BALNEO RESEARCH JOURNAL
English Edition
eISSN 2069-7619 pISSN 2069-7597 ROMANIAN ASSOCIATION OF BALNEOLOGY

Skeletal manifestations in end-stage renal disease patients and relation to FGF23 and Klotho

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Balneo Research Journal DOI: http://dx.doi.org/10.12680/balneo.2020.352 Vol.11, No.3, September 2020 p: 274–278

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Abstract

Chronic kidney disease affects patients of all ages and, as it progresses, it greatly affects their lives, especially with the complications it causes. One major complication is renal osteodystrophy (ROD) which starts to develop from the early stages of the disease, but becomes most apparent in patients in need of renal replacement therapy. Diagnosing ROD in the early stages remains a challenge, which brings up the need to find novel biomarkers. Studies are focusing on the role of fibroblast growth factor 23 and Klotho in the bone and mineral homeostasis, but the results are conflicting. ROD remains a major complication in CKD patients, therefore we need to gain a better understanding from the pathophysiological point of view, in order to be able to adjust the medical therapy.

Key words: *FGF 23, Klotho, osteodystrophy,*

Introduction

Chronic kidney disease (CKD) represents a major health problem with a great impact on the patients' quality of life (1). Emerging complications are early, common and numerous, making CKD an important cause of global morbidity and mortality (2). One of the main concerns regarding CKD is the development of renal osteodystrophy (ROD) which consists of a large spectrum of bone abnormalities. ROD is considered to be part of the mineral and bone disorders that occur in CKD (CKD-MBD) (3). ROD starts to develop in the early stages of CKD, but becomes most apparent in patients with end-stage renal disease (ESRD) in need of renal replacement therapy (RRT). The bone disorders that are most common in CKD are categorized according to the rate of bone turnover into high turnover (osteitis fibrosa cystica) and low turnover diseases (osteomalacia, adynamic bone disease) (Table 1). Mixed forms may also be encountered in these patients (4). The trend in the last decades shows an increasing prevalence of low turnover disorders (5). This is an important observation since the treatment of those chronically ill patients needs to address these bone abnormalities. The parathyroid hormone (PTH) is considered to be one of the main culprits for ROD development (6), therefore the plasma levels of PTH together measurement of phosphorus, calcium and alkaline phosphatase represent the main tools used in clinical practice to diagnose and to treat ROD (7, 8). Bone biopsy is required in order to obtain a definitive diagnosis (3,9), but since it represents an invasive procedure it is not frequently used in the clinical setting. Bone biopsy and bone histomorphometry remain the gold standard methods for diagnosing ROD. The need for discovering other reliable biomarkers that can be utilized to dynamically evaluate a chronically ill patient led to more research in this field, with promising results.

Table 1. Main types of bone disorders in patients with CKD

	Bone disorder	*Main cause*	*Characteristics*
High turnover	Osteitis fibrosa cystica	Mild/sever hyperparathyroidism	Increased activity of osteoclast and osteoblast Peri-trabecular fibrosis
Low turnover	Osteomalacia (10)	Chronic severe metabolic acidosis Aluminum deposition	Decreased number of osteoblasts and osteoclasts Defective mineralization of osteoid
	Adynamic bone disease (11) (12)	Mostly in peritoneal dialysis patients Associated diabetes	Abnormal low turnover Osteoporosis Osteopenia Increased osteoid formation

Fibroblast growth factor 23 and Klotho in human physiology

PTH is the main hormone that regulates the plasma levels of phosphorus and calcium. Its secretion is enhanced in response to hyperphosphatemia, hypocalcemia and low serum levels of 1,25-dihydroxyvitamin D (1,25(OH)2D). PTH secretion is suppressed by high levels of calcitriol, calcium and Fibroblast growth factor 23 (FGF23). In CKD patients, the oscillatory secretion of PTH tends to be blunted (13). When GFR starts to decline, the renal elimination of phosphorus also declines, leading to compensatory increased secretion of PTH. In the beginning, serum levels oh phosphorus are maintained within the normal range, but when the glomerular filtration rate (GFR) becomes 25-40% of the normal value, phosphorus starts to accumulate and hyperphosphatemia becomes continuing. This further leads to low levels of free calcium in the serum, which also stimulates PTH secretion. Hyperphosphatemia similarly decreases the renal calcitriol production, causing decreased intestinal absorption of calcium and secondary hypocalcemia, which in turn stimulates the secretion of PTH. Hyperphosphatemia leads to resistance of the parathyroid glands to the actions of calcitriol, which also stimulates the secretion of PTH, but also leads to resistance of the bone to the actions of PTH. Hyperphosphatemia is also responsible for directly and independently stimulating the PTH secretion. Consequently, the parathyroid glands become hyperplasic (Figure 1) (14,15,16,17,18,19,20,21).

