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Pathophysiology of chronic kidney disease-mineral and bone disorder

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ABSTRACT

Chronic kidney disease (CKD) alters the metabolism of several minerals, thereby inducing bone lesions and vessel-wall calcifications that can cause functional impairments and excess mortality. The histological bone abnormalities seen in CKD, known as renal osteodystrophy, consist of alterations in the bone turnover rate, which may be increased (osteitis fibrosa [OF]) or severely decreased (adynamic bone disease [AD]); abnormal mineralization (osteomalacia [OM]), and bone loss. Secondary hyperparathyroidism is related to early phosphate accumulation (responsible for FGF23 overproduction by bone tissue), decreased calcitriol production by the kidneys, and hypocalcemia. Secondary hyperparathyroidism is associated with OF. Other factors that affect bone include acidosis, chronic inflammation, nutritional deficiencies, and iatrogenic complications.

1. Introduction

Chronic kidney disease (CKD) causes early alterations in phosphorus and calcium metabolism that eventually lead to secondary hyperparathyroidism (HPT II). CKD affects many other functions, including blood pH regulation and nutrition, and also results in varying degrees of inflammation, which combine to induce bone lesions of variable specificity. Thus, the bone lesions seen in CKD result from an accumulation of toxic effects related to CKD, as well as from iatrogenic factors in some patients. The pathophysiology of CKD-mineral and bone disorder (CKD-MBD) extends far beyond the abnormalities in phosphorus and calcium metabolism long viewed as the sole culprits. In the past, the bone symptoms and phosphorus/calcium metabolism dyshomeostasis seen in CKD were known as "renal osteodystrophy". In 2006, the kidney disease improving global outcomes (KDIGO) consensus conference suggested the term CKD-MBD instead, to designate the systemic disorder of mineral and bone metabolism due to CKD [1]. CKD-MBD produces clinical features (calcifications of the vasculature and soft tissues, fractures, and growth disturbances in pediatric patients), histological abnormalities seen on bone biopsy specimens (now called renal osteodystrophy), and laboratory abnormalities (or serum calcium, phosphorus, parathyroid hormone [PTH], and vitamin D). This new concept is warranted because the pathophysiological mechanisms of the various manifestations are closely interlinked. Here, we will discuss only CKD-MBD in adults without renal transplantation.

2. Patterns of chronic kidney disease-mineral and bone disorder (CKD-MBD)

Table 1 lists the main alterations seen in the four patterns of CKD-MBD. The KDIGO panel suggested the TMV classification, where T stands for turnover rate, M for mineralization, and V for bone volume (or mass).

The turnover rate is measured by the bone formation rate (BFR) and may be normal, high, or low. High bone turnover is associated with increased levels of bone resorption markers. The parameters used to assess primary mineralization are the amount of osteoid tissue (collagen that is not yet mineralized), mineralization rate, and mineralization lag time (MLT). Primary mineralization may be normal or diminished. Bone volume (or mass) is evaluated based on the bone volume/tissue volume ratio for cancellous bone and on thickness and porosity for cortical bone. Bone volume is normal, high, or low. Various combinations of turnover and mineralization alterations produce four patterns of bone disease: osteitis fibrosa (OF), adynamic bone disease (AD), osteomalacia (OM), and mixed bone disease. In each of these four patterns, bone mass may be increased or decreased. Bone lesions characterized by low turnover are more common in CKD than those characterized by high turnover.

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Table 1
The four patterns of chronic kidney disease-mineral and bone disorder.

Turnover Masse	Bone turnover rate	Primary bone mineralization	Osteoid tissue	Bone mass
Osteitis fibrosa	↑ or ↑↑	N or ↑	↑ or ↑↑↑	N or ↑ or ↓
Adynamic bone disease	↓	N	0 or ↓	N or ↑ or ↓
Osteomalacia	↓	↓↓	↑↑↑	N or ↑ or ↓
Mixed bone disease	↑ or ↑↑↑	↓ or ↓↓	↑↑↑	N or ↑ or ↓

N: normal.

3. Pathophysiology of chronic kidney disease-mineral and bone disorder

3.1. Fibroblast growth factor 23, parathyroid hormone, and vitamin D: the three key hormones in chronic kidney disease-mineral and bone disorder

