Secondary hyperparathyroidity in patients with progressive chronic kidney disease

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Abstract

In patients with end-stage chronic kidney failure, there are a number of disorders that cause bone damage. In particular, secondary hyperparathyroidism (SHPT) is related to chronic kidney failure, a calcium-phosphorus metabolism disorder that causes bone disorder. Secondary HPT occurs when parathyroid hormone(PTH) is continuously produced in response to chronically low serum calcium levels, commonly seen in patients with progressive chronic kidney disease. In this article we present a case of secondary HPT causing facial and thoracic bone changes.

Key words: *end-stage chronic kidney failure, chronic kidney, secondary hyperparathyroidism (SHPT).*

1. INTRODUCTION

In patients with chronic kidney disease, there is a spiral of calcium-phosphorus disorders involving the kidney-gut axis: insufficient 1,325-(OH)2D3 produced in kidneys, causing vitamin D to not be absorbed, leading to low serum calcium levels and increased PTH response of the parathyroid glands, eventually causes secondary hyperparathyroidism. In chronic renal failure, secondary or tertiary hyperparathyroidism may occur. Secondary hyperparathyroidism can affect many different bones and is most common in flattened bone plates that change the pattern of bone trabeculae. In its most severe forms, it can cause bone hypertrophy or fibrocystic osteomyelitis, all of which are collectively known as renal osteomalacia [1].

In this article, we introduce a case of secondary HPT related to changes in the maxillofacial and thoracic bones:

Case report:

A 29-year-old male patient with end-stage chronic kidney disease has been receiving peritoneal dialysis for about 5 years. He comes to our department to do tests preparing for a kidney transplant. While examined, the patient was found to have abnormally deformed bone areas, mainly focusing on flat bone areas: jawbone, sternum, ribs, unrelated to trauma. The patient has no other medical history. The deformed bone areas have appeared for nearly 3 years but he was no pain, had no other symptoms and had not received any treatment. The results of dental and facial examination showed no abnormalities other than cystic jaw bone changes.

Figure 1. patient with face deformity

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He was then given tests related to bone metabolic disorders in people with CKD. The result is a severe Ca-P disorder as figure below

Blood test	Patient result	Normal range
Calcium	1.86	2.15 - 2.50 mmol/l
Phosphorus	1.64	0.8 - 1.6 mmol/l
Alkaline Phosphatase	520	30 - 120 U/l
PTH	3204	15 - 65 pg/ml

Accompanied by images of bone dystrophy and severe bone cysts in the jaw and sternum areas. In addition, measuring bone density also detects osteoporosis in the bones of the spine. Ultrasound and MRI scan detected parathyroid adenoma.

