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Secondary hyperparathyroidism in chronic kidney disease: pathomechanism and current treatment possibilities

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Abstract

Secondary hyperparathyroidism (SHPT) is one of the most common metabolic complications resulting from chronic kidney disease (CKD). The complexity of calcium and phosphate disorders associated with CKD is defined by the *Kidney Disease Improvement Global Outcomes* (KDIGO) working group as CKD-related mineral and bone disorders (CKD-MBD). The last update of the KDIGO guidelines on the conduct in CKD-MBD was published in 2017. The treatment of SHPT is based on 2 strategies: counteracting hyperphosphataemia and suppressing parathyroid hormone (PTH) secretion. Therapy should be based on optimally selected drugs, taking into account additional effects to reduce the risk of chronic complications and side effects. The creation of new drugs with a better safety profile, significant reduction of side effects, and greater efficiency in achieving target serum phosphorus and PTH values forces the gradual replacement of existing treatment with new pharmacotherapies. The aim of this study is to discuss the latest issues (in connection with the latest KDIGO guidelines) regarding the pathomechanism of secondary hyperparathyroidism and the current directions of the therapy in these disorders. **(Endokrynol Pol 2023; 74 (5): 490–498)**

Key words: *secondary hyperparathyroidism; chronic kidney disease; calcium and phosphate balance; Klotho; FGF-23*

Introduction

Secondary hyperparathyroidism (SHPT) is one of the most common metabolic complications resulting from chronic kidney disease (CKD). There are 5 stages in the course of CKD (G1-G5), which are determined on the basis of the glomerular filtration rate (GFR). It is believed that one of the first disorders in the development of SHPT in the course of CKD is the impairment of phosphate excretion by the kidneys. It takes place in the G2 stage of CKD, when the GFR is 89–60 mL/min. Consequently, parathyroid cells are stimulated to secrete more PTH, which in turn reduces phosphate reabsorption in the proximal tubule. Therefore, the serum phosphorus concentration is still within the normal range. Elevated serum phosphate levels usually occur at the G4 stage of CKD, when GFR is less than 30 ml/min. These changes cause other disorders, including hypocalcaemia. Hyperphosphataemia with hypocalcaemia stimulates parathyroid cells to proliferate, leading to hypertrophy of these glands and excess secretion of PTH. Therefore, all processes stimulate one another, generating a vicious circle. It should be emphasized here that the results of recent studies indicate that fibroblast growth factor 23 (FGF-23) and Klotho protein are the factors whose concentrations changes appear the earliest in the development of SHPT.

The main and most dangerous complications of SHPT involve the skeletal and cardiovascular systems. Calcium and phosphate imbalances associated with CKD are defined by the Kidney Disease Improvement Global Outcomes (KDIGO) group as chronic kidney disease-metabolic bone disease (CKD-MBD). CKD-MBD includes bone complications that can lead to chronic pain syndromes and mobility limitations, cardiovascular complications, significantly increasing mortality in this group of patients, and soft tissue calcifications [1, 2, 3]. The last guidelines for the treatment of SHPT in the course of CKD were published by KDIGO in 2017 and have not been updated. This manuscript is a review of the literature published mainly after 2017, paying special attention to potentially new therapies that seem to be promising in the treatment of SHPT.

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Parathyroids and parathormon — importance in maintaining calcium-phosphate homeostasis

The parathyroids are endocrine glands located most often on the posterior surface of the thyroid gland, directly below its upper and lower poles. They normally have a spherical shape, are yellowish/brownish in colour, weight approx. 35 g, and do not exceed 5 mm in size. There are usually 4 parathyroid glands in humans, but there may be more; occasionally there may be 3. Variability may also apply to the location of the parathyroid glands. Apart from the typical location mentioned above, the parathyroid glands may be located inside the thyroid gland, in the thymus gland, in the pericardium, or in the anterior or posterior mediastinum. Main parathyroid cells have calcium receptors (CaR) on their surface; therefore, they are highly sensitive to changes in the concentration of calcium ions in the extracellular environment. CaR-bound calcium affects both PTH secretion and parathyroid cell proliferation. Under physiological conditions, the parathyroid glands maintain very rigorously the correct concentration of calcium ions in the extracellular fluid and blood serum. In response to a low serum calcium concentration, PTH secretion increases within a few seconds to a few minutes, which enables a very quick response to calcium homeostasis disturbances. The half-life (T1/2) of PTH in the blood is approximately 2–4 minutes. With a high concentration of calcium, the release of PTH is inhibited and its degradation to inactive, shorter fragments occurs, which are excreted by the kidneys or the liver [3, 4].

PTH is a linear polypeptide composed of 84 amino acids. The precursor of PTH 1-84 is the 115 amino acid prepro-PTH polypeptide encoded by the PTH gene located on chromosome 11 (locus 11p15). The PTH molecule, after binding to the metabotropic receptor in target organs, activates adenylate cyclase, which results in the formation of cyclic AMP (cAMP), which is an intracellular signal transmitter that activates specific protein kinases. The entire PTH 1-84 molecule or its N-terminal fragment PTH 1-29 is abbreviated as CAP (cyclase activating PTH), while PTH fragments lacking 6 amino acids at the N-terminus (PTH 7-84, so-called iC-terminal fragments) are abbreviated as CIP (cyclase inhibiting PTH). CAP increases bone turnover, calcaemia, and phosphaturia, and reduces phosphataemia, while CIP has an antagonistic effect on CAP. About 10–20% of blood particles are PTH 1-84, while the remainder are PTH 1-29 and CIP [6, 7]. The second-generation diagnostic kits enabled the determination of the so-called intact PTH (iPTH), which is the sum of the concentrations of PTH 1-84 and PTH 7-84. Because the biological activity of PTH depends on the N-terminal fragment of PTH consisting of 34 amino acids, third-generation kits have been introduced for parathyroid diagnostics, enabling determination of the concentration of PTH 1-84 and biologically active N-terminal fragments of this hormone and CIP [7]. PTH, as the main regulator of calcium homeostasis in the body, maintains the correct concentration of calcium ions in the extracellular fluid by mobilizing calcium and inorganic phosphate from the bones by inducing differentiation and activation of osteoclasts. Calcium release is accompanied by an increase in inorganic phosphate in the extracellular fluid, but this does not normally lead to an increase in blood phosphate, because PTH reduces phosphate reabsorption from the proximal renal tubule by 85% and thus increases phosphaturia. In addition, it stimulates the reabsorption of calcium from the primary urine, which protects against excessive loss of calcium with the final urine. The effects of PTH also include the stimulation of the synthesis of calcitriol (the active form of vitamin D3), which stimulates the absorption of calcium and phosphate from the small intestine. Calcitriol, after binding to a specific receptor (VDR, vitamin D receptor) in the cell nucleus, affects the transcription of transport proteins and calcium channels important in maintaining calcium homeostasis in the body. Therefore, PTH has an indirect effect on the increase in the absorption of exogenous calcium by the intestinal mucosa [5–7].

