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Mini-Review

Parathyroid gland function in dialysis patients

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Abstract

Parathyroid disorder, is a common consequence of end-stage kidney disease (ESRD) and maintenance dialysis patient. This article, aims to investigate parathyroid disorders consisting symptoms, signs, laboratory findings, prevention and its treatment in dialysis patients. Directory of Open Access Journals (DOAJ), Google Scholar, PubMed, and Web of Science has been searched. Secondary hyperparathyroidism is one of disorders in minerals metabolism in ESRD patients, resulted from calcium reduction in blood due to a decrease in synthesis of active vitamin D, acidosis, and an increase in blood phosphorus, and also 1-alpha-hydroxylase deficiency that can cause bone demineralization as well as renal osteodystrophy with symptoms such as bone pain and fractures, and even vessels and soft-tissue calcification which can affect duration of hospitalization, hospital costs and length and quality of life. The findings show that with accurate measurement of serum level of laboratory values of alkaline phosphatase, calcium, and phosphorous monthly, and parathormone every six months, training the dialysis patients, recommending a diet with low phosphorous and appropriated use of phosphate binding agents will improve the outcome of hemodialysis patients.

Keywords: Parathormone, Hyperparathyroidism, Dialysis, Renal osteodystrophy

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Introduction

Parathyroid glands are four glands located along the posterior of thyroid lobes. The function of these glands is distinct from parathyroid. These glands produce parathyroid hormone (PTH) that controls calcium level of body with vitamin D and calcitonin hormone which is secreted by thyroid (1). Calcium is involved in various actions such as normal work of nerves and muscles, bone metabolism, blood clotting and natural permeability of cell membrane, while its abnormal decrease or increase has several effects (2). PTH causes the bones to release calcium into blood and increases the activity of osteoclasts cells. It also prevents calcium excretion from kidneys and increases calcium absorption in the intestine with activating vitamin D. The typical interaction ion for calcium is phosphate. PTH increases renal phosphate clearance and prevents the genesis of supersaturate concentration of calcium and phosphate in plasma (3). Hypoparathyroidism is caused by low PTH levels that leads to reduction of ionized calcium in serum and increase in phosphate level. Overproduction of PTH is called hyperparathyroidism that leads to an increase in blood calcium. Hyperparathyroidism may be primary (due to gland cell hyperplasia with unknown reason, small benign tumors or parathyroid adenoma) or secondary (due to chronic hypocalcemia, reduction of vitamin D as a result of other diseases) or third (due to long-term secondary hyperparathyroidism) (4). This article aims to investigate parathyroid disorders, signs, laboratory findings, prevention, and treatment of dialysis patients. We searched Directory of Open Access Journals (DOAJ), electronic databases, including Google Scholar, PubMed, and Web of Science with keywords relevant to parathyroid hormone, hyperparathyroidism, PTH and dialysis for studies between December 1990 and December 2014.

Parathyroid disorders in dialysis patients

In the early 1960, dialysis was used for the first time for patients of end-stage renal disease (ESRD) due to advantages such as patients' longevity (5). Now, in the US about 400 thousand people suffer ESRD and the number is increasing (6). In Iran, the prevalence has risen from 238 per million in 2000 to 357 per million in 2006 which show an increase of 28% during six years. Total incidence of ESRD is about 260 per million (7). Mortality rate in ESRD has alarmingly risen despite science advancement in this field, and in the US 20% of these patients die annually (8). Secondary hyperparathyroidism (SHPT) is one of the first disorders in minerals metabolism in ESRD patients and over 50% of dialysis patients influenced this disorder

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Implication for health policy/practice/research/ medical education

Accurate measurement of serum level of laboratory values of alkaline phosphatase, calcium, and phosphorous monthly, and parathormone every six month, training the dialysis patients, recommending a diet with low phosphorous and appropriated use of phosphate binding agents with improve the outcome of hemodialysis patients.

