REVIEW ARTICLE

Renal Disease and Transplantation Forum
2023, vol. 16, no. 3, 65–80

ISSN 2720–2771
e-ISSN: 2720-4189
DOI: 10.5603/rdtf.96819

Maksymilian Hryciuk, Zbigniew Heleniak, Alicja Dębska-Ślizień

Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdansk

Management of chronic kidney disease — mineral and bone disorder

Abstract

Chronic kidney disease (CKD) is a growing global health problem due to increased prevalence over the last few years. It is estimated, that more than every ten person suffers from CKD, that can leads to many organ complications. One of the most common is calcium- phosphate metabolism disorders, actually it is known as mineral bone disease (CKD-MBD). This is broad term, that includes abnormalities of parathormone (PTH), vitamin D, calcium and phosphorus metabolism; abnormalities in bone turnover, mineralization, volume, linear growth, or strength; or vascular or other soft tissue calcification. This important clinical complication of CKD continues to be studied, in order to improve the understanding and management of this complex disease. A major disadvantage in CKD-MBD management is significant variation in goals therapy among international guidelines. Large-scale, well-designed clinical studies should be performed to harmonize recommendations. In this article, we tried to present pathophysiological mechanisms underlying these abnormalities, symptoms, diagnosis and treatment strategies based on new reports and updated recommendations.

Renal Disease and Transplantation Forum 2023, vol. 16, no. 3, 65–80

Key words: chronic kidney disease, mineral bone disease, calcium, phosphate, secondary hyperparathyroidism, vitamin D

INTRODUCTION

Chronic kidney disease (CKD) is multi-symptomatic disease syndrome as a result of permanent damage or loss of active nephrons and intestitial tissue, that often leads to end-stage renal disease (ESRD). The National Kidney Foundation — Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) defined CKD as the presence of structural and functional abnormalities of renal damage for at least three months with or without a decreased glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2 [1].

The kidney have many functions, including excretory, endocrine and metabolic functions and thus it is crucial organ to maintaining body homeostasis.

Therefore number of complications such as anemia, arterial hypertension, acid-alkaline balance or calcium-phosphate-vitamin D metabolism disorders can occur in patients with CKD. The last of the above mentioned factors, actually is known as mineral bone disease (CKD- MBD). This is broad term, that includes abnormalities of parathormone (PTH), vitamin D, calcium and phosphorus metabolism; abnormalities in bone turnover, mineralization, volume, linear growth, or strength; or vascular or other soft tissue calcification [2]. The most often occurring biochemical abnormalities in CKD-MBD are hypocalcemia, hyperphosphatemia, hypovitaminosis D and hyperparathyroidism. This wide spectrum of laboratory abnormalities can give rise to a variety of mixed clinical manifestations. An understanding of these abnormalities pathogenesis then becomes essential to develop a rational approach to the prevention of these disorders and their treatment.

EPIDEMIOLOGY

CKD is a growing global health problem due to increased prevalence over the last few years [3]. It is estimated, that more than every

Address for correspondence:
Maksymilian Hryciuk
Department of Nephrology, Transplantology and Internal Diseases — Medical University of Gdańsk
Dębinki 7, 80-952 Gdańsk, Poland
e-mail: maks.hryciuk@gmail.com

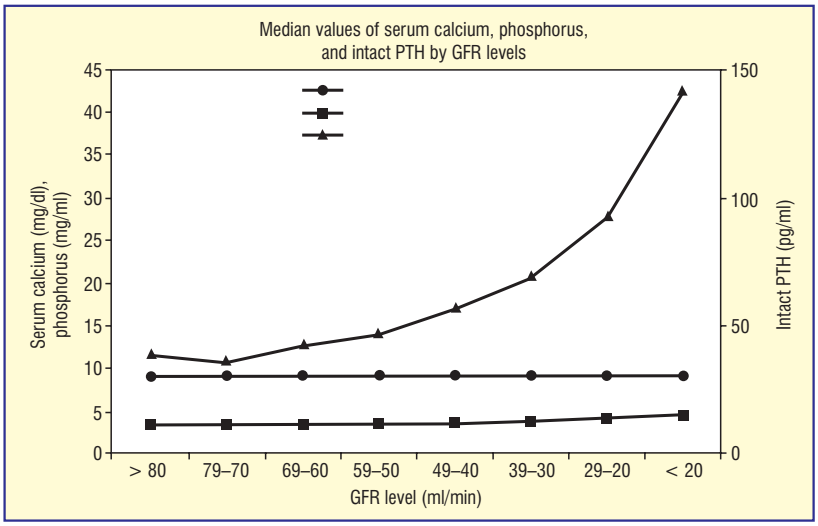

Figure 1. Median values of serum calcium, phosphorus, and iPTH by eGFR levels. Increases in iPTH preceded changes in serum calcium and phosphorus [12]

ten person suffers from chronic kidney failure [4]. In the United States, the prevalence of CKD was estimated to be 11% according to data from the Third National Health and Nutrition Examination Survey [5]. More recent work, has found that estimating CKD prevalence can be approximately 13.4% of the world's population [6]. CKD stage III is the most common CKD stage, with a rate reaching 30% in patients older than 70 years of age [7].

Assuming the above data, it can be estimated that at present around 600 million people in the world suffer from CKD. In Poland, the prevalence of CKD was estimated over 4 million people [8].

The growth in the number of patients with CKD is probably caused by an increased aging population and prevalence of type 2 diabetes (T2DM), atherosclerosis and hypertension that contribute to development of CKD [9].

However not all patients with CKD present biochemical abnormalities characteristic for CKD-MBD. The more severity disorders is directly proportional to the stage of advanced CKD [10, 11]. According to Levine study in CKD patients (stage III–V), calcium and phosphorus values don't become abnormal until glomerular filtration rate (GFR) was below 40 mL/min/1.73 m^2, and were relatively stable until GFR fall below 20 mL/min/1.73 m^2 [12] (Fig. 1). Frequency of hypocalcemia and hyperphosphatemia in CKD (3–5D) patients is 23.8% and 55.4 %, respectively [11]. However in patients with ESRD, the prevalence of hyperphosphatemia can reach about 70% [11, 13]. What is noteworthy, the most common disorder of mineral metabolism is vitamin D deficiency. More than 90% CKD patients have at least insufficiency level 25 OH D3 (< 30 ng/mL; < 75 nmol/L). As regards the secondary hyperthyroidism, elevated level of PTH is noticed from 64 to even 82% patients with CKD [8, 9]. Frequency of elevated PTH level is strongly correlated with stage of CKD. High PTH (> 65 pm/dL) occurred in 12% with eGFR > 80 mL/min/1.73 m^2, but almost 60% of patients with GFR < 60 mL/min/1.73 m^2 had elevated PTH levels [12].

PHYSIOLOGY

Total amount of calcium in the body is 1.5% of body weight, 99% of that is a part of hydroxyapatite. The remaining part of calcium is located in extracellular fluids mainly (thousand times higher level than in cells). Calcium is transported (in blood) as bound to serum albumin or inorganic anions and as dissolved ions. Reference range for calcium in serum is this: 8.5 to 10.5 mg/dl (4.3 to 5.3 mEq/L or 2.2 to 2.7 mmol/L) and ionized calcium 1,1–1,4 mmol/l [14,15].

Average content of calcium in diet is 1000 mg/24 h, 20% of that is absorbed. Transient receptor potential channel, of the vanilloid subtype (TRPV6) is responsible for intestinal calcitriol-dependent calcium absorption. This process can be impaired by phosphate, oxalates and phytates. More than 95% of the filtered calcium is reabsorbed along renal tubules, mostly in the proximal tubule (65%), but the most complex regulation of calcium excretion occurs in the distal convoluted tubules and connecting tubules (via TRPV 5, TRPV6 permeable ions channels). In this part of nephron calcium absorption rises in response of PTH (TRPV5), calcitriol (TRPV 5 and 6), alkalosis, low calcium diet and it falls as result of metabolic acidosis, that induces hypercalciuria. There is reabsorbed around 15% filtered calcium [16, 17]. It is worth adding, that around 20% of calcium is reabsorbed in thick ascending limb by paracellular pathways. The driving force is provided by sodium reabsorption through the sodium/potassium/chloride cotransporter (NKCC2), that is activated by calcium sensing receptor (CaSR). The higher blood calcium level is, the more reduced activity NKCC2 causing directly more calcium to remain in urine (and also sodium, chloride and potassium ions). It explains polyuria effect of

hypercalcemia. At this point it is worth to take note of loop diuretics inhibit NKCC2 also [18].

Phosphate comprise of 1% of body weight. 85% of that occurs in bone (inorganic), the remaining around 15% found in soft tissue and only 1% in extracellular fluid. Average amount of absorbed phosphate from diet is 800–1500 mg daily. Phosphate absorption is significantly dependent on calcitriol, that increases the expression of sodium phosphate cotransporter (NaPi-IIb) and contributes to more effective phosphate uptake. In the kidney is reabsorbed almost 90% filtered phosphate [21].

This process takes place in proximal convoluted tubule (in Henly's loop there is no reabsorption of phosphate at all) through Sodium Phosphate Cotransporters NaPi- IIa, and NaPi-IIc. FGF 23 inhibits the expression of NaPi-IIa, and in turn PTH causes internalization of NaPi-IIa and NaPi-IIC cotransporters leading to phosphaturia [19, 20].