Pathomechanism and consequences of secondary hyperparathyroidism

Secondary hyperparathyroidism (SHPT) occurs most often in the early stages of CKD. Previously it was believed that the main factors in the development of SHPT are primarily hypocalcaemia, hyperphosphataemia, and decreased calcitriol levels. As early as in the initial stage of CKD (stage G2), the concentration of calcitriol decreases, which is associated with a decrease in the activity of 1-alpha-hydroxylase in the kidney, as a result of increased concentration of inorganic phosphates in the serum. In addition, due to reduced glomerular filtration, the amount of 25-hydroxycholecalciferol (25(OH) D3) reaching the proximal tubule is reduced. However, results of studies have shown that other factors are probably crucial in the development of SHPT, namely Klotho protein deficiency and an increase in the serum concentration of fibroblast growth factor 23 (FGF-23) [8].

FGF-23 is a protein hormone with a mass of 32 kDa, which is produced mainly in osteoblasts and osteocytes. It is a 251 amino acid polypeptide chain in which the 24 amino acid initial fragment undergoes organic proteolysis during secretion of

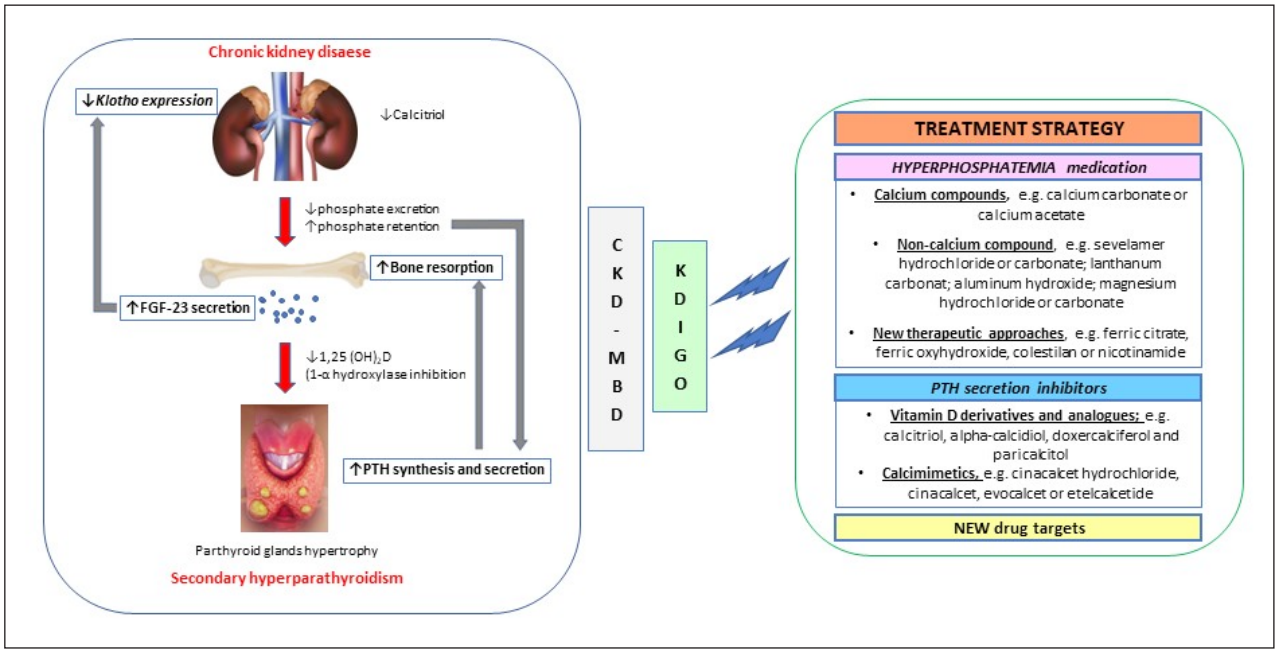

Figure 1. *Pathomechanism and treatment of secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD). FGF-23 — fibroblast growth factor 23; 1,25(OH)$_2$D — calcitriol; PTH — parathyroid hormone*

REVIEW

the hormone into the blood. The physiological role of FGF-23 is associated with the reduction of serum phosphate concentration by enhancing phosphaturia by PTH-independent inhibition of the expression of sodium-phosphate co-transporters in the renal tubules [FGF-23 reduces the expression of primarily NPT2a co-transporters (Na/Pi co- transporter type IIa) and NPT2c (Na/Pi co-transporter type IIc), which are present mainly in the proximal tubules]. In addition, FGF-23 reduces the concentration of the active form of vitamin D3 in the serum both by inhibiting the activity of 1-alpha-hydroxylase and by enhancing the activity of 24-hydroxylase, which results in the formation of 24, 25-dihydroxycalciferol (a metabolically inactive compound). It has been shown that the concentration of FGF-23 in the serum increases in the early stages of CKD, preceding the changes in the concentration of phosphates and calcaemia associated with this disease. FGF-23 works with the participation of a cofactor of renal origin: the Klotho protein, which, when combined with fibroblast growth factor receptor type 1 (FGFR1), converts it into a receptor specific for FGF-23. Klotho protein is expressed primarily in the parathyroid glands and kidneys (mainly in the distal tubule). It is a 1012 amino acid transmembrane protein with an extracellular domain, a single transmembrane unit, and a short intracellular domain. The extracellular fragment of the membrane protein Klotho can be "cleaved" by proteases ADAM 10 and ADAM 17 (a-disintegrin and metalloproteases) associated with the cell membrane and get into the serum and urine. The normal concentration of Klotho protein in the serum of healthy people is 239–1266 pg/ml and decreases with age. Urinary excretion of Klotho protein decreases in the early stages of CKD (stage G1), and it seems to be the first bioindicator of the onset of calcium and phosphate metabolism disorders. Therefore, it is highly probable that the elevated concentration of FGF-23 in the serum is the result of reduced expression of the Klotho protein [9–11].

