REVIEW ARTICLE

Port J Nephrol Hypert 2018; 32(2): 159-164 • Advance Access publication 22 June 2018

The role of bone biopsy in the management of patients with CKD - MBD

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Received for publication: Nov 21, 2017
Accepted in revised form: May 30, 2018

ABSTRACT

The gold standard for diagnosis and classification of bone disorders is the transiliac crest bone biopsy. This is a well-tolerated invasive technique, with few complications and is the only accurate method to assess bone metabolism and to evaluate treatment effects. This article will discuss the current role of bone biopsy in the assessment and management of renal osteodystrophy.

Keywords:

INTRODUCTION

Chronic kidney Disease-Mineral and Bone Disorder (CKD-MBD) characterizes a syndrome occurring in CKD patients involving disturbances in mineral and bone metabolism, which are often accompanied by vascular and tissue calcifications[1]. This entity is related to poor outcomes in the CKD population and proper recognition and management is fundamental. Increased fracture risk and cardiovascular mortality are two main issues contributing to a high morbidity and mortality in these patients[1-3]. The ideal assessment and management of CKD-MBD is not completely clarified[4]. Issues related with phenotype variations along the spectrum of CKD (including dialysis and transplantation) are not well established. The CKD patient is often elderly, with multiple comorbidities, and especially endocrine and rheumatoid disorders can have a profound impact in the skeleton and so the drugs used to treat them[5]. In this review, we will focus on bone and mineral metabolism and will discuss the role of bone biopsy in renal osteodystrophy.

RENAL OSTEODYSTROPHY

The term Renal Osteodystrophy (ROD) was used to denominate bone disease related to CKD and has been limited to histological analysis, implying the use of bone biopsy. There are four major types of bone disease that occurs in CKD: hyperparathyroid-mediated high turnover bone disease (traditionally called renal osteitis fibrosa cystica), osteomalacia, mixed uremic osteodystrophy and adynamic bone disease[1,4]. Each of these forms is associated with typical histological findings and only can be accurately distinguished by histomorphometric and imunohistoquimic analysis of bone tissue. Current classification is based on "TMV" system (turnover, mineralization, and volume). As CKD progresses, a

reduction in bone volume frequently occurs and bone turnover (high in hyperparathyroidism and mixed disease and low in adynamic bone disease and osteomalacia) and mineralization rate (prolonged in osteomalacia and mixed disease) are also typically affected[6]. ROD may result in fractures, bone pain, deformities in growing children, reduced growth velocity/peak bone mass and abnormal height. In addition, it has indirect effects on vascular calcification and increased mortality[7]. New evidence suggests that the bone acts as an endocrine organ that also plays a role in cardiovascular complications and metabolic abnormalities occurring along the progression of CKD[8]. A group of bone-derived substances have been implicated, particularly Fibroblast Growth Factor 23 (FGF23), osteocalcin, bone morphogenetic proteins and Wnt inhibitors such as sclerostin and Dickkopf-related protein 1 (Dkk1)[9,10].

FGF23 is a major bone-derived phosphatonin secreted by osteocytes, which along with its co-receptor Klotho, regulates phosphate homeostasis through inhibition of renal phosphate reabsorption, vitamin D activation and PTH secretion. FGF23 levels rises very early in CKD, driven by a positive phosphate balance, and increases as CKD progresses. Gradual loss of Klotho expression also parallels CKD progression, which contributes to resistance to FGF23 actions, further promoting its synthesis. FGF23 is an important regulator of bone metabolism. High levels have been associated with reduced osteoid thickness and mineralization, through inhibition of tissue alkaline phosphatase activity, increased pyrophosphate levels, reduced inorganic phosphate levels and expression of osteopontin, a known mineralization inhibitor[11]. Bone loss also occurs through a klotho-dependent mechanism and via stimulation of the osteoblast Wnt inhibitor Dkk1[10]. Several studies have supported an additional role in vascular calcification and myocardial hypertrophy, with important implications in cardiovascular mortality in CKD[9-11]. In future, it is possible that FGF23 levels will be used as an earlier and more accurate marker of CKD-MBD and cardiovascular risk, enabling new treatment strategies[11].