Parathormone is polypeptide hormone, secreted by parathyroid glands in response to low serum calcium, hyperphosphatemia and deficiency in the active form of vitamin D levels. On the other hand, high calcium serum, hypophosphatemia and 1.25 (OH) D3 decreased PTH secretion. Moreover magnesium deficiency diminishes secretion of PTH and furthermore impaired release calcium from bone on path increased resistance bone to PTH [21, 22].

Parathormone increases calcium level cause of reduction renal loss of these ions with urine. Second way is enhance release calcium from bone on path resorption bone by osteoclasts (as result indirect stimulation of osteoclasts). The next mechanism works indirectly through upregulates the activity of 1-α-hydroxylase enzyme, that contributes to converts 25-hydroxycholecalciferol into active form of vitamin D (1.25-dihydroxycholecalciferol) (Figure 2), that enhance dietary calcium and phosphate absorption [13]. We should note that PTH has dual effects in phosphate homeostasis as it also increases gastrointestinal (GI) phosphate absorption indirectly by increasing activation of vitamin D, but contrary to that, FGF-23 decreases serum phosphate level by inhibiting its GI absorption and increasing its renal excretion [19].

VITAMIN D

Vitamin D is a group of fat-soluble secosteroids, the most important for human are

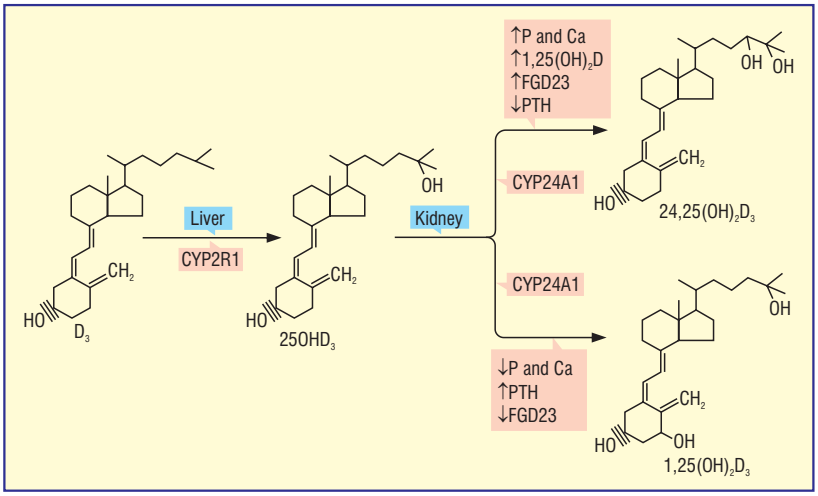

Figure 2. The metabolism of vitamin D [23]

ergocalciferol (D2, from plants food) and cholecalciferol (D3, from animal foods). The main natural source of the vitamin D is synthesis of cholecalciferol in the skin cells as result of chemical reaction that is dependent on sunlight, specifically UVB radiation (7-dehydrocholesterol is converted by reductase into cholecalciferol). In the first step cholecalciferol is converted by 25 alpha- hydroxylase in the liver to calcifediol (25-hydroxycholecalciferol) and next calcifediol is hydroxylated by 1α hydroxylase to 1,25-dihydroxycholecalciferol (calcitriol) [23]. The secondary hydroxylation is regulated by many factors (Fig. 2), the most important is likely PTH, that stimulates the production of 1-alpha-hydroxylase in the proximal convoluted tubule. 1,25(OH)2D3 limit its own production by inhibiting CYP27B1 as feedback inhibition and increasing the expression of CYP24A1, which encodes the 24-hydroxylase inactivating calcitriol. The phosphaturic FGF23 also increase activity of renal CYP24A1 resulting in calcitriol inactivation and is also main inhibitor of 1 alfa hydroxylase [24]. Without calcitriol, only 10 to 15% of dietary calcium and about 60% of phosphorus are absorbed. Vitamin D (in optimal level) enhances calcium and phosphorus absorption by 30–40% and 80%, respectively [25].

PATHOPHYSIOLOGY

Hyperphosphatemia is observed in patients with impaired excretion by the kidneys and leads to formation of insoluble salts with calcium, resulting in decreased plasma calcium [19]. In addition it contributes to increased

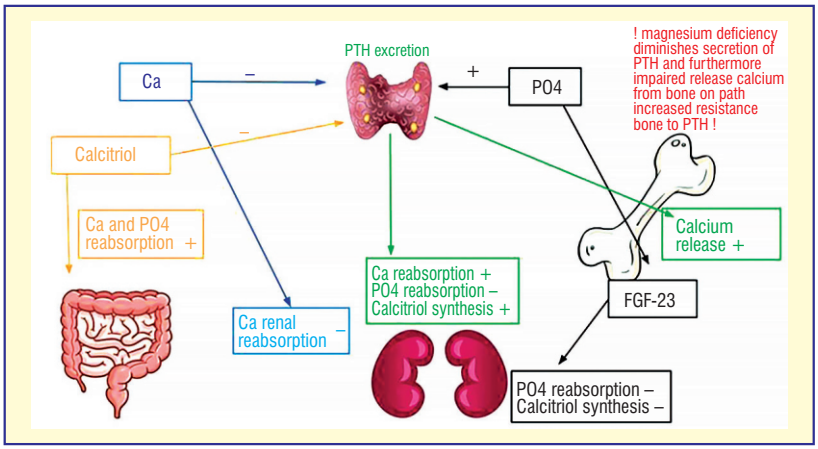

Figure 4. Calcium, phosphorus, PTH, FGF-23 homeostasis

release FGF23 from bone cells as well as PTH and suppression calcitriol renal synthesis. Despite of reduced phosphate clearance, increased phosphate level occurs usually in advanced CKD stages, because initially PTH and FGF 23 decrease the proximal tubular reabsorption of phosphate and maintain normophosphatemia. When GFR falls below 30 mL/min/1.73 m^2 (CKD stage IV), the compensatory increase PTH and FGF23 becomes inadequate, due to small number of active nephrons [26].

Moreover hyperphosphatemia is a major risk factor for vascular calcification in CKD. High phosphate level triggers transformation of the vascular smooth muscle cell in the osteoblastic cells and directly contributes to arterial stiffness and cardiovascular calcification. The association between higher serum phosphorus levels and vascular calcification has been reported in patients with CKD stage 3–4 [27]. Vascular calcification is associated with significant cardiovascular mortality in patients with CKD [27, 28]. Increased serum phosphorus levels stimulates osteoblastic transition into vascular smooth muscle cells and directly contributes to extraskeletal mineralization (such as calcification of atherosclerotic plaques and tunica media), as result of an elevated calcium-phosphorus product [28–30].

According to recent reports, it seems to that elevated level of FGF 23 is one the earliest biomarkers of CKD-MBD prior to changes in the serum calcium or PTH levels and it is mainly responsible for deficiency of calcitriol by inhibition of 1 alpha-hydroxylase enzyme and stimulation the 24-hydroxylase enzyme, which converts calcitriol to inactive metabolites [31]. Moreover FGF 23 enhances phosphaturia and decreases PTH excretion. In course of impairment calcitriol synthesis, there is significantly decreased absorption of calcium leading to hypocalcemia. There are further factors contributing to increased release PTH (low levels of calcium and calcitriol) to maintain optimal serum calcium and phosphate levels, leading to secondary hyperparathyroidism (SHP). The next important trigger is underexpression of the calcium-sensing receptor (CaSR) and vitamin D receptor (VDR) in parathyroid cells, which causes inadequately intensified PTH excretion in response to relatively small hypocalcemia. This disorder appears to stem from high phosphate concentration [32] (the ratio of CKD-MBD biomarker's values over time is shown on Figure 3.

Nevertheless, increased PTH production usually is not enough to normalize calcemia and phosphatemia usually, thereby the most often constellation of laboratories abnormalities in CKD-MBD include hypocalcemia, hyperphosphatemia and significantly elevated PTH. In response to hyperphosphatemia, high level of PTH osteocytes produce FGF-23, which enhances phosphaturia and inhibits production of calcitriol acting as an additional driver to secondary hyperparathyroidism (Fig. 4). It is assumed that weak phosphaturic effect FGF 23 in course of CKD is associated with αKlotho deficiency [19]. The membrane bound αKlotho is produced by the kidneys, is not only biomarker for CKD, in addition Klotho enhances phosphaturic effects by inhibiting renal NaPi-2a and NaPi-2c in the renal proximal tubule and reduces soft tissue calcification [33].

Renal osteodystrophy (often known as CKD-MBD) occurs commonly in patients with CKD, although the disease processes may differ in patients. There is a histological classification into low or high bone turnover states.

