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A systematic review of the pharmacotherapy of secondary hyperparathyroidism (SHPT) in grades 3-5 Chronic Kidney Disease (CKD)

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Abstract. – OBJECTIVE: The data on the treatment of secondary hyperparathyroidism (SHPT) provided in scientific publications are divergent and contradictory. Therefore, the aim of our systematic review was to evaluate the efficacy of SHPT treatment in (chronic kidney disease) CKD.

MATERIALS AND METHODS: The Cochrane, PubMed, and Scopus databases were searched independently by two authors. The search strategy included controlled vocabulary and keywords. The effectiveness and side effects of calcifediol, ergocaliferol, calcitriol, paricalcitol, and cinacalcet were compared and analyzed.

RESULTS: Extended-release (ER) calcifediol raised the total serum 25-hydroxyvitamin D level over the threshold of 30 ng/mL in 80% of the patients analyzed in the study. It is the level required for intact PTH (iPTH) suppression. ER calcifediol reduced the iPTH level by 30% in about 30% of the patients, whereas only 2.1% of them had hypercalcemia. Calcitriol significantly decreased the iPTH values. It was the cause of hypercalcemia in 1.7% of the patients. The reduction of the iPTH level by more than 30% was observed in 85.7% of the patients in the paracalcitol group after 48-week supplementation. Paricalcitol was the cause of hypercalcemia in 1.9% of the patients. The cinacalcet therapy resulted in the highest percentage of patients with the iPTH level within the limits recommended by the KDOQI (70-110 ng/L for stage 4 CKD and 150-300 ng/L for stage 5 CKD). 92% of the patients met the KDOQI guidelines and the mean decrease in the serum iPTH level was 68%.

CONCLUSIONS: Calcifediol ER, paricalcitol, and cinacalcet significantly decreased the iPTH level in the patients under study. Paricalcitol increased the serum calcium concentration the most of all the drugs under analysis. It is noteworthy that only cinacalcet does not carry the risk of hypercalcemia.

Key Words:
Secondary hyperparathyroidism, Chronic kidney disease, Pharmacotherapy.

Introduction

Chronic kidney disease (CKD) is a global public health problem with increasing incidence, poor outcomes, and high cost of treatment. A gradual decrease in the glomerular filtration rate (GFR) may progress to end-stage renal disease (ESRD) and require renal replacement therapy, including dialysis or transplantation[1]. Chronic kidney disease-mineral and bone disorder (CKD-MBD) causes increased serum concentrations of phosphorus and parathyroid hormone (PTH) and decreased serum concentrations of calcium and active vitamin D[2,3]. Vitamin D is a steroid hormone, traditionally acknowledged as a regulator of calcium, phosphorus, and bone metabolism. It can be derived from dietary sources (ergocalciferol – D_2 and cholecalciferol – D_3) or produced by the skin exposed to UVB radiation (D_3). After synthesis D_3 is 25-hydroxylated to 25-hydroxyvitamin D [25(OH)D; calcifediol] in the liver and then it undergoes 1-alpha-hydroxylation to its active form, i.e., 1,25-dihydroxyvitamin D [1,25(OH)2D – calcitriol]. The latter hydroxylation is catalyzed by CYP27B1 and occurs both in the kidneys and extrarenal sites, such as the skin and lymph nodes. The binding of 1,25(OH)2D to the intracellular vitamin D receptor (VDR) alters gene transcriptional profiles and mediates its downstream effects. There is increasing experimental evidence that