The consequence of SHPT is mineral and bone disorders, which include renal osteodystrophy and calcifications in blood vessels leading to cardiovascular complications. Renal osteodystrophy is not a disease entity. The clinical picture includes bone and joint pain, spontaneous bone fractures and tendon ruptures, muscle weakness, and soft tissue calcification. We distinguish high-turnover bone disease, which is characterized by increased osteolysis and (to a lesser extent) osteogenesis, and in severe cases, progressive fibrosis involving the medullary cavity (osteitis fibrosa cystica). It is the result of secondary hyperparathyroidism and the effect of high concentrations of PTH in bone (usually > 800 pg/mL). Low-turnover bone disease, on the other hand, is characterized by reduced osteoid mineralization (osteomalacia, aluminium osteopathy) or impaired osteoid production and mineralization (adynamic bone disease). The second aspect of CKD-MBD is the formation of extraosseous calcifications associated with the pathogenesis of the disease and with traditional methods of SHPT therapy. The most serious problem is calcification in

the cardiovascular system, the presence of which significantly contributes to the increase in mortality in patients with end-stage renal disease. Hyperphosphataemia, PTH hypersecretion, calcitriol deficiency, and high serum FGF-23 levels contribute to the deposition of calcium salts in the vascular wall and are risk factors for increased all-cause and cardiovascular mortality in patients with CKD [12–14].

Pharmacological treatment strategies for secondary hyperparathyroidism

There are 2 strategies of SHPT treatment. The first is based on the use of drugs that lower serum phosphate levels, and the second is based on the suppression of PTH secretion by the parathyroid glands.

Medications lowering serum phosphate level

Drugs that bind phosphate in the digestive tract are among the most commonly used in patients with advanced CKD. The guidelines of European nephrological societies suggest lowering the concentration of phosphate in the blood to normal values in CKD stage G3a, and in dialysis patients as close as possible to these values [15]. Medications lowering the serum phosphate level can be classified into 2 subgroups: calcium compounds, such as calcium carbonate or calcium acetate; and non-calcium compounds, such as sevelamer hydrochloride or carbonate, lanthanum carbonate, aluminium hydroxide, and magnesium hydrochloride or carbonate. Among the new therapeutic possibilities, iron preparations have also appeared in recent years, such as ferric citrate, sucroferric oxyhydroxide, colestilan, or nicotinic acid amide [16].

Calcium carbonate is the most commonly used in the group of patients with CKD, including dialysis patients. It is widely available and cheap. It should be noted, however, that the guidelines suggest that the daily amount of elemental calcium taken both in the diet and in phosphate binding preparations should not exceed 1500 mg due to the risk of hypercalcaemia, which leads to calcification in soft tissues and blood vessels. Moreover, the main side effect of this group of drugs is constipation [17]. Many literature data support the advantage of calcium-free drugs in patients with CKD treated with phosphate binders in the gastrointestinal tract. Unfortunately, the results of these studies are also inconclusive [16]. In a meta-analysis by Palmer et al., the safety of sevelamer, calcium, lanthanum, iron, magnesium, colestilan, bixalomer, and nicotinamide preparations was compared. Seventy-seven studies involving a total of 12,562 patients were analysed, of which 11,009 were on renal replacement therapy. It concluded that there is currently no conclusive evidence of a reduction in mortality from treatment with phosphate binders in the gastrointestinal tract compared to placebo. However, it was noted that sevelamer, as a representative of non-calcium drugs, reduced all-cause mortality compared to calcium preparations. In addition, it was concluded that iron-based drugs have a greater potential in lowering serum phosphate concentrations compared to other preparations [18]. Another meta-analysis by Habbous et al., including 51 studies and a total of 8829 CKD patients, showed that sevelamer reduced all-cause mortality compared to calcium phosphate binders, and sevelamer was associated with lower rates of hospitalization and lower incidence of hypercalcaemia. The analysed studies focused mainly on the analysis of biochemical indices, hence the lack of data on clinical events, such as vascular calcification, fractures, or cardiovascular events. Therefore, there is a need for new studies on the efficacy of sevelamer focusing on clinical data to draw clear conclusions [19].

In recent years, based on numerous clinical observations, it has been concluded that iron-based phosphate binders may be very promising. In a retrospective observational study by Coyne et al., which aimed to compare sucroferric oxyhydroxide with other non-ferrous phosphate binders in a population of dialysis patients, over a period of 2 years of follow-up, patients treated with an iron preparation reached target serum phosphate concentrations faster, were hospitalized less often, and took half as many tablets of the preparation compared to the rest of the available phosphate binders [20]. In turn, the multicentre study with the acronym VELREAL included a 6-month follow-up of 220 dialysis patients previously treated with phosphate binders other than sucroferric oxyhydroxide. This study confirmed that treatment of these patients with sucroferric oxyhydroxide resulted in a decrease in serum phosphate levels and an increase in the proportion of patients who achieved adequate control of serum phosphate levels with fewer tablets than other drugs of this type [21]. Iron preparations were also the subject of a meta-analysis, which included 19 studies involving a total of 4719 patients. Compared to placebo, the serum phosphate concentration was significantly reduced after the use of ferric citrate, the haemoglobin concentration increased significantly, and the parameters of iron metabolism improved, while sucroferric oxyhydroxide had no effect on the serum haemoglobin concentration. It has also been noted that iron citrate and sucroferric oxyhydroxide decrease serum PTH levels [22]. Other phosphate binders have also been studied in recent years, such as colestilan (a non-absorbable resin that binds phosphate and bile acids in the intestine). In a meta-analysis of 4

studies in dialysis patients, comparing colestilan with placebo, a significant reduction in serum phosphate concentration was found after colestilan; however, this drug caused significant gastrointestinal symptoms in a 2-year follow-up [23].

