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Phosphorus and Calcium Metabolism Disorders Associated with Chronic Kidney Disease Stage III-IV (Systematic Review and Meta-Analysis)

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1. Introduction

Kidneys play an important role in maintenance of the calcium and phosphorus balance. Renal failure is associated with disorders of all phases of the phosphorus and calcium turnover. The decrease of glomerular filtration rate (GFR) under 60 ml/min/1.73 m² is associated with phosphorus filtration rate decrease with further elevation of its serum level that results in parathyroid hormone (PTH) secretion stimulation. PTH suppresses phosphorus reabsorption; therefore, it returns its serum level to normal. However, when the GFR falls below the 30 ml/min/1.73 m² level, this mechanism becomes ineffective and persistent hyperphosphatemia develops. The latter enhances the PTH secretion. Hyperphosphatemia is associated with inhibition of 1 α -hydroxylase effect in proximal renal tubules and the decrease of serum 1,25(OH)₂D₃ (calcitriol) level. Calcitriol deficiency results in calcium absorption disorders in small intestine; as a result, hypocalcemia develops. Persistent hypocalcemia results in parathyroid glands hyperplasia (PTGH) that is associated with excessive PTH production and secretion. PTH hyper-production and hyperphosphatemia are the manifestations of secondary hyper-parathyroidism (SHPT). Hypocalcemia, vitamin D deficiency and hyperphosphatemia are the main factors responsible for secondary hyperparathyroidism. Hypocalcemia, vitamin D deficiency and hyperphosphatemia develop at the initial stage or renal dysfunction – Chronic Kidney Disease (CKD) III (GFR 60-30 ml/min/1.73 m²); they progress with the increasing severity of renal failure (GFR 29-15 ml/min/1.73 m², CKD IV-V). Disorders of calcium and phosphorus balance associated with CKD result in bone diseases, generally called renal osteodystrophy. At the same time numerous cohort studies have broadened the focus of CKD-related mineral and bone disorders to include cardiovascular disease (which is the leading cause of death in patients at all stages of CKD). All three of these processes (abnormal mineral metabolism, abnormal bone and extra skeletal calcification) are closely interrelated and together make a major contribution to the morbidity and mortality of patients with CKD.

Since the publication of the 2003 K/DOQI guidelines for bone and mineral metabolism, there has been tremendous advancement in our understanding of mineral metabolism in CKD patients. Major modifications of K/DOQI bone guidelines are essential and should

reflect our improved understanding of calcium and phosphorus metabolism. At the same time there is a desperate need for randomized trials for better informed decision making and further optimization of care of CKD patients.

The aim of the review is to provide a literature summary concerning the diagnosis and treatment of mineral metabolism disorders in CKD, which will serve an action plan for clinicians.

2. Methods

Literature searches were made of 10 major databases, among which were: Medline, Pubmed, Embase, Cochrane Library and CINAHL. The search was carried out to capture all articles relevant to the topic of CKD and mineral metabolism, bone disorders, and vascular/valvular calcification/. This search encompassed original articles, systematic reviews and meta-analyses.

2.1 Agreed criteria for article inclusion have been

- Articles should be full-text. Brief publications and abstracts were not included.
- Research should be at least 10 patients in each group. The minimum mean duration of study was 6 months.
- Analyzed literature over 15 years.
- The article is detailed research protocol for assessing of its quality
- Patient examination and treatment protocol must meet K / DOQI guidelines protocol and KDIGO Clinical Practice for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) ---First of all articles included a high level of evidence:
 - Randomized controlled trials
 - Prospective nonrandomized without matching controlled trials
 - Retrospective nonrandomized without matching controlled trials

Today, these are standard principles in dealing with the introduction into clinical practice of new diagnosis and treatment methods.

