
Study on the Performance of Calcium - or Non-Calcium - Based Phosphate Binder in the Treatment of Hyperparathyroidism Secondary to Chronic Renal Failure

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ABSTRACT

Secondary hyperparathyroidism is one of the most prevalent complications in the advancement of CKD which specifically appears when glomerular filtration rate decreases to a level lower than 80 cc per minute for a period of longer than three months. Physicians in charge of CKD and pre-dialysis patients should be attentive to investigate and correct all the conditions that cause the compensating increase of parathyroid hormone (PTH). In this respect the first action is to correct hypophosphatemia, which at first stages is corrected through monitored diet, and then with calcium- or non-calcium-based phosphate binders.

KEYWORDS

Hyperparathyroidism; Secondary hyperparathyroidism; Glomerular filtration rate; Cardiovascular disease; Calcium; Hemodialysis; Calciphylaxis; Chronic kidney disease; Endstage renal disease.

1. Introduction

Secondary hyperparathyroidism is one of the most prevalent complications in the advancement of chronic kidney disease (CKD) which specifically appears when glomerular filtration rate (GFR) decreases to a level lower than 80 cc per minute for a period of longer than three months (1). Severe hyperparathyroidism may cause kidney functionality to deteriorate and the decrease in the GFR to intensify. It may also lead to calciphylaxis and cardiovascular disease and even death in case of CKD and end-stage renal disease (ESRD) (2). In this paper, we intended to review the mostly recent data regarding chronic kidney disease- mineral and bone disorder (CKD-MBD).

2. Materials and Methods

For this mini-review, we used a diversity of sources by searching through PubMed/ Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and or their equivalents; hyperparathyroidism, secondary hyperparathyroidism, glomerular filtration rate, calciphylaxis, chronic kidney disease- mineral and bone disorder (CKD-MBD), cardiovascular disease, calcium, hemodialysis, chronic kidney dis-ease and end-stage renal disease. Titles

and abstracts of articles were investigated of review article, clinical trials, cohort studies, case-control studies, and report that relevance to the intended topic.

3. Secondary Hyperparathyroidism and Chronic Kidney Disease

The medical treatment of secondary hyperparathyroidism and its prevention is rather uncomplicated and economical. This, with an appropriate treatment may be stopped from developing into severe secondary hyperparathyroidism (tertiary) – which may need surgery to be treated. Therefore we decided to clarify the right method of prevention and treatment in order to make a step forward in improving these conditions of the patients suffering it. Vitamin D is a nutrient essential for calcium hemostasis and the optimal bone health (3). The essential vitamin D form for calcidiol circulation is 25-hydroxy vitamin D which needs a hydroxylase to activate and turn into calcitriol activated form (4).

In response to the low level of calcium, parathyroid hormone (PTH) increases 1-alpha-hydroxylase activity (5). In CKD patients, parathyroid gland is able to produce the activated form of vitamin D (calcitriol or 1.25(OH)₂D) in its local form Shahnazari B et al Physicians in charge of chronic kidney disease (CKD) and pre-dialysis patients should be attentive to investigate and correct all the conditions that cause the compensating increase of parathyroid hormone (PTH). In this respect the first action is to correct hypophosphatemia, which at first stages is corrected through monitored diet, and then with calcium- or non-calcium-based phosphate binders. (paracrine autocrine) and consequently inhibit PTH (6,7). Some other tissues such as colon, skin, placenta and prostate contain 1-alpha-hydroxylase (IOH) and this role of autocrine/paracrine supports the adjustment of 1.25(OH)₂D. The production of local calcitriol (anti proliferative) is effective in stopping cancer growth (8). Since in CKD the kidney functionality decreases, PTH increases to compensate, so that blood calcitriol level reaches an adequate level for an optimal absorption of calcium through bowels (9).

The chronic increase in PTH which is called secondary hyperparathyroidism, along with changed phosphorus metabolism may lead to renal osteodystrophy (10). Therefore a deficiency in 25-hydroxy vitamin D serum level may worsen secondary hyperparathyroidism in CKD patients (11).

For healthy people and CKD patients, there is an inverse correlation between hydroxyvitamin D and PTH (12-14). Medical treatment of secondary hyperparathyroidism Physicians in charge of CKD and pre-dialysis patients should be attentive to investigate and correct all the conditions that cause the compensating increase of PTH. In this respect the first action is to correct hypophosphatemia, which at first stages is corrected through monitored diet, and then with calcium- or non-calcium-based phosphate binders (15).

Although most resources including NKF recommend that the measurement of vitamin D serum level should be due to a PTH increase higher than the respective reference range of CKD (15) (Table 1), it seems that since there is a high prevalence in vitamin D serum level deficiency in Iran, it is better, according to the IMOS study (16), to Table 1. Target range of intact plasma PTH by stage of CKD check 25-hydroxy vitamin D level primarily and in case it was normal, to utilize the preventing dosage. Additionally it is recommended that in stages 2 and 3 of kidney failure to begin the treatment according to Table 2.

When treating using inactive form of vitamin D, we should pay attention to phosphorus and calcium levels and PTH target range for different stages of the disease should be taken into account.