In patients not yet subjected to dialysis (stage G3-5 CKD), both the benefits and risks of reducing serum phosphate are not fully understood. Some studies have shown that phosphorus still in normal values is already an indicator of the risk of death in patients with CKD. In turn, other studies demonstrated no association between phosphate levels and an increased risk of death [16]. Similarly with phosphate binders in CKD G3-5 patients not dialysed, there are also no conclusive data on the effectiveness of their use. Overall, few long-term studies on the use of phosphate binders in CKD in stages G3-5 have been conducted. In the COMBINE study published in 2019, including 205 patients with CKD in stage G3b/G4, lanthanum carbonate was prescribed for 12 months at a dose of 1 g 3 times a day, with no decrease in serum phosphate concentration, only a decrease in their concentration in the urine together with the concentration of FGF-23 [24]. Similarly, in the double-blind, placebo-controlled FRENCH study, which used sevelamer for 12 weeks and included 96 patients with CKD stage G3b-4, there was no significant decrease in serum phosphate, but there was a decrease in phosphaturia [25]. In addition, in the randomized IMPROVE-CKD study of 278 patients with CKD stage G3b-4 divided into 2 groups on lanthanum carbonate versus placebo for 96 days, there were no significant differences between the groups in phosphate and FGF-23 levels as well as the presence of calcifications in the aorta or arterial stiffness [26, 27]. Therefore, in patients with CKD who are not on dialysis, the role of drugs lowering blood phosphate levels is uncertain, and additional studies are needed to confirm their effectiveness in this group of patients. In turn, in dialysis patients, many studies indicate a definite relationship between serum phosphate levels and the risk of death [16]. Over the past decade, direct relationships between serum phosphate levels and mortality in dialysis patients have been reported, and there is increasing evidence that phosphate overload shortens the survival of dialysis patients through adverse effects on the skeletal and cardiovascular systems [28]. However, studies have not shown a reduction in mortality with phosphate binders compared to placebo. In the above-mentioned meta-analysis by Palmer et al., it was found that there is currently no evidence that treatment with phosphate binders in the gastrointestinal tract reduces mortality in the population of CKD patients, including dialysis patients, compared to placebo [18].

Drugs that inhibit the secretion of PTH by the parathyroid glands

The second treatment strategy for SHPT is to lower serum PTH levels. The optimal level of PTH in CKD patients with stage G3-5 not treated with dialysis is not known, while in patients on dialysis most nephrology scientific societies recommend maintaining the level of the hormone within the range of 2–9 times the upper limit of normal values (usually 140–600 pg/mL). Due to the risk of adynamic bone disease, PTH levels should not be allowed to fall below this range. Active vitamin D derivatives and its analogues (calcitriol, alfacalcidol, paricalcitol) and calcimimetics (cinacalcet) are used to reduce serum PTH levels [29, 30].

Vitamin D derivatives and its analogues

Vitamin D is defined as fat-soluble sterol compounds having a biologically inactive form of prohormones — mainly cholecalciferol (vitamin D3) and to a lesser extent ergocalciferol (vitamin D2). Vitamin D3 is derived from 2 sources: from the skin synthesis of dehydrocholesterol under the influence of ultraviolet radiation (which gives about 80% of the vitamin D found in the body) and from foods such as fatty fish and chicken egg yolk. In turn, vitamin D2 is found in plant foods and mushrooms. Biologically inactive forms achieve full hormonal activity through 2-stage hydroxylation – first in the liver, where 25-hydroxycholecalciferol (25(OH)D, calcidiol) is formed, and then in the kidneys, where 1.25-dihydroxycholecalciferol (1.25(OH)2D, calcitriol) is formed. Calcidiol is the main metabolite of vitamin D with a long half-life (up to several weeks), and its plasma concentration is considered the main indicator of the body's supply of vitamin D, which is why it is used in clinical practice to monitor vitamin D concentration and the effects of its supplementation. Calcitriol, on the other hand, is a biologically active form with a short half-life (several hours) [31–34]. The active form of vitamin D increases the absorption of calcium and phosphate in the intestines and kidneys, stimulates osteoblasts and bone resorption by osteoclasts, and inhibits the secretion of PTH [34]. The presence of the cytoplasmic calcitriol receptor (VDR) has been demonstrated in most tissues and organs, indicating a potential effect on the function of cells other than those involved in calcium and bone homeostasis. Therefore, vitamin D supplementation is supposed to lead to many positive health effects of a pleiotropic nature, including those related to the cardiovascular, immune, nervous, and respiratory systems [30]. Unfortunately, the clinical use of calcitriol is significantly limited by its calcaemic activity causing hypercalcaemia, which has stimulated the synthesis of many new analogues in search of derivatives with a much more favourable profile of