Wnt signaling is fundamental for bone cellular activities and mineralization processes, such as bone repair in fractures[9-11]. Wnt inhibitors are secreted by osteoblasts and osteocytes and their synthesis is stimulated in CKD. They act in a paracrine/autocrine way but can also behave like hormones, with systemic effects. The most studied are sclerostin and Dkk1, that can already be measured in blood[9]. Overexpression of these inhibitors promotes bone sclerosis and reduced bone formation rate mainly through downregulation of Wnt/b-catenin pathway, decreasing osteoblast function. PTH actions in bone are inversely related with sclerostin activity and this can be particularly relevant in Adynamic Bone Disease[9]. Sclerostin expression also has been shown in calcified valves, vascular smooth muscle cells and calcified tissue in calciphylaxis, possibly reflecting a key role of Wnt signaling in vascular atherosclerosis and arteriosclerosis[9].

Osteocalcin is a calcium-binding bone-matrix protein secreted by osteoblasts in response to vitamin D and PTH stimulation. It's one of the most abundant proteins in bone and regulates mineralization and bone remodeling, though feedback modulation of osteoblasts and also osteoclasts in a vitamin-K dependent way. The abnormal metabolism of vitamins D and K in CKD relates with disturbances in osteocalcin secretion and function, with implication in bone turnover and mineralization[9].

Bone morphogenetic proteins (BMPs) are not exclusively produced by bone and many have clinical implications in several disorders, including vascular calcification, obesity, diabetes and cancer. BMP 2 is an important induction factor of calcification (particularly vascular calcification) and its levels are increased in inflammatory conditions such as CKD. BMP7 acts like a calcification inhibitor, possibly implicated in bone disease in CKD[9].

THE ROLE OF BONE BIOPSY

The gold standard for diagnosis and classification of bone disorders is the transiliac crest bone biopsy, performed after tetracycline labeling[4,6]. Biomarkers and imaging techniques lack sensitivity and specificity and bone biopsy remains the only currently available tool to evaluate bone pathology and different effects of therapies[4,7,13-16]. The EU-ROD Initiative was recently created under the ERA-EDTA CKD-MBD working group to revitalize this procedure as a useful tool for CKD-MBD workup and to facilitate research[7]. Bone biopsy is an invasive technique, usually performed in the iliac crest (either the left or right) because it is easily accessible, has fewer complications and allows to obtain cortical and trabecular bone samples[12]. The procedure, despite being safe and well-tolerated, is globally underused because of the lack of specialized centers with training and expertise to interpret bone samples[13]. The total incidence of complications reported from more than 9,000 bone biopsies was only 0.6% and pain was the most feared complication that occurred only in 0.2% of patients, significantly ameliorated by previous sedation[14]. Histomorphometric measurements of bone

TMV can be determined using static and dynamic parameters[12,13]. Main structural parameters are trabecular bone volume, cellular elements (osteoblasts and osteoclasts) and fibrosis. Main dynamic parameters are bone formation rate, osteoid maturation time and mineralization lag time[13]. Tetracycline labeling before biopsy allows the assessment of the dynamic aspects of bone turnover, including bone formation rates and mineralization defects[13]. Usually, tetracyclines at low dose are given twice for 3 day periods, separated by 10 to 20 days (normally 20 days) and the bone biopsy must be performed after 5 days since the last pill. Tetracyclines chelate calcium on bone surfaces and are deposited within the bone at sites of active mineralization[13,15]. They have intrinsic fluorescent properties and a double-labeling contour can be seen at fluorescence light circumscribing the new bone formed during the labeling interval, reflecting bone formation rate[13,15]. Bone remodeling rate can be estimated with activation frequency, which represents the number of times per year that a new remodeling cycle is initiated at any point on the bone surface and can be calculated dividing the bone formation rate per bone surface (BFR/BS)[13]. Other elements such as osteoid and erosion surfaces, number of osteoblasts and osteoclasts and presence of fibrosis contributes to classify turnover[13]. Mineralization is measured by mineralization lag time or osteoid maturation time, both related with osteoid width and distance between tetracycline labels[13]. Bone volume can be assessed by cortical and trabecular bone thickness and is associated with severity and duration of disease process[13]. Recently, studies in the field of osteoporosis and CKD-MBD are changing the focus from trabecular to cortical bone (about 80% of fractures occur at sites with large amounts of cortical bone, such as vertebra) which can have important therapeutic implications in CKD-MBD[11,13,16].

