Bone biopsy: an ally in the management of fragility fractures in chronic kidney disease

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ABSTRACT

Patients with chronic kidney disease (CKD) have an increased susceptibility to fracture and this risk gradually rises as renal disease progresses. Chronic kidney disease–mineral and bone disorder (CKD-MBD) encompasses the mineral, bone, hormonal and calcific cardiovascular abnormalities that develop in these patients. Renal osteodystrophy (ROD) corresponds to the histopathologic description of bone lesions associated with CKD-MBD. Fragility fracture approach in CKD stages 1-3a may be similar to that of the general population. However, in stages 3b–5, osteoporosis cannot be established by the World Health Organization (WHO) criteria based on bone mineral density (BMD) or the presence of fragility fractures, because low BMD and fractures can also occur in the different forms of ROD. The gold standard for the diagnosis and classification of ROD is tetracycline double-labelled transiliac bone biopsy, with bone histology and histomorphometric analysis. By informing on bone turnover, mineralization and volume, it is a valuable tool that may help guide the management of CKD patients with fragility fractures, as therapeutic measures are distinct depending if the patient has osteoporosis or one of the forms of ROD.

For patients with stages 1–3 CKD, without biochemical abnormalities suggestive of CKD-MBD, who sustained low-trauma fractures, any therapeutic approved for use in osteoporosis could be used. However, there is little evidence for the efficacy and safety of conventional anti-osteoporotic agents in patients with more advanced CKD stages, so currently the approach is opinion-based and must be patient-tailored depending on the presence or absence of ROD.

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INTRODUCTION

Chronic kidney disease (CKD) and fragility fractures are important public health concerns, both increasing as the population ages and co-occurring frequently. Fracture susceptibility and incidence are increased in CKD and this risk gradually rises as renal disease progresses[1,2]. Of note, morbidity and mortality associated with fractures are also higher in these patients[3,4].

The increased fracture risk in CKD is multifactorial. On one hand, CKD patients have impaired bone strength due to deterioration of both bone volume and bone quality (incorporating changes in turnover, mineralization, cortical porosity and trabecular bone architecture) that increase in severity as the disease progresses[5]. On the other hand, these patients are commonly elderly with multiple comorbidities, such as diabetes mellitus, also associated with increased fracture risk, along with sarcopenia and cognitive dysfunction leading to higher risk for falls[1,6]. In addition, previous fracture is a known risk factor for a subsequent one[7].

The management of a CKD patient with one or more fragility fractures is challenging, first due to the need to determine whether the patient has osteoporosis and/or the various forms of metabolic bone disease and secondly to choose the therapeutic approach. Herein the authors review the contribution of bone biopsy with histomorphometric analysis in the management of these patients.

OSTEOPOROSIS AND CKD–MINERAL AND BONE DISORDER (CKD-MBD)

Osteoporosis has been mechanistically defined as a metabolic skeletal disorder characterized by compro-

mised bone strength that predisposes to an increased risk of fracture, with bone strength being determined by both bone quantity and bone quality[8]. Bone quantity can be represented by bone mineral density (BMD), a surrogate measure of bone mass assessed by dual X-ray absorptiometry (DXA). Bone quality can be evaluated by bone biopsy and includes several variables such as microarchitecture, bone remodelling abnormalities, collagen content and structure, microdamage accumulation and mineralization properties[9].

The definition of osteoporosis established by World Health Organization (WHO) is based on a T score of -2.5 or less, in other words, a BMD measured by DXA that is 2.5 standard deviations (SD) or more below the mean for young healthy women[10].

The Disease Outcome Quality Initiative (KDOQI) of the National Kidney Foundation (NFK) has classified the categories of CKD according to the glomerular filtration rate (GFR) [11] as follows:
- Stage 1 - GFR 90 mL/minute/1.73 m^2 or higher;
- Stage 2 - GFR 60 to 89 mL/minute/1.73 m^2;
- Stage 3a - GFR 45 to 59 mL/minute/1.73 m^2;
- Stage 3b - 3B – 30 to 44 mL/minute/1.73 m^2;
- Stage 4 - GFR 15 to 29 mL/minute/1.73 m^2;
- Stage 5 - GFR lower than 15 mL/minute/1.73 m^2, or if the patient is on dialysis (in this latter case called 5D).

There is evidence that CKD is associated with low bone mass and accelerated bone loss as well as with decreased bone quality. Several studies have reported that kidney function is significantly associated with declines in BMD measured by DXA[12-14]. Nikolas et al[15] showed that CKD 2-5D patients have significant cortical bone loss, with lower BMD in total hip, ultradistal radius measured by DXA and significant declines in cortical area, density, and thickness and increased porosity evaluated by high-resolution peripheral quantitative computed tomography[14]. There are also studies showing a gradual increase in bone resorption associated with decreased bone formation and impairment in bone mineralization on histomorphometry, as CKD progresses[16-18].