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many vitamin D target tissues, including immune and intestinal epithelial cells, express CYP27B1 and the VDR. According to recent data, local production of 1,25(OH)2D is required to obtain maximal calcium absorption, expression of antimicrobial peptides, and anti-inflammatory effects. Because 25(OH)D is the immediate precursor of 1,25(OH)2D, low serum 25(OH)D concentrations are hypothesized to prevent the production of 1,25(OH)2D in the target tissues. A low concentration of 1,25(OH)2D potentially promotes inflammation and reduces the pleiotropic effects of vitamin D[4]. Vitamin D insufficiency, defined as 25(OH)D serum levels <30 ng/mL, affects up to 75% of CKD patients[5]. Secondary hyperparathyroidism (SHPT) is one of the most common complications of CKD. An elevated concentration of serum intact parathyroid hormone (iPTH) is observed early in the development of CKD. It is associated with insufficient levels of active vitamin D (calcitriol)[1,6], because renal CYPR27B1 is reduced in patients with CKD, and it is basically absent from patients with ESRD[4]. Additionally, chronic kidney disease is accompanied by hyperphosphatemia, which is a secondary cause of hypocalcemia due to the precipitation of calcium phosphate. Calcitriol synthesis decreases in direct response to the decreased renal function. Calcitriol has a direct inhibitory effect on the pre-proparathyroid hormone gene transcription. A deficiency of this hormone results in a cascade of events, including decreased calcium absorption and increased parathyroid hormone (PTH) production[6]. In addition, the authors of recent studies suggest that fibroblastic growth factor 23 (FGF23) and FGF23-Klotho axis play an important role in the pathogenesis of SHPT. FGF23 reduces renal phosphate reabsorption through the downregulation of the sodium phosphate co-transporter in the proximal tubules. Simultaneously, FGF23 suppresses residual renal calcitriol production by decreasing the renal 1α-hydroxylation of calcifediol to calcitriol and by increasing its degradation (24-hydroxylation)[2].

Mineral metabolism imbalances increase the risk of bone fractures, renal osteodystrophy, and vascular calcification. This increases the risk of cardiovascular diseases and results in higher mortality rates among CKD patients[1,2,6-8]. Thus, the effective management of SHPT, which involves the maintenance of recommended serum PTH, calcium, and phosphorus levels, plays a key role in CKD treatment[2]. The data on the treatment of SHPT provided in scientific publications are divergent and contradictory. Therefore, the aim of our systematic review was to evaluate the efficacy of SHPT treatment in CKD.

Materials and Methods

The search strategy included controlled vocabulary and keywords. The Cochrane, PubMed, and Scopus databases were searched independently by two authors. The main search criteria were 'secondary hyperparathyroidism' and 'chronic kidney disease'. Studies published in the last 10 years were considered for this review (Table I-III)[9-16]. The PRISMA Checklist was checked during the draft of the review.

Results

Calcium supplements, phosphate binders, and active vitamin D compounds are widely used to improve the biochemical markers of mineral and bone metabolism. Vitamin D therapy has historically been based on alfacalcidol or calcitriol[6]. SHPT is traditionally treated by oral or intravenous administration of an active vitamin D analogue. It can inhibit PTH synthesis and secretion through high affinity to the vitamin D receptor (VDR) of the parathyroid gland and further attenuate parathyroid hyperplasia. There is a wide range of vitamin D receptor activators (VDRAs), including active (calcitriol, alfacalcidol, paricalcitol) and inactive ones (ergocalciferol, calcifediol)[8]. VDRAs

Table I. Databases: Cochrane, PubMed, Scopus

Stage	Action	Results
I	Key words ("secondary hyperparathyroidism" and "chronic kidney disease")	6378
II	2012-2021 (10 years)	2785
III	Clinical trial	153
IV	Independent verification and inclusion of research by two authors inclusion criteria: parathyroid hormone value before and after study time of examination ≥ 24 weeks stage of CKD (3-5) control group (placebo or comparator) exclusion criteria: time of examination < 24 weeks stage of CKD (1-2) patients receiving hemodialysis patients after kidney transplant	9

Table II. Selected information about the analyzed studies[14-21].

