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Secondary hyperparathyroidism: Update

Erick Alexander Cabrera Estrada *, Epitafio Rafael Mestre Sequeda, Iván Alberto Salas Pinzón, Olivia del Carmen Silva Sánchez, Iris Michell Racedo Segura, Diana Carolina Caicedo Sánchez, Eduard Orlando Vargas Plazas, Carlos Mario Moscote Terán, Gabriela Lucia Lara Barreto and Hilda Steffi Pineda Padilla

Department of Internal Medicine, Faculty of Health Sciences, Universidad Libre, Barranquilla, Colombia.

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Abstract

Secondary hyperparathyroidism is a clinical condition characterized by an increase in the synthesis and secretion of parathyroid hormone (PTH). Its presentation will be conditioned by the development of stimuli such as hyperphosphatemia, hypocalcemia, vitamin D deficiency, and PTH resistance. The most common cause of secondary hyperparathyroidism is chronic kidney disease, a pathological condition in which all the afore mentioned stimuli converge.

Secondary hyperparathyroidism is evidenced by an increase in the size of the parathyroid glands, favored by cellular hyperplasia and hypertrophy. At the bone level, there will be an increase in the quantity and activity of osteoblasts and osteoclasts, leading to bone with unusual structural characteristics.

Symptoms related to the disease include itching, bone pain, concentration alteration, and depression. In the long term, patients have a higher risk of cardiovascular mortality. Therapeutic options include calcimimetics, phosphate binders, vitamin D supplements, and surgery.

Keywords: Hyperparathyroidism; Hyperphosphatemia; Hypercalcemia; Parathyroid hormone

1. Introduction

PTH plays a fundamental role in calcium and skeletal metabolism. The most relevant stimuli in PTH secretion are hypocalcemia and hyperphosphatemia. Conversely, PTH secretion is reduced by 1,25-dihydroxy vitamin D3. Secondary hyperparathyroidism results from increased PTH secretion due to parathyroid hyperplasia caused by metabolic alterations such as hypocalcemia, hyperphosphatemia, or decreases in vitamin D levels. The most common cause of secondary hyperparathyroidism is chronic kidney disease, which encompasses all the mentioned metabolic disorders. As a consequence of increased PTH secretion, serum calcium levels will rise, impacting bone, intestinal, and renal levels [1].

2. Methodology

A systematic review was conducted by selecting original articles, available research reviews, written in English and/or Spanish, through recognized databases such as PubMed, Scielo, ScienceDirect, Wiley, PLOS ONE, among others. Regardless of the publication year, the search terms used included hyperparathyroidism, hyperphosphatemia, hypercalcemia, parathyroid hormone.

* Corresponding author: Erick Alexander Cabrera Estrada

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3. Results

3.1. Parathyroid Physiology

The secretion of PTH by the chief cells of the parathyroid glands is primarily regulated by calcium concentration. Calcium-sensing receptors (CaSR) are located on the surface of chief cells; when calcium binds to these receptors, PTH secretion and PTH gene expression are inhibited. When serum calcium levels are elevated, the degradation of PTH into inactive fragments is also induced. Conversely, when serum calcium levels are low, PTH gene expression and PTH secretion are increased.[2]

The active form of vitamin D, 1,25-dihydroxyvitamin D, binds to vitamin D receptors located in the chief cells of the parathyroids, inhibiting PTH gene expression and parathyroid cell proliferation [3]. Other regulatory mechanisms of PTH secretion include lithium, transforming growth factor α, prostaglandins, inorganic phosphate, and fibroblast growth factor.[4]

The production of PTH begins with the generation of a pre-pro-PTH polypeptide consisting of 115 amino acids, which is cleaved in chief cells into the active 84-amino acid intact PTH peptide. The 34-amino acid fragment of its NH2-terminal end constitutes the biologically active part of intact PTH and binds to the PTH/PTHrP type 1 receptor coupled to G protein (PTHR1). This receptor is also highly expressed in bones and kidneys [5].Maximum PTH secretion occurs when extracellular calcium concentrations are low and maximum suppression occurs when extracellular calcium concentrations are high [6].

At the renal level, PTH acts on the ascending limb of the loop of Henle and the distal convoluted tubule, where it increases calcium reabsorption, inhibits phosphate reabsorption, and increases phosphate excretion. Additionally, PTH promotes the conversion of 25-hydroxyvitamin D into its active metabolite calcitriol (1,25[OH]2D) by activating 1α-hydroxylase. Calcitriol enhances calcium absorption from food in the small intestine [7].