3. Pathogenesis of calcium and phosphorus turnover disorders in patients with CKD stages III-IV

3.1 Hyperphosphatemia

The serum level of phosphorus is based on the ratio of phosphorus absorption in gastrointestinal tract, mobilization rate in bones (bones serve as calcium and phosphorus reservoirs) and renal excretion. Dietary consumption of phosphorus is about 1000-1200 mg; about 800 mg of this amount is being absorbed in intestines (phosphorus turnover pool). The turnover pool is subdivided into cell cytoplasm compartment (70%), bone compartment (29%) and serum (less than 1%). Phosphorus balance is maintained by kidneys. Usually, kidneys filter about 9 g of phosphorus; about 8 g (90%) are reabsorbed in proximal tubules. Reabsorption is mediated by three transporters: Na^+/Pi^- co-transporters types I, II and III [Ermolenko, 2009; Lederer, 2011]. Transporters types I and II are located on the apical membranes of canalicular epithelium cells, while transporter type III is located on their basal membrane. Phosphorus reabsorption is associated with Na^+ transport and depends on the number of Na^+/Pi^- co-transporter molecules on the cell's membrane [Farrow E, 2010; Lederer, 2011; Quarles,2008].

High level of extracellular phosphorus is associated with suppression of $1\alpha\text{OHD}_3$ -hydroxylase (enzyme mediating conversion of $25(\text{OH})\text{D}_3$ to $1,25(\text{OH})_2\text{D}_3$); low level of phosphorus results in opposite effect. The effect of extracellular phosphorus on enzyme's activity is independent of PTH or Na^+/Pi co-transporter. CKD can also result in hypophosphatemia associated with malabsorption, excessive use of phosphate-binding drugs, hyperventilation, vitamin D deficiency or long term glucocorticoid treatment. Chronic phosphate deficiency results in increased renal reabsorption mediated by formation of new Na^+/Pi co-transporter. It is associated with simultaneous $1,25(\text{OH})_2\text{D}_3$ hyperproduction and increased plasma Ca^{2+} level. Increased intestinal absorption of Ca^{2+} and renal reabsorption result in suppression of PTH secretion and enhanced renal reabsorption of phosphorus. Therefore, the factors regulating phosphorus and calcium metabolism are interlinked. Calcitriol increases the phosphorus absorption through enhancement of its uptake by vesicles of enterocytes brush border [Hruska, 2008; Lederer, 2011]. Persistent hyperphosphatemia is found when GFR falls below $60 \text{ ml/min/1.73 m}^2$. Severe renal dysfunction (GFR under $30 \text{ ml/min/1.73 m}^2$) is associated with permanent hyperphosphatemia. CKD-associated phosphorus retention mediates hypocalcemia both through direct effect of hyperphosphatemia on plasma level of calcium, and indirectly - through an effect on parathyroid glands. The results of experiments demonstrate that hyperphosphatemia can stimulate secondary hyperparathyroidism; the process is unrelated to hypocalcemia and/or vitamin D3 deficiency. Therefore, in patients with CKD the plasma phosphorus level should be $2.7\text{-}4.6 \text{ mg/dl}$ ($0.87 - 1.49 \text{ mmol/l}$); and $3.5\text{-}5.5 \text{ mg/dl}$ ($1.13 - 1.78$) in patients with CKD V [Fukumoto, 2008; Gutierrez, 2005; Hruska, 2008; Lederer, 2011; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease., 2003; KDIGO,2009].