Moreover, there are systemic bone and mineral metabolism disturbances that arise early in the course of CKD and increase in frequency and severity as the disease progresses, which are associated with significant morbidity (including cardiovascular events and fractures) and mortality[19]. In 2006, the Kidney Disease Improving Global Outcomes (KDIGO) Working Group classified these disorders as a single clinical designated CKD–mineral and bone disorder (CKD–MBD) manifested by either one or the combination of: laboratory abnormalities of bone and mineral metabolism, including altered calcium, phosphorus, parathyroid hormone (PTH), or vitamin D metabolism; abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and/or bone disease and vascular and other soft-tissue calcifications[19].

Renal osteodystrophy (ROD) corresponds to the morphological description of bone lesions occurring in the context of CKD-MDB assessed by histomorphometric analysis of bone biopsy[19].

According to the KDIGO Working Group, the WHO definition of osteoporosis can be applied for the diagnosis and management of stages 1 to 3a CKD, as long as there are no biochemical abnormalities suggesting CKD-MBD[20].

However, diagnosis of osteoporosis in stages 3b-5 CKD (or in earlier stages if CKD-MBD is suspected) is more complex and an exclusionary one[1]. In these stages, patients have significant alterations in mineral metabolism and the probability of having features of ROD is high[20]. These are associated with bone strength impairment and may lead to low BMD and/or fragility fractures. Thus, the WHO criteria are not valid in these situations[21].

The 2017 KDIGO clinical practice guidelines state that, in patients with CKD stage 3-5D, it is reasonable to perform a bone biopsy if knowledge of type of ROD will impact treatment decisions[22].

Indeed, in CKD patients with fragility fractures it is important to exclude ROD and, if present, discriminate between the different types (adynamic bone disease, hyperparathyroid bone disease, osteomalacia and mixed bone disease) because management is distinct in each condition.

Currently, biochemical markers and imagiological tests are not accurate predictors of bone histology[23-26]. Thus, the gold standard for the diagnosis and specific classification of renal osteodystrophy (ROD) remains the histomorphometric analysis of the bone biopsy[19].

BONE BIOPSY AND HISTOMORPHOMETRY

Bone histomorphometry provides qualitative and quantitative information on bone structure, bone remodelling and turnover in histological sections of mineralized (undecalcified) bone [27]. It enables the understanding of metabolic bone diseases'

physiopathology and evaluation of the effects of specific drugs on bone tissue[27]. Transiliac bone biopsy is a well-tolerated procedure associated with very low morbidity and no mortality[17,28]. Bone histomorphometry is classically performed on trabecular bone. However, it should be noted that cortical bone quality is also an important factor, and cortical abnormalities take place in CKD patients, such as increased porosity and reduced thickness, so recent studies have focused in cortical bone analysis[5,23].

Several static and dynamic parameters are evaluated. Static histomorphometric measurements include osteoid thickness, osteoid surface, osteoblast surface and osteoclast surface. Conversely, bone formation rate, bone activation frequency, osteoid maturation time and mineralization lag time are dynamic measurements[23,27,29].

To obtain information about dynamic parameters such as bone formation rate and mineralization state, double tetracycline labelling of the bone surface with fluorochrome compounds such as demeclocycline or tetracycline (the latter being the only available in Portugal) needs to be performed prior to the bone biopsy procedure[17]. Tetracycline naturally fluoresces, which enables its visualization under a fluorescent microscope, and characteristically attaches to calcium, being co-deposited on active mineralization sites [27]. The distance between labels corresponds to the new bone formed during the interval of tetracycline administration[23]. The usual schedule consists of two dosing periods, 3 days on (e.g. 500 mg tetracycline BID), 10 days off, and 3 days on (e.g. 500 mg tetracycline BID), after which the biopsy is performed within the next 4 to 14 days[17].

After the biopsy procedure, the sample is submitted to a complex process including fixation, dehydratation, and embedding in methylmethacrylate to make the distinction between calcified and uncalcified bone, and to allow the study of the mineralization process. Subsequently the sample is cut in a microtome, with tungsten knives and stained, more frequently with Goldner trichrome technique or toluidine blue[27,29]. Afterwards, the bone slides are visualized in a microscope equipped with a camera and bone histomorphometric measurements are obtained numerically by using one of several commercialized computerized image analysis systems[27,29].

