SCIENTIFIC REVIEW

sciendo

10.2478/AMB-2019-0009

CALCIUM-PHOSPHATE METABOLISM DISORDERS IN PATIENTS WITH RENAL FAILURE – CLINICAL SIGNIFICANCE, DIAGNOSIS AND TREATMENT

V. Grozeva, A. Kundurzhiev

Clinic of Nephrology, University Hospital "Sv. Ivan Rilski", Department of Internal Medicine, Medical University – Sofia, Bulgaria

Abstract. *Chronic kidney diseases (CKD) are commonly associated with calcium and phosphorus metabolism disorders. The general term of "renal osteodystrophy" (ROD) encompasses a complex spectrum of abnormalities in bone and mineral metabolism in CKD. This is one of the most serious and debilitating complications of CKD. It is related to disproportionately high direct and indirect costs of healthcare, thus posing a major burden on society. The development of ROD begins too early in the course of CKD. Some mechanisms involved in the pathogenesis of ROD are reduced calciferol production, calcium deficiency and hyperphosphatemia. Clinically, ROD occurs with varied manifestations – osteomalacia, osteoporosis, adynamic bone disease. The diagnosis and the treatment are a challenge for the physician and effort should be made to prolong the duration and quality of life of the affected patients.*

Key words: *calcium-phosphate metabolism, chronic kidney diseases, hyperparathyroidism*

Corresponding author: *Vania Grozeva MD, Clinic of Nephrology, University Hospital ,,Sv. Ivan Rilski", Department of Internal Medicine, Faculty of Medicine, Medical University – Sofia, Blvd ,,Acad. Ivan Geshov" 15, Sofia, 1431, Bulgaria, tel: 0889452271, e-mail: vanyagrozeva@yahoo.com*

INTRODUCTION

Chronic kidney diseases (CKD) are commonly associated with calcium and phosphorus metabolism disorders. These disorders are present at an early stage in the course of CKD as they occur quietly and asymptomatically [1, 2]. The general term of "renal osteodystrophy" (ROD) encompasses a complex spectrum of abnormalities in bone and mineral metabolism in CKD [1]. This is one of the most serious and debilitating complications of CKD. It is related to disproportionately high direct and indirect costs of healthcare, thus posing a major burden on society [3,7]. Practically, ROD affects all CKD patients and should be diagnosed and treated to improve the prognosis of these patients [3]. Children and women are particularly susceptible to ROD development. Patients with fast-progressing kidney diseases and those with autosomal dominant tubulointerstitial disease are also at increased risk [3].

ROD is a complex of pathogenetically diverse diseases and conditions. These include secondary and tertiary hyperparathyroidism, impaired vitamin D metabolism, bone resistance to parathormone (PTH), patients' immobilization, amyloidosis, hypogonadism, toxic osteodystrophy from aluminum or poor dialysis, iatrogenic osteodystrophy from treatment with high doses of calcium and vitamin D and others [3].

PATHOGENETIC FACTORS FOR ROD DEVELOPMENT

The development of ROD begins too early in the course of CKD. The major pathogenetic mechanism – **reduced calciferol production**, readily occurs when the GFR drops below 90 ml/min/1.73 m^2 [7]. It is well known that calcitiriol (1,25(OH)2D) decreases as a result of reduced tubular transformation of 25(OH)D into 1,25(OH)2D due to intracellular accumulation of phosphate, resulting in a decrease in alpha hydroxylase activity [1, 9]. Progressive loss of nephrons and the presence of concomitant acidosis also play a role in this process. When GFR declines to 65-70 ml/min/1.73 m^2, the fall in calcitriol values is already highly significant, and approximately at the same time PTH begins to increase, thus leading to the development of secondary hyperparathyroidism. At GFR of about 35 ml/min/1.73 m^2, or earlier if the progression of chronic renal insufficiency occurs slowly, there is already clinically proven secondary hyperparathyroidism [3].

The second pathogenetic factor for the development and progression of ROD, which occurs relatively early in the course of CKD, is **calcium deficiency**. Several factors contribute to the development of calcium deficiency in patients with CKD: 1. decreased oral intake and/or impaired intestinal resorption; 2. skeleton resistance to PTH effect; 3. direct result from low levels of 1,25(OH)2D; 4. decreased calcium receptor expression in parathyroid glands (PTG).

