PRACTICAL ADVICE FOR PHYSICIANS

UDC: 616.61-06:616.447-02/-092
DOI: 10.2298/VSP141218024P

Secondary hyperparathyroidism in chronic renal disease – etiopathogenesis, diagnosis and treatment

Sekundarni hiperparatireoidizam u hroničnoj bolesti bubrega – etiopatogeneza, dijagnostika i lečenje

Mileta Poskurica*†, Mina Poskurica†, Dejan Petrović*†

***Department of Urology and Nephrology, Clinical Center Kragujevac, Kragujevac, Serbia; †Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia**

Key words:
kidney failure, chronic; hyperparathyroidism, secondary; diagnostic techniques and procedures; therapeutics.

Ključne reči:
bubreg, hronična insuficijencija; hiperparatireodizam, sekundarni; dijagnostičke tehnike i procedure; lečenje.

Introduction

Chronic renal failure (CRF) is usually slowly progressive and irreversible impairment of the functional unit of the kidney – the nephron. According to the agreed and established criteria (National Kidney Foundation / Kidney Disease Outcomes Quality Initiative – NKF / KDOQI) there is a five-stage classification, so that in I^0 stage glomerular filtration rate (GFR) > 90 mL/min/1.73m^2 and morphological and functional abnormalities may exist. Mild, moderate and pronounced reductions in GFR correspond with the stages II^0–IV^0, and GFR < 15 mL/min/1.73m^2 means end-stage renal failure [1].

Progressive decrease in GFR leads to a number of adaptive changes on tubular processes which maintain the external balance of substances and water. Biological 'price' of exhausted compensatory mechanisms is expressed as the disorder of internal balance – homeostasis along with the development of azotemia, hyperkalemia, hypocalcemia, hyperphosphatemia, and a number of consequential changes in all organs [2, 3].

Mineral and bone disorder (MBD) related to renal osteodystrophy (ROD), occurs relatively early in the course of chronic kidney disease (CKD-MBD) and includes: abnormal levels of serum calcium (Ca), phosphate (P), parathyroid hormone (PTH) and vitamin D; lower rates of bone turnover, mineralization, structure, strength and linear growth; vascular and soft tissue calcification [4].

Secondary hyperparathyroidism (SHPT) is a disorder of increased bone turnover, which is pathophysiological and can combine all the above mentioned disorders.

Etiopathogenesis of secondary hyperparathyroidism in chronic renal disease

According to the traditional concept of pathophysiology of SHPT, PTH hypersecretion is a compensatory measure for the correction of hypocalcemia resulted from transient hyperphosphatemia, which appears relatively early in the course of chronic renal disease (CRD) (GFR ≤ 60 mL/min/1.73m^2). PTH hypersecretion stimulates 1-α hydroxylase activity and enhances the synthesis of calcitriol, which promotes intestinal absorption of calcium and phosphorus. Synthesis of phosphaturic hormone is stimulated in osteocytes (FGF 23), and thus 'temporarily' disturbed homeostasis is restored.

With progression of chronic renal failure (CRF), hyperphosphataemia becomes more common, and after the reduction of GFR ≤ 25–30 mL/min/1.73m^2 it becomes permanent [5]. Serum calcium values therefore progressively decrease and it consequently lowers ionized calcium fraction (Ca^{2+}), thus stimulation of PTH synthesis and secretion becomes permanent, partly due to the absence of inhibitory effects of calcium and vitamin D for lower receptor density (CaSR/VDR) for these ligands in chief cells of the parathyroid gland [5].

Correspondence to: Mileta Poskurica, Department of Urology and Nephrology, Clinical Center Kragujevac, Zmaj Jovina 30, 34 000 Kragujevac, Serbia. E-mail: mileta.poskurica@gmail.com

Reduced serum calcium and calcitriol values and increase in circulating PTH have been encountered in 40% of patients with GFR < 40 mL/min/1.73m^2 and in 80% of cases with GFR < 20 mL/min/1.73m [2, 3, 6].