In the 2009 KDIGO guidelines, bone biopsy was suggested in patients with CKD stages 3 to 5 in several settings, including unexplained fractures, persistent bone pain, unexplained hypercalcemia or hypophosphatemia, possible aluminum toxicity and when considering therapy with antiresorptive agents. In a recent survey analyzing bone biopsy patterns across Europe[7], the majority of nephrologists (≥ 50%) agreed on the following indications: low-impact fracture, unexplained bone pain, prior to parathyroidectomy (to confirm high bone turnover) or initiation of antiresorptive drugs (to exclude low bone turnover), unexplained hypercalcemia or radiologic abnormalities, suspected or proven overload or toxicity to heavy or rare metals and a discordance between parathyroid hormone (PTH) and alkaline phosphatase. Most considered a stand-alone PTH outside the KDIGO target range or before initiating PTH suppressive therapy insufficient indication to proceed with a bone biopsy. The new 2017 KDIGO guidelines[4] also consider valid to perform this technique when there is suspicion of oteomalacia, an atypical response to standard therapies for elevated PTH or progressive decreases in bone mass density despite standard therapy. They also add "if knowledge of the type of CKD-MBD will impact treatment decisions (not graded)" and "the magnitude of the abnormality, its reversibility and CKD progression should also be considered (2D)". In sum, bone biopsy should be considered if the etiology of clinical symptoms and/or biochemical abnormalities is not clarified and when biopsy results may conduct to changes in attitudes or therapy.

■ The Spectrum of ROD with progression of CKD

Although high-turnover and mixed disease were the predominant forms of ROD in the 1960s and early 1970s, the pattern changed dramatically in the 1980s because of aluminum toxicity derived from water contamination used for hemodialysis and oral intake of high amounts of aluminum-containing phosphate binders[8]. Osteomalacia and adynamic bone disease progressively became more frequent, often accompanied by encephalopathy and microcytic anemia[18]. Also, the increasing use of active vitamin D analogues in subsequent years has contributed to change patterns. Better dialysis and water purification and the switch from aluminum to calcium-based phosphate binders rapidly reduced the incidence of these "iatrogenic" diseases[8].

The majority of ROD studies have been carried out in ESKD patients over the latest two decades,, implying long-term exposure to the uremic milieu, multiple therapeutic drugs and dialysis[15]. Cumulative evidence seems to suggest that adynamic bone disease is the predominant bone pattern, especially in early stages of chronic kidney disease and even in patients who have not been exposed to therapy like phosphate binders or vitamin D[19]. In renal transplant patients, the prevalence of low–turnover disease and low bone volume is very high. In following section, we will present a synthesis of major evidence regarding renal osteodystrophy in the different stages of CKD.

■ Pre-Dialysis Stage

Knowledge of the development and progression of renal bone disease across CKD stages 3-5 before dialysis is relatively scarce. One of the first studies was