Calcium deficiency is an incentive both for over-secretion of PTH and for PTG hyperplasia [1]. In recent years, due to the massive use of calcium-containing agents, the pathogenetic role of hypocalcemia in the development of ROD has remained in the background [3]. Moreover, according to some authors, a more frequent phenomenon in patients with CKD is iatrogenic hypercalcemia and its consequences – vascular calcification affecting the brain, carotid and coronary vessels. The vascular walls have reduced compliance, making them rigid, increasing the risk of thrombus formation and development of atherosclerotic plaques. All of this leads to fatal accidents and determines the prognosis of the patients [2, 10].

The third important pathogenetic factor for ROD, which is later involved in the course of CKD, is **hyperphosphatemia**. It occurs at GFR values of about 35-30 ml/min/1.73 m^2. However, according to more recent studies, this refers to extracellular phosphorus levels. Intracellular phosphates increase at GFR 70-60 ml min/1.73 m^2 [9]. This leads to reduced activity of 1-alpha hydroxylase and, as a consequence, decreased calciferol levels. In advanced CKD, high extracellular phosphorus is a major cause of ROD progression and the greatest obstacle to its complete treatment. By direct and indirect actions, hyperphosphatemia leads to secondary hyperparathyroidism [11]. Direct actions are as follows: 1. increased synthesis and secretion of PTH; 2. PTG hyperplasia. The indirect effects of hyperphosphatemia are as follows: 1. reduced levels of calcitriol; 2. Reduced ionized calcium; 3. Skeletal resistance to calcitriol and PTH [1].

More recently, a factor that contributes to the maintenance of serum phosphorus and that is synthesized from osteoblasts – fibroblast growth factor – 23 (FGF23), was identified. It functions in conjunction with its co-factor Klotho-protein. Its basic role is to reduce plasma phosphorus by reducing tubular phosphate reabsorption, a mechanism similar to that of PTH. However, in contrast to PTH effect, FGF23 reduces the renal synthesis of calcitriol. On the contrary, calcitriol and PTH increase the serum level of FGF23. The level of FGF23 – Klotho protein complex progressively increases with progression of CKD, accentuating the deficiency of calcitriol, and this contributes to the development of secondary hyperparathyroidism. Therefore, FGF23 reduces calcitriol, increases PTH, which in turn induces even higher levels of FGF23. This vicious circle is a result of hyperphosphatemia and is characteristic of the later stages of CKD [1]. Other factors increasing the risk of bone disease and its severity in CKD include hypogonadism, malnutrition, older age and low physical activity. All of these factors are more common with CKD, moreover they are part of the clinical picture [3].

CLINICAL FORMS OF ROD

Two main forms of ROD are clinically recognized: 1) high turnover bone disease in secondary hyperparathyroidism (SHPT) and 2) low turnover bone disease also referred to as adynamic bone disease [11].

Most often the two forms transfuse into one another, especially with advancing of CKD, so some authors also review a third form of ROD – a mixed bone disease that may be dominated by high or low turnover bone sections [3]. In ROD with increased bone turnover there are high levels of intact PTH (iPTH) – 25-30 pmol/l, while in the second form – PTH levels are < 15 pmol/l [4]. Compared with PTH 150-300 pg/ml, all-cause mortality was higher for PTH 301-450 pg/ml and greater than 600 pg/ml, with PTH greater than 600 pg/ml also associated with an increased risk of cardiovascular mortality and cardiovascular hospitalizations. PTH less than 50 pg/ml was associated with adverse outcomes and a high proportion of these patients were continued on therapy for SHPT, increasing their risk of adynamic bone disease. With a suggestion that a

PTH more than 300 ng/ml is associated with increased risk of death and hospitalization, the trend towards increased PTH in dialysis patients worldwide may have clinical consequences [30].

The histological picture of the bone is quite varied – from transitions of salient adynamic bone with complete lack of osteoblast and osteoclast activity through osteomalacia to all degrees of marked increase in osteoclasts and osteoblasts function – in severe secondary hyperparathyroidism [13]. The risk of high turnover bone disease correlates with the severity of hypocalcaemia, hyperphosphatemia, and deficiency of calcitriol that lead to high PTH /secondary hyperparathyroidism/ and prevailing of bone resorption over bone formation as a consequence [3]. The factors leading to relativistic hypoparathyroidism and the development of low turnover bone disease are – hypodynamics, older age, concomitant diseases such as diabetes mellitus, aggressive treatment with calcium-containing phosphorus-binding drugs, peritoneal dialysis, overdose with active vitamin E metabolites [14, 15]. In all these cases bone formation is reduced. In the past, aluminium intoxication was a common cause of adynamic bone disease. Nowadays, the most common causes are uremia, malnutrition, chronic inflammation related to the CKD and dialysis treatment.