The manifestation of high turnover bone disease involves osteitis fibrosa cystica, characterised by increased osteoblast and osteoclast activity and peritrabecular fibrosis. Low turnover bone disease includes adynamic bone disease (ABD) or heavy metal-induced osteomalacia. The high turnover bone disease is associated with parathormone overproduction and histologically is known as (in advanced stage) osteitis fibrosa cystica. In this condition, PTH indirectly induces osteoclast activity which leads to release calcium from bone tissue and bone resorption, cortical bone destruction, and fibrous cysts formation. In localised regions where bone loss is particularly rapid, osteoclasts-like giant cells, with active,

vascular, proliferating fibrous tissue may replace the bone marrow contents, resulting in brown tumours [34]. Low-turnover bone disease commonly is characterised by an extremely slow rate of bone formation. It is the result from excessive suppression of parathyroid glands by active forms of vitamin D3 and ionised calcium serum. ABD is characterised histopathologically by reduced number of osteoblasts and osteoclasts with proportionally reduced osteoid formation and the subsequent mineralization of bone collagen (the width of osteoid seems is normal or diminished). The osteomalacia differs from ABD in a relative osteoid excess cause of mineralization defect. Nowadays osteomalacia is rare, but until 1980' was significantly more frequent diagnosis because increase use of aluminium-containing drugs as phosphate binders, leading to aluminium-related bone disease (particular to osteomalacia) [35, 36].

The latter form of renal osteodystrophy is mixed uremic osteodystrophy characterised by either high or low bone turnover and by abnormal mineralization. In addition, there is one more type of uremic bone disease, mostly independent from vitamin D, PTH, calcium and phosphate metabolism, occurs in dialysed patients and it is result from beta2-microglobulin amyloid deposits [36].

SYMPTOMS

Generally, in course of CKD there don't occur characteristic signs, usually in last stages appear first nonspecific symptoms like general and muscle weakness, fatigue, dyspnea, peripheral edema, loss of appetite, nausea, vomiting, headache (as result from progressive hypertension or metabolic acidosis), malnutrition, pruritus and bone pain. Only the last two of above mentioned are characteristic for CKD-MBD [37].

Disorders of mineral and bone metabolism in setting of CKD that can be manifested by any one or a combination of the following: 1) vascular or soft tissue calcification, 2) abnormalities of phosphorus, calcium, parathyroid hormone, and vitamin D metabolism; 3) abnormalities of bone turnover and mineralization.

First group of symptoms should be associated with cardiovascular diseases, so symptoms may result from clinical features of atherosclerosis (like coronary artery disease, transient ischemic attack, stroke, peripheral artery disease). Serious complication of soft tissue calcification is calcific uremic arteriolopathy (CUA), also known as calciphylaxis. It is a syndrome of calcification of small vessels within skin and fat tissue, often complicated by thrombosis, open wound and secondary infections. It carries a high mortality rate due to sepsis and ischemia resulting in skin necrosis. Calciphylaxis is caused by high PTH levels, hyperphosphatemia and hypercalcaemia induced by high calcium in the dialysate and use of calcium-containing phosphate binders. Warfarin intake, diabetes, obesity, hypoalbuminemia enhance the risk of this process [38].

The next group of symptoms is consequence of biochemical abnormalities. Patients who develop hypocalcemia gradually (mostly nephrologist patients) are more likely to be asymptomatic, nevertheless low calcium level is manifested by increased neural excitability, that result in latent (Chvostek's and/or Trousseau's sign) and generalized tetany. Muscle spasms, cramps, even laryngospasm are equivalent to tetany. In addition can occur circumoral and peripheral paresthesia, cognitive impairment and personality disturbances. Hypocalcemia has also significant effect on cardiovascular system, because it can lead to disturbances of the electrical rhythm. Low calcium level has a negative inotropic effect (reduction in blood pressure) and will delay ventricular repolarization and thus prolong the Q-T interval. This may contribute to 2:1 heart block [14, 39].

Hyperphosphatemia is a common laboratory abnormality encountered by nephrologists and relatively rare result in symptoms, one of them are red eye syndrome, cataracts and pruritus, In view of the fact, that phosphate bind ionized calcium in plasma, thereby indirectly resulting in hypoglycemia symptoms. It is worth noting again, that hyperphosphatemia enhances vascular calcification leading to the development of cardiovascular disease and excess mortality [22, 28, 30].

The last group of symptoms is the consequence of bone turnover abnormalities. In setting of this disorders patients are often asymptomatic and symptoms appear only late in its course, but part of them can suffer from bone pain, fractures, pain and stiffness in joints, spontaneous tendon rupture, and proximal muscle weakness. A similar set of symptoms may take place in both the low- and high-turnover type [40]. According to KDIGO patients suffering from CKD 3-5D have increased fracture rates than general population.

However patients with bone biopsy-proven ABD (excluding aluminium-related bone disease) have lower frequency musculoskeletal symptoms, compared with patients with secondary hyperparathyroidism. Symptoms like muscle pain and weakness or bone pain occur less commonly [41].

Currently we observe decreased prevalence of high- turnover MBD among CKD patients, while non-aluminium low-turnover MBD occurs more often than earlier. This trend most likely is result from multiple factors, among other, associated with treatment: the more common usage of vitamin D analogues, high-dialysate calcium concentrations, calcium-containing phosphate binders or demography: older population and increased number of diabetic patients, which is steadily growing [36, 40, 42].

DIAGNOSTIC

In according to KDIGO recommendations from 2009, CKD MBD is defined by presence at least one of the following conditions: vascular or other soft-tissue calcification, abnormalities in mineralization, volume, linear growth, strength or bone turnover , abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism. There are no strict diagnosis criteria for MBD, it is therefore considered appropriate to base on KDIGO definition. Taking this into account it seems that CKD-MBD includes most patients with CKD.

KDIGO (MBD) work group suggest that a lateral abdominal radiograph can be utilized to detect presence or absence of vascular calcification. It is not necessary to use CT for this purpose (if don't exist another indications), because X-ray is more available and is a more cost- effective solution. According to some authors radiograph enables detect only extensive vascular calcification, The sensitivity of radiograph is almost less than half the EBCT (Electron Beam Computed Tomography), specificity is uniformly high [43]. Nevertheless screening towards vascular and tissue calcification in every patient with CKD is not recommended by KDIGO.

A dual-energy X-ray absorptiometry (DEXA) may be used to measure bone mineral density (BMD), although studies have not shown this to be very useful. [44]. Nevertheless updated KDIGO recommendations indicate validity DXA BMD in patients with CKD 3A–5 and evidence of MBD (to evaluate risk of fracture), if results will impact treatment decisions. This is major change compared to previous KDIGO recommendations.

On the other hand, a significant limitation is the lack of useful data on fracture prevention by treatment using in osteoporosis in advanced CKD G5-G5D. Recently published meta-analysis of 13 trials, that included patients with CKD stages 3 to 5D, showed that the impact of medications for osteoporosis (denosumab, bisphosphonates, teriparatide and raloxifene) on BMD, fracture risk, and safety in CKD were not clear [45].

Nevertheless DXA BMD is not able to distinguish types of renal osteodystrophy (lack of information on bone mineralization, turnover and microarchitecture), and the diagnostic usefulness of biochemical markers is limited by poor sensitivity and specificity [46]. The laboratory diagnosis of CKD–MBD includes the use of laboratory testing of serum PTH, calcium (ideally ionized calcium but most frequently total calcium, possibly corrected for albumin), and phosphorus following the KDIGO recommendations. In addition to the measurements of calcium and phosphorus concentrations, which in their own right can contribute to hyperparathyroidism, it is essential to obtain a direct index of parathyroid activity by measurements of PTH.

In clinical practice PTH and alkaline phosphatase (ALP) are biomarkers used to distinguish between high and low bone turnover. Whereas plasma iPTH levels at the extremely low or high, are usually associated with ABD and high-turnover bone disease, respectively, PTH levels greater than 500 pg/mL are highly indicative of osteitis fibrosa, whereas adynamic lesion is suspected when the levels are below 100 pg/mL [36, 47]. PTH greater than 300 pg/mL has positive predictive value 62% for the diagnosis of high turnover, however, while the low level of PTH (< 150 pg/mL) provided a positive predictive value of 83% for identifying low bone turnover [48]. The serum alkaline phosphatase level may be elevated in hyperparathyroidism indicating increased osteoblastic activity [36].

Bone-specific alkaline phosphatase (bsALP) is an indicator of osteoblastic activity. Low levels of bsALP can suggest a low bone turnover disease. Elevated levels of bsALP virtually exclude an adynamic renal bone disease, therefore ALP can be said to be a negative predictive value of high turnover bone disease. ALP can be combined with PTH to help establish

the diagnosis type of BMD [21, 36, 49].

However KDIGO the Work Group noticed that, iPTH, whole PTH, and ALP levels were associated with bone turnover, but neither of above biomarkers singly or in combination was sufficient to diagnose low, normal, and high bone turnover in an individual patient. KDIGO encourages use of trends in PTH rather than single value to manage treatment.

In the light of the latest KDIGO recommendations bone biopsy still remains gold standard for the definitive diagnosis of renal osteodystrophy, but it should be performed if knowledge of the type of renal osteodystrophy will affect treatment decision. Bone biopsy should be considered in patients with unexplained fractures, refractory hypercalcaemia, an atypical response to standard therapies for elevated PTH, or progressive decreases in BMD despite standard therapy. Bone biopsy is not widely used in clinical practice because of the invasive nature. The real obstacle appears to be widespread lack of availability of well-trained staff to perform and evaluate bone biopsies in many clinical centres [40, 50].

