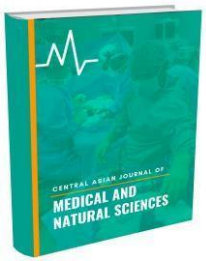

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Article

Secondary Hyperparathyroidism In Chronic Kidney Disease: Mechanism Of Development

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Abstract: This study explores the mechanisms of secondary hyperparathyroidism (SHPT) development in chronic kidney disease (CKD) and its implications. SHPT arises due to chronic hypocalcemia and is exacerbated by disturbances in calcium-phosphorus metabolism and vitamin D deficiency. A literature review methodology was used, analyzing peer-reviewed studies to understand SHPT's pathophysiology, diagnostic markers, and treatment strategies. Findings indicate that SHPT results in elevated parathyroid hormone (PTH) levels, causing systemic skeletal damage, vascular calcification, and renal osteodystrophy. Early diagnosis involves assessing serum PTH, calcium, and phosphorus levels, alongside imaging and histomorphometric bone analyses. Treatment includes dietary phosphorus restrictions, phosphate binders, vitamin D analogs, calcimimetics, and parathyroidectomy in severe cases. These interventions aim to regulate PTH levels and prevent complications like fractures and calciphylaxis. This research underscores the necessity of a multidisciplinary approach for effective management and highlights the importance of innovative therapies for long-term SHPT control in CKD patients.

Keywords: Secondary Hyperparathyroidism (SHPT), Chronic Kidney Disease (CKD), Calcium-Phosphorus Metabolism

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1. Introduction

Secondary hyperparathyroidism (SHPT) is a condition that occurs in response to chronic hypocalcemia (low blood calcium levels) and is linked to a higher release of parathyroid hormone (PTH) by the parathyroid glands. This disease is most often a compensatory reaction of the body to calcium deficiency caused by various pathologies, especially chronic kidney disease or impaired calcium metabolism.

2. Materials and Methods

This review article compiles existing knowledge on SHPT in CKD. The authors conducted a literature search to identify relevant studies published in peer-reviewed journals. The search strategy focused on keywords such as "secondary hyperparathyroidism," "chronic kidney disease," "calcium-phosphorus metabolism," "renal osteodystrophy," and "treatment." The retrieved articles were critically appraised to ensure their scientific merit and relevance to the topic (references to be added).

3. Results

Mechanism of Development.

The main mechanism of hyperparathyroidism (HPT) development is an increase in PTH secretion, which maintains serum calcium concentration within narrow limits through direct effects on the kidneys, bones and indirectly through effects on the gastrointestinal tract, as well as regulates phosphorus metabolism [1,2]. Parathyroid hormone increases the concentration of Ca++ and phosphates in the blood. The synthesis, secretion, and hydrolytic cleavage of parathyroid hormone is regulated by the concentration of calcium. A decrease in the level of calcium in the blood leads to stimulation of the synthesis and release of the hormone, and an increase causes the opposite effect. PTH 1-84 (intact - "whole") and the N-terminal fragment of PTH 1-34 have biological activity. The biological effect of PTH on bone tissue is to enhance bone resorption by stimulating osteoclasts. In the kidneys, PTH increases the production of 1,25-dihydroxyvitamin D. It additionally enhances the reabsorption of calcium in the distal tubules and reduces the reabsorption of phosphorus in the proximal tubules. PTH increases the absorption of calcium and phosphorus in the intestine by stimulating the production of 1,25-dihydroxyvitamin D. Calcium has a negative effect on the digestive tract through a calcium-sensitive receptor. Phosphorus has a direct stimulating effect on the parathyroid glands [3,4,5]

The most common causes of HPT are chronic kidney disease (CKD), vitamin D deficiency and metabolic disorders, malabsorption syndrome in gastrointestinal diseases and bariatric operations in which the reabsorption of fat-soluble vitamins is impaired. Factors such as vitamin D and calcitriol deficiency, decreased activity of calcium-dependent (CaSR) and vitamin D-dependent receptors (VDR) of the parathyroid glands play a major role in the development of secondary hyperparathyroidism.

The main reason for the decrease in bone mass in patients after bariatric surgery is vitamin D deficiency. The prevalence of vitamin D deficiency after surgery depends on many factors: the type of surgery performed, patient management tactics and patient compliance with vitamin D recommendations [6]. A decrease in vitamin D levels leading to an increase in PTH production is observed in patients in the long term after bariatric surgery. The increase in PTH level depends on the length of the diverting intestinal loop after gastric bypass surgery [7].