Histologic abnormalities observed in CKD-MBD are heterogeneous and may vary in the same patient along with the progression of CKD[17,24,26]. In order to standardize biopsy reports and allow comparison between studies, "TMV" classification system, which comprises bone turnover (T), mineralization (M) and volume (V), is used[19].

Turnover is a representative measure of bone remodelling, which can vary from low to very high in CKD patients. In this regard, the most important dynamic parameter to evaluate is bone formation rate, however other dynamic measurements – such as bone activation frequency, which corresponds to the probability that a new remodelling cycle will be initiated at any point on the bone surface - and static ones – namely osteoblast and osteoclast surface and number, osteoid and erosion surfaces - can help to define turnover[23].

Mineralization can be normal or abnormal (delayed or disorganized). It is classified based also on dynamic parameters as mineralization lag time and osteoid maturation time, and static parameters including osteoid thickness[23].

Volume can be low, normal or high across the different ROD categories and, although it has not been previously considered in their definition, its importance in the pathophysiology of fragility fractures in CKD has been recognized[30]. Bone volume is related to bone strength and is also usually associated to the severity and duration of CKD-MBD[23]. Accordingly, it has been demonstrated that patients with low bone volume have an increased fracture risk[23].

Based on TMV classification, ROD is classified into different histopathological patterns: hyperparathyroid bone disease, mixed bone disease, osteomalacia and adynamic bone (Table I).

High-turnover disease encompasses the spectrum of hyperparathyroid bone disease (from mild hyperparathyroid-related bone disease to osteitis fibrosa) and mixed uremic bone disease. The first one is attributable to secondary hyperparathyroidism and is characterized by an increased bone formation rate, a high number of osteoclasts and osteoblasts, an increased number of resorption lacunae and increased amount of osteoid albeit with normal mineralization (Figure 1). In severe forms there can also occur marrow fibrosis (osteitis fibrosa)[17]. Mixed uremic bone disease combines increased bone remodelling and abnormal mineralization with low to normal volume (Figure 2)[17,31].

Low-turnover disease includes osteomalacia and adynamic bone disease. Osteomalacia was formerly associated with aluminum toxicity and common in dialysis patients, but its incidence has significantly decreased

TABLE I. HISTOMORPHOMETRIC FINDINGS IN DIFFERENT METABOLIC BONE DISEASES

Bone disease	Turnover	Mineralization	Volume
Renal osteodystrophy			
Osteomalacia	Low	Abnormal	Low to normal
Adynamic bone disease	Low	Normal/Abnormal	Low to normal
Hyperparathyroid bone disease	High	Normal	Low, normal or high
Mixed uremic osteodystrophy	Normal to high	Abnormal	Low to normal
Osteoporosis	Low, normal, or high	Normal	Low

and nowadays is rarely seen[32]. Other potential etiologies of osteomalacia can also occur in CKD patients, including 25-hydroxyvitamin D deficiency, metabolic acidosis and hypophosphatemia[17]. It is characterized by increased osteoid volume and thickness, increased osteoid maturation time, longer mineralization lag time and low to medium bone volume (Figure 3).

In adynamic bone disease the main findings include the absence or reduced number of osteoclasts and osteoblasts, markedly reduce bone formation rate and activation frequency, along with normal to decreased amount of osteoid, normal mineralization and low or normal volume (Figure 4)[17]. This may be the result of a relative hypoparathyroidism caused by an overtreatment of hyperparathyroidism with vitamin D and calcium supplementation and/or calcimimetics[17]. Its prevalence is steadily increasing, especially in patients on peritoneal dialysis[23,32,33]. Other risk factors comprise advanced age, corticosteroid use and *diabetes mellitus* [32].

In spite of being a valuable tool, bone biopsy is underused due to a variety of factors: invasiveness of the procedure, the lack of technical training, the limited number of specialized centres with expertise to interpret and process bone samples and costs[17]. Moreover, the clinical relevance of the information provided by bone biopsy in this context is underestimated by most of practising physicians.

MANAGEMENT IMPLICATIONS FROM BONE BIOPSY RESULT

The KDIGO working group recommends to treat osteoporosis in patients with stages 1-3a CKD as the general population, as long as there are no accompanying biochemical abnormalities indicative of the presence of CKD-MBD, since there is evidence from clinical trials that included patients with similar renal impair-
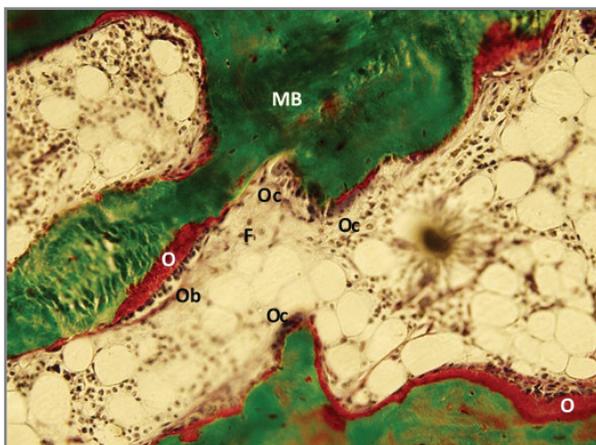