Therefore, the aim of the research is to develop techniques to better identify patients at risk of fracture. One such technique is Impact Microindentation (IMI) which uses the Osteo-Probe® (device measuring Bone Material Strength Index (BMSi) to measure the material properties of cortical bone *in vivo* (different components of bone than DXA) and may provide information not captured by routine assessments of BMD. This parameter quantifies how well a bone resists microindentation. As the probe indents the bone, it induces microfractures. The more easily the bone is fractured, the deeper the probe indents and the lower the BMSi. This is a new, minimally invasive, well accepted by patients and promising technology, use of it in research is growing. Advantages include that the device is portable and generates no ionising radiation, unlike DXA. It is also a quick measurement (~10 min). The assessment of the clinical utility of this technology for assessing fracture risk in CKD patients is currently in progress [87, 88].

Accordingly, a biochemical assessment of disorders of bone and mineral metabolism is fundamental for the diagnosis and treatment. The biochemical diagnostic of MBD should be carried out from stage 3. CKD. KDIGO suggest in 3. CKD: monitor of calcium and phosphate every 6–12 months and frequency of PTH should base on clinical needs and CKD progression. In CKD stage 4: for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months. In CKD stages 5, including 5D: for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months. Moreover KDIGO recommend monitor level of ALP activity, every 12 months, or more frequently in the presence of elevated PTH.

Serum calcium measurement can be expressed in three different ways: ionized, total and corrected calcium [addition of 0.8 mg/dL (0.2 mmol/L) for every 1 g decrease in serum albumin below 4 g/dL (40 g/L)]. The 'corrected calcium' formula is commonly used by many dialysis laboratories and in most clinical trials. Unfortunately, recent data have shown that albumin-corrected tCa does not predict iCa better than noncorrected tCa [51].

However, ionized calcium measurement is dependent on acid-alkaline balance, is not routinely available and, in some instances, measuring may require additional costs. Presently there is an absence of data revealing differences in treatment approach or clinical outcomes when using corrected vs total or ionized calcium, thus KDIGO did not recommend that corrected calcium measurements be abandoned at present. Phosphate serum normal range for adults is generally 2.5 to 4.5 mg/dL. False elevated phosphate level may be result of hemolysis during sample collection. Phosphorus is routinely measured in clinical laboratories with colorimetric methods. The assay is generally reproducible and precise.

The measurement of serum 25(OH)D currently is regarded as the best measure of vitamin D status, because of its long half-life (3 weeks). Total 25(OH)D measure is the sum of 25(OH)D2 (ercalcidiol) and 25(OH)D3 (calcifediol). These metabolites have a similar biological effects, thus there is absence of medical indications to differentiate these metabolites [52, 53]. Based on some studies, 25(OH)D deficiency may be an underlying cause of elevated PTH, and thus there is a rationale for measuring and supplementing calciferol in CKD patients [54]. KDIGO suggests that vitamin D deficiency and insufficiency be evaluated and treated using strategies recommended for the general population. According to recommendations of American Endocrinology Society vitamin D deficiency should be defined as a 25(OH)D below 20 ng/mL, insufficiency as

Table 1. Target levels of serum phosphorus, calcium, and parathyroid hormone in dialysed patients, presented by different guidelines; modified after [67]

	Phosphorus [mg/dL]	Calcium [mg/dL]	Intact PTH [pg/mL]
KDIGO [2017]	Towards normal range	Avoiding hypercalcemia	2–9× normal range
ERBP [2010]	2.4–4.5	Towards normal range	100–800
UKRA [2011]	2.78–4.64	8.8–10.0	Not mentioned
KDOQI [2003]	3.5–5.5	8.4–9.5	150–300
JSDT [2013]	3.5–6.0	8.4–10.0	60–240

ERBP — European Renal Best Practice; JSDT — Japanese Society for Dialysis Therapy; KDIGO — Kidney Disease: Improving Global Outcomes; KDOQI — Kidney Disease Outcome Quality Initiative; UKRA — United Kingdom Renal Association

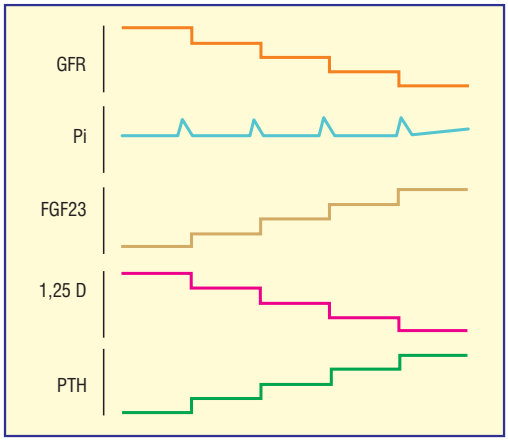

Figure 3. Pathophysiologic processes of hyperphosphatemia [59]

a 25(OH)D of 21–29 ng/mL, and sufficiency as a 25(OH)D of 30–100 ng/mL [25]. Due to the fact that the assays for 25(OH)D are not well standardized, clinicians should recommend (for patients) use the same laboratory for measurement of these levels. It is commonly known that serum 1.25(OH)2D concentration decreases as chronic kidney disease (CKD) progresses. According to Levine study, low 1.25 OH2 D3 was evident at all estimated glomerular filtration rate (eGFR) levels: 13% in those with eGFR > 80 mL/min/1.73 m^2, > 60% in those with eGFR < 30 mL/min/1.73 m^2 [12].

On the other hand, routine measurement of 1,25(OH)2D levels is not recommended by KDIGO. Normal range this vitamin D form shall be 60–108 pmol/L (25–45 pg/mL)[54]. Circulating level of 1,25(OH)2D is approximately thousand times smaller than 25(OH) D3, but this ratio is very variable, what may be affected by stores of 25(OH)D, short- half-life (4-6h), supplementation of calcitriol and vitamin D analogues, and the multiple factors that regulate activity of 25(OH)D 1a-hydroxylase enzyme (the renal CYP27B1 is regulated by nearly every hormone involved in calcium homeostasis) and 24(OH)D hydroxylase enzyme. Moreover there don't exist well- standardized assays, and there are no data indicating that the measurement is helpful in guiding therapy or predicting outcomes [55].

Accurate assessment of PTH assays remains problematic, even though the assays for PTH have become increasingly sensitive over the past few decades. The most commonly used assay for PTH, the two-site immunoradiometric assay (IRMA) is known as „intact" PTH. Unfortunately, there is evidence indicating that this 'intact' PTH assay also (apart from 1-84 PTH) detects accumulated large C-terminal fragments (7–84). More recently, a third generation of assays has become available that is highly specific for full-length PTH-(1–84), and it does not cross react with PTH-(7–84) [56].Thus, plasma PTH levels in patients with ESRD invariably are lower when evaluated by use of the highly specific IRMA assay for PTH-(1–84), compared with values obtained with conventional IRMA PTH assays. The disparity between plasma PTH levels measured by these assays ranges from 40 to 80% [57]. However, they are expensive, not yet widely available, and accordingly, there is much more reliance on conventional "intact PTH" assays, which seem to perform well in clinical practice. This is also KDIGO's position. There is significant variation in the results that are obtained with assays (intact-PTH) from different producers, mainly because of standardization and antibody specificity. This issue raises significant concerns with regard to the validity of absolute levels of PTH, because the various assays may result in quantitative differences in values. Thus, it seems inappropriate to expect rigid recommendations for target PTH levels [40]. KDIGO in 2009 suggested (this approach was maintained) that reference range for PTH in ERSD patients should be maintaining iPTH levels in the range of approximately 2 to 9 times (upper limit for general population is 65 pg/mL). In addition they suggested also using trends in levels PTH, rather than single values should be used in management of CKD-MBD. National Kidney Foundation K/DOQI clinical practice guidelines from 2003 defined normal range for PTH in ESRD: 150 to 300 pg/mL (Tab. 1), < 110 pg/mL in CKD stage 4 and < 70 pg/mL in CKD stage 3. KDIGO 2017 update notes, that there is still an absence of RCTs that define an optimal PTH level for patients with CKD G3a to G5 and suggest that the updated threshold

Table 5. Phosphorus binders; modified after [59]

Phosphorus binder	Dose [mg]	PBED of 1 tablet to 1 g of calcium carbonate	Formulation	Advantages	Disadvantages
Calcium carbonate	500 (200 calcium) — 3500	0.75	Swallowed and chewable tables	Low cost, over the counter	Calcium burden, constipations
Calcium acetate	667 (169 calcium) — 6000	0.67	Swallowed tables	Less calcium than calcium carbonate	Calcium burden, needs prescription
Lanthanum	500–3750	1.0	Swallowed and chewable tables (can be crushed)	Low pill burden	Expensive
Sevelamer	800–8000	0.6	Swallowed and chewable tables and granule packets	Lowers LDL cholesterol	High pill burden
Ferric citrate	210–2500	2.0	Swallowed tables	Improves iron parameters	Expensive

PBED — phosphorus binder equivalent dose

should be PTH levels that are "progressively rising or persistently above the upper normal limit".

Measurement FGF-23 level is not recommend by KDIGO as standard marker to diagnostic and evaluation of progression in setting CKD- MBD, although FGF 23 (near to PTH) is associated with faster worsening renal function independently from basal eGFR and albuminuria. KDIGO in 2017 recognized the necessary to investigations contributing to the understanding of the usefulness of FGF 23 as a complementary marker for treatment indications and direct treatment target [58].