The active substance	Dosage	Time study [weeks] *completed	Study group (n) GFR after *completed	Control group (n)	Placebo or comparator	GFR before	GFR after
Extended-release (ER) calcifediol	30 or 60 µg/day	26	285 *237	144	Placebo	30.6	29.93
Oral ergocalciferol oral calcitriol	50.000 units/week (through 3 months) then 50.000 units once monthly, according to their blood 25(OH)D levels	~133	104	Comparator		41.56	no data
	0.25 µg/d (start) then dose was regulated thereafter in response to the changes in blood levels of 25(OH)D, Ca, P, and intact PTH (iPTH)	~133	100			42.91	no data
Paricalcitol calcitriol	1 µg/d paricalcitol increasing to 4 µg/d	24	54 *45	Comparator		27.8	24
	0.25 µg/d calcitriol increasing to 1 µg/d	24	56 *45			27	22.6
Paricalcitol	1 µg/day reduction to 3 times/ week if serum calcium exceeded 11 mg/dL	24	93	93	Placebo	40	no data
	2 µg/day reduction to 3 times/ week if serum calcium exceeded 11 mg/dL		95			42	no data
Paricalcitol	2 µg/d, dose reduction to 1 µg/d if serum calcium exceeded 11 mg/dL	48	115 *84	112 *85	Placebo	31	26.91
Paricalcitol	1 µg/day or 2 µg/day	52	30	30	Placebo	19.7	15.21
Paricalcitol	1 µg/day	6	24	Comparator		24.6	22
	1000UI/day (D3)		23			30	29
Cinacalcet	30 mg/day	6	26	no data	comparator (calcitriol 0,25 µg/day or paricalcitol 1 µg/day)	13.8	13.34

inhibit PTH in a dose-dependent manner, regardless of the stage of CKD[17]. However, the treatment with non-selective VDRAs elevates calcium and phosphate levels by increasing intestinal calcium and phosphate absorption. It mobilizes calcium and phosphate from the bones and thus potentially enhances the risk of ectopic vascular calcification and cardiovascular mortality[2]. In addition, hypercalcemia may lead to over suppression of PTH. This results in low turnover bone disease or adynamic bone disease, in which abnormally low bone formation results in defective bone mineralization, which limits the therapeutic dosage of vitamin D[8]. The Kidney Disease Improving Global Outcome (KDIGO) guidelines do not recommend the routine use of calcitriol or its analogues in G3a-G5 CKD due to the risk of hypercalcemia and the lack of clinically significant improvement. According to the KDIGO, calcitriol and vitamin D analogue therapy may be considered for patients with progressive and severe SHPT. The therapy should start at low doses, regardless of the PTH levels. Then the

Table III. Changes in the serum concentration of PTH, calcium, phosphorus and the value of albumin or information about corrected serum calcium concentration based on albumin level[14-21].

The active substance	PTH before the study [pg/mL]	PTH after the study [pg/mL]	Phosphorus serum before [mmol/L]	Phosphorus serum after [mmol/L]	Calcium serum before [mmol/L]	Calcium serum after [mmol/L]	Albumin (serum calcium concentrations were corrected for albumin level)
Extended-release (ER) calcifediol	148.9	112.5	1.19	1.26	2.3	2.35	< 4.0 g/dL
	109.7	96.5	1.15	1.27	2.29	2.31	41.29 g/L (baseline)
Oral ergocalciferol oral calcitriol	89.5	108.1	1.14	1.25	2.31	2.33	*vs.* 42.29 g/L (final) 41.78 g/L (baseline) *vs.* 42.71 g/L (final)
Paricalcitol	176	124	1.18	1.25	2.33	2.42	< 4.0 g/dL
calcitriol	209	163	1.21	1.3	2.34	2.41	< 4.0 g/dL
Paricalcitol	97	71.1	1.26	1.27	2.32	2.36	Yes
	91	38.3	1.23	1.32	2.35	2.46	Yes
Paricalcitol	100	16.87	1.19	1.27	2.4	2.48	< 4.0 g/dL
Paricalcitol	156	51	1.35	1.37	2.32	2.39	43.1 g/L (baseline) *vs.* 41.8 g/L (final)
Paricalcitol	161	137.5	1.13	1.16	2.27	2.37	No data
	80.8	110	1.11	1.19	2.37	2.30	No data
Cinacalcet	506.4	163.3	1.45	1.49	2.5	2.45	No data

drug dosage can be modified according to the PTH response[18].