Biological effects of parathyroid hormone

PTH is a polypeptide containing 84 amino acids, which is normally secreted by the chief cells of four parathyroid glands, 50–300 mg weight each. Proteolytic degradation of prepro-PTH in the endoplasmic reticulum and Golgi apparatus creates the final form ($^{1–84}$ iPTH) which is deposited on secretory granules. Release from the depot is encouraged by the same stimuli as its synthesis, primarily by low extracellular concentration of Ca^{2+} ions. It disintegrates rapidly in the liver and kidneys (T½ = 2–4 minutes) into biologically active N terminal amino acids (33-84, 36-84N), and various biologically inactive C carboxylate terminals ($^{7–84, 34–84, 37–84, 41–84, 43–84}$ C) [7, 8].

PTH exerts its effects on tissues through PTH_1/PTH_2 receptors. Correction of hypocalcemia involves rapid release of Ca^{2+} ions along with pumping-out a so-called 'bone fluid' located on the peripheral zone of bone matrix and slow-rate and long-term release of calcium deposited in the mineral matrix. Osteoclastic-induced enzymatic degradation of apatite is stimulated by cytokines (TNF-α and IL-1) and growth factors acting locally (TGFß, IGF, FGF). PTH stimulates reabsorption of Ca^{2+} and Mg^{2+} in kidney cells; it inhibits reabsorption of P and stimulates calcitriol synthesis by stimulating α 1-hydroxylase. Indirectly, stimulating the synthesis of vitamin D, PTH promotes the intestinal absorption of Ca^{2+} and P for the increased expression of genes responsible for NaPT2b transporter synthesis [9, 10].

Nontraditional target organs of PTH are other tissues and organs with PTH1/PTH2 receptors, which are not directly or indirectly involved in maintaining Ca^{2+} and P ion homeostasis. Maladaptive changes in blood vessels, myocyte hypertrophy, increased extracellular matrix, myocardial fibrosis, dyslipidemia, proatherogenic and proinflammatory effects, vascular and soft tissue calcifications, increased intracellular Ca^{2+} concentration, impaired compliance of arteries and arterioles are some of the harmful consequences of SHPT and related disorders leading to increased mortality in patients on dialysis [11, 12]. According to the relevant data from the DOPPS (Dialysis Outcomes and Practice Patterns Study), there was an increased mortality in patients on dialysis with Ca^{2+} > 10.0 mg/dL, P > 7 mg/dL, and PTH > 600 pg/mL [13].

Regulation of parathyroid hormone synthesis and secretion

Variation in the extracellular ionized Ca^{2+} concentrations is the most important mechanism of regulation of PTH synthesis and secretion. It is independent of the effects of vitamin D and is accomplished through a complex sensing receptor CaSR. Intracellular domain of the receptor complex (β-region) directs through adenylate cyclase the production of energy substrates ATP and cAMP which stimulate the synthesis of PTH under conditions of extracellular hypocalcemia. Otherwise, intracellular α- domain of CaSR and phospholipase C is activated, which finally inhibits mRNA transcription in PTH synthesis in a cascade process [14].

Experimental hyperphosphataemia stimulates PTH synthesis (and secretion), regardless of the concentration of calcium in the vicinity of parathyreocytes, by phospholipase A2-mediated post-transcriptional induction of PTH mRNA synthesis. Indirectly, it leads to hypocalcemia but also to stimulation of 1-α hydroxylase and the synthesis of phosphaturic hormone FGF23, thereby providing a feedback control of hyperphosphatemia [4].

Through its nuclear receptor (VDR) vitamin D directly inhibits PTH mRNA synthesis, and in different ways it indirectly controls biologically available PTH: it stimulates CaSR expression and the synthesis of FGF23 in osteocytes, encourages maturation of osteoblasts and synthesis of bone matrix (utilization of Ca^{2+} and P), stimulates osteoclastogenesis (liberation of Ca^{2+} and P), intestinal absorption of Ca^{2+} and P, renal reabsorption of Ca^{2+} and Mg, and excretion of phosphates [15].