TREATMENT

KDIGO suggests that mild and asymptomatic hypocalcemia can be tolerated in order to avoid inappropriate calcium loading in adults.

Despite a lack of evidence from randomized controlled trials (RCTs) showing that reducing phosphate level improves clinical outcomes, KDIGO, basing on observational and experimental data, recommend suggest lowering elevated phosphate levels toward the normal range (between 2,5 to 4,5 mg/dl, *2C, figure 4.*). On the other hand, the KDOQI work group emphasises that no studies have shown that lowering serum phosphate concentrations improves clinical outcomes, such as mortality, for any CKD stage [60].

Phosphate restriction is a mandatory element of treatment. The ways to correct increased phosphate level include reducing intake with food, both dietary restriction and oral phosphate binders (Fig. 5 and 6). Dialysis is also an effective method to remove phosphate (in patients with CKD stage 5D) [61].

The most common prescribed phosphate binders are calcium agents such as carbonate, acetate, gluconate, the next one drug is sevelamer (chloride or carbonate) and next is lanthanum carbonate. Calcium-based binders are effective, relatively cheap (unlike sevelamer, lanthanum) and easily accessible but their potential contributing to total body calcium overload, hypercalcaemia and vascular calcification is an important long-term clinical problem. Moreover these drugs can result in gastrointestinal disorders often such as constipations. KDIGO in 2017 recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analogue in the presence of persistent or recurrent hypercalcaemia and suggest restricted them in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low (2C). Sevelamer is effective in reducing serum phosphate, not absorbed systemically, and does not increase calcium level. On the other hand sevelamer binds bile acids, is not an efficient phosphate binder in an acidic environment, moreover sevelamer chloride may cause metabolic acidosis. Lanthanum carbonate is a highly selective phosphate binder that holds high affinity for phosphate almost independently of pH values, does not bind bile acids or contribute to metabolic acidosis, and has the potential to reduce pill burden. According to the latest studies (data sources included MEDLINE and EMBASE Trials from 1996 to February 2016.), phosphate binders such lanthanum or sevelamer decreases the intestinal

calcium loading, and it provided reduced mortality in contrast to the calcium-based phosphate binder. [62–64]. Based on the newest KDIGO recommendations treatment phosphate lowering should start when progressively or persistently elevated serum phosphate is. "Preventive" phosphate-lowering treatment is currently not supported by data.

Second strategy for correcting hyperphosphatemia is reducing the daily phosphate intake in the diet, this is relatively hard to achieve because phosphorus is omnipresent in food. There are actually 2 major sources of phosphates: natural phosphates (as cellular and protein constituents) contained in raw or unprocessed foods, phosphates additives to foods during processing [65] Phosphate content in food is still growing (between 2001 and 2014, there was a statistically significant 7.4% increase in phosphorus density). Average phosphorus amount in typical diet (in United States) is over 1300 mg/day with an increasing trend in last period [66]. The daily phosphate intake in diet should be limit to 800 mg daily. This position is in the line with recommended low- protein diet in non- dialysed CKD patients, but it can be difficult as it is usually incompatible with the recommended by KDOQI daily protein intake of 1.2–1.3 g/kg/day in dialysed CKD patients, because majority of high-biological-value proteins have high phosphate content, it is not simple to create a dietary plan that lowers dietary phosphate intake without reducing protein intake and exposing to malnutrition [67]. In this point it is worth nothing that phosphate bioavailability is essential, the intestinal absorption of inorganic phosphate (in additives and beverages) is almost 100%, while that of animal-based phosphate is between 40-60% and plant phosphate, mostly associated with phytates, is absorbable in 20–50% [66, 67]. For this reason, consumption of more raw, organic, and less-processed foods should be emphasized by medical staff, including especially dietetics.

Third way (in CKD-5D patients) to reduce serum phosphate is dialysis. Almost all phosphate exists in bone tissue, only 1% of it is in blood, this is why the amount of P removed using dialysis is extremely limited. Conventional HD (3 times x 4 h per week) removes approximately 2.3–2.6 g/week, and the amount removed by PD (4 times/d, 2-L exchanges) is 2.0–2.2 g per week. Thus, even if the daily phosphate intake with food is obeyed (to 800 mg), the amount of P removed through weekly standard dialysis is around 50% of the dietary intake, which explains the necessity of administering phosphate binders. However, in Culleton's study, compared the effect of a nocturnal prolonged-duration HD six times weekly with that of standard HD given thrice weekly for 4 h each session. The authors found significant decreases in serum phosphorus and iPTH in patients allocated to frequent nocturnal HD, as compared with those on standard HD treatment [68, 69].

The secondary hyperparathyroidism (SHPT) treatment is based on suppression of parathyroid gland hormonal activity. The KDIGO guideline update emphasises, that treatment SHPT should not be based on a single elevated value of PTH, because: 1) the optimal PTH is still not known; 2) a modest increase in PTH concentration is an appropriate adaptive response that contributes to phosphaturia in CKD and may therefore be beneficial for maintenance of normal serum phosphate levels as GFR decreases; 3) increased resistance to skeletal effects of PTH. The KDOQI work group agrees with the update and its justification [50, 70].

VDRAS (VITAMIN D RECEPTOR ACTIVATORS)

Vitamin D is one of the oldest form treatment for SHPT. 1.25 dihydroxycholecalciferol deficiency is major contributor to SHPT, hence active vitamin D analogues supplementation is effective in suppressing high levels of PTH through the vitamin D receptor (VDR). Contrary to popular belief, we observe a similar effect in the population with CKD (especially in stage 3. and 4.) after administration „standard" vitamin D (like a cholecalciferol or ergocalciferol), because 1.25(OH)2D deficiency in ESRD is partly also a consequence of 25(OH)D deficiency, rather than solely due to reduced 1α-hydroxylase activity as suggested by current treatment strategies [54]. A clear confirmation of this are several studies assessing the effect of PTH-lowering nutritional vitamin D and comparing it with calcitriol or vitamin D analogs in CKD patients [71, 72]. Thus, both KDIGO and KDQOI recommendations state that vitamin D supplementation (cholecalciferol and ergocalciferol) should be used in SHPT in non- dialysed patients (especially when serum level of 25-hydroxyvitamin D is < 30 ng/mL) [60, 70].

KDIGO suggest, that calcitriol and vitamin D analogues (paricalcitol, doxercalciferol,

Table 6. Approved therapies for the treatment of SHPT in CKD patients. Arrows indicate the effect of single therapies on the principal metabolic biomarkers and effectors of SHPT; modified after [85]

		Therapies for SHPT			
		P	Ca	PTH	FGF-23
Nutritional therapy [79–81]		↓	↑	↓	↓
Nutritional vitamin D [55, 82]	Ergocalciferol	↑	↑	↓	↑
	Cholecalciferol				
	Calcifediol				
VDRA [55, 83–90]	Calcitriol	↑↑	↑↑	↓↓	↑
	Paricalcitriol				
	Alfacalcidol				
	Doxercakciferol				
Calcimimetric [60, 61, 76–78, 83, 85, 87, 90, 91, 92	Cinacalcet	→	↓	↓↓	↓
	Etelcalcetide				
	Evocalcet				
P binders [48, 54, 93–96]	Calcium carbonate	↓	↑	↓↓	↑ →
	Calcium acetate				
	Magnesium carbonate				
	Sevelamer carbonate				
	Sevelamer HCl	↓	↓	↓	↓
	Lanthanum carbonate				

alphacalcidol) not be routinely used (2C) in non-dialysed patients with CKD 3–5 (in contrary to own recommendations from 2009), these drugs are indicated to treatment severe and progressive hyperparathyroidism in CKD patients. The PRIMO and OPERA RCTs studies had significant impact on change of above recommendations by demonstrating a significantly increased risk of hypercalcemia in patients treated with paricalcitol, compared with placebo, in the absence of beneficial effects on cardiac endpoints [70].

The increased intestinal absorption of calcium and phosphorus after administration of calcitriol contributed to the development of selective agents that have more affinity to the kidney rather than intestinal receptors like a paricalcitol (19-nor-1,25-dihydroxy vitamin D2), that cause less hypercalcaemia and hyperphosphatemia than traditional calcitriol and decrease the cardiovascular morbidity and mortality (16% less than calcitriol) [73]. The fundamental differences are the route of administration of the drug and widely understood availability, calcitriol is oral medication (likely as alfacalcidol), relatively cheap and easily accessible. The start dosage is 0.25 mcg daily usually, dose should be adjusted (every 2–4 weeks) rather to serum PTH trends than single value. However paricalcitol is given (not more than every dialysis) only intravenously as a slow infusion (or into hemodialysis catheter) and its availability is limited to drug programmes often. The initial dose is related to PTH and is chosen between iPTH/120 and 0.04–0.1 μg/kg. The dose may be adjusted at 2–4 week intervals, based on relationship between subsequent iPTH levels and baseline iPTH level, up to 0.24 μg/kg per dialysis. It is recommended to discontinue VDRs if the PTH level is less than 100 pg/mL [67]. Frequent results of using VDRAs could be hypercalcemia, hyperphosphatemia and excessive PTH suppression, which can lead to development of adynamic bone disease.