Calcifediol

VDRA therapy is initiated in CKD patients when vitamin D supplementation cannot lower the PTH level. Although VDRAs effectively lower the plasma PTH level, they leave serum 25-hydroxyvitamin D uncorrected and potentially lower, because they reduce the CYP27B1 expression. Oral or intravenous bolus injection of VDRA causes supraphysiological spikes in blood vitamin D levels, resulting in undesirable increases in vitamin D catabolism dependence on FGF23 and CYP24A1. Both of them contribute to the development of resistance to vitamin D therapy. Immediate release (IR) calcifediol does not cause a clinically significant reduction in the PTH level (≥30% of the level before treatment) in patients with stage 3 or 4 chronic kidney disease. Two studies were analyzed to assess the efficacy of ER calcifediol in the treatment of SHPT. Two 26-week randomized double-blind placebo-controlled trials (n=429) showed that daily doses of 30 μg (study A) or 60 μg (study B) of ER calcifediol increased both the total serum 25-hydroxyvitamin D level to ≥30 ng/mL in 80% of the patients (weeks 20-26) *vs.* placebo ≤7% (p<0.0001) and the serum 1,25-dihydroxyvitamin D level. In both studies the ER calcifediol treatment resulted in a higher percentage of patients who achieved at least a 30% reduction in the plasma iPTH level than the placebo treatment (33% *vs.* 8% in study A (p<0.001) and 34% *vs.* 7% in in study B (p<0.001)), regardless of the fact whether the CKD stages were combined or analyzed separately. Moreover, the iPTH suppression increased upon continued ER calcifediol treatment and reached 50% after 52 weeks. After 26 weeks the iPTH level decreased by at least 10% in 72% of the patients treated with ER calcifediol. ER calcifediol, unlike any commonly prescribed vitamin D dietary regimen, increased the total serum 25-hydroxyvitamin D level and reached the mean level of 50-67 ng/mL required for iPTH suppression (25-hydroxyvitamin D concentration required to control the serum iPTH level in CKD >30 ng/mL). There were six episodes of hypercalcemia (2 consecutive serum Ca values >10.3 mg/dL), which were not associated with the use of ER calcifediol. The study did not reveal any adverse effects of the drug on the kidney function[12].

Ergocalciferol

Another study (n=204) showed the effect of treatment with ergocalciferol and calcitriol on PTH suppression during a 36-month follow-up. The treatment groups did not differ significantly in the rates at which the target iPTH levels were achieved at different stages of CKD. 58.7% of stage 3 CKD patients, 47.6% of stage 4 CKD patients, and 50% of stage 5 CKD patients (p=0.397) in the group receiving ergocalciferol achieved the target or lower iPTH levels, whereas in the group receiving calcitriol these were 55.2% of stage 3 CKD patients, 53.4% of stage 4 CKD patients, and 57.2% of stage 5 CKD patients (p=0.522). It is important to note that the authors did not provide the target value. In this study ergocalciferol was administered at a dose of 50,000 units per week for the first month and 50,000 units per month for the following months, at a blood concentration of 25(OH)D (target level – 30 ng/mL). This ergocalciferol dosing strategy increased the vitamin D level to 37.32 ± 10.49 ng/mL, which was significantly higher than the level of 18.08 ± 7.55 ng/mL in the calcitriol group (p<0.001). The rate of hypercalcemia in the patients with stage 4 CKD was significantly higher in the ergocalciferol group than in the calcitriol group (40.0% *vs.* 9.5%, p=0.036). The study did not prove vascular calcification, which is a high risk at vitamin D supplementation. It is necessary to conduct extensive multicenter research to confirm the effectiveness of ergocalciferol[14].

Calcitriol

The aim of the multicentre study was to compare the rate of hypercalcemia between the patients receiving calcitriol and paricalcitol, while reducing the PTH level by 40-60%. Patients with stages 3-4 CKD (n=110) with PTH levels >120 pg/mL were recruited and randomized to 0.25 μg/d calcitriol or 1 μg/d paricalcitol. Subsequent dose adjustments were made per protocol to achieve 40-60% PTH suppression below the initial value (albumin-corrected serum calcium <10.5 mg/dL). The primary endpoint was the rate of confirmed hypercalcemia >10.5 mg/dL in the groups. Forty-five patients in each group completed 24 weeks of treatment. Both drugs effectively inhibited PTH (-52% with paricalcitol and -46% with calcitriol; p=0.17). The paricalcitol group achieved a 40% reduction in the PTH level earlier (after 8 weeks *vs.* after 12 weeks). Small increases in the calcium and phosphorus levels were observed in both groups as well as a significant decrease in alkaline phosphatase, a marker of bone turnover. There were three episodes of hypercalcaemia in the paricalcitol group and one episode in the calcitriol group (p=0.36). This result can be partly explained by avoiding a prolonged excessive increase in the PTH concentration. It is important to note that in clinical practice patients with high serum calcium levels cannot undergo a VDRA dose adjustment because of the risk of hypercalcemia. This fact limits their ability to achieve the optimal SHPT control. The downside of this study was the use of albumin-corrected rather than ionized calcium, although this was done to mimic the clinical practice routine[18].