In bone, PTH has both anabolic and catabolic effects. PTH binds to osteoblasts via the PTHR1 receptor, leading to the formation of new bone matrix and its mineralization. However, osteoblast activation also leads to the production of regulators of osteoclast formation, such as the nuclear factor-kB activator receptor, the ligand of the nuclear factor-kB activator receptor, and osteoprotegerin [8]. PTH indirectly increases osteoclastic activity through the effects of the ligand of the nuclear factor-kB activator receptor and osteoprotegerin, resulting in increased bone resorption with the release of calcium and phosphate ions [9].

The half-life of PTH is 3-5 minutes, although variations between 1 and 21 minutes can occur. The liver and parathyroid cells break down PTH into fragments that are subsequently excreted at the renal level. Renal clearance of PTH is slower than degradation; therefore, 80% of circulating PTH corresponds to inactive fragments, with only 20% being biologically active intact PTH [10].

3.2. Etiopathogenesis

Secondary hyperparathyroidism encompasses one of the most common complications in chronic kidney disease and generally occurs from the early stages of the disease. One of the initial mechanisms leading to parathyroid gland overstimulation is phosphate retention, resulting from decreased excretion in the proximal tubule due to reduced renal mass [11]. Prolonged exposure to hyperphosphatemia, combined with reduced serum calcium levels and elevated levels of fibroblast growth factor (FGF)-23, induces the parathyroid glands to produce and excrete more PTH [12].

Another indirect mechanism through which phosphorus can stimulate PTH synthesis by the parathyroid glands is the inhibition of the enzyme 25(OH)D-1α-hydroxylase, which is involved in calcitriol synthesis in the proximal renal tubule. Decreased levels of calcitriol stimulate PTH secretion and production [13]. Phosphorus also stimulates fibroblast growth factor-23 (FGF23), which, in turn, stimulates PTH secretion through pathways that have not yet been fully elucidated. [14]

In some experimental studies, another additional mechanism secondary to hyperphosphatemia has been considered: an increase in the expression of the calcium-sensing receptor (CaSR), the main promoter of PTH secretion and synthesis [15].

The primary function of vitamin D is to maintain adequate bone homeostasis by inducing increased intestinal calcium absorption and reducing PTH synthesis through genomic and non-genomic effects [16]. Chronic kidney disease is characterized by a continuous reduction in multifactorial vitamin D levels, progressive reduction in the number of nephrons, inhibition of CYP27B1, irregular cytokine signaling, and decreased levels of αKlotho [17].

While the main cause of secondary hyperparathyroidism is renal disease and associated metabolic disorders, other less prevalent causes have been described, such as malabsorption syndrome, celiac disease, cystic fibrosis, congenital disorders, among others, as included in Table 1.[18].

Table 1 Causes of Secondary Hyperparathyroidism

Chronic renal failure
Deficiency of 25-hidroxyvitamin D.
Malabsorption syndromes Celiac disease Cystic fibrosis Short bowel syndrome Bariatric procedures
Medicaments Lithium Diuretics (hydrochlorothiazide, furosemide)
Metabolic disturbances Hypermagnesemia Hyperphosphatemia
Congenital disorders Transient neonatal hyperparathyroidism DiGeorge syndrome

Adapted from: Sabiston. Textbook of Surgery: The Biological Basis of Modern Surgical Practice, 21st edition.

3.3. Clinical Manifestations

Initially, secondary hyperparathyroidism tends to be asymptomatic. In more advanced stages, clinical manifestations are variable and nonspecific. Patients may present with severe bone pain, itching, pathological fractures, and muscle weakness. However, they may also develop vague symptoms such as memory loss, difficulty concentrating, sleep disorders, and emotional lability. The Parathyroidectomy Symptom Score (PSS) system synthesizes all the important clinical manifestations of secondary hyperparathyroidism [19].

In chronic kidney disease (CKD), secondary hyperparathyroidism causes alterations in bone remodeling, mineralization, volume, and growth, known as renal osteodystrophy. Bone alterations are classified based on the degree of remodeling and mineralization into mild forms, fibrous osteitis, osteomalacia, adynamic bone disease, and mixed bone disease [20].