3.2 Hypocalcemia

Dietary consumption of calcium in adults is $1.0 - 1.5 \text{ g/day}$. Most of this amount is absorbed in duodenum and proximal part of small intestine. Calcium absorption rate depends on its content in food and bone mineralization rate. Administration of calcium-based drugs with meals is associated with better absorption rate [Ermolenko, 2009; Fukumoto, 2008; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO, 2009]. Renal filtration rate is about $5\text{-}7 \text{ g/day}$; about $95\text{-}97.5\%$ of calcium is reabsorbed in renal tubules. Bone tissue is the main calcium reservoir, containing up to 98% of total body calcium. In serum, about one-half of calcium is represented by free ions, while the rest of calcium is bound to plasma proteins (mainly with albumin) or to other cations. Plasma level of calcium ions regulates all its biological effects. CKD IV-V is associated with gastro-intestinal absorption disorders resulting in low calcium absorption that results in low plasma level of total calcium or calcium ions [Ermolenko, 2009; Fukumoto, 2008]. Meat and dairy products are the main sources of dietary calcium. Dietary calcium is protein-bound. Calcium is released in GIT by proteases. The Ca^{2+} absorption rate in duodenum depends on the level of calcium-binding protein - calbindin - in cytoplasm of the enterocytes. Active transport of Ca^{2+} ions is regulated by calcitriol that interacts with intra-cellular receptors, which controls the transcription of over 60 genes. These genes encode calbindin and Ca^{2+} pump proteins [Foley, 1998; Parfey, 2000; KDIGO,2009]. The factors influencing intestinal absorption of calcium are listed in Table 1.

Increase	Decrease
Vitamin D	Age
Low calcium uptake	High calcium uptake
High sodium uptake	Low sodium uptake
Phosphate deficiency	Glucocorticosteroids
Growth hormone	Phosphate loading
Estrogens	Thyroid hormones
Pregnancy, lactation	Metabolic acidosis
Furosemide	Thiazide diuretics

Table 1. Factors influencing intestinal absorption of calcium

In healthy patients Ca^{2+} excretion rate is 40-300 mg/day [Ermolenko, 2009; K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; Quarles, 2008]. Hypophosphatemia results in decrease in plasma calcium ions level, both through direct binding and decreased renal production of $1,25(\text{OH})_2\text{D}_3$. Calcium is the main regulator of PTH secretion. Even short-term hypocalcemia results in increased PTH secretion due to activation of Ca-receptors located on the surface of parathyroid gland. Persistent hypocalcemia results in increased level of PTH matrix RNA and pre-pro-PTH gene transcription that is associated with PTH hyperproduction and secondary hyperparathyroidism. The latter results in PTH hyper-production and hyper-secretion. In hypocalcemia PTH stimulates the production of $1,25(\text{OH})_2\text{D}_3$ in kidneys that is associated with increased calcium absorption in gastro-intestinal tract [Fukumoto, 2008; Gutierrez, 2005]. In CKD IV-V the relationship of calcium level and PTH secretion is disordered, therefore, higher level of calcium ions is required to suppress the PTH production. Therefore, it is preferable to maintain the serum level of calcium ions within the ULN [Ermolenko, 2009; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO, 2009, Patel, 2009]. The calcium level in dialysis fluid for patients receiving haemo- and peritoneal dialysis should be 2.5 mEq/l (1.25 mmol/l). In patients with CKD IV-V the adenylate-cyclase of parathyroid glands is less sensitive to calcium inhibitory effect. Glucocorticoids suppress calcium absorption by inhibiting the transformation of 25OHD_3 to $1,25(\text{OH})_2\text{D}_3$; phosphates provide the same effect by forming insoluble complexes and oxalates [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO, 2009].

3.3 PTH and calcitonin hyperproduction

3.3.1 PTH molecule (structure and effects)

PTH molecule contains 84 amino acid derivatives (1-84) and contains short N-terminal fragment (PTH 1-34) and long C-terminal fragment (PTH 7-84). The molecular weight of PTH is 9425 Da. The gene mediating PTH synthesis is located on 11-th chromosome. Both whole PTH molecule and its N-terminal fragment possess biological effects [Block, 1998; Kestenbaum, 2005, Lederer, 2011].