The order of appearance of the various factors that induce or exacerbate CKD-MBD remains debated (Fig. 1). Fibroblast growth factor 23 (FGF23) is a hormone produced by osteocytes and, to a lesser extent, osteoblasts. FGF23 production is increased by hyperphosphatemia and vitamin D, and probably also by PTH [2], although this last point is controversial [3]. In CKD, phosphorus accumulation worsens gradually as the ability of the residual nephrons to excrete phosphorus declines. Consequently, serum phosphorus levels increase despite FGF23 elevation. Serum FGF23 increases as glomerular filtration diminishes, due to both increased production and decreased renal excretion. A positive correlation has been reported between serum FGF23 and phosphorus levels [4]. Serum FGF23 is about 50 RU/mL normally, 500 RU/mL in early CKD, and greater than 10 000 RU/mL in patients on chronic dialysis. One hypothesis is that serum FGF23 elevation may increase the excretion of phosphorus by the residual nephrons, thereby keeping the serum phosphorus level within the normal range in early CKD [5]. In addition, FGF23 may inhibit PTH production by the parathyroid glands (negative feedback loop) [6]. Finally, FGF23 decreases serum calcitriol levels by inhibiting the enzyme 1-alpha hydroxylase required for calcitriol synthesis and by stimulating 25-hydroxyvitamin D-24-hydroxylase, which inactivates this enzyme [7].

Nephron loss results in decreased calcitriol production by the kidneys, despite the increase in PTH, which activates renal 1-alpha hydroxylase. The increase in intracellular phosphorus levels diminishes the efficacy of 1-alpha hydroxylase, thereby worsening the calcitriol deficiency [8]. Calcitriol deficiency decreases the intestinal absorption of phosphorus (which is beneficial in this situation) and of calcium (which is deleterious). Another deleterious change is a reduction in genomic calcitriol effects that diminish PTH production by the parathyroid glands. However, serum calcitriol does not come only from the kidneys: patients with CKD remain capable of a non-negligible level of vitamin D activation by 1-alpha hydroxylase found in other tissues [9,10].

Secondary hyperparathyroidism is due to multiple interlinked factors (Fig. 1). The intracellular phosphorus level in the

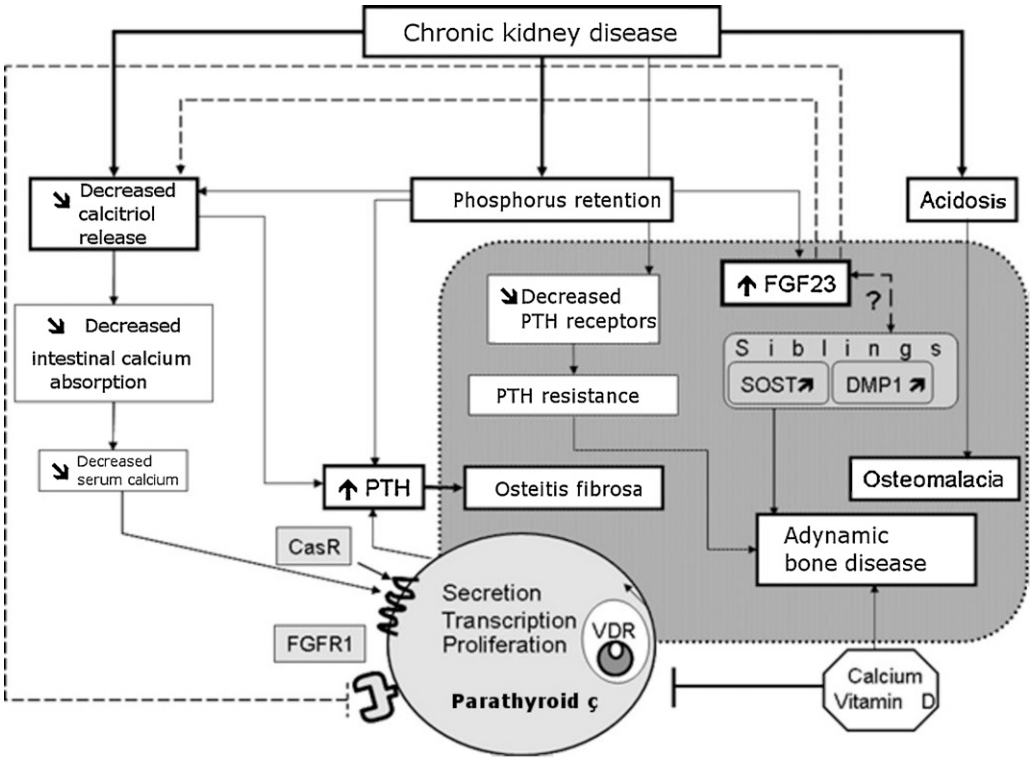

Fig. 1. Pathophysiology of chronic kidney disease-mineral and bone disorder.
The dark gray zone represents the bone compartment.
The dashed lines (------) represent the effects of FGF23. ----I: inhibition; ↘: stimulation; ç: cell; PTH: parathyroid hormone; FGF23: fibroblast growth factor 23.
CKD is characterized by diminished parathyroid cell (ç) expression of calcium-sensing receptor (CaSR), vitamin D receptor (VDR), and FGF23 receptor (FGFR1). Dentin matrix protein 1 (DMP1) and sclerostin (SOST) are expressed by osteocytes. Their links with FGF23 are incompletely understood (?) and are detailed in Fig. 3.