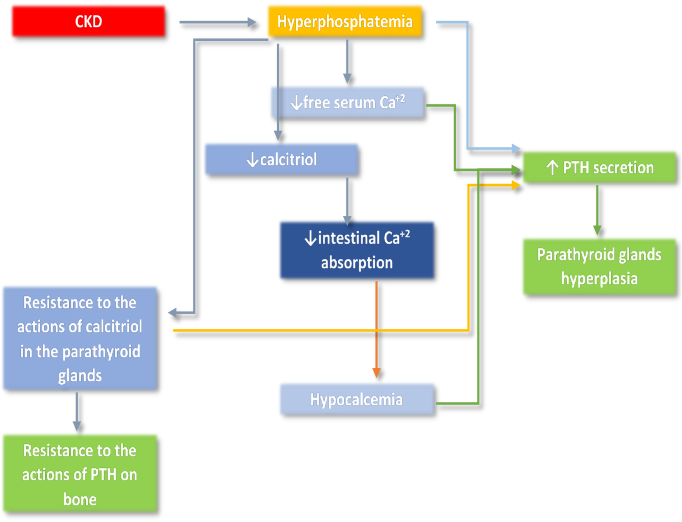

***Fig. 1**. Pathophysiology mechanisms of secondary hyperparathyroidism in CKD*

FGF23 represents a hormone with proteic structure that presents phosphaturic properties and is mainly secreted by osteoblasts and osteocytes. Its secretion is stimulated by increased plasma levels of phosphate, calcium, 1,25(OH)2D and PTH (22). It inhibits the sodium-phosphate cotransporter and the activity of 1-α-hydroxylase which leads to a reduction in the reabsorption of phosphate in the proximal tubule and, respectively, to diminished 1,25(OH)2D production. PTH and FGF23 are in a loop with constant negative feedback: FGF23 inhibits the production of PTH, while PTH increases the synthesis of FGF23 (23,24). Therefore, FGF23 presents three major effects: it decreases PTH levels, it decreases 1,2(OH)2D levels and it inhibits phosphate reabsorption (Figure 2).

***Fig. 2**. The effects of Fibroblast growth factor 23*

Klotho represents a protein that can be found both in a soluble state, as a secreted protein (α-Klotho), and as a transmembrane protein which presents a wide extracellular domain that can act as an endocrine factor when it is shed by secretases from the cell surface (25). Transmembrane Klotho is involved in antiaging and it also acts as a coreceptor for FGF23, with most of its expression being located in the renal and parathyroid tissues (26), while α-Klotho is involved in antiaging, antioxidation, control of PTH and vitamin D, and many others**Error! Bookmark not defined.**. When it comes to the calcium-phosphate metabolism, Klotho has its own role: it increases renal calcium reabsorption, and it increases PTH synthesis when hypocalcemia is present (27,28).

So far, studies have shown that in patients with CKD there is decreased Klotho expression in the kidneys, as early as the first stage. With the progression of CKD, the concentration of Klotho decreases constantly, which causes FGF23 resistance, with consequent accumulation of FGF23 (29,30).

FGF23, Klotho and bone mineralization

Animal studies have shown that both Klotho knockout mice and FGF23 knockout mice develop ectopic calcifications and decreased bone density, at the same time with hypercalcemia, hyperphosphatemia and high serum levels of

1,25(OH)2D (31,32). These results founded the idea of interplay between these two entities.

Klotho plays an essential role in the biologic activity of FGF23 as it is required for FGF23-mediated receptor activation, *in vivo* (33). The Klotho-FGF-Receptor complex is best expressed in the kidney, especially in the distal tubules (34,35).

Studies have shown that the overexpression of FGF23 *in vitro* is able to suppress the differentiation of osteoblasts as well as the mineralization of the bone matrix, in an independent manner from its effects on the metabolism of phosphate (36). In contrast, another study found a link between raised serum levels of FGF23 and a better bone mineralization, in CKD patients of pediatric age who undergo peritoneal dialysis (37). Other studies have shown that in CKD patients there is a deregulation of FGF23 metabolism, concluding that its plasma levels increase with the decrease of GFR, before the serum phosphate and PTH levels are even altered (38,39), even in the very early stages of CKD, like stage 2 or 3 (40,41). As CKD develops, the serum levels of FGF23 are correlated in a positive manner with phosphate and in a negative manner with 1,25(OH)2D and PTH (42,43).

One prospective study showed that serum levels of FGF23 were directly correlated to an increased risk of fractures, but another study that focused more on cardiovascular health showed that raised levels of FGF23 were not associated with increased risk of fractures, but instead were associated with greater bone density (44,45). The results were conflicting even when Klotho was assessed, as it has also been associated with bone density in both a negative and a positive way (46,47).

Conclusions

Renal osteodystrophy definitely benefits from the novel therapeutic strategies that are available for CKD patients, as seen with the decrease in high turnover ROD prevalence, due to a better control of the secondary hyperparathyroidism. Nevertheless, ROD remains an entity that affects these patients from the early stages of the disease. The gold standard diagnosis techniques remain bone biopsy and bone histomorphometry, but it is still mainly diagnosed using the serum levels of PTH, calcium, phosphorus and vitamin D. This is not convenient at all times since the serum levels might fluctuate in the early stages, and the chronic state of hyperphosphatemia is not reached until the GFR levels drops under 40% of the normal values. Both prospective cohort and experimental studies are focusing on finding new serum biomarkers that could improve the biological monitoring of these patients, in order to obtain a diagnosis of bone disorder while still in the early stage of CKD. FGF23 and Klotho have been the subject of many experimental studies, but with controversial results regarding their role in the bone physiology. Klotho and FGF23 are closely interconnected, with Klotho acting as a coreceptor for FGF23. More studies are needed in order to conclude exactly what role FGF23 and Klotho play in the bone mineralization.

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