PTH regulates the plasma level of Ca^{2+} . Elevated Ca^{2+} plasma level suppresses the PTH synthesis [Block, 1998; Kestenbaum, 2005; Marchais, 1999; Slinin, 2005]. This feedback enables the constant plasma level of Ca^{2+} . PTH maintains constant Ca^{2+} plasma level through the following mechanisms:

- Stimulation of bone tissue resorption resulting in calcium passage to blood.
- Stimulation of renal reabsorption of calcium, resulting in lower excretion in urine.
- Increase of calcium absorption in small intestine (mediated by $1,25(\text{OH})_2\text{D}_3$ synthesis stimulation).

Calcium level is regulated mainly by PTH-mediated effect on bone tissue; to a lesser extent it is regulated by effect on renal excretion of calcium. Long-term maintenance of calcium balance is mediated mainly by the PTH effect on $1,25(\text{OH})_2\text{D}_3$ synthesis and, therefore, on the rate of calcium absorption in gastro-intestinal tract. The daily level of blood and bone tissue calcium turnover is about 500 mg. PTH is the main regulator of this turnover [Block, 2007; Quarles, 2008].

PTH provides several direct and indirect effects on bone tissue. Persistent PTH level elevation results in bone tissue cells increase (primarily - of the osteoclasts) and intensive bone remodeling. The rate of PTH secretion by parathyroid glands depends on plasma level of Ca^{2+} . Magnesium provides similar but less pronounced effect on PTH secretion. In fact, the physiological changes of magnesium level do not impact the PTH secretion; however, pronounced decrease of intra-cellular magnesium level results in increased PTH secretion [Block, 2007; Craver, 2007; Lederer, 2011].

The effect of Ca^{2+} on PTH secretion is mediated through its interaction with Ca receptors (CaR) that are bound to G-proteins and have a large extracellular domain for binding to low-molecular weight ligands. Activation of receptors associated with high Ca^{2+} plasma level suppresses the PTH secretion. This inhibitory effect is mediated by secondary facilitators - inositol 1,4,5-triphosphate (IF3) and 1,2-diacylglycerine. CaR are found in parathyroid glands cells, in C-cells of the thyroid gland that secrete calcitonin, and also in brain and kidney cells. C-terminal fragments provide the anabolic effect on bone tissue [Ermolenko, 2009; Ketteler, 2011]. Normally, PTH and its fragments are excreted by kidneys and metabolized in cells of terminal tubules. Parathyroid gland produces both the complete PTH molecules, and their fragments. Complete molecules are subject to faster plasma elimination compared to C-terminal fragments. GFR decrease and metabolism disorders associated with CKD result in accumulation of C-terminal fragments in plasma. Intact PTH and its fragments can't be determined by I generation PTH tests; their results reflect the levels of inactive fragments. Recently, immuno-radiometry with double kit of antibodies to N-terminal and C-terminal epitopes has been introduced to measure the iPTH level. CKD IV-V is associated with iPTH level increase mostly due to hyper-secretion. iPTH hyper-secretion is promoted by P_i level elevation and decrease of serum Ca^{2+} level in extracellular fluid. iPTH interacts with membrane adenylatecyclase-bound receptor in proximal and distal renal tubules and causes phosphaturia, hypophosphatemia and enhances calcium reabsorption in distal renal tubules [Kestenbaum, 2005; Marchais, 1999; Lederer, 2011; Slinin, 2005]. Simultaneously, iPTH stimulates $1,25(\text{OH})_2\text{D}_3$ synthesis in renal parenchyma. The decrease of bone tissue sensitivity to iPTH-mediated calcemia is found at initial GFR decrease ($<85 \text{ ml/min/1.73 m}^2$). It does not regress during treatment. The same effect is found in many recipients of kidney grafts with decreased function (GFR under $70 \text{ ml/min/1.73 m}^2$) or in patients with acute renal failure. Acute renal failure is usually associated with hypocalcemia. It manifests during the oliguric stage and is present throughout the polyuric stage. Hypocalcemia regresses after the renal function normalization. Skeletal resistance to iPTH calcemic effect is associated with vitamin D3 deficiency and down-regulation of iPTH receptors. PTH effects osteogenesis through activation of osteoblasts while bone resorption is mediated through activation of osteoclasts.