action [31]. Available vitamin D analogues include calcitriol, alpha-calcidiol, doxercalciferol, and paricalcitol (19-nor-1-alpha-25-dihydroxyvitamin D2). Paricalcitol and calcitriol have a similar suppressive effect on parathyroid cells, but the binding strength of paricalcitol to the VDR in the intestine is 3.5 times weaker than that of calcitriol, so its effect on the risk of hypercalcaemia is lower. The most common side effects of paricalcitol are gastrointestinal complaints and rash, dizziness, dysgeusia, muscle spasms, and elevated liver enzymes in blood serum in laboratory tests [32]. A meta-analysis by Geng X et al. published in 2020, including 15 studies (involving 110,544 patients), examined the efficacy and safety of paricalcitol compared to other vitamin D analogues. The conclusions of this meta-analysis indicate that paricalcitol is superior to other analogues in mortality and lower serum PTH levels, but no difference in the incidence of side effects was found [33]. In the treatment and prophylaxis of vitamin D deficiency in the general population, cholecalciferol is used, while vitamin D analogues are indicated, e.g., in disorders of vitamin D hydroxylation in the liver or kidneys. In patients with CKD taking active metabolites of vitamin D or its analogues, it is recommended to take native vitamin D in parallel, to ensure its beneficial pleiotropic effect [34]. It should be emphasized here that during the supplementation and treatment of vitamin D deficiency with active vitamin D metabolites or analogues, including alfacalcidol, calcitriol, and paricalcitol, the vitamin D concentration should not be monitored in clinical practice by measuring serum 25(OH)D [34, 35]. The meta-analysis by Lu et al. analysed the effect of vitamin D supplementation on overall mortality in patients with CKD and cardiovascular mortality in this group of patients. Thirty-eight studies with data from 223,429 patients were analysed, with observational and randomized studies considered separately. In observational studies, treatment with vitamin D was associated with a marked reduction in mortality; however, such a significant relationship was not found in randomized controlled trials, which proves that further large randomized trials are needed to assess the effect of treatment with vitamin D on mortality [32]. On the other hand, the meta-analysis by Christodoulou et al. considered 22 randomized placebo-controlled trials involving adults with CKD but not on dialysis, who were taking any type of vitamin D. It was shown that calcidiol, calcitriol, and vitamin D analogues caused a significant suppression of PTH secretion. However, the authors were concerned about the fact that the use of vitamin D analogues also increased the concentration of FGF-23, which is already elevated in patients with CKD and is a predictor of vascular calcification and cardiovascular disease [36]. In meta-analysis by Karimi et al., the effect of vitamin D supplementation on FGF-23 concentration in patients with CKD was investigated, but it was finally concluded that there was no evidence of the effect of vitamin D supplementation on the concentration of this factor [37].

Calcimimetics

Calcimimetics are the drugs of first choice for hypercalcaemia or uncontrolled hyperphosphataemia. They act on the parathyroid cells by stimulating the CaR and thus inhibiting the secretion of PTH. The only currently available preparation from the group of calcimimetics in Poland is cinacalcet hydrochloride, which is a second-generation calcimimetic. Cinacalcet hydrochloride is an allosteric activator of transmembrane CaRs, sensitizing these receptors to calcium. This means that they are activated at lower calcium concentrations than under physiological conditions. As a result, within 2–4 hours after administration of cinacalcet hydrochloride, the concentration of PTH decreases by enhancing its intracellular degradation and by reducing the transcription of the gene encoding it. This is accompanied by a decrease in calcium and phosphate levels; therefore, regular monitoring of serum calcium levels is necessary during treatment. The risk of hypocalcaemia is greatest in the first weeks of treatment, especially in patients with very high PTH levels, but later, hypocalcaemia is less frequent and is usually moderate. The drug is generally well tolerated; the most common side effects concern the gastrointestinal tract. Usually, 6 months of treatment allows the effectiveness of the drug to be determined. An important advantage of using cinacalcet hydrochloride is the possibility of adding vitamin D to the treatment. Firstly, it has been shown that the combination of cinacalcet hydrochloride with low doses of active vitamin D metabolites increases the effectiveness of the treatment of SHPT and allows the target PTH values recommended by KDIGO to be achieved. Secondly, patients with CKD are deficient in calcitriol, and ensuring its adequate concentrations is very important to the bone tissue and parathyroid glands and also for the functioning of many other systems due to the pleiotropic effect [38–40]. The effectiveness of cinacalcet in the treatment of SHPT has been evaluated in numerous studies. In the randomised, double-blind EVOLVE study, cinacalcet was compared with a placebo for a reduction in the risk of all-cause mortality and cardiovascular events. It was conducted in a group of 3883 patients with moderate to severe SHPT receiving haemodialysis. This study did not demonstrate a reduction in the risk of all-cause mortality and cardiovascular events, including myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular events, in

patients taking cinacalcet compared to placebo [39]. In a randomized, open study by Susantitaphong et al., it was shown that cinacalcet significantly reduces PTH levels in patients dialysed with SHPT; moreover, patients treated with cinacalcet have improved bone turnover parameters, reduced FGF-23 levels, and stable vascular calcifications [41]. In turn, in a meta-analysis by Xu et al., covering a total of 7 studies and 456 patients using paricalcitol and 412 patients treated with cinacalcet, the effectiveness of these drugs in lowering PTH levels in patients with SHPT was compared. There were no differences in the potential to lower PTH levels in the 2 analysed groups, a similar effect of both drugs on phosphate metabolism was found, and hypocalcaemia was observed much more often in the cinacalcet group [42]. In contrast, a comparison of the effects of 3 calcimimetics (cinacalcet, evocalcet, and etelcalcetide) based on 36 studies (11,247 participants; median follow-up = 26 weeks) the majority of dialysis patients (excluding 4 studies) showed that etelcalcetide had the best effect in lowering serum PTH levels, but causing more hypocalcaemia compared to other calcimimetics. Considering the impact on the reduction of deaths (including deaths due to cardiovascular causes), no significant differences were found between the individual groups [43]. Interestingly, Akizawa et al. showed that evocalcet, a newly approved calcimimetic in Japan, has better bioavailability than cinacalcet, equivalent efficacy at a lower dose, and a lower rate of GI-related adverse events. The incidence of hypocalcaemia and electrocardiogram QT prolongation was similar between evocalcet and cinacalcet. Overall, the results of these studies indicate that evocalcet is safer than cinacalcet [44]. Similar conclusions can also be drawn from the study by Koiwa et al., which compared patients using evocalcet after cinacalcet therapy and evocalcet without prior cinacalcet treatment. Overall, the results of the study suggest that evocalcet treatment is effective and safe, regardless of prior cinacalcet treatment. Given the concerns about long-term exposure to high blood-PTH concentrations, these results suggest that patients may benefit if they start evocalcet treatment in the early stages of SHPT [45]. In turn, in a direct comparative study of dialysis patients in Japan using evocalcet and cinacalcet, it was found that evocalcet was as effective in lowering serum PTH levels as cinacalcet, but it caused fewer side effects and fewer drug interactions [46]. Considering the above conclusions, it seems inevitable that in the future cinacalcet will be replaced on a large scale by newer drugs from the group of calcimimetics.