(9,10). In ESRD patients, increase of parathormone is caused by acidosis, resistance to calcitriol, increase of blood phosphorous, decrease of blood calcium due to reduction of 1,25(OH)2D3 synthesis (active form of vitamin D) and 1-alpha hydroxylase deficiency (11).
In 1920, vitamin D was introduced as an essential vitamin for calcium hemostasis (12). On the way to convert vitamin D into its biological active form, first, vitamin D3 binds vitamin D binding protein or albumin in blood circulation and is transported to the liver to be converted into 25(OH)D3 by cytochrome P-450 enzyme (13). Then 25(OH)D3 is converted into the active form of 1,25(OH)2D3 by CYP27B1 (a mitochondrial cytochrome P-450 enzyme) (14). Kidney is the main place of 1,25(OH)2D3 production; that is released from kidney into blood and transported to target sites throughout the body (15). 1,25(OH)2D3 inhibits PTH synthesis and prevents cell proliferation of parathyroid gland (16). In contrast, PTH in different physiological conditions such as low level of blood calcium, stimulates renal conversion of 25(OH)2D3 to 1,25(OH)2D3. Dialysis patients are not capable to produce 1,25(OH)2D3; as a result, PTH level in blood circulation is high in these patients. Reduction of kidney glomerular filtration leads to phosphate retention that also leads to an increase in PTH secretion and fibroblast growth factor 23. Fibroblast growth factor 23 inhibits the activity of renal 1alpha-hydroxylase (17,18). In a study, Carlson *et al.* (19), explained that chronic renal failure patients suffer numerous hormonal disorders which certainly include increasing parathormone concentration and decreasing testosterone hormone; however, prolactin and growth hormones increase. The study conducted by Young *et al.* (20), showed that the prevalence of hyperphosphatemia was high in dialysis patients and in 52% of patients serum phosphate levels were higher than 5.5 mg/dl. Owda *et al.* (21), examined the race and hyperparathyroidism prevalence in 122 dialysis patients in Michigan for a year and concluded that 78% of patients faced the increase of parathyroid hormone with average of 481 ρg/ml. Moreover, parathyroid hormone average was more in black patients compared to white patients.

Hyperparathyroidism symptoms in dialysis patients

Increase of parathyroid hormone levels in dialysis patients is considered as a toxin of uremia that can stimulate rapid bone absorption and reabsorption causing bone demineralization and renal osteodystrophy (22). It can cause symptoms such as bone pain, joint problems, fracture, itch, or even soft-tissue calcification (lung, blood vessels, joints, and skin) that all affect duration of hospitalization, treatment costs as well as length and quality of life (11). Studies have shown that patients with high levels of parathyroid hormone experience high risk of cardiovascular diseases (due to calcium-phosphate deposition in the artery wall) and death (23,24).

Laboratory findings of hyperparathyroidism in dialysis patients

Alkaline phosphatase

The serum level of bone alkaline phosphatase increases and reaches as much as 10 times the maximum normal range. Alkaline phosphatase comes from other sources in addition to the bone the most important ones including liver, intestine, and kidney.

Calcium

Total and ionized calcium concentration is normal or slightly low. Hypercalcemia may emerge during overzealous treatment with calcium or vitamin D analogues.

Phosphorous

It increases to about 6-7 mg/dl or more before dialysis.

Parathyroid hormone

Measurement of normal (intact) hormone shows that serum PTH level increases completely. The amount of 150-300 ρg/ml is in the normal range and levels higher than 300 show color Doppler sonography, the gland volume changes are detected (25).

Clinical guidelines of national kidney foundation kidney disease outcomes quality initiative (NKF-K/DOQI) in calcium, phosphorus, and parathyroid hormone metabolism in different stages of chronic kidney disease are presented in Table 1 (25,26).

Prevention and treatment

To prevent problems created by SHPT, there is a need to examine and analyze the methods used to reduce parathyroid hormone:
The first and most important step in maintaining serum phosphorus in normal range by diet and use of phosphate binders such as calcium carbonate, calcium acetate and renagel (27).
The second step is controlling PTH in the normal range that is done with the help of active vitamin D compounds: calcitriol, zemplar, calcimimetic cinacalcet HCL (Sensipar/Mimpara) (that affects calcium-sensing receptors and increases its sensitivity to calcium and leads to the reduction of parathyroid hormone secretion consequently) (Table 2) (28,29).
Moe *et al.* (30), introduced long-term treatment (100 weeks) with cinacalcet HCL as a reason for reduction of parathyroid hormone without increasing calcium

Table 1. Calcium, phosphorus and parathyroid hormone metabolism in different stages of chronic kidney disease.

