fletcher et al. found a negative relationship between severity of osteitis fibrosa and BMD. Patients with high turnover, as others with MUO (3%), had a higher mean BMD measurement than patients with adynamic bone disease or normal histology [61]. Hence, up to now, it is not possible to establish any association between MUO and bone fractures by using DEXA.

Vascular calcification and mortality

Vascular calcification (VC) has been considered an integral part of CKD-MBD. Even though it has been hypothesized that both low and high bone turnover states may contribute to ectopic calcification, most studies have reported an association mostly between adynamic bone disease and vascular calcification [62, 63]. Importantly, bone biopsy-based studies in CKD patients have generally reported an inverse association between bone microarchitecture, such as trabecular bone volume and thickness, and both low and high bone formation and VC; but not with abnormal bone mineralization [10, 64–66]. To the best of our knowledge, no study has reported any association between MUO and VC, though. In fact, there is a lack of data supporting an association between this type of ROD and mortality.

Management

Considering that MUO is part of the spectrum of high turnover bone disease and the scarcity of studies in which the management of CKD-MBD was guided by the subtype of ROD, the current approach to treat MUO target the hyperparathyroidism state based on the PTH levels which, together with total or bone-specific alkaline phosphatases, has also been used as a surrogate marker of bone turnover [60]. It must be acknowledged that modest increases in PTH may represent an appropriate adaptive response to declining kidney function, due to phosphaturic effects and increasing bone resistance to PTH. Therefore, treatment should not be

Table 4 Available anti-MUO medications

Drug	Action
Calcium supplements	Used for maintaining normocalcemia in patients with symptomatic mild and/or asymptomatic moderate/severe hypocalcemia.
Ergocalciferol and cholecalciferol	Used in repleting vitamin D levels in patients with vitamin D deficiency (25 OH vitamin D < 20 ng/ml).
Calcitriol and synthetic vitamin D analogs (VDA)	Used in controlling hyperparathyroidism in patients to keep the iPTH 2-9 folds upper limit of normal levels.
Calcimimetics	They increase the sensitivity of the CaSR to calcium, so reducing plasma PTH to the same VDA target level (above).
Anti-osteoporotic drugs (bisphosphonates, denosumab, and SERM, teriparatide, abaloparatide, and romosozumab)	May help to prevent further bone loss and decrease fracture risk. The long-term efficacy and safety are not well-studied.

based on a single elevated PTH value, but on the levels of PTH progressively rising or persistently above the upper normal limit aiming to maintain its levels in CKD stage 5D patients, between 2 and 9 times above the normal range [67]. Additionally, it is critical to target mineral abnormalities and nutritional conditions that may lead to abnormal bone mineralization, such as hypophosphatemia, hypocalcemia, and hypovitaminosis D. In this regard, adequate nutritional intake, vitamin D analogs, and/or supplementation, in a case-by-case approach, have a pivotal role in the treatment of MUO. Anti-osteoporotic medications might help to prevent further bone loss and decrease fracture risk in patients with MUO. However, their long-term efficacy and safety are not well-studied. Table 4 shows the most common contemporary medications used in MUO management.

Conclusion

Despite MUO being a frequent bone pathology abnormality among patients with CKD, it is a poorly studied entity that needs special consideration to identify its consequences and precise management. The contemporary lack of non-invasive tools encourages healthcare providers to perform more bone biopsies to diagnose MUO.

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Declarations

Conflict of interest None.

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