CLINICAL PICTURE

Clinically, ROD occurs with spontaneous fractures and deformities leading to severe disability, resulting in reduced quality of life but also reduced survival. Renal osteodystrophy also may present with nonspecific signs and symptoms, including weakness, bone pain, and skeletal deformity. Presentation varies markedly with age. Adults may present with findings of osteomalacia, while children typically show growth retardation. As a result, complications differ depending on the patient's age. The most common complication of renal osteodystrophy is fracture, which may be insufficiency fracture through osteomalacic bone or pathologic fracture through brown tumors or amyloid deposits. Dialysis patients may experience carpal tunnel syndrome, osteomyelitis, septic arthritis, and osteonecrosis. Renal transplant patients may experience osteonecrosis, tendinitis, tendon rupture, and fracture [25]. In dialysis patients, the average age for fracture of the femoral neck was 10-15 years lower compared to the general population, with the mortality rate for these patients being 2-2.5 times higher than in the general case [3]. ROD also has out-of-skeleton manifestations. Both secondary hyperparathyroidism and hyperphosphatemia itself are independent risk factors for increased cardiovascular morbidity and mortality in dialysis patients [16]. The cause is the development of vascular and soft tissue calcifications that are a direct consequence of hyperphosphatemia. Two-thirds of dialysis (HDD) patients after 5-10 years have radiograph-visible calcifications [6]. Secondary hyperparathyroidism is associated with resistance to treatment with human recombinant erythropoietin. That is to say, secondary hyperparathyroidism leads to worsening of anemia in CKD patients [17]. ROD is the only complication of CKD, where no significant improvement occurs after a successful kidney transplantation. On the contrary, the loss of bone mass continues after the transplantation. Characteristically, markers of increased bone resorption remain high even 10 years after transplantation [18].

DIAGNOSIS AND TREATMENT

The findings of renal osteodystrophy diagnosed with conventional radiography include osseous resorption, soft tissue calcification, osteopenia, amyloid deposition, and fracture [27]. Essential for the optimal treatment of ROD is the correct diagnosis, in particular the differentiation of high turnover bone disease characteristic of secondary hyperparathyroidism and adynamic bone disease. Contemporary treatment of ROD is directed to high turnover bone disease. Carrying out similar treatment in adynamic bone disease would lead to negative results. The accurate diagnosis is possible only with the help of the morphological picture. Bone biopsy is considered the gold standard for diagnosis and classification of renal osteodystrophy [28]. Clinical indications for bone biopsy in patients with CKD stages 3-5, based on Kidney Disease Improving Global Outcomes (KDIGO) and Kidney Disease Outcomes Quality Initiative (KDOQI), are as follows: 1. unexplained fractures; 2. unexplained hypercalcemia; 3. unexplained hypophosphatemia; 4. persistent bone pain; 5. suspected aluminum toxicity based upon clinical symptoms or history of aluminum exposure; 6. previous therapy with bisphosphonates; 7. inconsistency among biochemical parameters, thereby preventing definitive interpretation; 8. severe progressive vascular calcification; 9. prior to parathyroidectomy, if a history of aluminum exposure exists or if the biochemical determination is inconsistent with advanced secondary or tertiary hyperparathyreoidism; 10. intact plasma parathyroid hormone (iPTH) levels between 100 and 500 pg/mL (in CKD stage 5) in association with unexplained hypercalcemia, severe bone pain, or unexplained increase in bone alkaline phosphatase activity [21, 22, 23].

CT is useful in the evaluation of pathologic fractures. Amyloidosis may cause erosion in and around a joint, resulting in subtle radiographic signs that are more clearly delineated with cross-sectional imaging techniques such as CT [26].

MRI helps evaluate the soft tissues for ligament rupture, and CT can help evaluate pathologic fractures. Amyloidosis may cause erosion in and around a joint, resulting in subtle radiographic signs, while amyloid deposits can be visualized directly on MRI [26].