HPT in CKD. A progressive decrease in the mass of active nephrons and a decrease in filtration capacity in CKD causes an increase in the level of phosphates and an associated decrease in the level of ionized calcium. Hyperphosphatemia causes hypocalcemia, since ionized calcium forms calcium phosphate with phosphorus (an insoluble complex), which leads to the development of extra-skeletal calcification and calcifylaxis, and hypocalcemia leads to stimulation of PTH production by the parathyroid glands. In addition, high phosphorus levels inhibit hydroxylase of the proximal renal tubules, which increases hyperphosphatemia in patients with CKD [8]. A progressive decrease in glomerular filtration rate leads to a decrease in vitamin D levels. Hyperphosphatemia and hypocalcemia directly stimulate the synthesis of PTH, which leads to bone remodeling, reduces bone strength and increases the number of fractures [9,10].

In recent years, studies have shown changes in specific biomarkers of CKD - FGF23 (Fibroblast Growth Factor) and Klotho proteins that participate in the metabolism of phosphorus, calcium and vitamin D. FGF23 (molecular weight is 32 kDa), located on chromosome 12, is secreted mainly by osteocytes to maintain the metabolism of phosphorus and minerals [11,12]. In addition, FGF23 affects vitamin D metabolism by inhibiting 1-α-hydroxylase, which converts 25(OH)D into the active form of 1,25(OH)2 D [13].

The Klotho protein, a transmembrane protein produced by the kidneys, is recognized as an early biomarker for chronic kidney disease (CKD) and may exert

additional independent effects on calcium and phosphate excretion, separate from FGF-23 [14, 15, 16]. In CKD, the buildup of both membrane-bound and soluble Klotho results in elevated serum FGF-23 levels because of reduced FGF-23 clearance, causing phosphate retention. The resistance to FGF-23's phosphate effects arises from Klotho deficiency, which becomes noticeable as phosphate retention increases with the progression of CKD. An animal study has indicated that Klotho deficiency can lead to a premature aging syndrome linked with ectopic calcification in soft tissues [17].

The main signs of HPT are systemic skeletal damage, the development of renal osteodystrophy, calcification of vascular walls and calcifylaxis. Clinical symptoms manifest as symptoms of chronic hypocalcemia, which include general weakness, fatigue, muscle cramps, tingling or numbness of the extremities. Prolonged hyperparthyroidism can lead to the development of itching, dryness and dull skin color. Vitamin D deficiency and hypocalcemia can lead to bone metabolism disorders and a decrease in bone mineral density, osteopenia and osteoporosis with the development of low-energy vertebral fractures and osteomalacia. Severe complications of secondary hyperparathyroidism include renal osteodystrophy, calcification of arteries and heart valves, ischemic necrosis of soft tissues, and bone fractures. Vitamin D deficiency is manifested by myopathy, especially in the proximal extremities, difficulty walking, loss of balance and falls when walking. A serious complication of hyperparathyroidism is the development of calcification - the deposition of calcium salts in the middle membrane of arteries of various calibers (mediacalcinosis). Studies show a direct relationship between an increase in parathyroid hormone levels and the severity of calcification in patients with HPT. An increase in PTH levels above 800 pg/ml increases the risk of cardiovascular mortality in dialysis patients [3,9].

The diagnosis of HPT includes: elevated blood PTH levels, low calcium levels (hypocalcemia) or normal, but with a deficiency of the active form of vitamin D, hyperphosphatemia (especially in CKD), a decrease in vitamin D levels, which is a key indicator when its synthesis or absorption is impaired.

Violations of phosphorus-calcium metabolism are the cause of the development of renal osteodystrophy. Assessment of bone changes and extra-skeletal calcification is performed using densitometry, parathyroid scintigraphy, echocardiography, CT or MRI. A reliable way to assess bone metabolism is a bone biopsy with histomorphological examination according to the standard nomenclature of the American Society for Bone and Mineral Research (ASBMR). The diagnosis of renal osteodystrophy is confirmed by histomorphometry of a bone biopsy [18,19,20].

An important stage of diagnosis is also the exclusion of primary hyperparathyroidism (hyperfunction of the parathyroid glands), which may have similar clinical symptoms, but is caused by a variety of causes, including tumors of the parathyroid glands.