FIGURE 1. Iliac crest biopsy histology with goldner staining. showing hyperparathyroid-related bone disease. (F: fibrosis; MB: mineralized bone; O: osteoid; Ob: osteoblasts; Oc: osteoclasts)
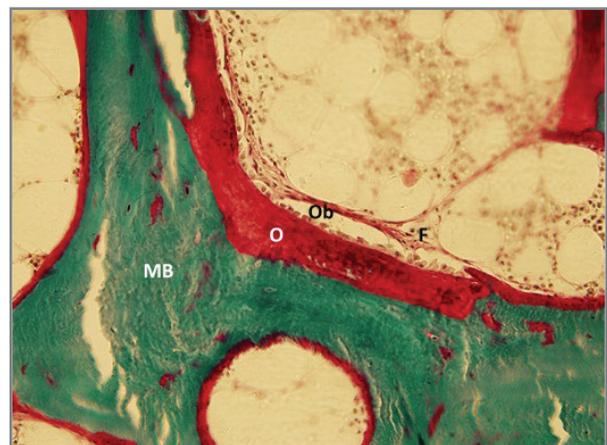

FIGURE 2. Mixed uremic bone disease with an increased extent and thickness of osteoid seams, activated osteoblasts and fibrosis (F: fibrosis; MB: mineralized bone; O: osteoid; Ob: osteoblasts)
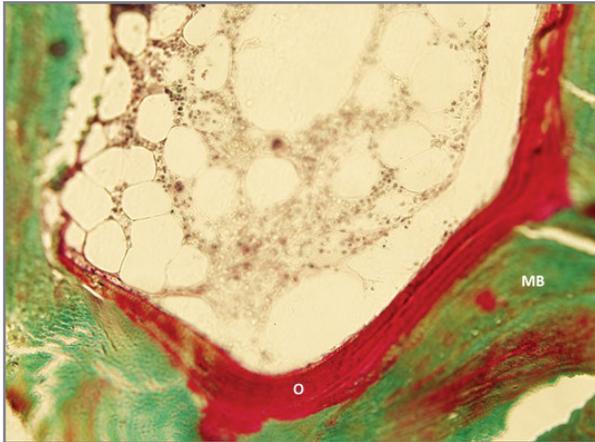
FIGURE 3. Osteomalacia showing increased extent and thickness of osteoid seams, without active bone cells (MB: mineralized bone; O: osteoid)

FIGURE 4. Adynamic bone disease showing marked reduction of bone volume and trabecular connectivity and absence of osteoid. (T: trabeculae)

ment, that efficacy and safety of anti-osteoporotic therapies are similar in both groups[22,34].

However, establishing the best therapeutic strategy in patients with severe CKD (stages 3b-5) or with CKD-MBD, who have sustained a low-trauma fracture, is more difficult[34-36].

In first place, it is essential to make the correct diagnosis and distinguish between the various forms of ROD and osteoporosis, especially if the physician is considering using anti-osteoporotic pharmacologic agents designed to improve bone strength and reduce the risk of fracture.

Nonetheless, there is an impressive lack of evidence for the efficacy and safety of these therapeutic agents in patients with more advanced CKD stages, which are the ones who present ROD more frequently.