In day-to-day clinical practice, differential diagnosis is very difficult. It is assumed that at PTH values below 65 pg/ml, it can certainly be considerered that it is an adynamic bone disease, and at PTH over 450 pg/ml – a high turnover bone disease. However, more than two-thirds of the patients are in the 65-450 pg/ml range [3]. Some indicators that, in combination, can help to make the right diagnosis are shown in Table 1.

Table 1. Bone markers in low and high turnover bone disease in CKD

	Low turnover bone disease	High turnover bone disease
PTH	low, normal, high	very high
ALP	Normal	High
Calcitonin	High	High
Serum calcium	high, normal	low, normal
Serum phosphorus	normal, high	high, very high
Z-score femur	Low	very low
Z-score spine	Low	very low
T-score	Low	very low

TREATMENT

There are five basic options for conservative treatment that can be combined: 1. Limiting the intake of phosphorus. 2. Supplementation with calcium. 3. Application of phosphate binders. 4. Application of vitamin D derivatives. 5. Treatment with calcimimetics.

The first treatment goal is to correct hyperphosphatemia and hypocalcaemia. In patients with high and very high levels of PTH and normal or low level of serum calcium, if calcium phosphorus does not exceed 1.8 mmol/l, calcitriol (Rocaltrol) or its synthetic analogue (Zemplar, Rayaldee), alpha-calcidol with or without calcium supplementation depending on the serum levels of calcium, are used. An undesirable effect of this treatment is hypercalcemia and hyperphosphatemia. The application of vitamin D analogues in early-stage CKD patients may delay the progression of bone disease, improve bone histology, and lead to a reduction in the incidence of secondary hyperparathyroidism. When used in stage 3 and 4 of CKD, they are effective in lowering PTH levels and improving bone mineralization [1].

Vitamin D analogues are recommended in patients with CKD stages 3-5 who are not on dialysis and in whom the serum parathyroid hormone (PTH) level is elevated or has been persistently rising. Vitamin D increases the absorption of calcium in the intestines and helps to prevent secretion of calcium in the kidneys. By increasing calcium levels in serum, it helps to decrease phosphate and PTH levels, as well as bone resorption [24].

Vitamin D analogues:

1. Calcitriol (Rocaltrol) – Calcitriol (1,25-dihydroxycholecalciferol or 1,25-dihydroxyvitamin D3), the potent active metabolite of vitamin D, can be used to suppress PTH production and secretion in secondary hyperparathyroidism. In addition, calcitriol can alleviate hypocalcemia in CKD by increasing intestinal calcium absorption and helping to prevent secretion of calcium in the kidneys.

– Chronic renal dialysis associated hypocalcemia: initial: 0.25 mcg p.o. q.d. to every other day; titrate by 0.5-1 mcg/day q.d. 4-8 weeks;

– Secondary hyperparathyroidism in moderate to severe kidney disease: 0.25 mcg/day p.o.; may increase to 0.5 mcg/day;

2. Paricalcitol (Zemplar) is a synthetic vitamin D analogue that binds and activates vitamin D receptors in the kidneys, parathyroid glands, intestines, and bones. It is used for the prevention and treatment of secondary hyperparathyroidism associated with CKD stages 3-4 and stage 5 patients on hemodialysis or peritoneal dialysis. It reduces PTH levels, improves calcium and phosphorus homeostasis, and stimulates bone mineralization.

In CKD stage 5:

– Paricalcitol is indicated for prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) stage 5 in patients on hemodialysis or peritoneal dialysis;

– Initial 0.04-0.1 mcg/kg i.v. 3 x/week, no more frequently than every other day;

– Titrate up or down by 2-4 mcg q2-4 weeks;

– Up to 0.24 mcg/kg p.o. have been administered.

In CKD stage 3 and 4:

– Paricalcitol is indicated for prevention and treatment of secondary hyperparathyroidism associated CKD;

- PTH ≤ 500 pg/mL: 1 mcg p.o. q.d. or 2 mcg p.o. 3 times/week;
- PTH > 500 pg/mL: 2 mcg p.o. q.d. or 4 mcg p.o. 3 times/week;
- Administer 3 times/week, no more frequently than every other day;
- Titrate dose based on response.