CKD Stage	GFR (ml/min/1.73m2)	Phosphorous (mg/dl)	Calcium (mg/dl)	Calcium × Phosphorus (mg^2/dl^2)	Intact PTH (ρg/ml)
3	30-59	2.7-4.6	8.4-10.2		35-70
4	15-29	2.7-4.6	8.4-10.2	Less than 55	70-110
5	Less than 15 or dialysis	3.5-5.5	8.4-9.5		150-300

CKD= Chronic kidney disease

Table 2. Drugs control parathormone secretion

Drug name	Indications	Side effects	Contraindication
Sensipar (cinacalcet) Tab 30,60 mg	• Helps to regulate calcium and phosphorus with increasing the sensitivity of parathyroid gland to calcium • Treating secondary hyperparathyroidism • Treating hypercalcemia in patients with parathyroid carcinoma	• Seizure (convulsions) • Swelling • Rapid weight gain • Nausea • Diarrhea • Vomiting (mild to moderate)	• Allergy to any ingredient in cinacalcet • Low blood calcium levels
Zemplar (paricalcitol) Cap 1,4 mcg	• Similar to vitamin D • Helps to lower high levels of parathyroid hormone • Preventing and treating secondary hyperparathyroidism	• Dizziness • Allergic reaction • Arthritis • Rash	• Allergy to any ingredient in paricalcitol • High levels of vitamin d or calcium in the blood
Rocaltrol (calcitriol) Cap 0.25,0.5 mcg	• A form of vitamin D • Managing certain conditions caused by high or low parathyroid hormone levels • Managing low blood calcium levels in patients who suffer chronic kidney dialysis	• Diarrhea • Allergic reaction • Bizarre behavior • Fever • Dizziness	• Allergy to any ingredient in rocaltrol • High levels of vitamin d or calcium in the blood
Hectorol (doxercalciferol) Cap 0.5 µg	• A synthetic form of vitamin D • Lowering elevated parathyroid hormone levels in patients undergoing kidney dialysis • Promoting the proper absorption and use of calcium and phosphate by the body	• Abscess • Difficulty sleeping • Joint pain • Upset stomach • Weight gain	• Allergy to any ingredient in Hectorol • Tendency toward high calcium levels or evidence of vitamin D overdose(eg, weakness, nausea, headache, drowsiness, vomiting, dry mouth, constipation, muscle pain, bone pain, loss of appetite) • High levels of calcium, phosphate, or vitamin D in the blood
Calcijex (calcitriol) Injection, solution 1µg/ml	• A form of vitamin D • Treating low calcium levels in dialysis patients' blood	• Fever • Allergic reaction • Bone pain • Bizarre behavior • Constipation	• Allergy to any ingredient in Calcijex solution • High levels of vitamin D or calcium in the blood

and phosphorus. Block *et al.* (31), performed a study to determine the effects of cinacalcet HCL in dialysis patients with PHT>3000 ρg/dl and concluded that daily use according to the need and prescription leads to reduction of parathyroid hormone, calcium, phosphorus, and Ca×P product.

Another method mentioned in studies is the use of vitamin C. The study conducted by Richter *et al.* (32), showed that there was a relationship between high levels of plasma vitamin C with low level of PTH. Vitamin C affects post-receptor events in calcium-sensing receptors on parathyroid cells which explain reverse interactions between vitamin C and PTH. However, Biniyaz *et al.* (33), in a double-blind, placebo-controlled study found that vitamin C has no beneficial effect on secondary hyperparathyroidism.

Sanadgol *et al.* (34), showed that the average of PTH serum level reduced at the end of two months intervention with vitamin C (200 mg, three times a week) compared to base time. However, this effect gradually decreased in the third month which may be due to the reduction of calcium-sensing receptors' sensitivity to parathyroid cells over time.

Partial or total parathyroidectomy with implantation of a part of parathyroid in arm is the last method used in patients who have iPTH>800 ρg/dl with hypercalcemia and hyperphosphatemia and dose not respond to medical treatment (35).

Conclusion

Since parathyroid hormone serum level is high in dialysis patients and on the other hand, excessive suppression

of parathyroid hormone with calcium-containing compounds and vitamin D leads to bone diseases, the serum level of laboratory values of alkaline phosphatase, calcium and phosphorus should be accurately measured monthly and PTH every six months (given that it is easier and more available compare to other assessment methods of bone disorders). Moreover, training the patients, recommending a diet with low phosphorus, and accurate treatment with phosphate-binding drugs, and calcitriol should be taken seriously. In this way, life quality of dialysis patients will increase through maintaining PTH level in recommended range and preventing the side effects of parathyroid hormone increase or decrease.

Authors' contributions

EA wrote the manuscript. AT and BE made substantial contributions to conception and design of the manuscript. EA prepared the final manuscript.

Conflict of interests

The authors declare no conflict of interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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