Phosphaturic hormone FGF 23 is formed in the osteocytes and is stimulated by PTH, vitamin D and hyperphosphatemia. It inhibits PTH synthesis and secretion on post-transcriptional level through mitogen-activated protein kinase (MAPK). It exhibits phosphaturic effect through internalisation of phosphate-transport proteins (NaPT2a and NaPT2c) [5].

Permanent PTH hypersecretion in advanced CRF and in dialysis patients is encouraged by intrinsic change in parathyroid glands. Combining thropic stimuli enables diffuse (polyclonal) proliferation of parathyreocytes and consequently reduces the density of CaSR and VDR, so that individual clones proliferate uncontrollably, which eventually ends up in formation of micronodule or encapsulated macronodule. They are relatively insensitive to inhibitory effects of vitamin D and the concentration of ionized calcium in the environment, which shifts the 'sensitivity of Ca^{2+}' to the right, i.e. to inhibit PTH synthesis higher serum (and extracellular) calcium levels are needed [16].

Skeletal resistance to PTH indicates an inadequate response to its pro-calcemic effects and is associated with abnormalities in uremic environment: hyper-P, hypo-Ca, hypovitaminosis D, lower density of VDR and CaSR, accumulation of $^{7–84}$ PTH fragment exerting effects that are opposing to iPTH etc. In addition, the accumulation of osteoprotegerin (which inhibits osteoclast differentiation and maturation) and of BMP-7 bone morphogenetic protein (incorporation of phosphate into skeletal matrix) suppresses the function of osteoclasts and osteoblasts in different ways [8, 9].

The diagnosis of secondary hiperparathyroidism

Clinical manifestations of SHPT are: itching, nausea, vomiting, confusion, various clinical manifestations of soft tissue calcification, painful bones and joints, fractures, and other [17].

Laboratory analyses of relevant parameters are shown in ranges of normal serum/plasma values [7, 18]: 1) serum intact PTH (iPTH), 15–60 pg/mL (iPTH > 450 pg/mL indicates rapid bone turnover); 2) markers of bone formation are: total

alkaline phosphatase (ALP), 90–120 IU/L; bone-specific ALP (bALP), 5–15 μg/L; osteocalcin (OC-bGP), 38–202 ng/mL; matrix Gla protein (m-GP): 6.2 ± 3.5 nmol/L; 3) markers of bone resorption: tartrate-resistant acid phosphatase (TRAP), 2.5 to 45 IU/L; C - terminal of procollagen Type I (ICTP), 1.8–5.046 ng/mL; N - terminal type I collagen (NTX), 6.2 ± 19.0 nmol/L; 4) other parameters of bone metabolism are: total serum calcium: 2.10–2.60 mmol/L (8.5–10.5 mg/dL); ionized calcium ($Ca^{2+)}$: 1.15–1:35 mmol/L (4.6–5.4 mg/dL); serum phosphate 0.84–1.45 mmol/L (2.5–4.5 mg/dL); product (Ca × P): < 4.40 $mmol^2/L^2$ (< 55 mg^2/dL^2); fibroblast growth factor (FGF23), 29 ± 28 pg/mL; serum 25(OH)D, 20–70μg/L; serum $1.25(OH)_2D$ serum: 25–45 pg/mL.

Radiological diagnostics

Radiological skeletal survey (dominant hand bones, long bones, spine and synarthrosis) can identify signs of bone resorption (subperiosteal, intracortical, endosteal and subchondral) bone sclerosis (vertebrae) and calcification of the blood vessels (continuous in the intima - discontinuous in the media of the blood vessels) and parenchymal organs [19].

Ultrasound examination of the parathyroid glands reveals their position and size (volume), which correlates well with the degree of activity, and examination of the heart and blood vessels provides information on cardiovascular changes.

Scintigraphy of parathyroid glands with ^{99m}TC-methoxyisobutyl isonitrile (MIBI) allows additional visualizing the glands and morphofunctional analysis.

Computed tomography (electron beam – EBCT and multi-slice – MSCT) are useful for the assessment of severity of coronary and valve calcification, as well as for locating parathyroid glands and estimation of their size [19].