Although available data shows a reduction in the rate of hip fractures and stabilization and even a slight de-
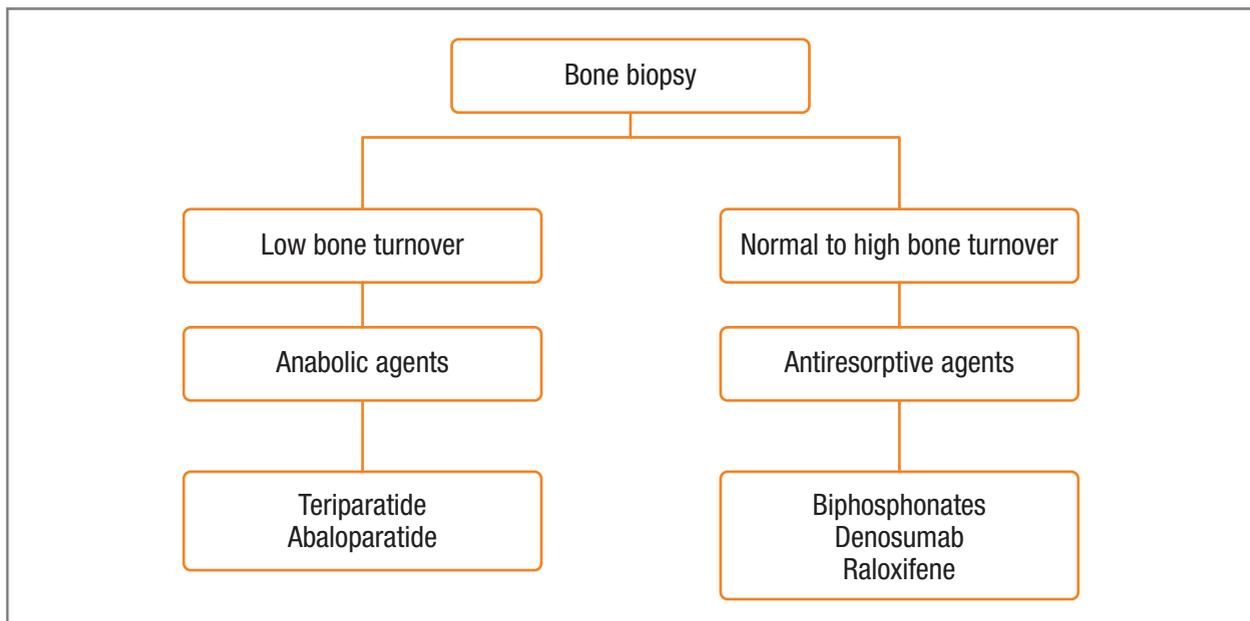

FIGURE 5. A conceptual model for selection of anti-fracture treatment based on bone biopsy histomorphometry. Drugs are mentioned as examples for each mode of action.

crease in the rate of hip and vertebral fractures between 2004 and, respectively, 2010 and 2009[37,38], in hemodialysis patients, the risk of fracture is still very high in this group of patients: 4–13 times higher in dialysis patients compared to the general population[6]. This suggests that these patients have unmet needs in relation to bone disease.

Overall treatment decisions should be guided by the presence of fractures and results from BMD as measured by DXA, and ideally the choice of agent should be based on transiliac bone biopsy (Figure 5)[34,35].

It should be highlighted that before initiating any antifracture therapy, CKD-MBD should be managed as recommended[22], and nonpharmacologic measures should be implemented in all patients, including adequate nutrition and sun exposure, fall prevention, regular weight-bearing exercise, avoidance of excessive alcohol intake and smoking cessation[39].

LOW BONE TURNOVER

As previously stated, low bone turnover states, namely adynamic bone disease, are steadily increasing[33]. Although there are no objective data to confirm it, administering an antiresorptive therapy in these context would, in theory, be harmful and deteriorate bone quality[21,35].

Conceptually, anabolic agents, such as teriparatide, a recombinant form of PTH could have a beneficial effect and improve bone remodelling in patients with low turnover bone disease[32,40]. However, the use of teriparatide is limited to up to 24 months and should be followed by the prescription of an antiresorptive, but that the latter will be contraindicated in the patient with low turnover bone disease, which renders teriparatide use difficult and perhaps explains the absence of enthusiasm for this drug in this context. Also the evidence supporting teriparatide use in patients with CKD 3-5D is anedoctal and comes from case reports and small observational studies[41-43]. Palcu et al. [41] reported a case of a patient under dialysis with multiple fractures and low turnover bone disease on biopsy that was treated with teriparatide 20 g/day for 24 months, with resolution of pain, increased BMD in femoral neck and total hip and improvements in histomorphometric parameters.

Cejka et al. administered teriparatide 20 g/day for 6 months to 7 patients with on haemodialysis with biopsy-proven adynamic bone disease, and showed a significant increase in lumbar BMD in 6 of the 7 patients[42]. In another study, lumbar spine BMD also increased after teriparatide was administered once weekly to patients on dialysis with hypoparathyroidism and a T score <-2.5 at the spine, hip, or forearm or a T score between -2.5 and -1.0 with a prevalent fragility fracture[43].

It is important to highlight that all but one of the cases included in the cited studies [41-43] were associated with true hypoparathyroidism, as well as the exception related to functional hypoparathyroidism.

Nevertheless, teriparatide effect on fractures is unknown. Regarding safety, patients may be more prone to hypercalcemia and cardiovascular security has not been evaluated[36,39].

Abaloparatide, an analogue of PTH-related peptide, is another promising osteoanabolic agent, with less risk of hypercalcemia. However, is has not been studied in patients with CKD-MBD[39].

