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Chronic kidney disease – mineral and bone disorder: a complex scenario

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ABSTRACT

The chronic kidney disease-bone and mineral disorders (CKD-MBD) represents a dinamic area of research. Recently, new factors such as FGF-23 have been added to the classic list of regulators of bone metabolism, which include calcium, phosphorus, PTH and calcitriol. Vascular calcification, one of the most important complication of CKD-MBD is regulated by a complex variety of promoters and inhibitors. The relationship between vascular calcification, bone loss and mortality, together with the existence of likely common signaling pathways are subject of interesting investigations.

Keywords: CKD-MBD. Vascular calcification. FGF-23. Bone demineralization. Secondary hyperparathyroidism.

El complejo escenario de las alteraciones de metabolismo óseo y mineral en la enfermedad renal crónica

RESUMEN

Las alteraciones del metabolismo óseo en el escenario de la enfermedad renal crónica (CKD-MBD) constituyen un dinámico campo de estudio. Al conjunto de reguladores clásicos del metabolismo óseo tales como calcio, fósforo, hormona paratiroidea (PTH) y calcitriol se ha añadido el factor de crecimiento fibroblástico 23 (FGF-23). La calcificación vascular, una de las complicaciones más importantes de la enfermedad renal crónica, está sujeta a una compleja regulación en la que intervienen factores promotores e inhibidores del proceso de mineralización. La asociación entre calcificación vascular, desmineralización ósea y mortalidad y la existencia de factores y vías de señalización comunes está siendo objeto de interesantes investigaciones.

Palabras clave: *CKD-MBD. Calcificación vascular. FGF-23. Desmineralización ósea. Hiperparatiroidismo secundario.*

INTRODUCTION

In healthy individuals kidneys regulate calcium and phosphorus homeostasis through tubular reabsorption mechanisms. Patients with chronic kidney disease have seriously compromised homeostatic mechanisms, giving rise to different adaptive changes in calcium (Ca), phosphorus (P), parathyroid hormone (PTH), vitamin D and fibroblastic growth factor (FGF-23) levels.

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Among all the CKD disorders, those related to bone and mineral metabolism have a significant impact on morbidity and mortality. Traditionally, these abnormalities are included within the term 'renal osteodystrophy'.[1] Recently, the collection of biochemical abnormalities such as calcium, phosphorus, vitamin D and PTH disorders, changes in bone morphology such as variation in turnover, volume and bone mineralisation, and vascular or other soft-tissue calcifications, have been included under the definition of "chronic kidney disease mineral and bone disorders" (CKD-MBD).[2-4] There are various clinical signs, although secondary hyperparathyroidism (SHPT), fractures, bone pain, vascular calcification and cardiovascular events are highlighted as causing lower quality of life with a high morbidity and mortality.[5]

This review pays special attention to the Ca-P-PTH-vitamin D-FGF-23 axis, SHPT, vascular calcifications and their relationship with bone-mineral density (BMD) in CKD-MBD.

CA-P-PTH-VITAMIN D-FGF-23 AXIS

The most important factors that regulate bone and mineral metabolism are PTH, Ca, P, FGF-23 and the vitamin D related compounds. These factors are also totally interrelated and their effects depend on the target organ studied. The progression of CKD is associated with an early increase in FGF-23 and with a reduced functioning kidney mass; both factors favour the decrease in alpha-1-hydroxylase, the enzyme responsible for calcitriol synthesis, a physiologically active form of vitamin D. The final result is that this hormone's levels are found frecuently decreased.[6] The decrease in calcitriol significantly affects the intestinal Ca absorption, favouring the serum calcium to decrease and stimulating PTH.[7] In the bone, PTH stimulates Ca and P release, whilst in the kidney, it stimulates Ca reabsorption and inhibits phosphate reabsorption. Furthermore, PTH increases alpha-1-hydroxylase expression, therefore favouring calcitriol synthesis which increases intestinal Ca and P absorption.[8] As a result of these changes, serum Ca increases and P decreases.[9]

Reduced renal function also directly affects P reabsorption. The kidney is not capable of filtering enough P, and its high level in blood directly stimulates the parathyroid gland which, in turn, stimulates FGF-23 synthesis and secretion by the osteocytes.[10-13] In principle, FGF-23 was described to inhibit renal P reabsorption and calcitriol production; these effects are synergic and contrary to those of PTH, respectively.[14] However, previous studies have shown that FGF-23 not only has an effect on renal tissue but also on the parathyroid gland, which under normal conditions activates the mitogen-activated protein kinase (MAPK) pathway, reducing PTH synthesis and secretion.[15] To do so, it needs to bind to its FGFR-1 and 3 receptors, and its co-receptor *Klotho*. The *Klotho* gene codes for a transmembrane protein whose deficiency in rats results in a premature ageing-like phenotype, characterised by atherosclerosis, osteoporosis, hyperphospatemia, calcifications in the vascular medial layer, cardiac muscle and other tissues.[16] *Klotho* expression determines the tissue-specificity of FGF-23 and is increased by FGF-23 in a feedback mechanism.