Treatment

Management of SHPT in CKD focuses on controlling serum calcium, phosphorus, and PTH levels. Dietary restrictions on phosphorus intake are crucial. Phosphate binders, such as aluminum hydroxide, calcium salts (acetate or carbonate), or sevelamer hydrochloride, are used to bind dietary phosphorus in the intestine and prevent its absorption. Vitamin D analogs like calcitriol help to improve intestinal calcium absorption and suppress PTH production. Calcimimetics, a class of drugs that increase the sensitivity of parathyroid glands to calcium, further suppress PTH secretion. In cases of severe or uncontrolled SHPT, parathyroidectomy, surgical removal of parathyroid tissue, may be considered. Treatment decisions are based on the stage of CKD and severity of SHPT. Target levels for calcium, phosphorus, and PTH may vary depending on the stage (reference needed for target levels). Treatment of SHPT in CKD should begin in stage III (estimated GFR of 60 ml/min). It is important to know the target levels of serum calcium, phosphorus and

intact PTH, depending on the stage of CKD. The management of secondary hyperparathyroidism primarily involves a low-phosphorus diet, phosphate-binding medications, vitamin D analogs, calcimimetics, and, when needed, parathyroidectomy. Nutrition plays an important role in the treatment of secondary hyperparathyroidism. Patients are advised to follow a diet with a restriction of phosphates and a sufficient amount of calcium. In some cases, it is necessary to exclude foods containing high levels of phosphorus from the diet (for example, meat products, cheeses, dairy products with high phosphorus content). Phosphate-binding drugs (aluminum hydroxide, calcium salts, sevelamer hydrochloride) are the basis for the treatment of HPT. Aluminum hydroxide forms insoluble aluminum-phosphorus compounds in the intestine and effectively reduces the severity of phosphatemia. In patients with vascular and/or soft tissue calcification, preference should be given to calcium-free phosphate-binding drugs. The most commonly used calcium salt preparations are calcium acetate and calcium carbonate. Calcium acetate provides just 169 mg of elemental calcium, while calcium carbonate offers between 200-600 mg. Calcium salts are not recommended for patients whose serum calcium levels exceed 10.5 mg/dl. Meanwhile, sevelamer hydrochloride is free of potassium, magnesium, and aluminum, and it acts as a cationic polymer that binds to dietary phosphorus via ion exchange. Sevelamer carbonate is as effective as hydrochloride, but has fewer side effects.

Vitamin D is one of the most effective means of treating HPT. It is known that calcitriol deficiency or the development of resistance to it is the main pathogenetic link in the development of HPT and drugs and supplements with vitamin D are used to suppress PTH levels. It should be borne in mind that calcitriol enhances the absorption of calcium and phosphorus in the intestine, increasing their concentration in the blood.

Calcimimetics are a group of drugs that increase the sensitivity of calcium-sensitive receptors to calcium in the parathyroid glands, thus suppressing the production of parathyroid hormone. Long-term use of cinacalcet leads to a decrease in the size of the OSH, reduces the rate of bone remodeling, and also reduces the risk of cardiovascular mortality in HPT [21,22].

Surgical treatment. If secondary hyperparathyroidism progresses to a severe degree and conservative treatment does not have an effect, surgical intervention may be required. Parathyroidectomy is performed if all conservative treatment methods are ineffective. Parathyroidectomy is indicated in the case of soft tissue calcification, severe hypercalcemia, and PTH levels above 800 pg/ml. Surgical treatment can be performed by subtotal parathyroidectomy, when the least altered part of the LV is left within the neck. Total parathyroidectomy with autotransplantation into brachioradialis or sternocleidomastoid muscle makes it possible to exclude cases of recurrence of hyperaparthyroidism and control the level of PTH. The prognosis after parathyroidectomy is favorable: bone pain, itching disappear, skin trophism improves in places of ischemic necrosis due to calcifylaxis. However, it should be borne in mind that a sharp decrease in PTH levels can lead to the development of "hungry bone syndrome" associated with a sharp decrease in blood calcium levels. Therefore, strict postoperative monitoring of the level of total and ionized calcium in the patient is very important.

The prognosis for secondary hyperparathyroidism depends on the timeliness of diagnosis and the effectiveness of treatment of the underlying disease. In the case of chronic kidney disease and other diseases accompanied by SHPT, it is very important to maintain control over the levels of calcium, phosphorus and vitamin D to prevent the development of osteoporosis, osteodystrophy and other complications.

4. Discussion

Early diagnosis and prompt treatment of SHPT in CKD patients are essential to prevent complications like osteoporosis, fractures, and calciphylaxis. A multidisciplinary approach involving nephrologists, endocrinologists, and nutritionists is crucial for effective management. Strict monitoring of serum calcium, phosphorus, and PTH levels is necessary to optimize treatment and prevent adverse effects.

5. Conclusion

Secondary hyperparathyroidism is a significant complication of CKD that disrupts calcium-phosphorus metabolism. Prompt diagnosis and a comprehensive treatment plan that addresses the underlying cause, dietary modifications, and pharmacological interventions are essential to prevent skeletal and extraskeletal complications and improve patient outcomes. Future research should focus on developing novel therapeutic strategies to achieve better long-term control of SHPT in CKD patients.

