



Management of adynamic bone disease in chronic kidney disease: A brief review

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ABSTRACT

The Kidney Disease: Improving Global Outcomes (KDIGO) work group released recommendations in 2006 to define the bone-related pathology associated with chronic kidney disease as renal osteodystrophy. In 2009, KDIGO released revised clinical practice guidelines which redefined systemic disorders of bone and mineral metabolism due to chronic kidney disease as chronic kidney disease-mineral and bone disorders. Conditions under this overarching term include osteitis fibrosa cystica, osteomalacia, and adynamic bone disease. We aim to provide a brief review of the histopathology, pathophysiology, epidemiology, and diagnostic features of adynamic bone disease, focusing on current trends in the management of this complex bone disorder.

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Introduction

Patients with end-stage renal disease (ESRD) requiring hemodialysis have an increased fracture risk, where the incidence of hip fractures in one study was fourfold greater in ESRD patients on dialysis when compared to non-dialysis patients [1]. Chronic kidney disease (CKD) is associated with various bone-related pathologies, each with unique histopathological findings. In spite of their varied underlying processes, the clinical presentations of the diseases which comprise chronic kidney disease-mineral and bone disorders (CKD-MBD) are oftentimes similar [2]. Patients with adynamic bone disease (ABD), a condition of low-bone turnover, and those with osteitis fibrosa cystica (OFC), a condition of high-bone turnover, are typically asymptomatic at the time of their diagnosis, though either can present with fragility fractures.

Histopathology

ABD is characterized by markedly low-bone turnover resulting from a reduced number of osteoclasts and osteoblasts without osteoid accumulation [3]. This distinguishes ABD from OFC, which in contrast, is a disorder characterized by increased bone turnover with a resulting increase in bone formation and resorption [4] [Fig. 1].

Pathophysiology

The underlying pathophysiology of ABD is both intricate and multi-factorial. Fundamentally, ABD is due to either the resistance of parathyroid hormone (PTH) on bone metabolism or the oversuppression of PTH release, though several events precede this outcome. One of the earliest biomarkers of CKD appears to be a decreased expression in α -Klotho, which is a co-receptor of the phosphatonin Fibroblast growth factor 23 (FGF-23) [5]. This peptide is secreted by osteocytes and osteoblasts in response to elevated phosphate and calcitriol levels thus allowing for increased excretion of phosphate [6]. The resistance to FGF-23 by the decreased expression of α -Klotho leads to an increase in FGF-23 production, a decrease in calcitriol, relative hypocalcemia, and secondary hyperparathyroidism [5,7]. This cascade eventually results in PTH receptor down-regulation with subsequent skeletal resistance to PTH action [8].

Oversuppression of PTH is an additional hallmark of ABD. While very high levels of PTH are associated with an increase in both fracture risk and mortality, normalizing the secondary hyperparathyroidism associated with early and late-stage CKD can also lead to similar increases in morbidity [9]. Patients with CKD and intact parathyroid hormone (iPTH) levels <195 pg/mL have been found to have a 22% increased risk of fractures as studied retrospectively by Atsumi *et al.* [10]. Hence, dietary phosphate restriction, the use of calcium-based phosphate binders, activated vitamin D analogs, and calcimimetics can all trigger PTH suppression thus creating a low-bone-turnover state [8,11].

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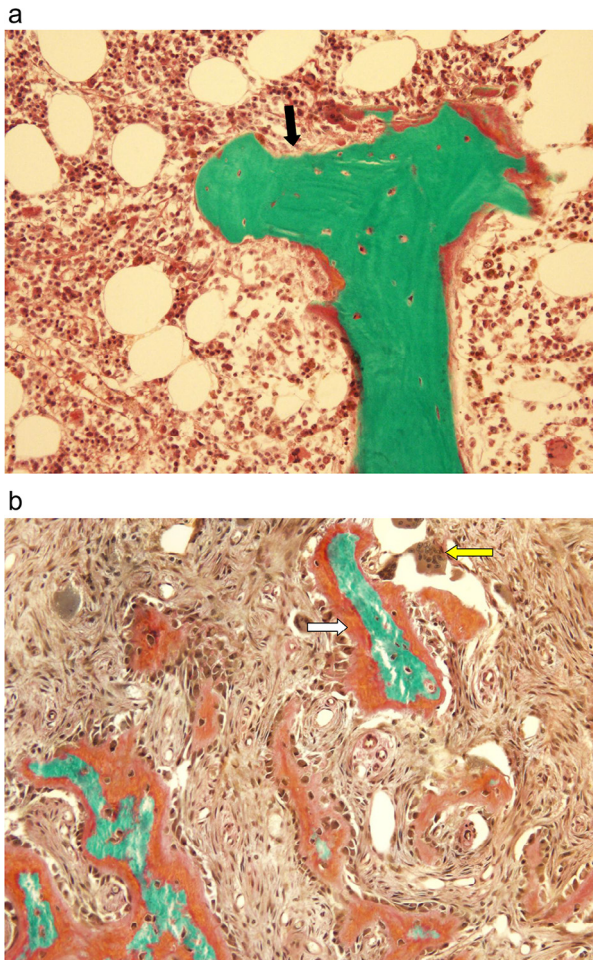