3. Calcifediol (Rayaldee) Extended-release formulation of calcifediol (25-hydroxyvitamin D3), a prohormone of the active form of vitamin D3. Calcifediol is converted to calcitriol by CYP27B1, also called 1-alpha hydroxylase, primarily in the kidney. Calcitriol binds to the vitamin D receptor in target tissues and activates vitamin D responsive pathways that result in increased intestinal absorption of calcium and phosphorus and reduced parathyroid hormone synthesis. It is indicated for secondary hyperparathyroidism associated with vitamin D insufficiency in patients with stage 3 or 4 chronic kidney disease (CKD) and serum total 25-hydroxyvitamin D levels.

Calcium mimetics (like Cinacalcet, Mimpara) resemble the action of calcium and bind to calcium-sensitive receptors (Ca-SR) in the parathyroid glands, resulting in decreased PTH secretion and lowering serum calcium levels. The calcimimetic agent Cinacalcet is approved for the treatment of secondary hyperparathyroidism in patients with terminal CRF who require hemodialysis [4].

Etelcalcetide is a new long-acting (intravenous) calcimimetic drug that binds and activates calcium-sensitive receptor (CaSR) in the cells of the parathyroid glands and thus reduces PTH secretion. It is used as a bolus injection in the venous dialysis system at the end of the hemodialysis treatment during the return of the blood or intravenously after the return of the blood. Initial dose of 5 mg. Possible dose range from 2.5 mg to 15 mg. Three times a week. Etelcalcetide is a calci-mimetic intravenous drug that shows better control of biochemical indications compared to placebo and cinacalcet-based regimens for the treatment of SHPT in CRF patients with hemodialysis. Overall, it has a good tolerability, profile of adverse events that is consistent with the pre-existing concomitant diseases typically associated with SHPT and the calcimimetes action mechanism. This auspicious benefit/risk profile combined with the easy way of intravenous application at the end of dialysis (which gives flexibility and application control to practitioners) means that ethcalcetide represents significant progress compared to existing therapies.

Serum phosphate levels can be controlled with phosphate binders such as sevelamer (Renagel) or calcium salts (calcium-based phosphate binders). Sevelamer binds to food phosphates entering the gastrointestinal tract and lowers serum phosphate levels in patients with chronic renal failure (CRF) on hemodialysis. It is a non-adsorbent polymer that does not contain calcium. It also acts as a sequestrant of bile acids (lowers LDL-cholesterol levels). The drug is indicated for control of hyperphosphatemia in adult patients on hemodialysis or peritoneal dialysis. Study data show that calcium salts (calcium carbonate, calcium acetate) and sevelamer achieve similar control of serum phosphate level in hemodialysis patients. Sevelamer leads, however, to a greater decrease in serum calcium (reduces the incidence of hypercalcaemia manifestations, probably because it does not contain calcium) and PTH as compared to calcium-based phosphate-binding agents [4]. As a result, sevelamer stops the progression of calcification of the coronary arteries and the aorta, whereas the calcium salts do not have a similar effect (the difference between the two types of phosphate binders is visible as early as the sixth month of treatment and remains significant until the end of the follow-up of patients for a period of one year).

Calcium salt additives were considered to be particularly effective in patients with terminal CRF not only because of their phosphate-binding properties but also due to their direct effects of normalizing or raising the level of serum calcium in secondary hyperparathyroidism and associated metabolic bone disease (as a result of increased bone remodeling and loss of bone mineral density). However, new data have shown that high doses of calcium salts may not be as useful in patients with end-stage renal failure as it was previously thought. The results of a study show that sevelamer, administered alone, resulted in a gradual decrease in intact PTH levels. This substance, used in combination with metabolites (analogues) of vitamin D, can improve the control of hyperparathyroidism. Serum phosphate, calcium and intact PTH levels are related to coronary artery and aortic calcification. Sevelamer treatment reduces the hypercalcemia manifestations, improves PTH level control, and slows the progression of coronary artery and aortic calcification compared to calcium salts [4].

Patients with chronic kidney disease are advised to avoid foods that are especially high in phosphate; high-phosphate foods include dairy products; meats, nuts, and other high-protein foods; processed foods; and dark colas [29].

In case of dual-energy X-ray absorptiometry (DEXA)-proven osteoporosis in patients with mild to moderate

CRF (stage 2-3), treatment is not different from that in menopausal women with normal renal function and drugs of choice are bisphosphonates (mainly alendronate and risedronate) as well as raloxifene, teriparatide and denosumab [5].