CALCIMIMETICS

Calcimimetic agents increase the sensitivity of CaSR to extracellular calcium ions. As a result of the receptor "thinking" there is sufficient calcium, PTH secretion will be reduced. Cinacalcet is the most common and was the first calcimimetic to be approved (in 2004 by FDA). Etelcalcetide (was approved in 2017 by FDA) is another calcimimetic agent and it appeared to be superior to cinacalcet in lowering PTH level, what's more is less

likely to cause hypercalcaemia [74]. Cinacalcet is a medication also used to treat tertiary hyperparathyroidism, parathyroid carcinoma, and primary hyperparathyroidism. Those who have serum calcium levels less than normal range should not begin therapy with cinacalcet (Fig. 6). Cinacalcet is partially metabolized by CYP3A4. Dose adjustment may be required if a patient is treated with a strong CYP3A4 inhibitors (clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, verapamil and grapefruit) Cinacalcet is a strong inhibitor of CYP2D6, which metabolizes, among others, metoprolol, and carvedilol. The recommended starting oral dose of cinacalcet is 30 mg once daily. Cinacalcet should be titrated no more frequently than every 2 to 4 weeks. Its side effects include gastrointestinal symptoms and QT prolongation, mostly related to hypocalcemia [75]. It has proved to be highly effective in lowering PTH level and improving calcium-phosphorus homeostasis in dialysed patients with SHPT [76, 77]. The results of treatment SHPT (lowering PTH) with either cinacalcet or vitamin D analogue were similar in RTC „PARADIGM" including 312 participants. It was found that hypocalcemia was more common in the cinacalcet arm, whereas hypercalcemia and hyperphosphatemia occurred more often in the vitamin D analogue arm. Nevertheless, cinacalcet don't significantly reduce the risk of death or major cardiovascular events in dialysed patients with moderate-to-severe SHPT in comparison to placebo group in large RCT from 2012. Hypocalcemia and gastrointestinal adverse events were significantly more frequent in patients receiving cinacalcet [78]. Promising treatment regimen could be combination of cinacalcet and VDRA, part of studies show better efficiency in PTH lowering comparing to monotherapy with calcitriol [79, 80]

Based on above data KDIGO (in update guidelines from 2017) lists the agents in an alphabetical order to emphasize that calcimimetics, calcitriol, or vitamin D analogues are all acceptable first-line options to treat SHPT and that there are no data showing superiority one agent over another. Given that superiority of cinacalcet over other agents has not been proven, K/DOQI suggest, that selection of PTH-lowering therapy in patients with CKD stage G5D may be based on cost, adverse events, and presence of other mineral metabolism abnormalities [50, 70]. Therefore calcitriol or other VDRA agents should be considered if the serum calcium is relatively low or refractory hyperphosphatemia does not occur (Fig. 7). On the other hand, in the case of hypercalcaemia cinacalcet is a better option to PTH suppression.

TERTIARY HYPERPARATHYROIDISM

The state of prolonged stimulation of parathyroid cell due to high phosphate, low calcitriol, and hypocalcemia, can leads to nodular hyperplasia and excess PTH. The stimulated parathyroid glands do not undergo involution, despite of the resolution of some triggering mechanisms, continuing to oversecrete PTH and assume an autonomous role akin to that seen in primary HPT. This condition is named tertiary hyperparathyroidism (THPT) and is common among patients with long-term chronic kidney disease, hemodialysis, and kidney transplantation. Risk factors for persistent high PTH level after transplantation are: high PTH values before transplant, long dialysis vintage, nodular hyperplasia of parathyroid glands. Characteristic biochemical disorders except of PTH excess are also hypercalcemia and hypophosphatemia (in transplant kidney recipients) [81, 82]. Treatments with active vitamin D or calcimimetic usually become uneffective and fail to work. Cinacalcet has been considered a potential treatment option, but its effectiveness has not been proven. Cinacalcet is a promising therapeutic option for patients with persistent hypercalcemia post transplantation at least as a bridging agent before parathyroidectomy [83].

PARATHYROIDECTOMY

Subtotal parathyroidectomy and total parathyroidectomy with autotransplantation are the representative surgical methods [67]. Given the lack of RCTs of medical and surgical therapy of HPT, KDIGO suggests these management strategies are difficult to compare.

For patients able to undergo surgery, parathyroidectomy is generally considered when HPT is severe and refractory to medical management (after treatment with calcitriol, a vitamin D analogue, or cinacalcet). Parathyroidectomy should also be considered when medical management to reduce levels of iPTH results in unmanageable levels of serum calcium and/or phosphorus (as occurs frequently using calcitriol or vitamin D analogues), when

medical management is not tolerated because of adverse effects, when parathyroid size is larger than 0.5 cm^3 in size, (determined by ultrasonography), X-ray findings of a bone disorder, severe bone and muscle pain, calciphylaxis, or soft tissue calcification [70, 84]. It is estimated that parathyroidectomy is required in about 15% of patients after 10 years and in 38% of patients after 20 years of ongoing dialysis therapy (despite the availability of pharmacological agents). Surgical complications are rare, and parathyroidectomy appears to be a safe treatment option for THPT [86]. The main posteopearative complication is hypocalcemia as a result lack of osteoclastic activity caused by decreased PTH, hence serum Ca levels should be monitored in postoperative period (even every 4–6 hours for 48–72 hours after surgery) and often it may be required change using drugs (for example replace sevelamer or lanthan with calcium phosphate binders) [67].

SUMMARY

The underlying mechanisms of bone loss and fractures in CKD patients are complex and remain insufficiently understood. Nevertheless, it is well known that abnormal calcium and phosphate metabolism leading to the development of SHPT and cardiovascular calcification can be complicated during the early course of CKD. Thus, early interventions in setting of CKD are important to reduce cardiovascular morbidity and mortality. On the basis of above data non- calcium phosphate binder may become key component of CKD therapy. On the other hand phosphorus diet restriction and cooperation with dieticians are equally important, especially since the patients do not seem appreciate the role of diet.

A major disadvantage in calcium phosphate disorders management is significant variation in goals therapy among international guidelines. Large-scale, well-designed clinical studies are required to harmonize recommendations. Undoubtedly improvement in the field of unification diagnosis and treatment poses a challenge for nephrologists.

CONFLICT OF INTEREST

None to declared.

References

1. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf.
2. Waziri B, Duarte R, Naicker S. Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD): Current Perspectives. Int J Nephrol Renovasc Dis. 2019; 12: 263–276, doi: 10.2147/IJNRD.S191156, indexed in Pubmed: 31920363.
3. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011). 2022; 12(1): 7–11, doi: 10.1016/j.kisu.2021.11.003, indexed in Pubmed: 35529086.
4. Mills KT, Xu Yu, Zhang W, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int. 2015; 88(5): 950–957, doi: 10.1038/ki.2015.230, indexed in Pubmed: 26221752.
5. Coresh J, Astor BC, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis. 2003; 41(1): 1–12, doi: 10.1053/ajkd.2003.50007, indexed in Pubmed: 12500213.
6. Hill NR, Fatoba ST, Oke JL, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One. 2016; 11(7): e0158765, doi: 10.1371/journal.pone.0158765, indexed in Pubmed: 27383068.
7. Centers for Disease Control and Prevention. Chronic Kidney Disease Surveillance System website. https://nccd.cdc.gov/CKD (2/19/2021).
8. Król E, Rutkowski B. Przewlekła choroba nerek – klasyfikacja, epidemiologia i diagnostyka. Forum Nefrol. 2008; 1: 1–6.
9. Evans M, Lewis RD, Morgan AR, et al. A Narrative Review of Chronic Kidney Disease in Clinical Practice: Current Challenges and Future Perspectives. Adv Ther. 2022; 39(1): 33–43, doi: 10.1007/s12325-021-01927-z, indexed in Pubmed: 34739697.
10. Căpuşă C, Chirculescu B, Vladu I, et al. The prevalence of biochemical abnormalities of chronic kidney disease. Mineral and bone disorders in untreated non- dialysis patients- a multicenter study. Acta Endocrinol (Buchar). 2016; 12(3): 282–290, doi: 10.4183/aeb.2016.282, indexed in Pubmed: 31149102.
11. Vikrant S, Parashar A. Prevalence and severity of disordered mineral metabolism in patients with chronic kidney disease: A study from a tertiary care hospital in India. Indian J Endocrinol Metab. 2016; 20(4): 460–467, doi: 10.4103/2230-8210.183457, indexed in Pubmed: 27366711.
12. Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int. 2007; 71(1): 31–38, doi: 10.1038/sj.ki.5002009, indexed in Pubmed: 17091124.
13. Leaf DE, Wolf M. A physiologic-based approach to the evaluation of a patient with hyperphosphatemia. Am J Kidney Dis. 2013; 61(2): 330–336, doi: 10.1053/j.ajkd.2012.06.026, indexed in Pubmed: 22938849.
14. Chambers D, Huang Ch, Matthews G. Endocrine Physiology. In: Basic Physiology for Anaesthetists. Cambridge University Press 2019.