Directions of the development of new therapies

In recent years, alternative solutions in the treatment of CKD-MBD have also been sought, and studies on the role of intestinal microbiota in the course of CKD seem to be particularly promising. The intestinal microbiota under normal conditions remains in symbiosis with the body and plays an important role in the fermentation of nutrients, the stimulation of the immune system, and the production of bioactive particles such as vitamins and short-chain fatty acids (SCFA). More and more data indicate a special effect on the body from the products of metabolism of intestinal bacteria, in particular SCFA, such as butyric, propionic and acetic acids. They play a significant role in the proper functioning of the immune system, showing a significant anti-inflammatory potential, and they are important in maintaining the proper function of the kidneys by affecting the expression of the Klotho protein and the proper functioning of the proximal tubules of the nephrons [47, 48]. On the other hand, the intestinal microbiota is responsible for the synthesis of uremic toxin precursors, of which trimethylamine N-oxide (TMAO), p-cresol sulphate (p-cresyl sulphate pCS), and indoxyl sulphate (IS) have been proven to damage blood vessels and kidneys and activate pro-inflammatory pathways [48, 51, 52]. Disturbances in the composition of the intestinal microbiota lead to disturbances in the homeostasis of the body and the development of various diseases in patients with CKD diagnosed primarily with a reduction in the population of microorganisms that produce SCFA with a relatively stable number of population-producing uremic toxin precursors [48–50]. These data require confirmation in larger studies involving populations of patients with CKD from various backgrounds; however, it seems that actions aimed at preserving the microbiota responsible for SCFA synthesis while reducing the microbiota population responsible for the synthesis of uraemic toxin precursors may be a key goal of CKD treatment in the future [47]. In addition, observations carried out in recent years indicate the existence of a relationship between the content of phosphates in the diet and the use of phosphate-binding drugs in the gastrointestinal tract and the composition of the intestinal microbiota. They also indicate the influence of the intestinal microbiota on the phosphate balance and the effect of PTH on the bones. However, the exact molecular mechanisms of these processes remain unclear and require further research, which may in the future help in the development of novel therapeutic approaches in the treatment of CKD-MBD [48].

Conclusions

The complex pathophysiology of calcium and phosphate metabolism disorders in the SHPT in the course of CKD leads to serious dilemmas during treat-

ment. Despite the increasing knowledge about the pathomechanisms of disorders and the therapeutic possibilities that we currently have, it is often difficult to properly compensate disorders of phosphate and calcium metabolism and to lower PTH and compensate vitamin D deficiency. When conducting treatment, we should remember about the optimal selection of available drugs, paying attention to their additional effects to reduce the risk of chronic complications, as well as side effects. Because calcium and phosphate metabolism disorders accompanying chronic kidney disease begin with an increase in FGF-23 secretion and a significant decrease in serum Klotho protein, it could be assumed that the new drugs will stimulate the expression of Klotho protein or block FGF-23.

