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FGF-23 and PTH, mirror hormones. Their role in bone metabolism

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Summary
FGF-23 and PTH are two fundamental proteins in bone metabolism closely related since FGF-23 directly regulates both the expression and secretion of PTH.
PTH is the main regulator of the RANK/RANKL/OPG system considered essential for bone shaping and remodeling, but it is also an important regulator of the Wnt pathway in the bone, key to bone formation. Decrease of Wnt pathway inhibitors in the bone due to high levels of PTH could contribute to maintaining bone health, but also favor vascular calcification in the vessels. On the contrary, the action of FGF-23 would be opposite to that of PTH as by inhibiting the Wnt pathway in the bone, it will contribute to the loss of bone mass, while attenuating vascular calcification in the FGF-23 vessel.

Introduction

Conventionally, calcium, phosphorus, calcitriol and PTH were considered the only regulators of bone and mineral metabolism. In recent years, this axis of regulation has been complicated due to emergence of other factors with a crucial role in bone and mineral metabolism, such as fibroblast growth factor 23 (FGF-23) and the so-called klotho anti-aging protein.

Biological actions of FGF-23 and PTH

Biological action of FGF-23

FGF-23 is a 251 amino acid protein synthesized and secreted by bone cells, mainly osteoblast[1]. FGF-23 has been identified as the main regulatory factor of phosphorus metabolism, a critical element for maintaining skeletal integrity and for the development of multiple enzymatic processes[2]. In addition, in the last decade it has been attributed a notable role in the pathophysiology of vascular calcifications[3] and cardiovascular disease (CV), both in the general population[4-6] and in patients with chronic kidney disease[7].

The biological action of FGF-23 depends on the expression of a gene that acts as its co-receptor, called klotho[8]. Klotho is a 130-kDa transmembrane protein predominantly expressed in the renal distal tubule and to a lesser extent in the parathyroid gland and choroid plexus[9]. Klotho increases the affinity between FGF-23 and its FGFR receptors, forming a klotho/FGFR complex[10]. The final action of FGF-23 is carried out through its binding to the klotho/FGFR complex, although FGF-23 is capable to act independently of klotho through the FGFR4 receptor via the calcineurin pathway in cardiac and liver tissue[11-13].

The biological actions of FGF-23 take place in different organs: parathyroid gland, choroid plexus, pituitary and the kidney, being the later the main target organ. At a bone level, FGF-23 indirectly influences mineralization through the control of serum phosphorus and calcitriol levels. At the same time, serum calcitriol levels are one of the main regulators of FGF-23 production. In animal models, it has been observed that calcitriol stimulates in a direct and dose-dependent way the secretion of FGF-23 by the osteoblast[14]. This system makes it possible to maintain serum phosphorus levels within narrow margins[15]. In those situations in which there is an increase in the levels of calcitriol and, therefore, in the gastrointestinal absorption of phosphorus, the stimulation of the production of FGF-23 by the osteoblast will favor phosphaturia to avoid hyperphosphatemia.

The increase in serum phosphorus levels stimulates the production of FGF-23 by the bone and vice versa[16]. Although in murine models, increments of phosphorus in the diet influence the serum concentration of FGF-23[14,16], clinical trials assessing the effect of phosphorus ingestion on the levels of FGF-23 and phosphaturia have shown contradictory results. While some authors have not found an association between FGF-23 levels and phosphorus overload[17,18], others have described notable increases in circulating FGF-23 levels after several days of following a diet high in phosphorus[19-21].

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This discrepancy between studies has been attributed to differences in sample size, duration of phosphorus overload, to the time FGF-23 levels were identified, and to the patients' diet control. A possible explanation for these results may be the fact that acute phosphorus overload leads to a rapid response in PTH secretion, which increases phosphaturia within a few hours, while FGF-23 secretion would decrease with chronic and sustained phosphorus overload[18,22].