In order to suppress the SHPT without increasing the calcium and phosphate levels selective VDRA was developed. Paricalcitol (19-nor-α-25-dihydroxyergocalciferol) is a synthetic, tissue-selective VDRA with higher affinity for the parathyroid gland than the intestine. When compared with placebo, paricalcitol treatment effectively reduces PTH levels in CKD patients, in both the dialysis and non-dialysis populations. Teng et al[19] found that the use of paricalcitol resulted in an adjusted 16% survival benefit, as compared with the use of calcitriol[19]. The other randomized controlled trial (RCT) showed that the addition of 2 mg/d paricalcitol to renin-angiotensin-aldosterone system (RAAS) blockers safely lowered residual albuminuria in patients with diabetic nephropathy[20]. However, paricalcitol may also increase the calcium and phosphorus levels and cause other adverse events associated with poorer cardiovascular and mortality outcomes[6]. Han et al[21] advised to cautiously administer any active vitamin D analogue to patients with CKD because of the potential risk of exacerbation of vascular calcification[21]. Other researchers observed that paricalcitol reduced hypercalcaemia and hyperphosphatemia. The use of paricalcitol and calcitriol resulted in a similar ≥50% reduction of PTH, calcium concentration, phosphate concentration, calcium phosphate, alkaline phosphatase, hypercalcaemia, secondary hyperparathyroidism, and adverse effects in dialysis patients[7].

Paricalcitol

In each of the studies under analysis paricalcitol effectively reduced the iPTH levels. Thadhani et al[9] observed that by the 48th week of treatment the iPTH level had decreased by more than 30% in 85.7% of the patients in the paricalcitol group and 16.5% of the patients in the placebo group (p≤0.001). However, paricalcitol increased the cal-

cium levels. The serum calcium levels increased on average by 0.32 mg/dL (95% CI, 0.19-0.45 mg/dL) in the paricalcitol group and decreased by 0.25 mg/dL (95% CI, 0.12-0.37 mg/dL) in the placebo group ($p \leq 0.001$). Episodes of hypercalcaemia were more frequent in the paricalcitol group than in the placebo group[9]. Coyne et al[10] observed a dose-dependent reduction in the iPTH level, which decreased by 26.9 pg/mL in the 1 μg/day group (20.9% reduction; $p<0.001$ *vs.* placebo) and by 52.7 pg/mL in the 2 μg/day group (48.9% reduction; $p<0.001$ *vs.* placebo). Approximately 3% and 1% of the patients treated with paricalcitol at doses of 2 and 1 μg/day, respectively, experienced hypercalcemia (at least two consecutive monthly calcium concentrations >10.5 mg/dL)[10]. Stancu et al[11] noted that after six weeks the iPTH level decreased by more than 30% ($p=0.6$) in 25% of the patients treated with paricalcitol and in 13% of the patients treated with cholecalciferol. Episodes of hypercalcemia (>10.5mg/dL) were more frequent in the paricalcitol group than in the placebo group (1.8% in the paricalcytol group *vs.* 0.6% in the cholecalciferol group, $p=0.5$)[11].

