Journal of Nephrology and Kidney Diseases
Volume 5 | Issue 1
ISSN: 2455-7633

Research Article Open Access

Approach to and Management of a Adynamic Bone Disease in Hemodialysis Patients-A Review

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Citation: : Athish KK, Chethan Reddy B, Shobhana Nayak-Rao (2024) Approach to and Management of a Dynamic Bone Disease in Hemodialysis Patients- A Review, J Nephrol Kidney Dis 5(1): 103

Received Date: April 03, 2024 **Accepted Date:** May 03, 2024 **Published Date:** May 08, 2024

Abstract

Chronic kidney disease (CKD) is now a global public health epidemic with increasing rates reported all over the world. Currently, more than 850 million people are estimated to live with CKD worldwide. Bone and mineral disorders (CKD-MBD) form an integral part of the management of CKD patients. CKD-MBD encompasses distinct abnormal pathology within the spectrum of Renal Osteodystrophy (ROD), including osteitis fibrosa cystica, osteomalacia, adynamic bone disease (ABD), mixed lesions, and osteoporosis. ABD is primarily characterized by decreased or absent bone formations along with low cellularity of both osteoblasts and osteoclasts as well as thin osteoid seams and minimal or absent peri trabecular/marrow fibrosis. ADB is also associated with a greater risk of vascular calcification and fractures negatively affecting patient outcomes. It is unclear if all forms of ABD are truly pathological or milder forms of ADB could be a compensatory mechanism to guard against bone loss. In this article, we describe a hemodialysis patient profile of ADB with a review of this entity.

Keywords: Chronic Kidney Disease; CKD-MBD; Adynamic Bone Disease; Fractures; Bone Biopsy

Introduction

Chronic kidney disease (CKD) is now a global public health epidemic with increasing rates reported all over the world. Currently, more than 850 million people are estimated to live with CKD worldwide. Bone and mineral disorders (CKD-MBD) form an integral part of the management of CKD patients. CKD-MBD encompasses distinct abnormal pathology within the spectrum of Renal Osteodystrophy (ROD), including osteitis fibrosa cystica, osteomalacia, adynamic bone disease (ABD), mixed lesions, and osteoporosis [1]. ABD is primarily characterized by decreased or absent bone formations along with low cellularity of both osteoblasts and osteoclasts as well as thin osteoid seams and minimal or absent peri trabecular/marrow fibrosis. The terms ABD and low bone turnover (LBT) are used, however, interchangeably. ABD was initially described in the early 1980's [2] and must be differentiated from osteomalacia where defects in bone mineralization exceed bone formation thereby causing osteoid excess. ADB is also associated with a greater risk of vascular calcification and fractures negatively affecting patient outcomes. It is unclear if all forms of ABD are truly pathological or milder forms of ADB could be a compensatory mechanism to guard against bone loss. In this article, we describe a hemodialysis patient profile of ADB and provide a current review of this entity.

Case Details: A 53 years old lady, known hypertensive and CKD-stage 5 D on hemodialysis treatment since 4 yrs on twice weekly basis was investigated in view of severe leg pains and back ache for which she was taking NSAID'S since few months. She denied weight loss, fever or any other systemic symptoms. She had attained menopause at the age of 45 yrs and was not taking any hormone replacement therapy. Her serum calcium ranged from 9.6mg/dl to 10.5 mg/dl, serum phosphorus was 2.2mg/dl with serum total alkaline phosphatase being 138 IU/L. Serum iPTH was low at 24.5 pg/l with two serial values below 30pg/L. Her serum TSH was also high at 18.6 IU/L with low T4 and normal T3. A bone densitometry study revealed T score of -1.9 at LS spine, -3.1 at right femur and -1.7 at left femur. She was diagnosed to have dynamic bone disease with associated hypothyroidism and started on thyroid supplementation at 25mcg /day along with teriparatide 20mcg s/c once daily for bone disease. Bone biopsy could not be done in our hospital due to absence of facilities.