Biopsy is not a routine procedure and is applied in accordance with K/DIGO (Kidney Disease: Improving Global Outcomes) recommendations, along with two-dose tetracycline 500 mg administered 20 and 10 days before the biopsy [19, 20]. It is recommended in cases of inconsistent laboratory findings, unexplained bone pain or the occurrence of fractures, progressive vascular calcification, unexplained hypercalcemia, suspicion of aluminum or other metals intoxication, and it also should be considered before the application of bisphosphonates [20–22].

Prevention and treatment

Preventive measures include slowing the progression of kidney disease, timely commencement and periodic monitoring of indicators of mineral status thereafter, serum levels of regulatory hormones, biochemical markers of bone turnover, and timely diagnostic procedures, Table 1 [19].

Treatment involves the implementation of measures to normalize serum Ca^{2+} and P, correction of calcitriol deficiency and other procedures applied to suppress PTH synthesis and secretion.

Oral phosphate binder

Treatment of hyperphosphatemia begins by protein-adjusted restricted dietary phosphate intake of 800–1000 mg/daily, usually not before GFR is reduced to 50–60% of its normal values.

If serum P cannot be reduced to the recommended limit in this way or PTH is increased, the use of calcium, and optionally, non-calcium-based phosphate binders may be considered (Table 2) [19, 20, 23].

For this purpose, natural metabolites of vitamin D can be used [ergocalciferol (D_2), cholecalciferol (D_3), calcitriol]; synthetic analogues of vitamin D_2 (paricalcitol, falecalcitriol, doxercalciferol) synthetic analogues of vitamin D_3 (alfacalcidol, maxacalcitol).

The use of vitamin D in the treatment of secondary hyperparathyroidism

If hyperphosphatemia is corrected as described above and target serum Ca^{2+} levels achieved are not sufficient to suppress hypersecretion of PTH, application of vitamin D may be taken into consideration (Table 3) [24].

Ergocalciferol [Calcidol®, Calciferol®, Vitamin D2®, Drisdol® caps. 1.25 mg (50,000 IU); Ergocalciferol® amp. 200.000/300.000/600.000 in 1 mL or 2 mL is now rarely used, and priority is given to calcitriol and its synthetic derivatives.

General recommendations for use of vitamin D to suppress SHPT are: if, after the initial dose serum PTH increases remains unchanged, or is reduced to less than 50%, the dose should be increased; if PTH is reduced by more than 50%, the dose does

Table 1

Recommended reference intervals for monitoring biochemical parameters of mineral bone disorder in chronic kidney disease (CKD)

Parameter	Check-up interval (in months)		
	CKD–III[0] (GFR 59–30 mL/min)	CKD–IV[0] (GFR 29–15 mL/min)	CKD–V[0] (GFR < 15 mL/min)
Ca	6–12	3–6	1–3
P	6–12	3–6	1–3
PTH	basal	6–12	3–6
ALP	not recommended	6–12	3–6
bALP	basal- not recommended		
25 OH D_3	basal when PTH levels increase		when needed

GFR – glomerular filtration rate; Ca – serum calcium; P – serum phosphate; PTH – parathyroid hormone; ALP – serum alkaline phosphatase; bALP – bone alkaline phosphatase.