In severe SHPT (serum PTH >300 pg/mL) medical management requires combination therapy: the use of vitamin D, which stimulates vitamin D receptors, and calcimimetic agents acting via calcium-sensing receptors. The clinical practice guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) provide weak recommendations based on the moderate quality evidence in favor of surgical parathyroidectomy if the PTH level remains constantly above 1,000 pg/mL[3]. Cinacalcet hydrochloride (cinacalcet) is a second-generation calcimimetic agent, approved for the treatment of SHPT patients by directly, allosterically binding to and activating calcium-sensing receptor (CaR) in the parathyroid gland. For this reason, cinacalcet could significantly increase sensitivity to extracellular calcium, thus suppressing PTH secretion without increasing the serum calcium and phosphate levels[1,8]. A growing number of randomized controlled trials (RCTs) indicated that cinacalcet effectively improved the biochemical parameters of SHPT patients and did not have negative influence on all-cause mortality and all adverse events. Since vitamin D compounds and cinacalcet act through distinct mechanisms, their combined use could lead to more effective control of PTH. Their offsetting effects on calcium and phosphate may reduce the risk of hypercalcemia and hyperphosphatemia, which accompany vitamin D therapy. However, according to the meta-analysis conducted by Palmer et al[22], the long-term effects of treating cardiovascular and skeletal complications are uncertain[22].

Cinacalcet

The recommended treatment with a combination of cinacalcet and vitamin D analogues (mainly calcitriol) was also described by Montenegro et al[1]. These researchers conducted a study on patients with stages 4-5 CKD who did not undergo dialysis. The vast majority of the patients were also administered oral phosphate binders (mostly calcium carbonate). All 26 patients included in the study had resistant SHPT, defined as a serum iPTH concentration >300 ng/L during the previous treatment with vitamin D analogues and oral phosphate binders. Regardless of the CKD etiology, the six-month combined therapy with cinacalcet (usually 30 mg/d) resulted in the effective management of SHPT since over 92% of the patients were within the limits of the serum iPTH concentration (70–110 ng/L in stage 4 CKD and 150–300 ng/L in stage 5 CKD) recommended by the KDOQI. The mean decrease in the serum iPTH level was 68%, which greatly surpassed the results of earlier trials. Notably, the diminished iPTH concentration was accompanied by an 8% increase in the serum phosphorus concentration and an 8% decrease in the serum calcium level. Unlike in other studies, there were only a few cases of hypocalcemia (2 episodes), which responded well to calcium supplementation (all of the patients completed the study). The counterbalancing actions of cinacalcet and vitamin D analogues on FGF23 were suggested as a mechanism preventing substantial hyperphosphatemia. There were no significant changes in the serum 25(OH) vitamin D_3 concentration as well as the systolic and diastolic blood pressure. The 6% GFR decrease was comparable to other studies and even lower than before the introduction of the combined treatment. Taken together, the addition of cinacalcet to the vitamin D analogue-based regimen proved utterly more effective than the standard treatment with vitamin D analogues or oral phosphate binders. Besides, the safety of the combined treatment including moderate doses of cinacalcet was confirmed in stages 4-5 CKD[16].

Conclusions

ER calcifediol increased the total serum 25-hydroxyvitamin D level to the value required for iPTH suppression (25-hydroxyvitamin D concen-

tration >30 ng/ml for 80% of patients). Approximately 30% of the patients treated with calcifediol ER achieved a 30% reduction in the iPTH level. Calcifediol ER was the cause of hypercalcemia in 2.1% of the patients. It significantly decreased the iPTH values, causing hypercalcemia in 1.7% of the patients. The paricalcitol treatment reduced the iPTH level by more than 30% in 85.7% of the patients by the 48th week. Paricalcitol was the cause of hypercalcemia in 1.9% of the patients by the 24th week. The serum iPTH concentrations of 92% of the patients receiving cinacalcet were within the limits recommended by the KDOQI (70-110 ng/L for stage 4 CKD and 150-300 ng/L for stage 5 CKD). The mean decrease in the serum iPTH level was 68%.

In conclusion, ER calcifediol, paricalcitol, and cinacalcet significantly decreased the iPTH levels in the patients described by the authors of the studies under analysis. Paricalcitol increased the serum calcium concentration the most of all the drugs under analysis. It is noteworthy that only cinacalcet does not carry the risk of hypercalcemia. A review of the results of other studies would enable a meta-analysis and more accurate conclusions.

Conflict of Interests

The authors declare that they have no conflict of interest.

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