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References

1. Koiwa F, Tokunaga S, Asada S, et al. Efficacy of Evocalcet in Previously Cinacalcet-Treated Secondary Hyperparathyroidism Patients. Kidney Int Rep. 2021; 6(11): 2830–2839, doi: 10.1016/j.ekir.2021.08.020, indexed in Pubmed: 34805635.
2. 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 (2011). 2017; 7(1): 1–59, doi: 10.1016/j.kisu.2017.04.001, indexed in Pubmed: 30675420.
3. Rodríguez-Ortiz ME, Rodríguez M. Recent advances in understanding and managing secondary hyperparathyroidism in chronic kidney disease. F1000Res. 2020; 9, doi: 10.12688/f1000research.22636.1, indexed in Pubmed: 32913635.
4. Mizobuchi M, Ogata H, Koiwa F, et al. New strategies for the treatment of secondary hyperparathyroidism. Am J Kidney Dis. 2003; 41(3 Suppl 1): S100–S103, doi: 10.1053/ajkd.2003.50095, indexed in Pubmed: 12612963.
5. Kužma M, Jackuliak P, Killinger Z, et al. Parathyroid Hormone-Related Changes of Bone Structure. Physiol Res. 2021; 70(Suppl 1): S3–SS11, doi: 10.33549/physiolres.934779, indexed in Pubmed: 34918524.
6. Chen T, Wang Yi, Hao Z, et al. Parathyroid hormone and its related peptides in bone metabolism. Biochem Pharmacol. 2021; 192: 114669, doi: 10.1016/j.bcp.2021.114669, indexed in Pubmed: 34224692.
7. Soliman M, Hassan W, Yaseen M, et al. PTH assays in dialysis patients: Practical considerations. Semin Dial. 2019; 32(1): 9–14, doi: 10.1111/sdi.12743, indexed in Pubmed: 30168196.
8. Memmos E, Papagianni A. New Insights into the Role of FGF-23 and Klotho in Cardiovascular Disease in Chronic Kidney Disease Patients. Curr Vasc Pharmacol. 2021; 19(1): 55–62, doi: 10.2174/1570161118666200420102100, indexed in Pubmed: 32310050.
9. Ho BB, Bergwitz C. FGF23 signalling and physiology. J Mol Endocrinol. 2021; 66(2): R23–R32, doi: 10.1530/JME-20-0178, indexed in Pubmed: 33338030.
10. Erben RG, Andrukhova O. FGF23-Klotho signaling axis in the kidney. Bone. 2017; 100: 62–68, doi: 10.1016/j.bone.2016.09.010, indexed in Pubmed: 27622885.
11. Muñoz-Castañeda JR, Rodelo-Haad C, Pendon-Ruiz de Mier MV, et al. Klotho/FGF23 and Wnt Signaling as Important Players in the Comorbidities Associated with Chronic Kidney Disease. Toxins (Basel). 2020; 12(3), doi: 10.3390/toxins12030185, indexed in Pubmed: 32188018.
12. 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.
13. Elias RM, Dalboni MA, Coelho AC, et al. CKD-MBD: from the Pathogenesis to the Identification and Development of Potential Novel Therapeutic Targets. Curr Osteoporos Rep. 2018; 16(6): 693–702, doi: 10.1007/s11914-018-0486-0, indexed in Pubmed: 30291515.
14. Sprague SM, Martin KJ, Coyne DW. Phosphate Balance and CKD-Mineral Bone Disease. Kidney Int Rep. 2021; 6(8): 2049–2058, doi: 10.1016/j.ekir.2021.05.012, indexed in Pubmed: 34386654.
15. Scialla JJ, Kendrick J, Uribarri J, et al. State-of-the-Art Management of Hyperphosphatemia in Patients With CKD: An NKF-KDOQI Controversies Perspective. Am J Kidney Dis. 2021; 77(1): 132–141, doi: 10.1053/j.ajkd.2020.05.025, indexed in Pubmed: 32771650.
16. Stróżecki P, Manitius J. Hyperphosphatemia in patients with chronic kidney disease. Forum Nefrol. 2018; 11(1): 1–8.
17. Chan S, Au K, Francis RS, et al. Phosphate binders in patients with chronic kidney disease. Aust Prescr. 2017; 40(1): 10–14, doi: 10.18773/austprescr.2017.002, indexed in Pubmed: 28246429.
18. Palmer SC, Gardner S, Tonelli M, et al. Phosphate-Binding Agents in Adults With CKD: A Network Meta-analysis of Randomized Trials. Am J Kidney Dis. 2016; 68(5): 691–702, doi: 10.1053/j.ajkd.2016.05.015, indexed in Pubmed: 27461851.
19. Habbous S, Przech S, Acedillo R, et al. The efficacy and safety of sevelamer and lanthanum versus calcium-containing and iron-based binders in treating hyperphosphatemia in patients with chronic kidney disease: a systematic review and meta-analysis. Nephrol Dial Transplant. 2017; 32(1): 111–125, doi: 10.1093/ndt/gfw312, indexed in Pubmed: 27651467.
20. Coyne DW, Ficociello LH, Parameswaran V, et al. Sucroferric Oxyhydroxide in Maintenance Hemodialysis: A Retrospective, Comparative Cohort Study. Kidney Med. 2020; 2(3): 307–316, doi: 10.1016/j.xkme.2020.01.009, indexed in Pubmed: 32734250.
21. Christodoulou M, Aspray TJ, Schoenmakers I. Vitamin D Supplementation for Patients with Chronic Kidney Disease: A Systematic Review and Meta-analyses of Trials Investigating the Response to Supplementation and an Overview of Guidelines. Calcif Tissue Int. 2021; 109(2): 157–178, doi: 10.1007/s00223-021-00844-1, indexed in Pubmed: 33895867.
22. Zhu Y, Rao J, Liao X, et al. Using iron-based phosphate binders in phosphate reduction and anemia improvement in patients receiving dialysis: a meta-analysis of randomized controlled trials. Int Urol Nephrol. 2021; 53(9): 1899–1909, doi: 10.1007/s11255-021-02820-y, indexed in Pubmed: 33675476.
23. Zhang Q, Li M, Chen J. Effect of colestilan on serum phosphorus in dialysis patients: A meta-analysis of the literature. Nephrology (Carlton). 2016; 21(3): 229–235, doi: 10.1111/nep.12588, indexed in Pubmed: 26272343.
24. Ix JH, Isakova T, Larive B, et al. Effects of Nicotinamide and Lanthanum Carbonate on Serum Phosphate and Fibroblast Growth Factor-23 in CKD: The COMBINE Trial. J Am Soc Nephrol. 2019; 30(6): 1096–1108, doi: 10.1681/ASN.2018101058, indexed in Pubmed: 31085679.
25. Liabeuf S, Ryckelynck JP, El Esper N, et al. FRENCH Study collaborators. Randomized Clinical Trial of Sevelamer Carbonate on Serum Klotho and Fibroblast Growth Factor 23 in CKD. Clin J Am Soc Nephrol. 2017; 12(12): 1930–1940, doi: 10.2215/CJN.03030317, indexed in Pubmed: 29074818.
26. Toussaint ND, Pedagogos E, Lioufas NM, et al. IMPROVE-CKD Trial Investigators. A Randomized Trial on the Effect of Phosphate Reduction on Vascular End Points in CKD (IMPROVE-CKD). J Am Soc Nephrol. 2020; 31(11): 2653–2666, doi: 10.1681/ASN.2020040411, indexed in Pubmed: 32917784.
27. Lioufas N, Toussaint ND, Pedagogos E, et al. IMPROVE-CKD Writing Committee.. Can we IMPROVE cardiovascular outcomes through phosphate lowering in CKD? Rationale and protocol for the IMpact of Phosphate Reduction On Vascular End-points in Chronic Kidney Disease (IMPROVE-CKD) study. BMJ Open. 2019; 9(2): e024382, doi: 10.1136/bmjopen-2018-024382, indexed in Pubmed: 30796122.
28. Cozzolino M, Galassi A, Ciceri P. Do we need new phosphate binders in dialysis? Clin Kidney J. 2021; 14(2): 474–475, doi: 10.1093/ckj/sfaa246, indexed in Pubmed: 33626110.
29. Bacchetta J. Treatment of hyperphosphatemia: the dangers of high PTH levels. Pediatr Nephrol. 2020; 35(3): 493–500, doi: 10.1007/s00467-019-04400-w, indexed in Pubmed: 31696357.
30. Haffner D, Leifheit-Nestler M. Treatment of hyperphosphatemia: the dangers of aiming for normal PTH levels. Pediatr Nephrol. 2020; 35(3): 485–491, doi: 10.1007/s00467-019-04399-0, indexed in Pubmed: 31823044.
31. Jean G, Souberbielle JC, Chazot C. Vitamin D in Chronic Kidney Disease and Dialysis Patients. Nutrients. 2017; 9(4), doi: 10.3390/nu9040328, indexed in Pubmed: 28346348.
32. Lu RJ, Zhu SM, Tang FL, et al. Effects of vitamin D or its analogues on the mortality of patients with chronic kidney disease: an updated sys-