Table 2

Recommendations for the application of phosphate binder

Dosage	Phosphate binder
	Calcium carbonate
Initial dose	2–3 × 0.5–1.0 g (Calcium carbonate® tablets. 0.5/1.0 g)
Titration: dose/interval	0.5–1.0 g/1–2 weeks
D.Th. max.	5.0–6.0 g (2.0 g elemental Ca daily)
Notes	Constipation, hyper-Ca, soft-tissue calcification, proven ABD or PTH ≤ 150 pg/mL constantly
	Calcium acetate (Phoslo® capsules 667 mg; Phosex® tablets 1000 mg; Renacet® tablets 475 mg)
Initial dose	2 × 667 mg; 3 × 475 mg
Titration: dose/interval	475–667 mg/1–2 weeks
MDD	3–4.0 g (2.0 g elemental Ca daily).
Notes	Constipation, hyper-Ca, soft-tissue calcification, proven ABD or PTH ≤ 150 pg/mL constantly
	Combination 435 mg calcium acetate and 235 mg magnesium carbonate (Osvaren® tablets)
Initial dose	3 × 1 tabl.
Titration: dose/interval	1–2 tabl. /1–2 weeks
MDD	10–12 tab.
Notes	Mg > 2 mmol/L, AV-block III°, bradycardia/bradyarrhythmias, customize the dialysate magnesium content, myasthenia
	Sevelamer hydrochloride (Renagel® tablets 800 mg) **Sevelamer carbonate** (Renvela® tablets 800 mg)
Initial dose	3 × 1 (P: 1.76–2.42 mmol/L); 3 × 2 (P > 2.42 mmol/L).
Titration: dose/interval	1–2 tab/week
MDD	4–6 g/daily
Notes	Cholesterol binder, compensation of liposoluble vitamins, hypo-Ca (correction of $CaCO_3$, vitamin D)
	Lanatanum carbonate (Fosrenol® tablets 500/750/1000 mg)
Initial dose	1–2 tab/daily
Titration: dose/interval	1–2 tab/week
MDD	1.5–3.0 g/daily
Notes	Less hypocalcemic state, likely tissue accumulation

MDD – maximum daily dose.

Table 3

Recommendations for supplementation of vitamin D

Dosage	Vitamin D
	Calcitriol (Rocaltrol® tablets -0.25/0–5 μcg; Calcitriol® ampoules 1 μcg)
Initial dose	p.o.: 0.25 μcg/daily or 0.1 μg/кg/weekly in 3 doses i.v.: 1–2 μcg/HD.
Titration: dose/interval	p.o.: 0.25 μcg/2–4 weeks i.v.: 0.5–1 μcg/2–4 weeks
MDD	In accordance with parameters (Ca, P, Ca × P and PTH) – app. 10 μcg
Notes	General contraindications
	Alfacalcidol (One-Alpha® capsules 0.25/0.5/1.0 μcg; ampoules 1.0/2.0 μcg)
Initial dose	p.o.: 1,0 μcg/daily i.v.: 1.0 μcg/HD
Titration: dose/interval	p.o.: 0.25/0.5 μcg./2–4 weeks i.v.**:** 0.5–1.0 μcg./2–4 weeks
MDD	In accordance with parameters (Ca, P, Ca × P and PTH)
Notes	General contraindications
	22-oxacalcitriol-OCT (Maxacalcitol® Oxarol ®; ampoules 5.0/10.0 μcg)
Initial dose	i.v.**:** 5 μcg (PTH ≤ 500 pg/mL); 10 μcg (PTH > 500 pg/mL).
Titration: dose/interval	i.v.**:** 5.0 μcg/2–4 weeks
MDD	In accordance with parameters (Ca, P, Ca × P and PTH)
Notes	Lower levels of hyper-Ca and hyper-P in relation to calcitriol Better control of bone metabolism Useful in refractoriness to calcitriol General contraindications
	Paricalcitol (Zemplar® capsules 1/2/5 μcg; ampoules 5.0/10 μcg)
Initial dose	p.o.: 1 μcg/daily; 2 μcg 3 times weekly (PTH < 500 pg/mL), p.o.: 2 μcg/daily; 4 μcg 3 times weekly (PTH > 500 pg/mL), i.v.: 5 μcg/HD
Titration: dose/interval	p.o.: 1 μcg/2 μcg/2–4 weeks i.v.: 2.5 -5 μcg/2–4 weeks
MDD	p.o.: μcg dose = PTH (pg/mL) : 60; (≤ 32 μcg/weekly) i.v.: μcg dose = PTH (pg/mL) : 80, (≤ 40 μcg/weekly)
Notes	Less calcemic than calcitriol General contraindications
	Doxercalciferol (Hectorol® capsules 0.5/1.0/2.5 μcg; ampoules 2.0/4.0 μcg)
Initial dose	p.o.: 3 × 1–2.5-10 μcg. i.v.**:** 3 × 4 μcg
Titration: dose/interval	p.o.: 2.5–5.0 μcg/8 weeks i.v.**:** 3 × 1–2 μcg/8 weeks
MDD	p.o.: 60 μcg/weekly i.v.: 18 μcg/weekly
Notes	General contraindications

P.o. – *per os*; i.v. – intravenous; MDD – maximum daily dose; PTH – parathyroid hormone; Ca – serum calcium; P – serum phosphate.

not change if PTH > 150 pg/mL; if PTH < 150 pg/mL treatment will be suspended temporarily, and after 1–2 weeks it will continue at a lower dose. It will be necessary to periodically monitor: Ca, P, Ca × P (at every 7-14 days) and PTH (1-2 times a month.) [25, 26].