NORMAL TO HIGH TURNOVER

On the other hand, the presence of normal to high bone turnover on bone biopsy would support treatment with an antiresorptive agent [32,40].

Bisphosphonates, which are the most commonly used antiresorptive drugs, have a high affinity for bone hydroxyapatite, and persist in the skeleton for many years. As their clearance depends on renal excretion, excessive accumulation of the drug in the skeleton in CKD is a particular concern[44]. There is limited data on bisphosphonates effects on BMD, fractures and safety in CKD 3-5D[36]. A randomized trial in stage 3–4 CKD comparing 18 months of alendronate 70 mg/week with placebo reported an increase in lumbar spine T-score[45]. However, this was a small study with 51 patients in which the primary endpoint was the effect of alendronate on vascular calcification, with BMD evaluated as secondary endpoint. Also, patients with creatinine clearance <25mL/min were excluded, resulting that mean GFR in the patients included was 35.1mL//min/1.73m^2. Thus, the population would be mostly in CKD stage 3. It is also important to remember that the observed effect on spine BMD as measured by anteroposterior DXA could potentially be affected by the presence of extensive abdominal aortic calcifications common in these patients[45]. Considering a dose reduction by 50% and shorter duration of treatment (2--3 years) has been recommended when administering

these drugs[34,35].

Denosumab, the monoclonal antibody against receptor activator of NF- B ligand (RANK-L), also inhibits osteoclast activity and proliferation, but has the advantage of not having GFR restrictions as it is not cleared by the kidney[44]. In small open-label uncontrolled pilot study, 12 patients on haemodialysis associated with severe secondary hyperparathyroidism (iPTH > 1000pg/mL) and low BMD (T-score < –1.0) received a single 60 mg subcutaneous dose of denosumab and after 6 months both lumbar spine and femoral neck BMD significantly increased [46]. Jamal et al. [47] showed that 73 and 2817 women in the FREEDOM Trial were in CKD stage 4 and 3, respectively. There was no interaction between treatment effect and kidney function, and adverse events did not differ by CKD stage. Denosumab increased BMD at the spine and hip and resulted in lower incidence of vertebral fractures in all patients except for CKD 4. Moreover, the incidence of nonvertebral fractures was lower among those randomized to denosumab compared with placebo but was not statistically significant for stages 3 and 4 CKD. It should be noted that the number of patients with CKD 4 was limited and there were no patients with stage 5.

There are some safety concerns with denosumab. The risk of hypocalcaemia, which can be more severe and prolonged, seems to be higher[36]. Therefore, prior to its administration, these patients must be supplemented with vitamin D, have adequate calcium intake and during treatment serum calcium levels must be carefully monitored[39]. It appears that infections and diarrhoea are also more common in these patients[36].

Raloxifene, a selective oestrogen receptor modulator with antiresorptive action, has been studied in postmenopausal women with varying degrees of CKD severity, including stage 5D[48-50]. One study[48], which was a subgroup analysis of a randomized, controlled trial, reported a significantly higher annualized percentage change in femoral neck BMD in the raloxifene group than in the placebo group. However, the other 2 studies did not report any statistically significant differences in femoral neck BMD absolute scores, T-scores, or Z scores [49,50]. One study compared raloxifene with placebo and reported reduced risk of vertebral fractures in postmenopausal women[48]. However this effect was only statistically significant for patients with GFR > 45 mL/min/1.73m².

None of these studies reported statistically significant differences between raloxifene and placebo in lumbar spine BMD, or incident nonvertebral fractures.

Regarding safety, there is the special concern of increased risk for venous thrombosis when using this drug [51].

CONCLUSION

CKD patients are particularly prone to fragility fractures, not only in the context of osteoporosis, whose diagnosis represents a true challenge in advanced stages, but also due to the presence of ROD. Tetracycline double-labelled transiliac bone biopsy with quantitative histomorphometric analysis is currently the only tool to differentiate between the various forms of ROD and to establish the diagnosis of osteoporosis, often by exclusion.

Although it has been recognized that management of patients with stages 1-3a CKD with fragility fractures can be similar to that of the general population, in more advanced CKD a bone biopsy should be considered prior to initiating treatment, in order to accurately recognize the type of bone disease present.

Additionally, there is little evidence to guide anti-fracture treatment in these patients, as this drugs have not been developed or conveniently studied in CKD-MBD, so there is an urgent need for further research in this area.