Epidemiology and Pathophysiology

The history of ABD goes back to the 1970's when aluminum intoxication was first described in patients undergoing maintenance hemodialysis [3]. In recent years, the intensive treatment of hyperparathyroidism with phosphate binders and the use of Vitamin D analogues continues to be the main contributing factors. Iatrogenic hypoparathyroidism caused by subtotal or total parathyroidectomy for severe secondary or tertiary hyperparathyroidism can lead to a severe form of ABD and aggravate cardiovascular calcification [4] It has been long believed that the most prevalent pattern of ROD in advanced CKD and those on HD is osteitis fibrosa cystica induced by secondary hyperparathyroidism [5] whereas ABD is more prevalent in peritoneal dialysis (PD) patients [6]. However in the last two decades, there has been a shift in ROD pattern from high turnover bone disease to ABD [7]. Prevalence rates in advanced CKD stages vary from 10-40% and 10-50% in dialysis patients. However in earlier CKD stages 3-4, prevalence rates show rising trend to about 18% [8, 9]. In a larger study in 630 hemodialysis patients, bone biopsy specimens revealed LBT in 58% of patients. Additionally, LBT was more prominent in white than in the black population [10]. Barreto et al also found a LBT pattern in 58 out of 97 (60%) patients on HD with inconsistent levels of parathyroid hormone, highlighting the poor specificity of PTH level in discriminating LBT and HBT [11]. Initial reports in pre-dialysis CKD demonstrated high prevalence of ABD ; however with progression of CKD , bone turnover moves towards a higher state because of progressive increase in PTH to overcome PTH resistance and bone-turnover –inhibitory factors. ABD might therefore a transitional stage before HBT overcomes it with a progressive rise in PTH [12]. The pathophysiology of ABD is certainly multifactorial, with patient –related and iatrogenic factors on a genetically predisposed background. Imbalance between low circulating levels of anabolic bone factors (e.g insulin--like growth factorIGF-1) and increased expression of bone-inhibitory factors such as Sclerostin and Dickkopf-related protein (D-kk-1)largely predominates. This imbalance represses bone formation by suppression of WNT/β-catenin signalling [13]. Inflammation caused by the uremic state and increased pro-inflammatory cytokine release also suppresses PTH synthesis and release.

Low PTH(<60pg/ml) was also found to be a surrogate marker of malnutrition in addition to low serum albumin and blood urea nitrogen levels in one Japanese study [14] .

Gonadal dysfunction is also one of the factors negatively impacting bone formation [15]. Decrease in serum testosterone in men and estradiol in women are known to impair bone health. In addition, low Vitamin D levels cause suppressed Vitamin D receptor (VD 12) expression [16], which is crucial in blocking osteoblast apoptosis and promoting osteoblast differentiation. Down –regulation of the PTH receptor with reduced bone-stimulating effect of PTH causing PTH resistance is ultimately responsible [13]. Prevalence of ABD is higher in diabetes mellitus with several histomorphometric studies proving that ABD is the pre-dominant type of diabetic osteodystrophy. Advanced glycation end products (AGE's interfere negatively with osteoblast and osteoclast activity. In addition, IGF-1 resistance and inhibitors of bone formation such as Sclerostin are also responsible.