Contraindications to vitamin D are: hypercalcemia (≥ 2.60 mmol/L), hyperphosphatemia (≥ 1.70 mmol/L), iPTH < 150 pg/mL, adynamic bone biopsy-proven disease, vascular calcification and calciphylaxis.

Treatment of secondary hyperparathyroidism with calcimimetics

Calcimimetics are drugs that bind to the transmembrane domain of CaSR in parathyrocyte and increase its sensitivity to the existing extracellular Ca^{2+} concentration, and thereby suppress PTH synthesis independently of vitamin D. Long-term use of calcimimetics substantially reduces the need for parathyroidectomy (PTx), and the risk of fractures and cardiovascular complications [27].

The drugs are indicated for dialysis patients with refractory SHPT including those with calciphylaxis if serum PTH > 800–1000 pg/mL despite standard therapy and surgical treatment is impossible. The main contraindication is hypocalcemia.

Cinacalcet (Mimpara®; Sensipar® tabl. 30/60/90 mg) is used to treat SHPT with phosphate binders and vitamin D. The starting dose was 30 mg/day and progressively increased by 30 mg every 2–4 weeks to a maximum of 180 mg/day. During the titration phase PTH should be measured every month, and every 3 months when the maintenance dose is achieved. In case of hypo-Ca, calcium supplements and vitamin D should be administered and dialysate concentration of calcium should be corrected.

To change the dialysis regime means, besides the use of membrane with higher phosphate clearance and longer dialysis duration, more frequent or daily/nightly dialysis until hyperphosphatemia has been corrected. To provide a more liberal application of vitamin D or its analogues, and, consequently, a more efficient suppression of PTH, 1.5 mmol/L or 1.25 mmol/L calcium dialysate is commonly used [28].

Surgical treatment of secondary hyperparathyroidism

Surgical or sclerosing PTx is a procedure for treatment of advanced SHPT that is refractory to combined drug therapy [28].

Indications for PTx are: persistent hyper-Ca despite the complete suspension of Ca-phosphate binder; persistent hypersecretion PTH (≥ 1000 pg/mL) refractory to medical treatment, especially if the gland/nodule is greater than 0.5 cm; progressive and symptomatic soft-tissue calcifications including uremic arteriolopathy (calciphylaxis); unbearable itching with increased levels of PTH [29].

Surgical methods are subtotal or total parathyreidectomy. Total PTx means simultaneous autoimplantation of parathyroid tissue which is not of nodular hyperplastic gland. Subtotal PTx involves removing all located parathyroid glands except the least and anatomically the best one, which is partially resected and reconstructed [29].

Ultrasound-guided percutaneous ethanol injection therapy (PEIT) is used to selectively destroy nodular hyperplastic glands, while the rest of diffuse-type hyperplastic parathyroid tissue can be medically controlled. Complications include pain, bleeding and laryngeal nerve paresis. The same procedure may also be used with administration of injectable calcitriol or analogues and effectively suppress diffuse-type hyperplastic glands, through apoptosis induction or toxic necrosis [30].

Conclusion

Excessive secretion of parathyroid gland already develops in moderate renal failure, and severe clinical consequences are usually seen in patients treated with dialysis. Initially, transient hypocalcemia and hyperphosphatemia trigger the excessive synthesis and secretion of parathyroid hormone, and when they have turned into permanent condition, vitamin D deficiency is already present. Besides biochemical indicators that should be periodically monitored in accordance with the recommendations, a variety of visualization techniques can be used for localization and assessment of the gland activity. Correction of hyperphosphatemia and hypocalcemia using calcium-based phosphate binders and vitamin D leads to the suppression of PTH hypersecretion. In clinically well-defined patients, application of calcimimetics may be useful and, if associated with pulse doses of active metabolites of the vitamin D, can significantly reduce the need for parathyroidectomy.