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REFERENCES
1. Pimentel A, Urena-Torres P, Zillikens MC, Bover J, Cohen-Solal M. Fractures in patients with CKD-diagnosis, treatment, and prevention: a review by members of the European Calcified Tissue Society and the European Renal Association of Nephrology Dialysis and Transplantation. Kidney Int 2017;92(6):1343--1355.
2. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, et al. Increased risk of hip fracture among patients with end-stage renal disease. Kidney Int 2000;58(1):396-399.
3. Kim SM, Long J, Montez-Rath M, Leonard M, Chertow GM. Hip Fracture in Patients With Non-Dialysis-Requiring Chronic Kidney Disease. J Bone Miner Res 2016;31(10):1803-1809.
4. Wakasugi M, Kazama JJ, Narita I. High rates of death and hospitalization follow bone fracture among hemodialysis patients. Kidney Int 2014;86(3):649.
5. Diamond T, Elder GJ. Is there a practical role for bone biopsy in chronic kidney disease? Nephrology (Carlton) 2017;22 Suppl 2:22-26.
6. Kazama JJ. Chronic kidney disease and fragility fracture. Clin

Exp Nephrol 2017;21(Suppl 1):46-52.

7. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone 2004;35(2):375-382.

8. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, March 7-29, 2000: highlights of the conference. South Med J 2001;94(6):569-573.

9. Babayev R, Nickolas TL. Bone Disorders in Chronic Kidney Disease: An Update in Diagnosis and Management. Semin Dial 2015;28(6):645-653.

10. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. Osteoporos Int 1994;4(6):368-381.

11. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1-266.

12. Ishani A, Paudel M, Taylor BC, Barrett-Connor E, Jamal S, Canales M, et al. Renal function and rate of hip bone loss in older men: the Osteoporotic Fractures in Men Study. Osteoporos Int 2008;19(11):1549-1556.

13. Jassal SK, von Muhlen D, Barrett-Connor E. Measures of renal function, BMD, bone loss, and osteoporotic fracture in older adults: the Rancho Bernardo study. J Bone Miner Res 2007;22 (2):203-210.

14. Fried LF, Shlipak MG, Stehman-Breen C, Mittalhenkle A, Seliger S, Sarnak M, et al. Kidney function predicts the rate of bone loss in older individuals: the Cardiovascular Health Study. J Gerontol A Biol Sci Med Sci 2006;61(7):743-748.

15. Nickolas TL, Stein EM, Dworakowski E, Nishiyama KK, Komandah-Kosseh M, Zhang CA, et al. Rapid cortical bone loss in patients with chronic kidney disease. J Bone Miner Res 2013;28(8):1811-1820.

16. Zheng CM, Zheng JQ, Wu CC, Lu CL, Shyu JF, Yung-Ho H, et al. Bone loss in chronic kidney disease: Quantity or quality? Bone 2016;87:57-70.

17. Evenepoel P, Behets GJS, Laurent MR, D'Haese PC. Update on the role of bone biopsy in the management of patients with CKD-MBD. J Nephrol 2017;30(5):645-652.

18. Graciolli FG, Neves KR, Barreto F, Barreto DV, Dos Reis LM, Canziani ME, et al. The complexity of chronic kidney disease-mineral and bone disorder across stages of chronic kidney disease. Kidney Int 2017;91(6):1436-1446.

19. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006;69(11):1945-1953.

20. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2009(113):S1-130.

21. Miller PD. Bone disease in CKD: a focus on osteoporosis diagnosis and management. Am J Kidney Dis 2014;64(2):290-304.

22. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. Kidney Int 2017;92(1):26-36.

23. Carvalho C, Alves CM, Frazao JM. The role of bone biopsy for the diagnosis of renal osteodystrophy: a short overview and future perspectives. J Nephrol 2016;29(5):617-626.

24. Sprague SM, Bellorin-Font E, Jorgetti V, Carvalho AB, Malluche HH, Ferreira A, et al. Diagnostic Accuracy of Bone Turnover Markers and Bone Histology in Patients With CKD Treated by Dialysis. Am J Kidney Dis 2016;67(4):559-566.

25. Evenepoel P, Bover J, Urena Torres P. Parathyroid hormone metabolism and signaling in health and chronic kidney disease. Kidney Int 2016;90(6):1184-1190.

26. Gal-Moscovici A, Sprague SM. Role of bone biopsy in stages 3 to 4 chronic kidney disease. Clin J Am Soc Nephrol 2008;3 Suppl 3:S170-174.

27. Vidal B, Pinto A, Galvao MJ, Santos AR, Rodrigues A, Cascao R, et al. Bone histomorphometry revisited. Acta Reumatol Port 2012;37(4):294-300.

28. Trueba D, Sawaya BP, Mawad H, Malluche HH. Bone biopsy: indications, techniques, and complications. Semin Dial 2003;16(4):341-345.