In a study involving patients with CRF and osteoporosis, treatment with risedronate significantly reduced the incidence of vertebral fractures and effectively maintained bone mineral density. Similar results were also seen with alendronate therapy. In addition, risedronate demonstrated a good safety profile – 5 mg of the drug per day over a period of more than two years was not associated with a significant change in serum creatinine [5]. No significant difference was observed between controls and participants in the therapeutic group in terms of renal function indicators (change in serum creatinine levels for two years of follow-up), regardless of base value of GFR (respectively the CRF stage). Similar data were also reported in the safety assessment of alendronate – the drug did not result in worsening of renal function in patients with GFR 15 ml/min/1.73 m^2 [5]. The efficacy and safety profile of bisphosphonates for intravenous administration (ibandronate and zoledronic acid) was monitored with first - third stage CRF patients. Temporary increase in serum creatinine levels as well as the development of acute renal failure (ARF) were reported after the introduction of zoledronic acid. To prevent such complications, zoledronic acid should be applied in a slow intravenous infusion (not shorter than 15 minutes), patients should be well hydrated and, if possible, co-administration of medications that reduce glomerular filtration (e.g. NSAIDs) should be avoided [5].

Raloxifene can be applied at all stages of CRF. PTH teriparatide derivative does not result in worsening of renal function in patients with mild to moderate CRF, but there are no data about the safety of the drug at GFR less than 30 ml/min. Since PTH is a vasodilator, administration of teriparatide may result in GFR increase. It is contraindicated in patients with CRF with hypercalcemia and increased base PTH levels. Denosumab was approved in 2010 for treatment of osteoporosis in postmenopausal women as first-choice therapy. It is a biological agent – a monoclonal antibody directed against RANKL (receptor activator of the nuclear factor kappa-B ligand, a key mediator in bone metabolism). The drug is not excreted via the kidneys, is metabolised in the reticuloendothelial system and is safe for CRF patients with glomerular filtration to 15 ml/min after three years of application. All patients with CRF and osteoporosis are advised to take additives of 1200-1500 mg calcium daily and adequate vitamin D intake to maintain a serum concentration of 25(OH) – Vitamin E above 30 ng/ml [5].

In severe forms of secondary hyperparathyroidism, surgical treatment is used. This is recommended for PTH serum levels above 600-800 pg./ml. In case the parathyroid gland is 5-10 mm and more, it is believed that there is autonomous growth, i. e. tertiary hyperparathyroidism has been developed. Then conservative treatment can not help, either. Subtotal parathyreoidectomy or total parathyreoidectomy with immediate autotransplantation is performed in order to avoid sustained hypoparathyroidism and adynamic bone disease [1].

An alternative to surgical treatment is local injection of alcohol or vitamin D derivatives. Intervention is performed under ultrasonographic control by manipulating the largest PTG [1].

In conclusion, ROD is leading cause of increased mortality and poor quality of life in patients with CKD. It is related to disproportionately high direct and indirect costs of healthcare, respectively of society.

Conflict of interests

The authors have nothing to disclose.

REFERENCES

1. Song L. Calcium and Bone Metabolism Indices. Adv Clin Chem. 2017;82:1-46. doi: 10.1016/bs.acc.2017.06.005. Epub 2017 Aug 7.
2. Cunningham J, Locatelli F, Rodriguez M. Secondary Hyperparathyroidism: Pathogenesis, Disease Progression, and Therapeutic Options. Clin J Am Soc Nephrol, 2011;6(4): 913-921.
3. Krivoshiev S., A.-M. Borissova. From Renal Osteodystrophy to Senile Osteoporosis. J Bulg Soc Endocrinol. 2003,8(2),68-75.
4. Edna D. Taniegra, M.D., Hyperparathyroidism. Am Fam Physician. 2004 Jan 15;69(2):333-339.
5. Nitta K, Yajima A, Tsuchiya K. Management of Osteoporosis in Chronic Kidney Disease. Intern Med. 2017 Dec 15; 56(24): 3271-3276.
6. Krivoshiev, St, E. Katerdzhieva, Ts. Baldev et al. Vascular calcifications in patients with terminal chronic renal failure treated with prolonged hemodialysis. Roentgenology and Radiology, 1994, Suppl., 39-42.
7. Martin, KJ, EA Gonzalez. Strategies to minimize bone disease in renal failure. Am J Kidney Dis, 38, 2001, 6, 1430-1436.
8. Llach F., F. V Forero. Secondary Hyperparathyreoidism in chronic renal failure: pathogenic and clinical aspects. Am J Kidney dis, 2001;38(5), Suppl 5, S20-S33.
9. Hsu, C.-Y., G. M. Ghertow. Elevations of serum phosphorus and potassium in mild to moderate chronic renal incufficiency. Nephrol Dial Transplant, 2002;17(6), 1419-1425.
10. Levey, A. S. Controlling the epidemic of cardiovascular disease in chronic renal disease:where do we start? Am. J. Kidney Dis., 1998;32(5), Suppl. 3, S5-S13.
11. Slatopolsky, E., A. Brown, A. Dusso. Phosphate control and osteodistrophy. Role of phosphorus in the pathogenesis of