However, osteoclasts have no PTH receptors, therefore, their stimulation is mediated by release of cytokines by osteoblasts. In experiments, the stimulation of osteoclast-mediated bone resorption by PTH was found in cell cultures containing both osteoclasts and osteoblasts [Block, 2007; Lederer, 2011; Marchais, 1999]. Cytokines IGF-1, IL-6, G-CSF mediate proliferation and differentiation of osteoclasts progenitor cells. Large multi-nuclear osteoclasts are formed. They start secreting organic acids and hydrolytic enzymes that dissolve the mineral matrix and organic substance of bone tissue. This process results in release of phosphorus, calcium and bicarbonate to extra-cellular fluid. Osteoblasts produce organic components (mostly - type I collagen); however, iPTH-mediated activation of resorption processes is more pronounced compared to activation of bone synthesis. As hypocalcemia develops, PTH removes calcium from bone tissue in order to maintain its constant level in extra-cellular fluid. Even mild elevation of iPTH level results in activation of mature osteoclasts and bone tissue resorption [Block, 1998; Kestenbaum, 2005; Lederer, 2011; Marchais, 1999; Slinin, 2005].

3.3.2 Calcitonin

Calcitonin is secreted by the inter-follicular cells of thyroid gland. In 30% patients with terminal CKD elevated plasma level of calcitonin is found. Calcitonin provides phosphaturic effect by inhibiting the phosphates reabsorption in proximal convoluted tubules and enhances the activity of 1α -hydroxylase by stimulating the production of $1,25(\text{OH})_2\text{D}_3$. Calcitonin decreases the Ca^{2+} serum and extra-cellular fluid levels, reduces the number of osteoclasts and suppresses their activity, and inhibits the process of osteolysis [Ermolenko, 2009; Lederer, 2011].

3.4 Vitamin D3 deficiency

Calcitriol (1,25-dihydroxycholecalciferol) is formed from vitamin D₃ (cholecalciferol) as a result of hydroxylation (addition of the OH group) to position 25 (in liver) or to position 1 (in proximal convoluted tubules of kidneys); the hydroxylation process is mediated by α 1-hydroxylase. In kidneys calcitriol induces Ca^{2+} and Pi reabsorption. In small intestine calcitriol enhances the production of calcium-binding protein that enhances Ca^{2+} absorption. In bone tissue calcitriol stimulates pre-osteoclasts proliferation and differentiation. Calcitriol induces the synthesis of organic bone matrix and regulates the process of bone tissue mineralization [Craver, 2007; Liu, 2006; Quarles, 2008]. In patients with CKD III relative deficiency of $1,25(\text{OH})_2\text{D}_3$ is found. When the GFR falls below 50 ml/min/1.73 m² (in children) or 30 ml/min/1.73 m² (in adults) relative deficiency is followed by absolute calcitriol deficiency [Craver, 2007; Liu, 2006; Zemchencov, 2009]. CKD progression is associated with the decrease of vitamin D receptors (VDR) and Ca-receptors of parathyroid gland that is associated with decreased sensitivity to effects of $1,25(\text{OH})_2\text{D}_3$ and Ca^{2+} . Patients with CKD IV-V have low $1,25(\text{OH})_2\text{D}_3$ plasma level, associated with renal hydroxylation process disorders. Such patients develop $1,25(\text{OH})_2\text{D}_3$ deficiency and are resistant to its effect. In patients with removed kidneys and patients receiving dialysis usually the plasma level of $1,25(\text{OH})_2\text{D}_3$ can't be detected by standard analyses. Low plasma level of 25-hydroxy vitamin D [$25(\text{OH})\text{D}_3$] is found in CKD patients with nephrotic proteinuria due to $25(\text{OH})\text{D}_3$ losses with urine, in patients receiving peritoneal dialysis - due to PTH diffusion into peritoneal solution and in patients with low dietary uptake of vitamin D. Limited dietary uptake of phosphorus associated with decreased GFR in CKD patients results in elevated plasma $1,25(\text{OH})_2\text{D}_3$ level and enhanced response of target organs to

