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Review

The pleiotropic effects of paricalcitol: Beyond bone-mineral metabolism☆

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ABSTRACT

Secondary hyperparathyroidism (SHPT) is a common complication in patients with chronic kidney disease (CKD) that is characterised by elevated parathyroid hormone (PTH) levels and a series of bone-mineral metabolism anomalies. In patients with SHPT, treatment with paricalcitol, a selective vitamin D receptor activator, has been shown to reduce PTH levels with minimal serum calcium and phosphorus variations. The classic effect of paricalcitol is that of a mediator in mineral and bone homeostasis. However, recent studies have suggested that the benefits of treatment with paricalcitol go beyond PTH reduction and, for instance, it has a positive effect on cardiovascular disease and survival. The objective of this study is to review the most significant studies on the so-called pleiotropic effects of paricalcitol treatment in patients with CKD.

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Efectos pleiotrópicos del paricalcitol, más allá del metabolismo óseo-mineral

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RESUMEN

El hiperparatiroidismo secundario (HPTS) es una complicación habitual en pacientes con enfermedad renal crónica que se caracteriza por unos niveles elevados de hormona paratiroidea (PTH) y una serie de anomalías en el metabolismo mineral-óseo. En pacientes con HPTS, el tratamiento con paricalcitol, un activador selectivo de los receptores de la vitamina D, ha demostrado reducir los niveles de PTH con mínimas variaciones del calcio y del fósforo séricos. El efecto clásico de paricalcitol es el de mediador en la homeostasis mineral y ósea. Sin embargo, estudios recientes han indicado que los beneficios del tratamiento con paricalcitol van más allá de la reducción de PTH, por ejemplo, ocasionando efectos positivos en la enfermedad cardiovascular y en la supervivencia. El objetivo del presente trabajo es revisar los estudios más significativos sobre los llamados efectos pleiotrópicos del tratamiento con paricalcitol en pacientes con ERC.

Introduction

The classic physiological role of the vitamin D hormonal system is in the essential regulation of bone mineral metabolism. 1α,25-dihydroxyvitamin D3 binds with a high affinity to vitamin D receptors (VDR) and regulates serum levels of calcium (Ca) and phosphorus (P) by increasing their absorption in the intestine, increasing calcium reabsorption in the renal tubules, and suppressing secretion of parathyroid hormone (PTH), which in turn is a key regulator of mineral metabolism.[1] The decrease in 1α,25-dihydroxyvitamin D3 levels is attributed to the increased production of FGF23 induced by the accumulation of phosphate, which stimulates FGF23 production, even without an evident increase in serum P concentration. Therefore, vitamin D deficiency plays a central role in the development of secondary hyperparathyroidism (SHPT), a common early complication in patients with chronic kidney disease (CKD)[2–4] that progresses as glomerular filtration rate decreases.[4] SHPT is characterised by high PTH levels and the presence of bone and mineral abnormalities.[1,2] SHPT and abnormal mineral metabolism lead to clinical consequences at 2 levels: in the musculoskeletal system and in the cardiovascular system. The consequences in the musculoskeletal system are due to increased bone remodelling, the most common condition being osteitis fibrosa. The consequences on the vascular system are related to the increased risk of vascular calcification.[2]

The usual treatment for SHPT involves dietary phosphorus restriction and drugs such as phosphate binders, VDR activators (selective and non-selective), and/or calcimimetics such as cinacalcet.[2,3]

The first commercial VDR activator (VDRA) was calcitriol.[2] Calcitriol is an important drug in the treatment of SHPT in patients with CKD. However, due to its potent effects on intestinal Ca and P absorption, this molecule frequently induces hypercalcaemia, hyperphosphatemia, and renal calculi formation, and increases the likelihood of calcification.

In 1998, paricalcitol was approved for the treatment of SHPT.[5] This third-generation vitamin D analogue emerged in view of the need for treatments that could inhibit high PTH concentrations in patients with SHPT, with a minimal effect on serum concentrations of Ca, P, and the calcium-phosphorus product (Ca × P), without renal toxicity.[4] Recently, paricalcitol has been reclassified by the World Health Organisation to H05BX (other antiparathyroid agents) rather than A11CC (vitamin D and analogues).

The beneficial effect of paricalcitol in reducing PTH levels in patients with CKD is widely established.[4] Its therapeutic efficacy is due to the tissue selectivity of its mechanism of action.[4] Paricalcitol is considered a selective VDR activator. The term "selective" refers to the differential binding of the ligand to the VDR. The synthesis of selective vitamin D receptor activators (sVDRA) such as paricalcitol and maxacalcitol came about because of the clinical need to broaden the therapeutic window of the classic vitamin D forms and to try to reduce the risk of hypercalcaemia and hyperphosphatemia associated with the non-selective derivatives calcitriol and alfacalcidol. Selective VDRAs allow more efficient inhibition of PTH synthesis and secretion, with a lesser effect on intestinal absorption of calcium and phosphorus.[6] The selectivity of paricalcitol is explained at a biochemical level by the C-terminal of the vitamin D receptor, which is the region that binds specifically to the ligand.[6]

Although current clinical practice guidelines for CKD limit the use of VDRAs to the treatment of SHPT,[7] the VDR has been identified in more than 30 different human tissues (Table 1).[8] This suggests the different actions that vitamin D may have, in addition to those related to bone and mineral homeostasis, giving what are known as the "non-classical" effects of vitamin D. Such effects include an anti-inflammatory immunomodulatory effect on cardiomyocyte remodelling,[9] a renal protective effect, and to a lesser degree, an effect on the progression of vascular remodelling, particularly in some derivatives.

The wide dissemination of VDRs in human tissues explains some potential effects in terms of improved cardiovascular