Impact of ABD on Bone Fracture/Osteoporosis and Mortality

Adynamic bone disease results in poor skeletal health, increased bone fragility and decreased ability to restore damaged bone. Delayed remodelling of bone promotes more secondary mineralization producing brittle bones that increase risk of atypical fractures [17]. Several studies have reported a J or U shaped association between PTH levels and mortality in patients on dialysis [18, 19]. Low PTH levels were associated with higher risk of mortality. In a subgroup analysis of 5387 patients on HD from the Dialysis Outcomes and Practice Patterns(DOPPS) study ,PTH levels <50pg/ml were associated with 25% higher mortality in comparison to those with PTH levels between 150-300pg/ml [20]. In the CORES study including 16,173 Latin American HD patients [19], PTH <150pg/ml was associated with increased all-cause and cardiovascular mortality. Association between low PTH and mortality in different patient populations is largely observational and a causal relationship cannot be established. The rule of residual confounders such as malnutrition and inflammation may influence clinical outcomes. Studies investigating association between biopsy –proven ABD and mortality are scarce. Data from the Brazilian Registry of Bone Biopsy(REBRABO) from patients with Stage 3-5 CKD who underwent bone biopsy and were followed up for 30 months did not find any association between hospitalization or mortality and type of ROD [21].

ABD and Association with Vascular Calcification (VC): Cardiovascular disease is the main cause of death in the CKD population. VC is common in both pre-dialysis and dialysis patients and has been linked to higher CKD related cardiovascular mortality [22]. ABD leads to reduced bone capacity to buffer calcium and inability to handle an extra load of calcium. Radiologically , VC may present as cardiovascular calcifications, chondrocalcinosis or peri-articular calcifications. ROD associated VC affects mainly the vascular media in contrast to atherosclerotic calcification which affects mainly vessel intima. There have been several clinical studies that have investigated a possible association between LBT and VC in CKD. In a study including 207 patients on HD, coronary artery calcification (CAC) was associated with significantly lower bone-formation rate [23]. In pre-dialysis patients, low bone formation rate also has been independently associated with VC, either on CT or plain X-ray (24). Calciphylaxis, a rarer type of VC associated with higher mortality rate also has been associated with biopsy-proven ABD [25].

Diagnosis of ABD

Bone biopsy is considered the gold standard for the diagnosis of ABD. The practical metric for ABD includes bone formation less than 97-108 μm2.mm2/day, osteoid volume less than 12-15%, and absent (minimal) fibrosis(Figure 1) [20,26]. Bone turnover markers (BTM's provide mild-to moderate precision evaluation of bone health in patients with CKD. These include a) Bone formation biomarkers such as serum total and bone specific alkaline phosphatase (TAP, BSAP) with BSAP being the more precise markers in discriminating bone-turnover status in dialysis patients. Pro-collagen type-1 N-terminal propeptide (P1NP) and procollagen Type-1 C-terminal propeptide (P1CP) are indicators of collagen synthesis rate [27]. However in patients with CKD, only intact P1NP is reliable and is not affected and is not affected by GFR. Sclerostin and DKK-1 are soluble inhibitors of Wnt-signalling pathway and the main promoter of bone formation with significant association between high sclerostin levels and ADB [28]. b) Bone-resorption Biomarkers includes tartrate-resistant acid phosphatase 5b(TRAP5b) with higher levels showing faster rate of cortical

bone loss [29].

Radiological Methods of Assessment: a) Use of Dual Energy X ray absorptiometry (DXA) scan: Patients with ABD may have either low or normal bone mineral density (BMD). Use of DXA scan may have several limitations including risk of confounding results due to soft-tissue calcification and osteoarthritis [30] as well as its inability to identify bone-turnover rates and ROD type. Use of Quantitative Computed Tomography (QCT) and High Resolution Quantitative CT (HR-Pqct) can precisely help in assessing bone microarchitecture (31). Positron Emission Tomography (PET) scan uses fluorine-Na-Sodium fluoride (18-F-Na F) , bone –seeking tracer for assessment of bone-turnover and osteoblast function. The sensitivity and specificity of this technique to discriminate LBT were 76% and 78% respectively.

Use of bone biopsy: Bone biopsy with mineralized bone histology is the gold standard for detection of ROD [10]. The classification is mainly based on the TMV system, which assesses bone turnover, mineralization of osteoid matrix, and bone volume [32]. In patients with ABD, bone histomorphometry reveals LBT with reduced number of both osteoblasts (Figure 1) and osteoclasts or low bone volume with normal mineralization [32]. The presence of thin osteoid differentiates ABD from 'osteomalacia'. Bone biopsy, although a very precise tool to assess metabolic bone disease has some limitations including high cost, lack of expertise and limited patient acceptability.