SECONDARY HYPERPARATHYROIDISM

The parathyroid gland is the main organ responsible for Ca homeostasis in the organism, it senses serum Ca concentration via the Ca receptor (CaR), and also has vitamin D receptors (VDR). Its main action is PTH production.[17] Extracellular ionic Ca is the main parathyroid regulator; low levels stimulate PTH secretion in a matter of minutes, whilst high levels inhibit hormone release and, furthermore, favour its degradation within the parathyroid cells.[18-20] The result is a sigmoidal response in the parathyroid gland, in which small extracellular ionic Ca changes provoke large variations in PTH, achieving maximum inhibition in hypercalcaemia. The effects of Ca on PTH are mediated by its specific receptor, CaR,[21] a receptor belonging to the family of G protein-coupled receptors, which are found at the cell membrane.

Calcitriol acts on the parathyroid gland via its specific receptor, VDR, a high affinity and specificity receptor that belongs to the family of steroid/thyroid receptors.[22] When calcitriol is bound to a receptor, the calcitriol/VDR complex is translocated to the cell nucleus, forming a heterodimer with retinoid-X receptor (RXR). The calcitriol/VDR/RXR complex is bound to *vitamin D responsive elements* (VDR-E) present in the PTH gene's promoter region, blocking its transcription. Furthermore, calcitriol is able to indirectly inhibit PTH secretion, increasing intestinal Ca absorption, and at the same time, stimulating the reabsorption of Ca deposits.[23-25]

In CKD, the incorrect control of PTH secretion has partly been attributed to the reduced VDR and CaR expression which occurs in parallel to parathyroid gland growth. Parathyroid gland hyperplasia and the consequent increase in PTH secretion are responsible for SHPT observed in CKD. In mild and moderate forms of SHPT, the parathyroid gland is still able to respond to its main regulators, such as Ca, P and FGF-23.[26,27] On the other hand, in more advanced stages, especially in tertiary HPT, an irreversible form of HPT which is common in patients undergoing dialysis for a long time and kidney transplant patients, the parathyroid gland has a scarce or null response to usual stimuli and presents a high degree of autonomy.[28]

FGF-23/*Klotho* and Ca/CaR act on the parathyroid gland via mechanisms similar to the MAPK pathway,[15] with the common objective of reducing PTH synthesis and secretion. Under normal conditions, FGF-23 reduces PTH levels, although in chronic renal failure FGF-23 and PTH levels increase. This is due to a reduction in *Klotho*/FGFR in uremic parathyroid glands so that FGF-23 fails to exert its inhibitory effect likely due to a decrease in MAPK activation.[29]

VASCULAR CALCIFICATIONS

Soft-tissue calcification occurs in a high percentage of CKD patients and it has been reported since the 19th

century. Tissues that are frequently affected are blood vessels, lungs, kidneys, myocardium, coronary arteries, the central nervous system and gastric mucosa. Calcifications are associated with many factors such as excessive doses of calcitriol, hyperphosphatemia, tobacco use, arterial hypertension, increase in CaxP product, calcium overload, diabetes and male gender.[30] In CKD, lesions are mainly observed in the medial layer, but also in the intima layer and may affect the flow and vascular stiffness, with the consequent increase in arterial pressure and pulse wave velocity.

Vascular calcifications in the artery intima layer are often associated with previous atherosclerotic plaques. They affect the medial layer of medium calibre arteries, the aorta, and coronary arteries, with concentric Ca precipitates in vascular smooth muscle cells, causing stiffness and atherosclerosis. A phenotypic differentiation from vascular to bone cells is produced in these calcifications, critically reducing the contractile ability of muscle cells. Vascular complications often precede bone alterations, which occur very late and insidiously.[31] Although all histological forms of renal osteodystrophy have been associated with a greater prevalence of vascular calcifications, the one with the most impact is that observed in low turnover renal osteodystrophy.

There is a large number of promoters and inhibitors involved in vascular calcification. Promoters favour vessel calcification but, under normal conditions, there are more vascular calcification inhibitors circulating in the blood. With older age and CKD, this process is reversed and calcification inhibitors are down-regulated, while promoters are up-regulated.