Among the most significant extra-skeletal manifestations are extraosseous deposits of hydroxyapatite crystals in soft tissues and various organs, as well as vascular structures, leading to vascular calcification of small vessels. Secondary hyperparathyroidism is a significant risk factor for the development of calciphylaxis, characterized by ischemia and necrosis, histologically characterized by arteriolar calcification in the dermis and subcutaneous adipose tissue [21]. In patients with CKD and hyperparathyroidism, coronary artery calcification can lead to cardiac ischemia, serving as a predictor of overall mortality and cardiovascular mortality [22]

3.4. Diagnosis

Assessment of renal function, serum levels of 25-hydroxyvitamin D, calcium, phosphate, magnesium, and 24-hour urinary calcium is essential for establishing the differential diagnosis between primary and secondary hyperparathyroidism. The diagnosis of hyperparathyroidism is based on the finding of absolute or relatively elevated

levels of PTH. The diagnostic differentiation between primary and secondary hyperparathyroidism is established based on high or low serum calcium levels, respectively. Additionally, in the context of normal renal function, both forms of hyperparathyroidism generally present with low serum phosphate levels due to the phosphaturic effects of PTH [23].

In patients with CKD, PTH levels usually rise when the glomerular filtration rate falls below 60 ml/min/1.73m^2, and hyperphosphatemia occurs when the rate falls below 30 ml/min/1.73m^2. Elevated PTH levels above 5 times the upper limit of normal reflect high-turnover bone disease [24].

PTH is the marker that provides the most information and is widely related to bone histology. Measurement of intact PTH (iPTH) is recommended, with values ranging from 10 to 65 pg/ml. These values should always be interpreted in the appropriate clinical context and associated with serum calcium and phosphate levels. In patients with CKD, higher PTH levels are needed to maintain adequate bone function, which can reach up to 4 times the upper limit of normal (125-250 pg/ml) in patients on renal replacement therapy [25].

Serum calcium levels are usually low or normal in most patients with secondary hyperparathyroidism and chronic kidney disease; however, in a small proportion of patients, calcium begins to rise to evident levels of hypercalcemia, typically associated with an increase in PTH levels. This condition is considered tertiary hyperparathyroidism and is characterized by a reduced inhibitory effect of calcium on PTH secretion, usually as a consequence of decreased CaSR expression in the parathyroid glands [26].

Secondary hyperparathyroidism with normal renal function is generally associated with low serum phosphate levels due to the inhibitory effect of PTH on sodium-phosphate cotransporters in renal tubules. However, this situation is not similar in patients with chronic kidney disease since, in addition to the decreased excretion of phosphate due to reduced glomerular filtration, there is also a resistance to the phosphaturic effect of FGF23 due to decreased αKlotho expression at the tubular level [27].

In patients with secondary hyperparathyroidism, alkaline phosphatase levels rise as a reflection of PTH action on bone. The clinical utility of this marker lies in its potential for monitoring disease progression and evaluating treatment response. A decrease in its levels may suggest bone remineralization. However, it should always be kept in mind that its origin may be extraosseous, for example, in the liver and intestine [28].

The importance of bicarbonate in bone metabolism is generally underestimated. Sustained low serum levels are associated with increased bone resorption and probably a higher prevalence of high-turnover bone disease. The goals are to maintain it at 20-23 mEq/l pre-dialysis and 26-28 mEq/l post-dialysis [29].

Imaging studies are important in the evaluation of secondary hyperparathyroidism; however, they are not mandatory. X-rays of the hands, skull, pelvis, and spine may show specific skeletal lesions of secondary hyperparathyroidism, such as bone resorption, fractures, periosteal new bone formation, osteosclerosis, and brown tumors. However, these findings have low sensitivity and specificity, especially in the early stages of the disease [30].

Assessment of bone mass and bone mineral density is adequately appreciated with dual-energy X-ray absorptiometry (DXA), through which we can establish the diagnosis of reduced bone mass, either osteopenia or osteoporosis, and it also serves as a reliable predictor of fracture risk. Advanced imaging techniques such as quantitative computed tomography and high-resolution peripheral quantitative computed tomography have greater value for diagnosis and prognosis. These aids provide a diagnosis very close to histological findings and predict fracture risk significantly. However, despite their good performance, these techniques are less available [31].

The study of the number of hyperplastic glands and the approximate calculation of their volumes is a fundamental step in determining the stage of secondary hyperparathyroidism in chronic kidney disease, and it is also a tool for surgical intervention planning when indicated. Different methods have been established for evaluating the morphological and functional characteristics of the parathyroid glands, such as high-resolution ultrasound with color Doppler, Tc-MIBI scintigraphy, computed tomography, magnetic resonance imaging, PET, and SPECT [32].