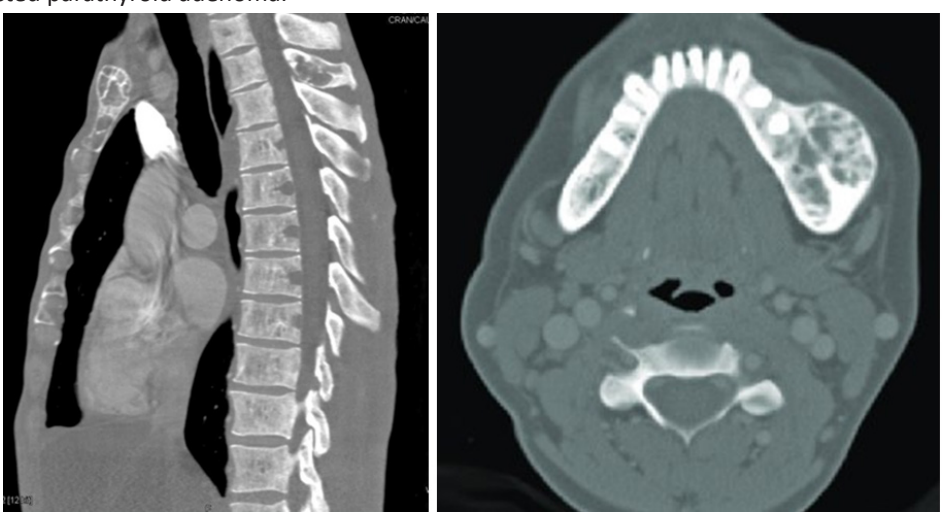


Figure 2. images on thoracic MRI and CT of patient's jaw

Ultimately, the patient was diagnosed with secondary hyperparathyroidism - a condition caused by a calcium-phosphorus disorder common seen in patients with progressive CKD and ESKD, he was received conservative medical treatment with calcitriol 0.25 mcg/day, cinacalcet 30 mg/day and sevelamer 800 mg/day. He was examined and retested every 3 months. Results after 3 months are as follow: Ca 1.65 mmol/l, Phosphorus 1.20 mmol/l, alkaline phosphatase 210 U/l, PTH 1500 pg/ml.

Discussion: *So what is secondary hyperparathyroidism in patient with CKD?*

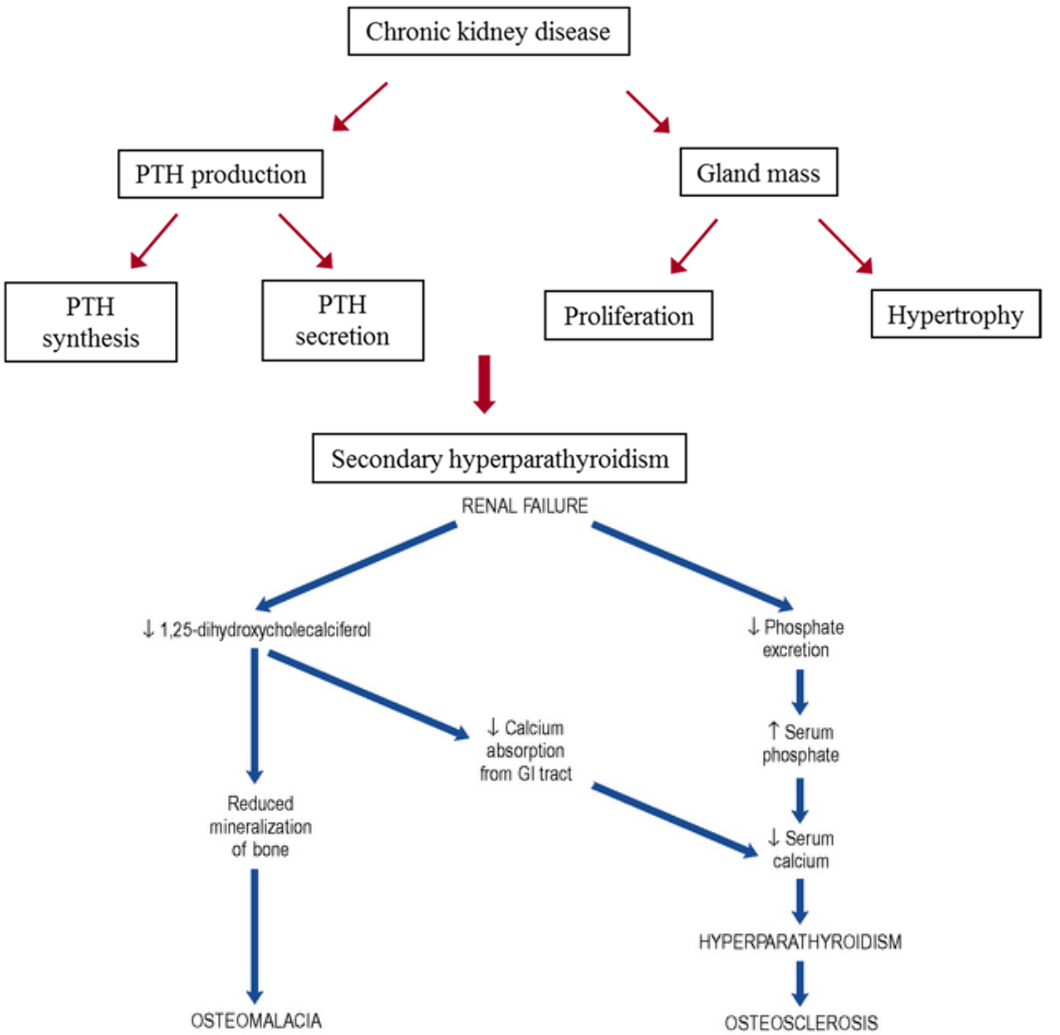
We know that hyperparathyroidism can be primary, secondary, and even have tertiary and quaternary. Among them, the primary type is mostly due to parathyroid adenoma (80–90% of cases), parathyroid hyperplasia, and parathyroid carcinoma.