tematic review and meta-analysis. Eur J Clin Nutr. 2017; 71(6): 683–693, doi: 10.1038/ejcn.2017.59, indexed in Pubmed: 28488689.
33. Geng X, Shi E, Wang S, et al. A comparative analysis of the efficacy and safety of paricalcitol versus other vitamin D receptor activators in patients undergoing hemodialysis: A systematic review and meta-analysis of 15 randomized controlled trials. PLoS One. 2020; 15(5): e0233705, doi: 10.1371/journal.pone.0233705, indexed in Pubmed: 32470067.
34. Marcinkowska Suchowierska E, Płudowski P. Niedobory witaminy D u osób dorosłych. Medycyna po Dyplomie. 2018;10. https://podyplomie.pl/medycyna/31352,niedobory-witaminy-d-u-osob-doroslych (03.05.2023.).
35. Kmieć P, Sworczak K. Korzyści i zagrożenia wynikające z suplementacji witaminą D. . Forum Medycyny Rodzinnej. 2017; 11(1): 38–46.
36. Christodoulou M, Aspray TJ, Schoenmakers I. Vitamin D Supplementation for Patients with Chronic Kidney Disease: A Systematic Review and Meta-analyses of Trials Investigating the Response to Supplementation and an Overview of Guidelines. Calcif Tissue Int. 2021; 109(2): 157–178, doi: 10.1007/s00223-021-00844-1, indexed in Pubmed: 33895867.
37. Karimi E, Bitarafan S, Mousavi SM, et al. The effect of vitamin D supplementation on fibroblast growth factor-23 in patients with chronic kidney disease: A systematic review and meta-analysis. Phytother Res. 2021; 35(10): 5339–5351, doi: 10.1002/ptr.7139, indexed in Pubmed: 33928687.
38. Eddington H, Chinnadurai R, Alderson H, et al. A randomised controlled trial to examine the effects of cinacalcet on bone and cardiovascular parameters in haemodialysis patients with advanced secondary hyperparathyroidism. BMC Nephrol. 2021; 22(1): 106, doi: 10.1186/s12882-021-02312-2, indexed in Pubmed: 33757437.
39. Cozzolino M, Messa P, Roggeri DP, et al. FARO Study Group. Pharmacological control of secondary hyperparathyroidism in hemodialysis subjects: a cost consequences analysis of data from the FARO study. J Med Econ. 2012; 15(6): 1110–1117, doi: 10.3111/13696998.2012.703632, indexed in Pubmed: 22702445.
40. Okuno S, Inaba M, Ishimura E, et al. Effects of Long-Term Cinacalcet Administration on Parathyroid Gland in Hemodialysis Patients with Secondary Hyperparathyroidism. Nephron. 2019; 142(2): 106–113, doi: 10.1159/000496808, indexed in Pubmed: 30712039.
41. Susantitaphong P, Vadcharavivad S, Susomboon T, et al. The effectiveness of cinacalcet: a randomized, open label study in chronic hemodialysis patients with severe secondary hyperparathyroidism. Ren Fail. 2019; 41(1): 326–333, doi: 10.1080/0886022X.2018.1562356, indexed in Pubmed: 31014177.
42. Xu W, Gong L, Lu J, et al. Paricalcitol *vs.* cinacalcet for secondary hyperparathyroidism in chronic kidney disease: A meta-analysis. Exp Ther Med. 2020; 20(4): 3237–3243, doi: 10.3892/etm.2020.9044, indexed in Pubmed: 32855693.
43. Palmer SC, Mavridis D, Johnson DW, et al. Comparative Effectiveness of Calcimimetic Agents for Secondary Hyperparathyroidism in Adults: A Systematic Review and Network Meta-analysis. Am J Kidney Dis. 2020; 76(3): 321–330, doi: 10.1053/j.ajkd.2020.02.439, indexed in Pubmed: 32475604.
44. Akizawa T, Ikejiri K, Kondo Y, et al. Evocalcet: A New Oral Calcimimetic for Dialysis Patients With Secondary Hyperparathyroidism. Ther Apher Dial. 2020; 24(3): 248–257, doi: 10.1111/1744-9987.13434, indexed in Pubmed: 31486206.
45. Koiwa F, Tokunaga S, Asada S, et al. Efficacy of Evocalcet in Previously Cinacalcet-Treated Secondary Hyperparathyroidism Patients. Kidney Int Rep. 2021; 6(11): 2830–2839, doi: 10.1016/j.ekir.2021.08.020, indexed in Pubmed: 34805635.
46. Fukagawa M, Shimazaki R, Akizawa T, et al. Evocalcet study group. Head-to-head comparison of the new calcimimetic agent evocalcet with cinacalcet in Japanese hemodialysis patients with secondary hyperparathyroidism. Kidney Int. 2018; 94(4): 818–825, doi: 10.1016/j.kint.2018.05.013, indexed in Pubmed: 30049473.
47. Liu X, Jiang C, Liu G, et al. Sodium butyrate protects against oxidative stress in human nucleus pulposus cells via elevating PPAR -regulated Klotho expression. Int Immunopharmacol. 2020; 85: 106657, doi: 10.1016/j.intimp.2020.106657, indexed in Pubmed: 32554208.
48. Favero C, Carriazo S, Cuarental L, et al. Phosphate, Microbiota and CKD. Nutrients. 2021; 13(4), doi: 10.3390/nu13041273, indexed in Pubmed: 33924419.
49. Lau WL, Chang Y, Vaziri ND. The consequences of altered microbiota in immune-related chronic kidney disease. Nephrol Dial Transplant. 2021; 36(10): 1791–1798, doi: 10.1093/ndt/gfaa087, indexed in Pubmed: 32437554.
50. Gryp T, Huys GRB, Joossens M, et al. Isolation and Quantification of Uremic Toxin Precursor-Generating Gut Bacteria in Chronic Kidney Disease Patients. Int J Mol Sci. 2020; 21(6), doi: 10.3390/ijms21061986, indexed in Pubmed: 32183306.
51. Gryp T, De Paepe K, Vanholder R, et al. Gut microbiota generation of protein-bound uremic toxins and related metabolites is not altered at different stages of chronic kidney disease. Kidney Int. 2020; 97(6): 1230–1242, doi: 10.1016/j.kint.2020.01.028, indexed in Pubmed: 32317112.
52. Pignanelli M, Just C, Bogiatzi C, et al. Mediterranean Diet Score: Associations with Metabolic Products of the Intestinal Microbiome, Carotid Plaque Burden, and Renal Function. Nutrients. 2018; 10(6), doi: 10.3390/nu10060779, indexed in Pubmed: 29914158.