performed in 1976, with histomorphometric analysis of 50 bone biopsies from German patients with CKD stages 2 to 5[21]. The results were inconclusive but suggested that mineralization defects and possibly low bone turnover may precede high turnover disease. A bigger study in 1983, with 327 bone biopsies from pre-dialysis patients, also showed a high percentage of cases with osteomalacia (34%), not associated with 25 – OH – vitamin D levels[22]. In 1996, Coen et al.[23] performed a cross-sectional retrospective study on 76 pre-dialysis patients that had never received steroids, native vitamin D, calcitriol or aluminum-containing phosphate binders. Mixed uremic osteodystrophy was the predominant pattern (63.1%), followed by normal bone histology (13.2%), adynamic bone disease (11.8%) and osteomalacia (9.2%). The latter was more frequent in more advanced stages, together with a tendency to hypocalcemia and severe metabolic acidosis. Adynamic bone disease was more frequent in early CKD stages. Further studies also have shown that mineralization defects and particularly low turnover status were among the most frequent findings in pre-dialysis patients [24-28]. A hypothesis is that adynamic bone disease could be a form of bone pattern that appeared concomitantly with skeletal resistance to increases in serum PTH and could be considered as transient stage in early CKD, to be eventually overcome by progressive secondary hyperparathyroidism to patterns of high-turnover and mixed osteodystrophy[19-22]. Coexistence of other conditions like vitamin D and sex hormones deficiency, diabetes, increased synthesis of Wnt pathway inhibitors and uremic toxins can further contribute to skeletal resistance to PTH in early stages[8,11].

Vitamin D deficiency diminishes intestinal calcium absorption leading to lower calcium levels and reduced expression of vitamin D receptors, particularly in parathyroid gland, which leads to resistance to calcitriol-mediated negative regulation of PTH secretion[8-11]. In CKD stages 2 to 5, serum 25 – OH – vitamin D levels correlated inversely with serum PTH levels. Calcifediol measurements above 40 ng/ml were associated with decreased bone turnover rate and for values higher than 48 ng/ml, the suppressed effect on PTH progressively vanished[11]. Sex hormones deficiency can negatively influence bone remodeling rate and bone mechanical strength, regardless of presence of CKD.

Phosphate is one of the most relevant uremic toxins and hyperphosphatemia is a well-known cause of reduced bone mass, increased fracture risk and ectopic calcifications across all CKD stages, with a major role as a potent induction factor of FGF23, as previously discussed[8-11].

■ Dialysis

Prevalence of low turnover disease continues to increase after dialysis initiation. Studies conducted in the last decade with large numbers of dialysis patients revealed that low turnover disease (58% to 80.6%) was the most frequent bone pattern, with mineralization defects and high turnover disease being the rarest patterns. Massy Z et al.[19] proposed that several patient-related factors (age, diabetes, ethnic and genetic background) and treatment-related factors (oral calcium overload, excessive treatment with vitamin D or derived vitamin D sterols, high dialysate calcium concentration and parathyroidectomy) may explain the current high prevalence of low-turnover disease and considered that absolute or relative hypoparathyroidism is the main cause. Data from peritoneal dialysis (PD) are scarce, but seems to be no differences of ROD distribution between dialysis modalities[33,34].

■ Transplantation

There are very few studies which addressed histomorphometric analysis in kidney transplant patients. Long term persistence of hyperparathyroidism and hypovitaminosis D, along with steroid and calcineurin inhibitors use may explain the very high prevalence of osteoporosis, low bone turnover and mineralization defects in kidney transplant patients, particularly after the first year[35-37]. In 2013, Neves et al.[38] performed bone biopsies about 2 years post-transplant in 47 patients with preserved kidney function and managed with steroid sparing protocols. About 82% of patients presented with alterations in at least one of the TMV parameters: 26% with high turnover, 26% with low turnover, mineralization defects in 48% (about 58% in those who had hypovitaminosis D) and low bone volume in 37%. In 2016, Carvalho C. et al.[39] reported the results of a prospective study that analyzed trabecular and cortical bone in 7 transplant patients that performed bone biopsy after 2 months of transplantation and repeated it after 2-5 years of follow-up. Globally, there was a reduction in bone activity, suggesting an increased risk for adynamic bone disease and loss of bone volume.

■ Effects of Medical and Surgical Treatment

The high prevalence of low cancellous bone volume, which is the mainly constitute of vertebrae, may predispose CKD patients to develop compression fractures

whereas high cortical porosity or thin cortices are more likely to promote hip fractures. Fractures are a major cause of morbidity and mortality among dialysis patients and the incidence of all fractures in this group was reported to be 28 fractures per 1000 patient-years, with hip fractures causing 18 events per 1000 patient-years. Erroneous treatment of ROD may worsen this problem and also promote vascular calcifications[1-10].