Phosphorus is the most significant and probably the most studied vascular calcification promoter and its action is facilitated by the Na/P cotransporter, called PiT-1. Ca, osteopontin, osteocalcin, bone morphogenetic proteins (BMP-2 and BMP4), bone sialoprotein, type I collagen, and alkaline phosphatase (ALP) and many transcription factors (CbfaI/RUNX2 and MSX-2) have been described as downs tream vascular calcification promoters.[32-37] Several types of proteins are vascular calcification inhibitors. Fetuin-A is a circulating molecule that inhibits the formation of hydroxyapatite crystals, and there is a correlation between decreased fetuin-A levels and an increased mortality in patients on haemodialysis and patients with heart diseases.[38] Osteoprotegerin (OPG) also participates in inhibiting vascular calcification. Studies on KO mice for OPG showed calcifications in the aorta, renal arteries and osteoporosis.[39] Studies on KO mice for bone Gla protein (BGP) found calcification in the medial layer and the cartilage.[40] Among the bone morphogenetic proteins (BMP), BMP-7 is associated with vascular calcification inhibition. In KO mice studies for low density lipoprotein (LDL), it was shown that the expression of vascular osteocalcin is down-regulated in animals treated with BMP-7.[41]

RELATIONSHIP BETWEEN DEMINERALISATION AND VASCULAR CALCIFICATION

Although this relationship was first described 20 years ago,[42] the relationship between osteoporosis and vascular calcification has been underestimated, possibly because demineralisation, osteoporosis and vascular calcification have always been considered as disorders secondary to ageing. Age can not be excluded as a favouring factor, but evidence of a frequent association between bone fragility and vascular calcification further suggests that there may be a causal relationship between the two. The pathogenic factors involved in both processes are still to a large extent unknown.[43]

In 2004, a study was conducted on 193 HD patients showing that vascular calcification progression was closely linked with bone loss.[44] Along the same lines, another recent study with a 4-year follow-up showed that the greatest progression in vascular calcifications was not only related to a greater decrease in bone mass, but also with a greater incidence in osteoporotic fractures.[45] Similar results have been published in patients on dialysis, showing a greater prevalence of vascular calcifications in medium- and small-sized vessels in patients with more vertebral fractures.[46]

As a result, information on this matter suggests that bone loss, increase in fractures, and greater prevalence of vascular calcifications could be associated, and not only age-dependent.[45,47-49] KO mice models have been of vital importance to help clarify the relationship between bone mass, vascular calcifications and factors involved. A good example of this is the KO mouse study for OPG, a soluble decoy receptor of tumour-necrosis-factor-alpha (TNF-alpha) that is involved in severe osteoporosis and medial and sub-intimal calcification, findings that indicate that the lack of this protein has paradoxical effects promoting bone loss and vascular calcification.[50] OPG binds to and inhibits the receptor activator of nuclear factor kappa B ligand (RANKL),[51] which activates RANK and is essential for the maturation of osteoclast progenitors. Mice with OPG deficiency present an increase in vascular calcification in arteries and osteoporosis attributed to the stimulation of osteoclast activity. The mechanisms by which OPG and RANKL influence vascular calcifications are still unknown, although new studies have implied BMP-4 as a mediator.[52]

The transmembrane protein *Klotho*, which is involved in ageing and plays a critical role in regulating Ca, P and vitamin D synthesis, has also been involved in this relationship.[53,54] KO mice for *Klotho* gene develop hyperphosphoraemia, vascular calcifications and abnormalities in osteoblasts and osteoclasts, which lead to low-turnover osteopenia.[16,55,56]

To conclude, new factors such as FGF-23-*Klotho* have been added to the complex scenario of CKD–MBD. Vascular calcification, one of the most important mineral and bone disorders is very closely associated with CKD patient mortality. Far from being a simple physiological or chemical process, it is regulated in a complex manner, and at present, much effort is being made to understand its regulation. Furthermore, aspects such as the inverse relationship between vascular calcification and bone demineralisation and the existence of common signalling factors and pathways, constitute a new research area.

KEY CONCEPTS

1. FGF-23 has been added to the list of bone metabolism regulators in chronic kidney disease, given its effects on the kidney, parathyroid gland and vitamin D metabolism.
2. Vascular calcification, an important chronic kidney disease complication, is subject to a complex regulation in which mineralisation promoters and inhibitors intervene.
3. Epidemiological, clinical and experimental studies have shown a relationship between vascular calcification progression and bone demineralisation, suggesting that between both processes there is an interrelation, involving common mediators, which goes beyond the known effect that age has on both alterations.

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