We mention the following points to explain the reason why we should use the inactive form of vitamin D with high dosage and to clarify why the common mistake in the prevention is using an insufficient dosage of calcitriol:

1. Due to the presence of bonding proteins for 25-hydroxy-vitamin D and 1,25- dihydroxy-vitamin D, the bonding with these proteins produce the reserve form of the vitamins while to suppress free form PTH, we need 1,25(OH)₂D (1,25-hydroxy-vitamin D). Therefore in cases of vitamin D deficiency through prescribing low dosage of Rocaltrol, this vitamin bonds with the protein and the adequate amount of its free form needed to suppress PTH would not be provided (17).

2. Due to autocrine/paracrine phenomenon explained earlier, higher doses of inactive vitamin D may turn into calcitriol (activated form).

3. According to Chandra treatment, consuming cholecalciferol (25-hydroxy-vitamin D) with a weekly dosage of 50000 units for 12 weeks, is an efficient way for the correction of vitamin D level in patients at stages 3 and 4 of CKD. In this study vitamin D level reached the adequate level of higher than 30 mg/L in a 6 week period and in 12 weeks of treatment there happened an average increase of 185% in vitamin D level compared to the 5% increase in the placebo setting (3). There also was a 31% decrease of PTH level after 12 weeks of treatment compared to the placebo being 7% (3). Armas et al have illustrated that prescribing cholecalciferol (the animal type) on a weekly basis is much more effective than ergocalciferol (herbaceous type) for increasing 25-hydroxy-vitamin D level (18).

In CKD, a phosphorus level is a cause of inhibition of kidney 1-alpha-hydroxylase and worsening of secondary hyperparathyroidism (19). Uremia also causes a decrease in the functionality of kidney 1-alpha-hydroxylase through decreasing the attacking protein 25-hydroxy-vitamin D to the kidney proximal tubule (20).

The important point is, slow change process of PTH after hypophosphatemia corrections and hypocalcemia and vitamin D deficiency, the patient should be monitored for at least six months, and if despite calcium correction, phosphorus, 25-hydroxy-vitamin D after 6 months, parathormone was still at a high levels, a treatment using active vitamin D analogs (Rocaltrol) for inhibiting PTH would be advised.

It should be remembered that no precise definition of the resistance to treatment with Rocaltrol was existed. However, in any case in CKD patients who do not respond to Rocaltrol, compounds imitating calcium, such as cinacalcet, can be of help (15). The active vitamin D dosage may vary depending on the stage of CKD and the level of serum PTH and blood calcium level (12) (Figure 1). The other issue that should be taken into account is that although the treatment using cinacalcet may reduce the risk of fracture and the need for parathyroidectomy, statistically speaking, it did not have any effect in respect of heart mortality and also in general (2,21). Therefore cinacalcet may not be a definitive treatment for severe secondary hyperparathyroidism. To answer the question that "In what circumstances in patients who did not respond well to medical treatments do we need to consider parathyroidectomy?" there is much controversy. In fact for the patients with no symptoms, there is not any reliable evidence that solely due to PTH not being inhibited, we may recommend parathyroidectomy. A study conducted in Japan considers the level of PTH cut off to be 500 μ g/mL, in order to recommend parathyroidectomy (22).

However, in the same respect, the nephrology guideline recommends parathyroidectomy for patients with severe and enduring hyperparathyroidism with a PTH level higher than 800 μ g/mL along with clinical symptoms and also the presence of hypercalcemia or hyperphosphatemia resistant to treatment (23).

Since there is no controlled study on medial hyperparathyroidism with an iPTH range of 300-800 μ g/mL, most of the patients in this range of PTH, even in case of symptoms being present are medically treated (24). Is the increase of absorption in Sestamibi scan an indication for parathyroidectomy (24)? The fact is that scanning in

secondary hyperparathyroidism is only recommended in cases that need investigating in respect of ectopic parathyroid before surgery (23).

Therefore it does not seem that for all the secondary hyperparathyroidism (SHPT) patients, scanning is necessary and if for any reason it is done, solely the increase of localized absorption is not an indication of surgery (25). Due to the studies reviewed, in CKD patients with hyperparathyroidism, initially all the factors that stimulate PTH, including hypoxemia, hyperphosphatemia and vitamin D deficiency should be corrected. If despite correcting these factors, especially making the level of 25-hydroxy-vitamin D to reach the adequate, a PTH level of 30 $\mu\text{g/mL}$ after at least 6 months, is still high. Hence, the treatment with Rocaltrol with calcium and phosphorus monitoring would be effective in decreasing serum PTH. There is no RCT available in case of comparing Cinacalcet with parathyroidectomy in severe hyperparathyroidism for CKD and ESRD patients. But apparently Cinacalcet may reduce the need for parathyroidectomy in these patients, although it does not affect mortality.

4. Conclusion

In deciding for patients suffering severe hyperparathyroidism that resist medical treatment, it seems that for carrying out parathyroidectomy, that the presence of hyperparathyroidism symptoms (e.g., skin pruritus, presence of pathological fracture, veins calcification, calciphylaxis) is more important than just the level of PTH. When patients with symptoms along with hypercalcemia or hyperphosphatemia in the presence of severe and enduring hyperparathyroidism, parathyroidectomy without the need for scanning may be recommended. But we should note that since there is not much randomized controlled trial (RCT) regarding this field, most of the recommendations are not well grounded and need more studies to be carried out, especially RCTs. hyperparathyroidism (19). Uremia also causes a decrease in the functionality of kidney 1-alpha-hydroxylase through decreasing the attacking protein 25-hydroxy-vitamin D to the kidney proximal tubule (20).

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