Secondary hyperparathyroidism is an acquired disorder, occurring secondary and commonly seen in patients with chronic kidney disease, especially patients with advanced chronic renal failure. Even though the patient has received renal replacement therapy. This disorder affects about 38% patients in Stage 3 and 68% patients in Stage 4 of chronic kidney disease [2].

Characteristics of HPT due to chronic kidney disease are increased parathyroid function in response to calcium-phosphorus imbalance caused by impaired kidney function.

In CKD, hyperphosphatemia and decreased 1,25 (OH)2 D3 production lead to decreased ionized calcium, causing the parathyroid glands to become stimulated (secondary hyperparathyroidism) and over time can become secondary or tertiary hyperparathyroidism [1].

One of the first changes of the Parathyroid gland in CKD is cell hyperplasia. These disorders continuously increase blood PTH levels, leading to increased CaxP products, increasing the risk of calcium deposition in tissues, causing excessive excretion of calcium and phosphorus through the kidneys. Consequences: urinary stones, chronic bone loss due to diffuse bone mineral loss, pathological fractures, cystic bone lesions (fibrous osteomyelitis and cystic fibrosis), renal osteodystrophy [1],[5].



A characteristic of SHPT is that PTH concentrations are always elevated above 5 times the normal value

Lab comparison between HPT types

Hyperparathyroidism	Calcium	PTH	Vitamin D	Phosphate
Primary	Elevated	Elevated/ normal	Elevated	Decreased
Secondary	Elevated/ normal	Elevated	Decreased	Elevated/ decreased
Tertiary	Elevated	Elevated	Decreased	Elevated

Clinically, this disorder often has a gradual, insidious onset and no obvious symptoms. Its appear when serum PTH levels increased very high, causing bone metabolism disorders, typically renal osteodystrophy. Common symptoms are:

- Bone pain: The level can range from very mild pain to very severe, unable to move. The pain is often vague, with deep pain in the lumbosacral area, hip joints, knees and both sides of the legs. Pathological fractures are possible, often occurring in the femoral neck and vertebrae collapse.

Muscle weakness: Muscle weakness, especially the proximal muscles, can reduce the patient's ability to move.

- Calcium-induced skin necrosis: Skin necrosis can occur due to peripheral ischemia or calcification of arterioles causing ulcers. Periarthritis: Patients have severe pain with swelling, redness and heat around one or more joints. Pain may occur in the ankle or foot without local signs of inflammation.[1][2]

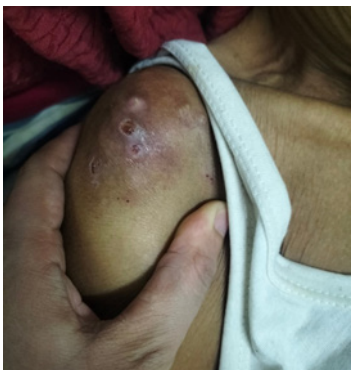


Figure 3. image of patient with calcium-induced skin necrosis- at Nephrology Department

- Spontaneous tendon rupture: Usually occurs in the quadriceps, triceps, and extensor digitorum tendons

- Bone deformities: Bending of the tibia, femur, deformity of the bone ends, often seeing bulging ends of long bones in adolescence.