secondary hiperparathyreoidism. Am J Kidney Dis, 2001;37 (1), Suppl. 2, S54-S57.
12. Coen, G., P. Ballanti, E. Bonucci et al. Taggi, Renal osteodystrophy in predialysis and haemodialysis patients: comparison of histologic patternsand diagnostic predictivity of intact PTH. Nephron, 2002;91(1), 103-111.
13. Hercz, G. Regulation of bone remodeling: impact of novel therapies. Semin Dial, 2001;14(1),55-60.
14. Hampson, G, Vaja S, Evans C et al. Comparison of the humoral markers of bone turnover and bone mineral density in patients on haemodialsysis and continuous ambulatory peritoneal dialysis. Nephron, 2002;91(1), 94-102.
15. Yamamoto, T, Ozono K, Miyauchi A et al. Role of advanced glycation end products in adynamic bone disease in patients with diabetic nephropathy. Am J Kidney Dis, 2001;38(4), Suppl. 1 S161-S164.
16. London, G. Cardiovascular disease in end stage renal failure: role of calcium-phosphate disturbances and hyperparathyreoidism. J. Nephrol, 2002;15(2), 209-210.
17. Rao, D.S., M.S. Shih, R. Mohini. Effect of serum parathyroid hormone and bone marrow fibrosis on the response to erythropoietin in uremia. N. Engl. J Med, 1993;328, 171-175.
18. Giannini, S, D'Angelo A, Carraro G et al. Persistently increased bone turnover and low bone density in long-term survivors to kidney transplantation. Clin Nephrol., 2001;56(5), 353-363.
19. Horwitz M. What medical options should be considered for the treatment of primary hyperparathyroidism? Clin Endocrinol. 2011;75(5):592-595.
20. Khan A., Bilezikian J., Kung A. et al. Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial. J Clin Endocrinol Metab 2004;89: 3319-25.
21. Moe S, Drüeke T, Cunningham J et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006;69(11):1945-53.
22. [Guideline] 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.
23. [Guideline] 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.
24. Chronic Kidney Disease, Article in Madscape, Pradeep Arora, MD Assistant Professor of Medicine, University of Buffalo State University of New York School of Medicine, july 2018.
25. 25. Imaging in Secondary Hyperparathyroidism, Article in Madscape, Ali Nawaz Khan, MBBS, FRCS, FRCP, FRCR Consultant Radiologist and Honorary Professor, North Manchester General Hospital, nov. 2015.
26. Sharma AK, Masterson R, Holt SG, Toussaint ND. Emerging role of high-resolution imaging in the detection of renal osteodystrophy. Nephrology (Carlton). 2016;21(10):801-11.
27. Henriques JC, De Melo Castilho JC, Jacobs R et al. Severe secondary hyperparathyroidism and panoramic radiography parameters. Clin Oral Investig. 2013 Jul 12.
28. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2017. 7:1-59.
29. Eleanor Lederer, MD, FASN Professor of Medicine, Chief, Nephrology Division, Director, Nephrology Training Program, Director, Metabolic Stone Clinic, Kidney Disease Program, University of Louisville School of Medicine; Consulting Staff, Louisville Veterans Affairs Hospital, 2017.
30. Andrew L. Lundquist; Sagar U. Nigwekar, Curr Opin Nephrol Hypertens. 2016;25(2):120-126.