Prevention and Treatment of ADB in CKD

The chief management strategy aims to increase PTH synthesis by the following mechanisms:

Switching from calcium-containing phosphate binders to non-calcium, non aluminium containing binders such as sevalamer and lanthanum carbonate. This helps in lowering total calcium load thereby stimulating PTH synthesis in a negative feedback loop.

Reduction of oral dietary calcium intake by calcium supplements to 1000-1200mg/day. As per current guide, daily intake of men aged 19-70 and women aged 19-50 yrs should be 1000mg and beyond that should be 1200mg /day [33]. Stoppage or reduction of active Vitamin D metabolites should also be done.

Lowering dialysate calcium to 125mmol/L or below helps in increasing bone formation rate from 18.1±5.6μm2/mm2/day to 159±59.4μm2/mm2/day in low calcium group over a 16 month period [34]. Benefits of low calcium dialysate include preventing an overall positive balance and resultant PTH stimulation. This helps in maintaining bone growth in these patients as well as slowing down the progression of vascular calcification.

Antiresorptives: Bisphosphonates may aggravate or induce LBT with long term use or in high doses. They are more likely to cause brittle and less tough bone leading to a higher risk of fractures. Denosumab leads to an early and profound decline in bone turnover with each dose which thereafter partially recovers before the subsequent dose administration. Studies evaluating the use of antiresorptive agents on bone remodelling in CKD are however scanty and it seems reasonable to consider these agents in CKD on a case-by case basis. Studies evaluating efficacy and safety of antiresorptives in patients with CKD are urgently needed.

Calcilytics are agents that are serve as antagonists of the calcium sending receptor. They are of undetermined value at present with ronacalcet [35], a calcilytic which allows bone formation through endogenous production of PTH showing encouraging results in postmenopausal women. There have been no trials in ABD of its use however.

Use of potential Bone-building agents: Teriparatide (PTH (1-34)) is recombinant PTH approved for treatment of patients at high risk of fracture [36]. It has been hypothesized that teriparatide would be effective for ABD based on its ability to promote osteoblas-

tic and osteoclastic activity. In trials, teriparatide showed efficacy in reducing risk of fracture and improving vertebral and femoral neck BMD. In an open label, prospective 6 month observational pilot study of HD patients with ABD and a median iPTH level of 22pg/ml, all patients received 20mcg teriparatide /day subcutaneously [37]. At the end of the study, calculated monthly changes in BMD improved significantly in both lumbar spine and femoral neck($p<0.02$).. Sumida et al [38] administered 56.5 μg s/c once weekly to 22 patients with serum PTH <60pg/ml. BMI at spine increased by 3.3±1.9% and 3.0±1.8% at 24 and 48 weeks respectively; however no significant changes in femoral neck and distal radius BMD was observed. Abaloparatide, another PTH –related peptide analogue has been approved in the US for the treatment of postmenopausal osteoporosis at high fracture risk. However potential benefits in ABD remain to be explored. Romosozumab is a monoclonal antibody that binds and inhibits sclerostin (Wnt-signalling pathway regulator).Sclerostin inhibits osteoblast recruitment and decreases bone recruitment [39]. Clinical studies in postmenopausal women has shown positive results, however efficiay studies are needed in CKD patients with ABD.

Conclusion

Adynamic bone disease is a complex disease process and its prevalence has been increasing in CKD, including dialysis patients. Management of ABD relies on prevention through judicious use of calcium containing phosphate binders as well as use of antiparathyroid agents.

Funding Information

None

Conflict of Interest

None declared

Ethical Approval

This is a review article and hence not required

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