-Extraskeletal calcification: Calcification of medium-sized arteries; juxtaarticular calcification and calcific tumor; calcification of internal organs: heart, lungs, kidneys...

- Developmental delay: Seen in children with chronic kidney failure

On diagnostic imaging:

- X-ray: Hyperparathyroidism leads to bone dystrophy. The earliest change in bone is subperiosteal bone resorption. The late stage has systemic osteoporosis, bone destruction, bone cavities and bone deformities.

- Bone density measurement: Bone density measurement results may show reduced bone density or osteoporosis.

- Parathyroid scan (Scintigraphy): Parathyroid scan using radioactive isotopes Iodine-123, Thallium-201 or 99mTechnetium - methoxyisobutylisonitrile (99mTc-MIBI) helps evaluate location, shape, size, and function of the Parathyroid Gland.

- Bone biopsy: Bone histopathology results help accurately diagnose bone disease due to hyperparathyroidism, mixed bone disease or osteomalacia

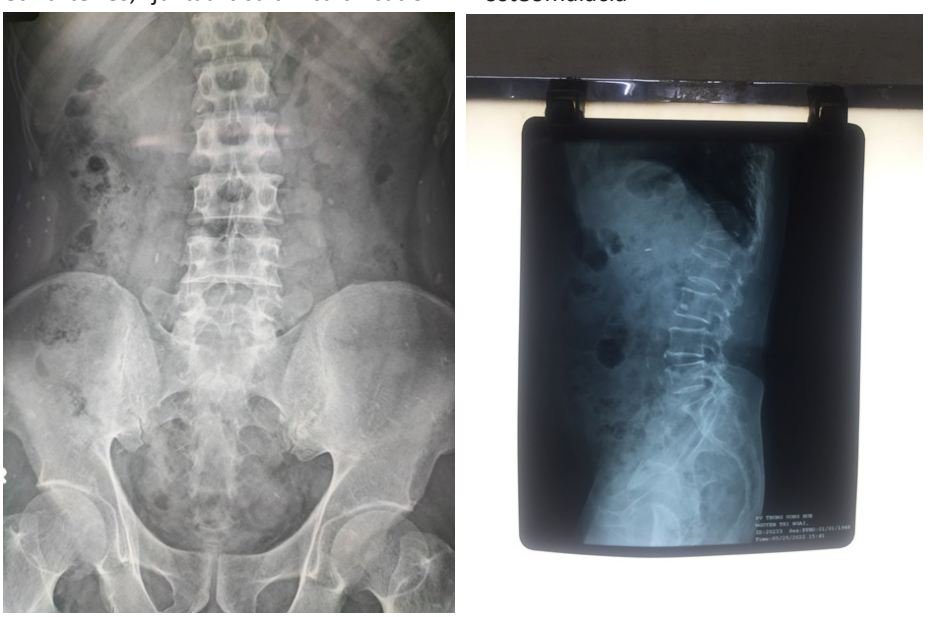


Figure 4. images of extra-skeletal calcification in patients with SHPT at the Department of Nephrology - Hue Central Hospital)

However, this disorder context also needs to be distinguished from other cases:

- Pseudohypercalcemia: hypercalcemia results may be due to laboratory errors or because the tourniquet time for blood collection is too long and the test always needs to be repeated. Hypercalcemia may be due to hyperproteinemia (as in dehydration), so serum calcium should be measured as albumin.

- Hypercalcemia due to malignant tumors: many malignant tumors (breast, lung, pancreatic, uterine, kidney cancer) can cause hypercalcemia. In some cases (especially breast carcinoma) there are bone metastases. Although other cancers have not seen bone metastases, blood calcium increases because these tumors secrete PTHrP (parathyroid hormone-related protein), a protein with a similar structure to tertiary PTH. PTHrP also causes osteolysis and hypercalcemia such as PTH. The clinical symptoms

of cancer-induced hypercalcemia are identical to those of hyperparathyroidism. Serum phosphorus is low but PTH levels are also low.