4. Treatment

The main goal of treating secondary hyperparathyroidism is to correct the triggering metabolic disorders previously described. One of the first strategies involves maintaining adequate phosphate levels, either by reducing its intake in the diet or its gastrointestinal absorption. However, it has been shown that dietary phosphate restriction, despite being a good strategy in these patients, confers a higher risk of malnutrition and mortality [33]. In patients with advanced

chronic disease and on renal replacement therapy, it is generally necessary to use medications that reduce gastrointestinal phosphate absorption. These medications can be classified as calcium-based and non-calcium-based phosphate binders; however, the former group has been associated with greater vascular calcification and, therefore, higher cardiovascular morbidity and mortality [34].

Previously, aluminum salts were used as phosphate binders due to their effectiveness in reducing serum phosphate levels; however, they are currently not considered first-line treatment due to their toxic effects on bone, the central nervous system, and bone marrow. This group of medications has been replaced by calcium-containing binders, such as calcium acetate and calcium carbonate [35].

Magnesium has been shown to act as a calcimimetic, regulating parathyroid function regarding PTH secretion and positively regulating receptor expression in the parathyroid glands. This leads to increased gland sensitivity to calcium action inhibitors, vitamin D, and FGF23 [36].

Recently, different non-aluminum and non-calcium phosphate binders have been developed, including sevelamer hydrochloride, a non-absorbable synthetic polymer that has demonstrated efficacy in adequately reducing phosphate levels. Additionally, various studies have shown the impact of this medication on reducing mortality from all causes at 36 months of follow-up [37].

There are other phosphate binders that have demonstrated efficacy in controlling hyperphosphatemia, including lanthanum carbonate, ferric citrate, sucroferric oxyhydroxide, and colestilan, which have shown adequate reduction in serum phosphate levels and improved survival [38] [39] [40].

Patients with chronic kidney disease and secondary hyperparathyroidism generally have reduced calcitriol levels, as a result of decreased renal mass unable to support adequate synthesis, in addition to the potent suppressive effect of FGF23 on 1α-hydroxylase. Therefore, vitamin D supplementation is a common strategy for treating hyperparathyroidism. KDIGO 2016 recommendations propose not to routinely use vitamin D analogs to avoid the risk of hypercalcemia and excessive PTH suppression; however, the use of active vitamin D is correct in patients with stage 4-5 chronic kidney disease with uncontrolled hyperparathyroidism [41].

Paricalcitol is an alternative for controlling serum PTH levels in patients with secondary hyperparathyroidism and chronic kidney disease with and without dialysis. Compared to calcitriol, paricalcitol suppresses PTH earlier and reduces the risk of hypercalcemia [42].

Treatment with calcimimetics is one of the main strategies in the management of secondary hyperparathyroidism. This group of medications are potent inhibitors of PTH secretion and proliferation of parathyroid gland cells. Calcimimetics act on the CaSR by simulating the effect of calcium, increasing the sensitivity of the parathyroid glands to calcium. This leads to a reduction in the calcium concentrations required to reduce PTH secretion by 50%. The calcimimetics currently available for the treatment of secondary hyperparathyroidism are cinacalcet, etelcalcetide, and evocalcet [43].

Cinacalcet has a rapid inhibitory effect on PTH, which occurs within several hours, unlike vitamin D receptor activators, which require several days to achieve adequate suppression. Cinacalcet also reduces serum calcium and phosphate levels by blocking the mobilization of calcium and phosphate from bone due to PTH suppression. Gastrointestinal symptoms such as nausea and vomiting are common adverse effects of cinacalcet use, in addition to hypocalcemia [44].

Surgical resection of the parathyroid glands is a therapeutic option in patients with secondary hyperparathyroidism refractory to treatment with calcimimetics and vitamin D receptor activators. The guidelines of the Japanese Society for Dialysis Therapy recommend parathyroidectomy in patients with secondary hyperparathyroidism with intact PTH levels > 500 pg/ml who are refractory to medical treatment [45]. Parathyroidectomy is associated with decreased mortality in patients with refractory secondary hyperparathyroidism, and it is also related to a decrease in the occurrence of coronary syndrome and peripheral arterial disease [46].

5. Conclusion

Secondary hyperparathyroidism is a common complication in patients with advanced chronic kidney disease; however, its origin can also be multifactorial. Its clinical manifestations are mainly secondary to the mineral and bone disorders that occur, but they can also present systemic manifestations that impact the morbidity and mortality of patients. Advances in the study and understanding of the pathogenesis of the disease have led to the development of new

therapeutic strategies that substantially impact disease management. However, there are still controversies that have not been fully resolved, and deciphering them may offer better strategies to improve the quality of life of patients.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflicts of interest.

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