Acknowledgments

Authors would like to express their deepest gratitude to the Serbian Ministry of Education, Science and Technological Development for their Grant No 175014, which was used as one of the sources to financially support the study.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

R E F E R E N C E S

1. *Levey AS, de Jong PE, Coresh J, El-Nahas M, Astor BC, Matsushita K*, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011; 80(1): 17−28.
2. *Bricker NS*. On the pathogenesis of the uremic state. An exposition of the "trade-off hypothesis". N Engl J Med 1972; 286(20): 1093−9.
3. *Poskurica M*. Imbalance of phosphate, calcium and magnesium ions in development of chronic renal failure [dissertation]. Belgrade: School of Medicine, University of Belgrade; 1993. (Serbian)
4. *Lewin E, Rodriguez M*. Abnormal parathyroid gland function in CKD. In: *Olgaard K, Salusky BI, Silver J*, editors. The spectrum of Mineral and Bone Disorders in Chronic Kidney Disease. 2nd ed. Oxford: University Press; 2010. p. 77−108.
5. *Naveh-Many T, Silver J*. Regulation of parathyroid hormone biosynthesis and gene expression. In: *Olgaard K, Salusky BI, Silver J*, editors. The spectrum of Mineral and Bone Disorders in Chronic Kidney Disease. 2nd ed. Oxford: University Press; 2010. p. 61-75.
6. *Poskurica M*. Dynamics of fractional phosphate excretion in chronic renal failure [thesis]. Belgrade: School of Medicine, University of Belgrade; 1989.
7. *Ureña P, Olgaard K, Martin K*. Biochemical markers of bone metabolism in CKD. In: *Olgaard K, Salusky BI, Silver J,* editors. The spectrum of Mineral and Bone Disorders in Chronic Kidney Disease. 2nd ed. Oxford: University Press; 2010. p. 173−98.
8. *Ritter CS, Armbrecht HJ, Slatopolsky E, Brown AJ*. 25-Hydroxyvitamin D(3) suppresses PTH synthesis and secretion by bovine parathyroid cells. Kidney Int 2006; 70(4): 654−9.
9. *Gonzaley AE, Martin JK*. Growth factors and cytokines in renal bone disease. In*: Olgaard K, Salusky BI, Silver J*, editors. The spectrum of Mineral and Bone Disorders in Chronic Kidney Disease. 2nd ed. Oxford: University Press; 2010. p. 137−44.
10. *Ott MS*. New aspects of normal bone biology. In: *Olgaard K, Salusky BI, Silver J*, editors. The spectrum of Mineral and Bone Disorders in Chronic Kidney Disease. 2nd ed. Oxford: University Press; 2010. p. 15−30.
11. *Petrovic D, Stojimirovic B*. Secondary hyperparathyroidism: risk factor for development of cardiovascular complications in patients on hemodialysis. Med Pregl 2010; 63(9−10): 674−80. (Serbian)
12. *Poskurica M, Lazarević M, Petrović D, Lazarević T, Milošević J*. Calcium and Phosphate Disturbances and its Regulating Hormones in Chronic Renal Failure. XXXVI Congress of EDTA-ERA, EDTA-ERA; Spain, Madrid; September 5–8: 1999; Abstract 38.
13. *Petrović D, Obrenović R, Trbojević-Stanković J, Majkić-Singh N, Stojimirović B*. Hyperphosphatemia - The Risk Factor for Adverse Outcome in Maintenance Hemodialysis Patients. J Med Biochem 2012; 31(3): 239−45. (Serbian)
14. *Cañadillas S, Canalejo A, Santamaría R, Rodríguez ME, Estepa JC, Martín-Malo A,* et al. Calcium-sensing receptor expression and parathyroid hormone secretion in hyperplastic parathyroid glands from humans. J Am Soc Nephrol 2005; 16(7): 2190−7.