Biological action of PTH

Parathyroid hormone (PTH) is an 84 amino acid peptide hormone synthesized in the main cells of the parathyroid glands. It is essential for the maintenance of serum calcium concentration within narrow limits through direct actions on bone and kidney, and indirectly through actions on the gastrointestinal tract[23]. PTH also regulates phosphorus metabolism[24], decreasing its serum levels by inhibiting renal phosphate reabsorption in the distal and proximal tubules, although the effect in the later is quantitatively the most important[25].

PTH is released from parathyroid cells in a pulsatile, circadian fashion. The synthesis and secretion of PTH are controlled by the calcium sensing receptor (CaSR) expressed on the membrane of parathyroid cells[26]. The signal for starting the production and secretion of PTH is a drop in the concentration of extracellular ionic calcium, while the signal for decreasing its production and secretion is an increase in extracellular ionic calcium. To a lesser extent, PTH secretion can also be stimulated by increasing phosphorus levels, either directly or by reducing calcium levels[25].

One of the key mechanisms by which PTH regulates calcium homeostasis is related to the direct actions of PTH on osteoblasts and osteocytes and its indirect effects on osteoclasts. Although PTH stimulates both bone resorption and formation, the end result of the net bone balance will depend on the dose and periodicity of the PTH signal. Continuous exposure to PTH produces catabolic effects in the skeleton, while low and intermittent doses of PTH produce anabolic effects in the bone[27]. The best characterized catabolic effect of PTH excess occurs in primary hyperparathyroidism, with bone loss at both cortical and trabecular levels[28-32]. On the contrary, the PTH amino terminal peptide 1-34, teriparatide, and PTH intact molecule (PTH 1-84) have an anabolic action on the treatment of osteoporosis when administered in low doses in a pulsatile or intermittent manner[33,34].

The actions of PTH are mainly mediated by a receptor called PTH1R. The two forms of administration of PTH, continuous and intermittent, can regulate different genes at the bone level in different ways, thus promoting bone resorption or formation[35,36].

Interaction between FGF-23 and PTH

FGF-23 regulates PTH secretion. Several studies, both in vivo and in vitro, have shown that FGF-23 has a direct inhibitory effect on PTH, decreasing the expression and protein secretion of PTH, in a dose-dependent manner[37,38].

As with calcitriol, serum PTH levels regulate FGF-23 levels. PTH can stimulate the secretion of FGF-23 by the osteoblast[39]. Studies in murine models with primary hyperparathyroidism show increases in FGF-23 levels that are reversed after parathyroidectomy. These same results have been reported by Carrillo-López et al. in rat models with secondary hyperparathyroidism, where parathyroidectomy can reduce FGF-23[40] levels by three times. PTH would act as a stimulator of FGF-23 production in hypercalcemia caused by hypersecretion of PTH. The boost of FGF-23 would increase the renal elimination of phosphorus, avoiding tissue damage by preventing the potential appearance of extraosseous calcification caused by the dangerous association of hypercalcemia and hyperphosphatemia.

FGF-23 and PTH. Its regulation in bone metabolism

RANK/RANKL/OPG system

PTH is the primary regulator of the receptor activator of NFkappa beta (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) system that controls bone remodeling by inducing RANKL synthesis by osteoblasts, and negatively regulating OPG production. Both mechanisms favor osteoclastogenesis and bone resorption through a mechanism driven by protein kinase A (PKA)[41-43], since PKA agonists mimic PTH regulation of RANKL and OPG gene expression[42,44].

The RANK/RANKL/OPG system was identified in the mid-1990s as an essential regulator of bone shaping and remodeling[45]. Its role in bone maintenance is well known, but recent studies give it an important role in the calcification of vascular smooth muscle cells.

In the bone, osteoblasts and osteocytes synthesize and secrete RANKL, which binds to its transmembrane receptor RANK on bone marrow-derived osteoclast progenitors, allowing osteoclast maturation, activation and survival in order to initiate bone resorption. In addition, osteoblasts secrete OPG, a soluble decoy receptor for RANKL, which prevents the binding of RANKL to RANK, thus attenuating osteoclastogenesis[46].