15. Goldstein DA. Serum Calcium. In: Walker HK, Hall WD, Hurst JW. ed. Chapter 143. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Butterworth, Boston 1990.
16. Lemoine S, Figueres L, Bacchetta J, et al. Calcium homeostasis and hyperparathyroidism: Nephrologic and endocrinologic points of view. Annales d'Endocrinologie. 2022; 83(4): 237–243, doi: 10.1016/j.ando.2022.05.003.
17. Jeon UnS. Kidney and calcium homeostasis. Electrolyte Blood Press. 2008; 6(2): 68–76, doi: 10.5049/EBP.2008.6.2.68, indexed in Pubmed: 24459525.
18. Moor MB, Bonny O. Ways of calcium reabsorption in the kidney. Am J Physiol Renal Physiol. 2016; 310(11): F1337–F1350, doi: 10.1152/ajprenal.00273.2015, indexed in Pubmed: 27009338.
19. Habas E, Eledrisi M, Khan F, et al. Secondary Hyperparathyroidism in Chronic Kidney Disease: Pathophysiology and Management. Cureus. 2021; 13(7): e16388, doi: 10.7759/cureus.16388, indexed in Pubmed: 34408941.
20. Chudek J, Więcek A. Zaburzenia gospodarki fosforanowej. Nefrologia. Wydanie II. Medical Tribune Polska, Warszawa 2017.
21. Małgorzewicz S, Jankowska M, Niemczyk S, et al. Practical aspects of a low-protein diet. Renal Disease and Transplantation Forum. 2022; 15(4): 161–165.
22. Na D, Tao G, Shu-Ying L, et al. Association between hypomagnesemia and severity of primary hyperparathyroidism: a retrospective study. BMC Endocr Disord. 2021; 21(1): 170, doi: 10.1186/s12902-021-00838-y, indexed in Pubmed: 34416890.
23. Bikle D, Christakos S. New aspects of vitamin D metabolism and action - addressing the skin as source and target. Nat Rev Endocrinol. 2020; 16(4): 234–252, doi: 10.1038/s41574-019-0312-5, indexed in Pubmed: 32029884.
24. Young K, Beggs MR, Grimbly C, et al. Regulation of 1 and 24 hydroxylation of vitamin D metabolites in the proximal tubule. Exp Biol Med (Maywood). 2022; 247(13): 1103–1111, doi: 10.1177/15353702221091982, indexed in Pubmed: 35482362.
25. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011; 96(7): 1911–1930, doi: 10.1210/jc.2011-0385, indexed in Pubmed: 21646368.
26. Saliba W, El-Haddad B. Secondary hyperparathyroidism: pathophysiology and treatment. J Am Board Fam Med. 2009; 22(5): 574–581, doi: 10.3122/jabfm.2009.05.090026, indexed in Pubmed: 19734404.
27. Kendrick J, Chonchol M. The role of phosphorus in the development and progression of vascular calcification. Am J Kidney Dis. 2011; 58(5): 826–834, doi: 10.1053/j.ajkd.2011.07.020, indexed in Pubmed: 21956015.
28. Goyal R, Jialal I. Hyperphosphatemia. [Updated 2022 Jun 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. https://www.ncbi.nlm.nih.gov/books/NBK551586/.
29. Mathew S, Tustison KS, Sugatani T, et al. The mechanism of phosphorus as a cardiovascular risk factor in CKD. J Am Soc Nephrol. 2008; 19(6): 1092–1105, doi: 10.1681/ASN.2007070760, indexed in Pubmed: 18417722.
30. Hruska KA, Seifert M, Sugatani T. Pathophysiology of the chronic kidney disease-mineral bone disorder. Curr Opin Nephrol Hypertens. 2015; 24(4): 303–309, doi: 10.1097/MNH.0000000000000132, indexed in Pubmed: 26050115.
31. Albanese L, Caliendo G, D'Elia G, et al. Diagnostic utility of FGF-23 in mineral bone disorder during chronic kidney disease. J Circ Biomark. 2022; 11: 1–4, doi: 10.33393/jcb.2022.2328, indexed in Pubmed: 35023876.
32. Centeno PP, Herberger A, Mun HC, et al. Phosphate acts directly on the calcium-sensing receptor to stimulate parathyroid hormone secretion. Nat Commun. 2019; 10(1): 4693, doi: 10.1038/s41467-019-12399-9, indexed in Pubmed: 31619668.
33. Hu MC, Shi M, Zhang J, et al. Klotho deficiency causes vascular calcification in chronic kidney disease. J Am Soc Nephrol. 2011; 22(1): 124–136, doi: 10.1681/ASN.2009121311, indexed in Pubmed: 21115613.
34. Parisien M, Silverberg SJ, Shane E, et al. Bone disease in primary hyperparathyroidism. Endocrinol Metab Clin North Am. 1990; 19(1): 19–34, indexed in Pubmed: 2192867.
35. Salusky IB, Goodman WG. Adynamic renal osteodystrophy: is there a problem? J Am Soc Nephrol. 2001; 12(9): 1978–1985, doi: 10.1681/ASN.V1291978, indexed in Pubmed: 11518793.
36. Brandenburg VM, Floege J. Adynamic bone disease-bone and beyond. NDT Plus. 2008; 1(3): 135–147, doi: 10.1093/ndtplus/sfn040, indexed in Pubmed: 25983860.
37. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. JAMA. 2019; 322(13): 1294–1304, doi: 10.1001/jama.2019.14745, indexed in Pubmed: 31573641.
38. Llach F. The evolving clinical features of calciphylaxis. Kidney Int Suppl. 2003(85): S122–S124, doi: 10.1046/j.1523-1755.63.s85.29.x, indexed in Pubmed: 12753282.
39. Fong J, Khan A. Hypocalcemia: updates in diagnosis and management for primary care. Can Fam Physician. 2012; 58(2): 158–162, indexed in Pubmed: 22439169.
40. Martin KJ, González EA. Metabolic bone disease in chronic kidney disease. J Am Soc Nephrol. 2007; 18(3): 875–885, doi: 10.1681/ASN.2006070771, indexed in Pubmed: 17251386.
41. Goodman WG, Coburn JW, Slatopolsky E, Salusky IB. Renal osteodystrophy in adults and children. In: Favus M. ed. rimer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 5th edn. American Society of Bone and Mineral Research, Washington, DC 2003: 430–447.
42. Changsirikulchai S, Domrongkitchaiporn S, Sirikulchayanonta V, et al. Renal osteodystrophy in Ramathibodi Hospital: histomorphometry and clinical correlation. J Med Assoc Thai. 2000; 83(10): 1223–1232, indexed in Pubmed: 11143489.
43. Johnson RC, Leopold JA, Loscalzo J. Vascular calcification: pathobiological mechanisms and clinical implications. Circ Res. 2006; 99(10): 1044–1059, doi: 10.1161/01.RES.0000249379.55535.21, indexed in Pubmed: 17095733.
44. Shah A, Aeddula NR. Renal Osteodystrophy. StatPearls Publishing, Treasure Island (FL) 2022.
45. Wilson LM, Rebholz CM, Jirru E, et al. Benefits and Harms of Osteoporosis Medications in Patients With Chronic Kidney Disease: A Systematic Review and Meta-analysis. Ann