29. Torres PU, Bover J, Mazzaferro S, de Vernejoul MC, Cohen-Solal M. When, how, and why a bone biopsy should be performed in patients with chronic kidney disease. Semin Nephrol 2014;34(6):612-625.

30. Ott SM. Renal Osteodystrophy-Time for Common Nomenclature. Curr Osteoporos Rep 2017;15(3):187-93.

31. Kulak CA, Dempster DW. Bone histomorphometry: a concise review for endocrinologists and clinicians. Arq Bras Endocrinol Metabol 2010;54(2):87-98.

32. Brandenburg VM, Floege J. Adynamic bone disease-bone and beyond. NDT Plus 2008;1(3):135-147.

33. Malluche HH, Mawad HW, Monier-Faugere MC. Renal osteodystrophy in the first decade of the new millennium: analysis of 630 bone biopsies in black and white patients. J Bone Miner Res 2011;26(6):1368-1376.

34. Miller PD. Fragility fractures in chronic kidney disease: an opinion-based approach. Cleve Clin J Med 2009;76(12):715-723.

35. West SL, Patel P, Jamal SA. How to predict and treat increased fracture risk in chronic kidney disease. J Intern Med 2015;278 (1):19-28.

36. Wilson LM, Rebholz CM, Jirru E, Liu MC, Zhang A, Gayleard J, et al. Benefits and Harms of Osteoporosis Medications in Patients With Chronic Kidney Disease: A Systematic Review and Meta-analysis. Ann Intern Med 2017;166(9):649-658.

37. Arneson TJ, Li S, Liu J, Kilpatrick RD, Newsome BB, St Peter WL. Trends in hip fracture rates in US hemodialysis patients, 1993-2010. Am J Kidney Dis 2013;62(4):747-754.

38. Wagner J, Jhaveri KD, Rosen L, Sunday S, Mathew AT, Fishbane S. Increased bone fractures among elderly United States hemodialysis patients. Nephrol Dial Transplant 2014;29(1):146-151.

39. Khairallah P, Nickolas TL. Management of Osteoporosis in CKD. Clin J Am Soc Nephrol 2018.

40. Cejka D, Haas M. Should teriparatide ever be used for adynamic bone disease? Semin Dial 2011;24(4):431-433.

41. Palcu P, Dion N, Ste-Marie LG, Goltzman D, Radziunas I, Miller PD, et al. Teriparatide and bone turnover and formation in a hemodialysis patient with low-turnover bone disease: a case report. Am J Kidney Dis 2015;65(6):933-936.

42. Cejka D, Kodras K, Bader T, Haas M. Treatment of Hemodialysis-Associated Adynamic Bone Disease with Teriparatide (PTH1--34): A Pilot Study. Kidney Blood Press Res 2010;33(3):221--226.

43. Sumida K, Ubara Y, Hoshino J, Mise K, Hayami N, Suwabe T, et al. Once-weekly teriparatide in hemodialysis patients with

hypoparathyroidism and low bone mass: a prospective study. Osteoporos Int 2016;27(4):1441-1450.

44. Khairallah P, Nickolas TL. Management of Osteoporosis in CKD. Clin J Am Soc Nephrol 2018;13(6):962-969.

45. Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG. Effect of alendronate on vascular calcification in CKD stages 3 and 4: a pilot randomized controlled trial. Am J Kidney Dis 2010;56(1):57-68.

46. Chen CL, Chen NC, Hsu CY, Chou KJ, Lee PT, Fang HC, et al. An open-label, prospective pilot clinical study of denosumab for severe hyperparathyroidism in patients with low bone mass undergoing dialysis. J Clin Endocrinol Metab 2014;99(7):2426--2432.

47. Jamal SA, Ljunggren O, Stehman-Breen C, Cummings SR, Mc-Clung MR, Goemaere S, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. J Bone Miner Res 2011;26(8):1829-1835.

48. Ishani A, Blackwell T, Jamal SA, Cummings SR, Ensrud KE. The effect of raloxifene treatment in postmenopausal women with CKD. J Am Soc Nephrol 2008;19(7):1430-1438.

49. Haghverdi F, Farbodara T, Mortaji S, Soltani P, Saidi N. Effect of raloxifene on parathyroid hormone in osteopenic and osteo-porotic postmenopausal women with chronic kidney disease stage 5. Iran J Kidney Dis 2014;8(6):461-466.

50. Hernandez E, Valera R, Alonzo E, Bajares-Lilue M, Carlini R, Capriles F, et al. Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. Kidney Int 2003;63(6):2269-2274.

51. Adomaityte J, Farooq M, Qayyum R. Effect of raloxifene therapy on venous thromboembolism in postmenopausal women. A meta-analysis. Thromb Haemost 2008;99(2):338-342.