15. *Koizumi M, Komaba H, Fukagawa M*. Parathyroid Function in Chronic Kidney Disease: Role of FGF23-Klotho Axis. In: *Razzaque MS*, editor. Phosphate and Vitamin D in Chronic Kidney Disease. Basel: Karger; 2013. p. 110−23.
16. *Lewin E, Garfia B, Almaden Y, Rodriguez M, Olgaard K*. Autoregulation in the parathyroid glands by PTH/PTHrP receptor ligands in normal and uremic rats. Kidney Int 2003; 64(1): 63−70.
17. *Levy J, Morgan J, Brown E*. Complications of ESRD: renal bone disease. In: *Levy J, Morgan J, Brown E*. Oxford handbook of dialysis. 2nd ed. New York: Oxford University Press; 2007. p. 653−82.
18. *Poskurica M*. Renal osteodystrophy in patients on peritoneal dialysis. In: *Nešić V*, editor. Peritoneal dialysis: A clinical problem. Belgrade: Faculty of Medicine; 2003. p. 167−95. (Serbian, English)
19. *Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group*. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2009; (113): S1-130.
20. *National Kidney Foundation*. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003; 42(4 Suppl 3): S1−201.
21. *Poskurica M, Lazarević M, Grubor M, Laković S, Mitrović N, Milošević J*. Metastatic calcification of the heart in patients with terminal renal failure. Medicinska istraživanja 1999; 13(2): 109−13. (Serbian)
22. *Applbaum YH*. Imaging of the skeleton snd the joints in CKD. In: *Olgaard K, Salusky BI, Silver J*, editors. The spectrum of Mineral and Bone Disorders in Chronic Kidney Disease. 2nd ed. Oxford: University Press; 2010. p. 199−216.
23. *D'Haese PC, Spasovski GB, Sikole A, Hutchison A, Freemont TJ, Sulkova S,* et al. A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. Kidney Int Suppl 2003; (85): S73−8.
24. *Poskurica M*. The importance of vitamin D in preventing progression and complications of terminal renal failure. In: *Stolic R*, editor. School of dialysis Leskovac, "Preventive Nephrology. Nis: University of Nis; 2004. p. 229−36. (Serbian)
25. *Park J, Rhee CM, Lau WL, Kalantar-Zadeh K*. Clinical uses of 1-alpha-hydroxy-ergocalciferol. Curr Vasc Pharmacol 2014; 12(2): 306−12.
26. *Cunningham J, Lewin E, Silver J*. Medical therapy in chronic kidney disease. In: *Olgaard K, Salusky BI, Silver J*, editors. The spectrum of Mineral and Bone Disorders in Chronic Kidney Disease. 2nd ed. Oxford: University Press; 2010. p. 463−83.
27. *Nemeth EF*. Calcimimetics and calcilytics in the treatment of chronic kidney disease-mineral and bone disorder. In: *Olgaard K, Salusky BI, Silver J*, editors. The spectrum of Mineral and Bone Disorders in Chronic Kidney Disease. 2nd ed. Oxford: University Press; 2010. p. 443−61.
28. *Argilés A, Mourad G*. How do we have to use the calcium in the dialysate to optimize the management of secondary hyperparathyroidism? Nephrol Dial Transplant 1998; 13 Suppl 3: 62−4.
29. *Sarfati E, Drueke BT*. Surgical management of secondary hyperparathroidism. In: *Olgaard K, Salusky BI, Silver J*, editors. The spectrum of Mineral and Bone Disorders in Chronic Kidney Disease. 2nd ed. Oxford: University Press; 2010. p. 543−59.
30. *Ogata H, Koiwa F, Shishido K, Takahashi K, Ito H, Kinugasa E,* et al. Effects of 22-oxacalcitriol and calcitriol on PTH secretion and bone mineral metabolism in a crossover trial in hemodialysis patients with secondary hyperparathyroidism. Ther Apher Dial 2007; 11(3): 202−9.

Received on December 18, 2014.
Accepted on February 23, 2015.
Online First February, 2016.