REFERENCES

[1] Silva BC, Bilezikian JP. Parathyroid hormone: anabolic and catabolic actions on the skeleton. Curr Opin Pharmacol. 2015;22:41-50. https://doi.org/10.1016/j.coph.2015.03.005

[2] Civitelli R, Ziambaras K. Calcium and phosphate homeostasis: concerted interplay of new regulators. J Endocrinol Invest. 2011;34:3-7

[3] Isakova T, Nickolas TL, Denburg M, Yarlagadda S, Weiner DE, Gutiérrez OM, Bansal V, Rosas SE, Nigwekar S, Yee J, Kramer H. KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Am J Kidney Dis. 2017 Dec;70(6):737-751

[4] Brown EM, Hebert SC. Calcium-receptor-regulated parathyroid and renal function. Bone. 1997;20:303–9

[5] Slatopolsky E, Finch J, Denda M, et al. Phosphorus restriction prevents parathyroid gland growth. High phosphorus directly stimulates PTH secretion in vitro. J Clin Invest. 1996;97:2534–40

[6] Slatopolsky E, Brown A, Dusso A. Role of phosphorus in the pathogenesis of secondary hyperparathyroidism. Am J Kidney Dis. 2001;37:S54–7. doi: 10.1053/ajkd.2001.20740

[7] Martin KJ, Floege J, Ketteler M. Bone and Mineral Disorders in Chronic Kidney Disease. In: Feehally J, editor. Comprehensive Clinical Nephrology. 6th ed. Springer; Berlin/Heidelberg, Germany: 2019

[8] Chakhtoura MT, Nakhoul NN, Shawwa K, et al. Hypovitaminosis D in bariatric surgery: A systematic review of observational studies. Metabolism. 2016;65(4):574-585. https://doi.org/10.1016/j.metabol.2015.12.004

[9] Johnson M, Maher J, DeMaria E, et al. The Long-term Effects of Gastric Bypass on Vitamin D Metabolism. Ann Surg. 2006;243:701–705

[10] Llach F. Secondary hyperparathyroidism in renal failure: the trade-off hypothesis revisited. Am J Kidney Dis. 1995;25:663–679

[11] Asci G, Ok E, Savas R, et al. The link between bone and coronary calcifications in CKD-5 patients on haemodialysis. Nephrol Dial Transpl. 2011;26:1010-1015

[12] Fang Y, Ginsberg C, Seifert M, et al. CKD-induced wingless/integration1 inhibitors and phosphorus cause the CKD-mineral and bone disorder. J Am Soc Nephrol. 2014;25:1760-1773

[13] Agoro R, White K. Regulation of FGF23 production and phosphate metabolism by bone-kidney interactions. Nat Rev Nephrol. 2023;19(3):185–193

[14] Garcia-Fernandez N, Lavilla J, Martín P, et al. Increased fibroblast growth factor 23 in heart failure: biomarker, mechanism, or both? Am J Hypertens. 2019;32(1):15–17. doi: 10.1093/ajh/hpy153

[15] Ho B, Bergwitz C. FGF23 signalling and physiology. J Mol Endocrinol. 2022;66(2):R23–R32. doi: 10.1530/JME-20-0178

[16] Kuro-O M. Nat Rev Nephrol. The Klotho proteins in health and disease. 2019;15:27–44

[17] Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Kuro-o M, Matsumura Y, Aizawa H, et al. Nature. 1997;390:45–51. doi: 10.1038/36285

[18] In vivo genetic evidence for klotho-dependent, fibroblast growth factor 23 (Fgf23) -mediated regulation of systemic phosphate homeostasis. Nakatani T, Sarraj B, Ohnishi M, et al. FASEB J. 2009;23:433–441. doi: 10.1096/fj.08-114397

[19] Moe S, Drüeke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006;69(11):1945-1953. https://doi.org/10.1038/sj.ki.5000414

[20] Moe SM. Renal Osteodystrophy or Kidney-Induced Osteoporosis? Curr Osteoporos Rep. 2017;15(3):194-197. https://doi.org/10.1007/s11914-017-0364-1

[21] Sprague SM, Bellorin-Font E, Jorgetti V, et al. Diagnostic Accuracy of Bone Turnover Markers and Bone Histology in Patients With CKD Treated by Dialysis. Am J Kidney Dis. 2016;67(4):559-566

[22] Okuno S, Inaba M, Ishimura E, et al. Effects of long-term cinacalcet administration on parathyroid gland in hemodialysis patients with secondary hyperparathyroidism. Nephron. 2019;142(2):106-13. doi: 10.1159/000496808

[23] Behets GJ, Spasovski G, Sterling LR, et al. Bone histomorphometry before and after long-term treatment with cinacalcet in dialysis patients with secondary hyperparathyroidism. Kidney Int. 2015;87:846-856. doi: 10.1038/ki.2014.349