Regarding treatment, calcium-phosphorus disorders are currently treated according to KDIGO 2017 guidelines [3].

a. Hypophosphatemia: Is the foundation of SHPT prevention and treatment. Dietary phosphate restriction and phosphate binders are effective means of controlling phosphate.

- Phosphate-restricted diet: A phosphorus-poor diet of 800 - 1000 mg/day (adjusted to a low-protein diet), limiting protein and avoiding dairy products is very important.

- Phosphate binders: Aluminum, magnesium, iron, calcium, lanthanum salts and non-absorbable intestinal polymers are effective drugs.

- Patients with CKD stage 3 - 4 often use calcium-containing phosphorus inhibitors (calcium carbonate, calcium acetate). CKD stage 5 can use a calcium-containing phosphorus scavenger and/or a calcium-free phosphorus scavenger (Sevelamer hydrochloride).

- The total dose of elemental calcium from calcium-containing phosphate binders must not exceed 1500 mg/day. Calcium-free phosphorus scavenger should be prescribed for dialysis patients with hypercalcemia or with PTH < 16.5 pmol/l or with severe extraskeletal calcification. When using calcium-containing phosphorus scavengers, there is a risk of aggravating hypercalcemia, then it is necessary to reduce the calcium concentration in the filtrate below 2.5 mEq/l.

b. Calcium control: When eGFR < 50 ml/min, calcium absorption in the digestive system is reduced due to reduced calcitriol synthesis in the kidneys. Providing adequate amounts of calcium to absorb phosphorus can help reverse the negative balance of calcium. If the patient has well adjusted phosphorus levels but has low blood calcium levels, calcium supplementation is still needed [4].

Treatment goals: According to recommendations of NKF - K/DOQI.

CKD stage 3 - 4: Calcium control within normal limits

CKD stage 5: Keep blood calcium concentration 2.1 - 2.37 mmol/l.

Product Ca x P < 55 mg2/dl2.

c. Control of PTH: diet, calcimimetics, phosphorus binders

CKD stage 3: keeps PTH at 35 - 70 pg/ml or 3.85 - 7.7 pmol/l. Measure serum PTH every 12 months

CKD stage 4: keeps PTH at 70 - 110 pg/ml or 7.7 - 12.1 pmol/l. Measure serum PTH every 3 months

CKD stage5/5D: keep PTH at 150 - 300 pg/ml or 16.5 - 33 pmol/l. Measure serum PTH every 3 months

d. Calcimimetics: Effective in treating hyperparathyroidism in ESKD. In dialysis patients, cinacalcet significantly reduces PTH concentrations. Cinacalcet is indicated in patients with serum iPTH > 300 pg/ml

e. Vitamin D: Supplement vitamin D (calcitriol) or vitamin D analogues (doxercalciferol, alfacalcidol, paricalcitol). Use of calcitriol depends on the severity of CKD and the degree of hyperparathyroidism. In the early stages, low doses of calcitriol may be sufficient to limit hyperparathyroidism. In patients with ESKD, high doses of calcitriol can be used.

f. When does the issue of parathyroidectomy arise?

Patients with ESKD, have severe hyperparathyroidism (usually PTH > 800 pg/mL and elevated AP) and additional symptoms:

- Persistent hypercalcemia
- Persistent hyperphosphatemia
- PTH increases continuously despite adequate treatment
- Progressive extraskeletal calcification, including calcifilaxis
- Persistent itching

Or, post-kidney transplant patients have increased PTH accompanied by hypercalcemia with unexplained decreased graft kidney function. These cases are called tertiary hyperparathyroidism and need to be resolved with partial parathyroidectomy [6].

5. CONCLUSION

SHPT is a very common condition in patients with advanced chronic kidney disease. Symptoms appear when parathyroid hormone level is increased. Early medical treatment is the optimal choice for patients.

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