Wnt/β-catenin pathway

PTH is also an important regulator of the Wnt/β-catenin pathway in the bone[47]. The activation of the signaling of the Wnt/β-catenin pathway is essential for bone formation[48,49] and has also been involved in the vascular calcification process[40,50-52].

The action on the Wnt pathway inhibitors in the bone is one of the most promising therapeutic goals in the prevention and treatment of the bone mass reduction, since the activity of this pathway is essential for the optimal remodeling and mineralization of the skeleton[53].

The rosozumab´s proven efficacy (an antibody against the best known Wnt pathway inhibitor, sclerostin (SOST)) in reducing bone loss in postmenopausal women, represents another therapeutic option for the treatment of these disorders[54]. SOST actions could include those on the vascular system. It is important to highlight that, in addition to its direct control of the bone remodeling and mineralization, SOST influences serum concentrations of calcitriol and FGF-23, both involved in the mineralization process[55].

Serum SOST increases in parallel with phosphorus, PTH and FGF-23[49,56,57], possibly due to its reduced renal clearance[58], and the use of anti-SOST monoclonal antibodies has been effective in preventing bone loss in normal rats or with chronic renal failure and low PTH[59]. However, anti-SOST therapy could not prevent bone damage in rats with the same degree of kidney damage, but with elevated PTH. These results contradict the finding by Cejka et al.[60], who suggested that serum SOST, a Wnt pathway inhibitor, could be an even more sensitive and accurate marker for bone remodeling than circulating PTH.

Studies in humans[56], in a mouse model with slowly developing polycystic disease[56,57] and in a model of chronic kidney disease with hyperphosphatemia[49], have shown that increased SOST in bone precedes serum increases in phosphorus, PTH and FGF-23. Increases in serum phosphorus, PTH, and FGF-23 simultaneously with the Wnt pathway signaling bone inhibition coincide with decreases in bone SOST, but with increases in other Wnt pathway inhibitors[49,56,57]. In fact, bone biopsies from patients with chronic kidney disease have shown that a greater inhibition of the Wnt pathway links to low levels of SOST in osteocytes[56], suggesting the contribution of other Wnt pathway inhibitors.

Our recent studies, analyzing the direct effect of PTH and FGF-23 on osteoblasts, have revealed that elevated PTH inhibits not only SOST increases, but also other Wnt pathway inhibitors, and that FGF-23 may have a direct inhibitory effect on the Wnt pathway in osteoblasts through the induction of DKK1[49].

SOST inhibition and other Wnt pathway inhibitors of the bone due to high levels of PTH could contribute to maintaining bone health, but it is important to note that the reduction of PTH of the Wnt pathway inhibitors in the vessels could favor vascular calcification. In fact, as mentioned above, recent studies in rats with chronic kidney disease fed a diet high in phosphorus, with both elevated and normal PTH levels (parathyroidectomy with supplementation of PTH 1-34 to avoid hypocalcemia) suggest that an elevated PTH favors vascular calcification. In contrast, normal circulating PTH levels were protective against aortic calcification despite elevated serum phosphorus[40]. In vitro studies confirmed this fact, showing that high doses of PTH in vascular smooth muscle cells subjected to a calcifying stimulus aggravated the calcifying process, while low doses of PTH were able to inhibit the calcification process, showing calcium content and osteogenic gene expression similar to those of cells not subjected to the calcifying stimulus[40].

On the contrary, the action of FGF-23 would be opposite to that of PTH, since, by inducing increases in DKK1, FGF-23 would inhibit the Wnt pathway in the bone, contributing to the loss of bone mass, while it could attenuate vascular calcification in the FGF-23 vessel.

Conclusion

The role of the regulatory axis consisting of calcium, phosphorus, calcitriol, PTH, FGF-23 and klotho exert on the activation or inactivation of the Wnt pathway, as well as the precision of the serum levels of Wnt activators and inhibitors to reflect its changes in a bone and vascular level, could allow the design of therapeutic strategies to prevent the bone-vessel axis deterioration.

Conflict of interests: The authors declare no conflict of interest.

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