Intern Med. 2017; 166(9): 649–658, doi: 10.7326/M16-2752, indexed in Pubmed: 28395318.
46. Barreto Fd, Costa CR, Reis LM, et al. Bone biopsy in nephrology practice. J Bras Nefrol. 2018; 40(4): 366–374, doi: 10.1590/2175-8239-jbn-2017-0012, indexed in Pubmed: 30525179.
47. Gonzalez EA, Martin KJ. Renal osteodystrophy. Rev Endocr Metab Disord. 2001; 2(2): 187–93.
48. Barreto FC, Barreto DV, Moysés RMA, et al. K/DOQI-recommended intact PTH levels do not prevent low-turnover bone disease in hemodialysis patients. Kidney Int. 2008; 73(6): 771–777, doi: 10.1038/sj.ki.5002769, indexed in Pubmed: 18185506.
49. Schwarz C, Sulzbacher I, Oberbauer R. Diagnosis of renal osteodystrophy. Eur J Clin Invest. 2006; 36 Suppl 2: 13–22, doi: 10.1111/j.1365-2362.2006.01666.x, indexed in Pubmed: 16884394.
50. Isakova T, Nickolas TL, Denburg M, et al. KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Am J Kidney Dis. 2017; 70(6): 737–751, doi: 10.1053/j.ajkd.2017.07.019, indexed in Pubmed: 28941764.
51. Gauci C, Moranne O, Fouqueray B, et al. NephroTest Study Group. Pitfalls of measuring total blood calcium in patients with CKD. J Am Soc Nephrol. 2008; 19(8): 1592–1598, doi: 10.1681/ASN.2007040449, indexed in Pubmed: 18400941.
52. Hollis BW. Editorial: The determination of circulating 25-hydroxyvitamin D: no easy task. J Clin Endocrinol Metab. 2004; 89(7): 3149–3151, doi: 10.1210/jc.2004-0682, indexed in Pubmed: 15240585.
53. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrinol Metab. 2008; 93(3): 677–681, doi: 10.1210/jc.2007-2308, indexed in Pubmed: 18089691.
54. Huish SA, Jenkinson C, Dunn JA, et al. Low serum 1,25(OH)2D3 in end-stage renal disease: is reduced 1 -hydroxylase the only problem? Endocr Connect. 2021; 10(10): 1291–1298, doi: 10.1530/EC-21-0372, indexed in Pubmed: 34519274.
55. Zittermann A, Ernst JB, Becker T, et al. Measurement of Circulating 1,25-Dihydroxyvitamin D: Comparison of an Automated Method with a Liquid Chromatography Tandem Mass Spectrometry Method. Int J Anal Chem. 2016; 2016: 8501435, doi: 10.1155/2016/8501435, indexed in Pubmed: 27127512.
56. Gao P, D'Amour P. Evolution of the parathyroid hormone (PTH) assay--importance of circulating PTH immunoheterogeneity and of its regulation. Clin Lab. 2005; 51(1-2): 21–29, indexed in Pubmed: 15719701.
57. John MR, Goodman WG, Gao P, et al. A novel immunoradiometric assay detects full-length human PTH but not amino-terminally truncated fragments: implications for PTH measurements in renal failure. J Clin Endocrinol Metab. 1999; 84(11): 4287–4290, doi: 10.1210/jcem.84.11.6236, indexed in Pubmed: 10566687.
58. Bullen AL, Katz R, Jotwani V, et al. Biomarkers of Kidney Tubule Health, CKD Progression, and Acute Kidney Injury in SPRINT (Systolic Blood Pressure Intervention Trial) Participants. Am J Kidney Dis. 2021; 78(3): 361–368.e1, doi: 10.1053/j.ajkd.2021.01.021, indexed in Pubmed: 33857535.
59. Sekar A, Kaur T, Nally JV, et al. Phosphorus binders: The new and the old, and how to choose. Cleve Clin J Med. 2018; 85(8): 629–638, doi: 10.3949/ccjm.85a.17054, indexed in Pubmed: 30102593.
60. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003; 42.
61. Bellinghieri G, Santoro D, Savica V. ing drugs for hyperphosphatemia. Expert Opin Emerg Drugs. 2007; 12: 355–365.
62. Sprague SM. A comparative review of the efficacy and safety of established phosphate binders: calcium, sevelamer, and lanthanum carbonate. Curr Med Res Opin. 2007; 23(12): 3167–3175, doi: 10.1185/030079907X242719, indexed in Pubmed: 17991307.
63. Sekercioglu N, Thabane L, Díaz Martínez JP, et al. Comparative Effectiveness of Phosphate Binders in Patients with Chronic Kidney Disease: A Systematic Review and Network Meta-Analysis. PLoS One. 2016; 11(6): e0156891, doi: 10.1371/journal.pone.0156891, indexed in Pubmed: 27276077.
64. Hou YC, Lu CL, Lu KC. Mineral bone disorders in chronic kidney disease. Nephrology (Carlton). 2018; 23 Suppl 4: 88–94, doi: 10.1111/nep.13457, indexed in Pubmed: 30298663.
65. Saliba W, El-Haddad B. Secondary hyperparathyroidism: pathophysiology and treatment. J Am Board Fam Med. 2009; 22(5): 574–581, doi: 10.3122/jabfm.2009.05.090026, indexed in Pubmed: 19734404.
66. McClure ST, Chang AR, Selvin E, et al. Dietary Sources of Phosphorus among Adults in the United States: Results from NHANES 2001-2014. Nutrients. 2017; 9(2), doi: 10.3390/nu9020095, indexed in Pubmed: 28146091.
67. Hwang E, Choi BS, Oh KH, et al. Management of chronic kidney disease-mineral and bone disorder: Korean working group recommendations. Kidney Res Clin Pract. 2015; 34(1): 4–12, doi: 10.1016/j.krcp.2015.02.002, indexed in Pubmed: 26484013.
68. Cupisti A, Gallieni M, Rizzo MA, et al. Phosphate control in dialysis. Int J Nephrol Renovasc Dis. 2013; 6: 193–205, doi: 10.2147/IJNRD.S35632, indexed in Pubmed: 24133374.
69. Culleton BF, Walsh M, Klarenbach SW, et al. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. JAMA. 2007; 298(11): 1291–1299, doi: 10.1001/jama.298.11.1291, indexed in Pubmed: 17878421.
70. 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. Kidney International Supplements. 2017; 7(3): e1, doi: 10.1016/j.kisu.2017.10.001.
71. Kovesdy CP, Lu JL, Malakauskas SM, et al. Paricalcitol versus ergocalciferol for secondary hyperparathyroidism in CKD stages 3 and 4: a randomized controlled trial. Am J Kidney Dis. 2012; 59(1): 58–66, doi: 10.1053/j.ajkd.2011.06.027, indexed in Pubmed: 21885174.
72. Thimachai P, Supasyndh O, Chaiprasert A, et al. Efficacy of High vs. Conventional Ergocalciferol Dose for Increasing 25-Hydroxyvitamin D and Suppressing Para-

thyroid Hormone Levels in Stage III-IV CKD with Vitamin D Deficiency/Insufficiency: A Randomized Controlled Trial. J Med Assoc Thai. 2015; 98(7): 643–648, indexed in Pubmed: 26267985.
73. Teng M, Wolf M, Lowrie E, et al. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med. 2003; 349(5): 446–456, doi: 10.1056/NEJMoa022536, indexed in Pubmed: 12890843.
74. Block GA, Bushinsky DA, Cheng S, et al. Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism: A Randomized Clinical Trial. JAMA. 2017; 317(2): 156–164, doi: 10.1001/jama.2016.19468, indexed in Pubmed: 28097356.
75. Sensipar - cinacalcet hydrochloride tablet, coated. Daily Med.
76. Block GA, Martin KJ, de Francisco ALM, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med. 2004; 350(15): 1516–1525, doi: 10.1056/NEJMoa031633, indexed in Pubmed: 15071126.
77. Chertow GM, Block GA, Correa-Rotter R, et al. EVOLVE Trial Investigators. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med. 2012; 367(26): 2482–2494, doi: 10.1056/NEJMoa1205624, indexed in Pubmed: 23121374.
78. Wetmore JB, Gurevich K, Sprague S, et al. A Randomized Trial of Cinacalcet versus Vitamin D Analogs as Monotherapy in Secondary Hyperparathyroidism (PARADIGM). Clin J Am Soc Nephrol. 2015; 10(6): 1031–1040, doi: 10.2215/CJN.07050714, indexed in Pubmed: 25904755.
79. Fishbane S, Shapiro WB, Corry DB, et al. Cinacalcet HCl and concurrent low-dose vitamin D improves treatment of secondary hyperparathyroidism in dialysis patients compared with vitamin D alone: the ACHIEVE study results. Clin J Am Soc Nephrol. 2008; 3(6): 1718–1725, doi: 10.2215/CJN.01040308, indexed in Pubmed: 18945995.
80. Messa P, Macário F, Yaqoob M, et al. The OPTIMA study: assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism. Clin J Am Soc Nephrol. 2008; 3(1): 36–45, doi: 10.2215/CJN.03591006, indexed in Pubmed: 18178780.
81. Palumbo VD, Palumbo VD, Damiano G, et al. The medical and surgical treatment in secondary and tertiary hyperparathyroidism. Review. Clin Ter. 2017; 168(2): e158–e167, doi: 10.7417/CT.2017.1999, indexed in Pubmed: 28383630.
82. Zhang LX, Zhang B, Liu XY, et al. Advances in the treatment of secondary and tertiary hyperparathyroidism. Front Endocrinol (Lausanne). 2022; 13: 1059828, doi: 10.3389/fendo.2022.1059828, indexed in Pubmed: 36561571.
83. Ważna-Jabłońska E, Gałązka Z, Durlik M. Treatment of Persistent Hypercalcemia and Hyperparathyroidism With Cinacalcet After Successful Kidney Transplantation. Transplant Proc. 2016; 48(5): 1623–1625, doi: 10.1016/j.transproceed.2016.01.044, indexed in Pubmed: 27496458.
84. Tominaga Y, Matsuoka S, Uno N. Surgical and medical treatment of secondary hyperparathyroidism in patients on continuous dialysis. World J Surg. 2009; 33(11): 2335–2342, doi: 10.1007/s00268-009-9943-3, indexed in Pubmed: 19247704.
85. Galassi A, Ciceri P, Fasulo E, et al. Management of Secondary Hyperparathyroidism in Chronic Kidney Disease: A Focus on the Elderly. Drugs Aging. 2019; 36(10): 885–895, doi: 10.1007/s40266-019-00696-3, indexed in Pubmed: 31304565.
86. Lau WL, Obi Y, Kalantar-Zadeh K. Parathyroidectomy in the Management of Secondary Hyperparathyroidism. Clin J Am Soc Nephrol. 2018; 13(6): 952–961, doi: 10.2215/CJN.10390917, indexed in Pubmed: 29523679.
87. Rufus-Membere P, Holloway-Kew KL, Diez-Perez A, et al. Normative Data for Lean Mass Using FNIH Criteria in an Australian Setting. Calcif Tissue Int. 2019; 104(4): 475–479, doi: 10.1007/s00223-018-0506-1, indexed in Pubmed: 30570670.
88. Holloway-Kew KL, Rufus-Membere P, Anderson KB, et al. Bone material strength index is associated with prior fracture in men with and without moderate chronic kidney disease. Bone. 2020; 133: 115241, doi: 10.1016/j.bone.2020.115241, indexed in Pubmed: 31954850.