Malluche et al.[40] reviewed the landmark studies that assessed the effects of treatment on bone histology. Major treatment modalities were phosphate binders, vitamin D compounds and calcimimetics. Overall, aluminum-containing phosphate binders are toxic to the bone because of negative effects in turnover, mineralization and bone volume. Use of calcium-based binders has been associated with the development of adynamic bone disease, bone loss and worsening of vascular calcifications. Non-aluminum and non-calcium binders (sevelamer hydrochloride and lanthanum carbonate) seems to improve bone histology, particularly bone turnover and volume[40-42]. Calcitriol replacement therapy by daily oral administration is associated with frequent hypercalcemia and turnover suppression in CKD stages 3 to 5. Pulse oral or intravenous calcitriol administration frequently induces hypercalcemia or hyperphosphatemia and achieves the same degree of correction of bone abnormalities[43]. There are presently no data about effects of paricalcitol or doxercalciferol on human bone but experimental data on animal models showed better PTH control without suppression of bone turnover, improved regeneration and de novo bone formation[44,45]. Calcimimetics lower PTH levels and bone turnover. Results of the recent BONAFIDE study[46] support this evidence. This was a multicenter, single-arm study and evaluated skeletal response to cinacalcet after 6-12 months of treatment in 110 dialysis patients with biopsy-proven high-turnover disease. There was a generally improvement in bone histology, with lowering of bone turnover and several biomarkers of high-turnover bone disease. A significant proportion of patients had a normal bone biopsy after cinacalcet treatment (26%). About 2.7% developed low-turnover disease secondary to treatment.

Araujo et al.[47] alerts to potential risks of treating low bone turnover by simply altering therapies to increase levels of PTH. This may reduce cortical thickness and increase cortical porosity, with potential to exacerbate fracture risk.

Regarding the effects of surgical treatment, to our knowledge, only three studies addressed the impact of parathyroidectomy on bone histology in CKD patients with severe secondary hyperparathyroidism. There seems to be a change from high to low turnover disease but definitive conclusions cannot yet be drawn.

In 2003, Yajima et al.[48] investigated early bone changes at 1 week after parathyroidectomy in 14 dialysis patients. The rapid decreased in serum PTH appeared to suppress bone resorption, caused transient increase in bone formation and an increase in normal lamellar osteoid seams. In 2010, the Yajima group[49] also studied the effects of parathyroidectomy on osteocyte number and mineralization before and 2 to 4 weeks after surgery in 18 dialysis patients. There was an increased osteocyte death rate and mineralization in association with rapid decline in PTH levels. In 2017, Hernandes et al.[50] investigated the impact of parathyroidectomy on bone remodeling and vascular calcifications in 19 dialysis patients at baseline and after 12 months of surgery. At 12 months, 90% of patients evolved to low turnover disease, coronary calcium score increased significantly and vascular calcifications progressed. Their results support the need for careful evaluation, also beyond ROD, before performing this surgical procedure.

CONCLUSIONS

Despite being considered the gold standard in diagnosing renal bone disease, there is a lack of enthusiasm among nephrologists to perform bone biopsy. The main reason for this is the fact that clinicians perceive the procedure as invasive, painful and burdensome, through clinically useful. However, bone biopsy is well tolerated, has few complications and is the only accurate method to assess bone metabolism and to evaluate treatment effects. Bone biomarkers and bone imaging techniques may help to complement bone assessment and predict fractures in CKD but do have major limitations and further studies are needed. Bone biopsies are presently no part of routine analysis or follow-up and are performed for specific cases in a limited number of places. A revival of the procedure is needed before results in complete disappearance of expertise.

Disclosure of potential conflicts of interest: none declared

Acknowledgments

We like to thank to Prof. João Frazão for all the knowledge, support and availability provided.

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