Figure 1. a: Adynamic bone disease. Depicts a classic bone biopsy featuring minimal osteoid (black arrow) and nearly no activity of osteoblasts or osteoclasts. Image courtesy of Avudai Maran, PhD and Bart Clarke, MD – Biomaterials and Histomorphometry Core Lab, Mayo Clinic, Rochester, MN. b: Osteitis fibrosa cystica. Characterized by thick osteoid production (white arrow) with increased osteoclast activity (yellow arrow). Image courtesy of Avudai Maran, PhD and Bart Clarke, MD – Biomaterials and Histomorphometry Core Lab, Mayo Clinic, Rochester, MN. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Epidemiology

Of the disorders which comprise CKD-MBD, ABD is by far the most prevalent and should therefore be at the forefront of metabolic bone disease management. In patients with CKD stages 3–5, there is an 18% prevalence of ABD [2]. This low-bone-turnover disease is seen in 50% of patients with CKD-MBD who receive peritoneal dialysis and in 19% of CKD-MBD patients receiving hemodialysis [2,8,12]. Several direct and indirect risk factors for ABD exist and include the use of calcium-based phosphate binders, activated vitamin D analogs, calcimimetics, peritoneal dialysis, high-calcium dialysate, glucocorticoid-induced osteoporosis, bisphosphonate use, diabetes, post-menopausal state, hypogonadism, increased age, malnutrition, parathyroidectomy, and systemic inflammation [2–8,12]. Of the aforementioned risk factors, the increased global prevalence of diabetes and ESRD, as well as the aggressive treatment of secondary hyperparathyroidism have greatly contributed to the growing prevalence of ABD over the past 20 years [3].

Diagnosis

Bone biopsy remains the diagnostic gold standard in distinguishing a disease of low-bone turnover such as ABD from other bone-related pathologies such as OFC which is characterized by a marked increase in bone turnover and remodeling [4]. Guidelines set forth by the KDIGO work group as well as the National Kidney Foundation: Kidney Disease Outcomes Quality Initiative (NKF KDOQI) recommend performing a bone biopsy in patients with CKD who also possess one or more of the following conditions [2,3,13]:

- Patients with iPTH levels between 100 and 500 pg/mL with unexplained hypercalcemia, bone pain, or increased bone-specific alkaline phosphatase (BSAP)
- Fragility fractures not explained by additional etiologies such as malignancy
- Prior to initiating bisphosphonate therapy
- Unexplained hypercalcemia
- Suspected aluminum toxicity
- Severe vascular calcification

Serological markers, though unable to solely confirm the diagnosis of ABD, can be helpful in guiding clinicians who are unsure of whether or not to proceed with a bone biopsy. This especially holds true in the case of an asymptomatic patient, as persistent bone pain and fragility fractures are seen in only a minority of patients at the time of their initial diagnosis [8]. Patients with PTH levels <150 pg/mL have a 97% positive predictive value for ABD, whereas PTH levels >450 pg/mL have a 100% positive predictive value for OF [14]. One serum marker directly implicated in assessing bone formation is BSAP [8]. BSAP of >20 ng/mL virtually excludes the diagnosis of ABD particularly when patients have a concurrent PTH >200 pg/mL. Patients with BSAP <12.9 ng/mL can further bolster the diagnosis of ABD as this is 100% sensitive and 93.7% specific [8,15,16].

Management

In spite of its underlying complexity, the traditional therapies geared toward managing ABD are firmly rooted in the prevention of CKD progression, management of ABD risk factors such as diabetes, and decreasing calcium and vitamin D load so as to relax PTH suppression in order to re-establish its activity [3,8].

Relaxing PTH suppression

As discussed earlier, several factors are involved in the suppression of PTH which can ultimately lead to ABD in patients with CKD. Though the most favorable PTH level to maintain in patients with CKD stages 3–5 is currently not known, the 2009 KDIGO Guidelines suggest maintaining iPTH levels for patients with CKD stage 5D between 2 and 9 times the upper limit of normal for the assay utilized [2].

The administration of activated vitamin D analogs can cause decreased bone turnover in patients with CKD. In a 1994 study by Goodman et al., 6 out of 14 study participants with end-stage renal disease developed biopsy-proven ABD following the administration of high dose calcitriol [17]. Therefore, limiting the use of calcitriol can assist in alleviating PTH oversuppression which is a driving force for the development of ABD. Similarly, the use of calcimimetics should be avoided in patients who have developed this low-bone-turnover disease seeing that these medications also serve to suppress PTH activity [8]. Consideration should also be given toward switching patients with ESRD receiving hemodialysis from a calcium-containing phosphate binder to a non-calcium-containing phosphate binder, as this could assist in relaxing PTH suppression and

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