calcitriol effect. Calcitriol inhibits the activity of PTH through direct effect on PTH gene. It inhibits gene transcription and PTH synthesis and stimulates the sensitivity of calcium receptors in parathyroid cells. The results of experiments prove that calcitriol deficiency can initiate secondary hyperparathyroidism even without hypocalcemia. Calcitriol deficiency results in calcium intestinal absorption disorders and suppression of calcemia effect on iPTH. Hypocalcemia results in hyperparathyroidism [Ketteler,2011; Lederer, 2011; Liu ,2006; Zemchencov , 2009].

3.5 CKD-associated ectopic mineralization

Several authors consider CKD-associated hyperphosphatemia to be a special syndrome associated with specific bone remodeling, heterotopic mineralization and cardiovascular complications [Ermolenko, 2009; Hruska, 2008; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003, KDIGO,2009; Zemchencov, 2009].

In patients with CKD and hyperphosphatemia the rate of arterial hypertension and mean blood pressure levels are significantly higher compared to patients with normal plasma level of phosphorus. These conditions are associated with vascular adaptation system disorders; therefore, high blood pressure can result in significant mechanical loading and loss of arterial wall elasticity [London, 2000; Parfey, 2000]. Direct statistically significant correlation between high $Ca \times P$ index (over $70 \text{ mg}^2/\text{dl}^2$) and the rate of hypertrophic cardiomyopathy [Block ,1998; Kestenbaum ,2005; Marchais,1999; Slinin, 2005] has been demonstrated. Hypertrophic cardiomyopathy along with myocardial ischemia are the main reasons of congestive heart failure in patients with CKD. Moreover, high phosphorus levels promote non-atherosclerotic arterial calcification associated with vascular smooth muscles cells (VSMC) transformation into osteogenous phenotype [Lederer, 2011; Shanahan C, 1994]. CKD-associated hyperphosphatemia development is also associated with bone tissue remodeling. CKD patients have a broad spectrum of bone remodeling; however they have similar features – excessive bone tissue resorption compared to formation. The experimental data prove that hyperphosphatemia is associated with block of phosphate reservoir function of bone tissue [National kidney Foundation; K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; Shanahan C,1994; Volgina, 2004]. However, the requirement of phosphorus in bone tissue increases. It results in phosphorus plasma level elevation. Soft tissues and blood vessels become new phosphorus reservoirs. Formation of phosphorus reservoirs in the walls of arteries result in their higher rigidity [Lederer, 2011; London,2000, National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO,2009; Parfey,2000; Zemchencov, 2009].

Recent studies have demonstrated that CKD patients with hyperphosphatemia ($>6.5 \text{ mg/dl}$) have a higher risk of cardiovascular mortality compared to patients with lower phosphorus levels ($<6.5 \text{ mg/dl}$). Therefore, maintenance of serum phosphorus level within $<6.5 \text{ mg/dl}$ limit seems to be an important therapeutic objective in these patients [Davies , 2003, 2005; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO,2009; Pletcher,2004; Wang,2006].

Two types of vascular calcification are typical for CKD: calcification of atherosclerotic neo-intimal plaques (intima calcification) and arterial tunica media calcification (media calcification) [London, 2000; Wang, 2006]. Both types of vascular calcification progress along with advancing CKD. Coronary arteries intimal calcification is the risk factor for of

myocardial infarction [London, 2000; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO, 2009]. In CKD patients the calcification of media is characterized by extensive diffuse lesions (atherosclerosis of Moenkenberg). It results in coronary damage with acute coronary syndrome development, ectopic calcification of large arteries with pulse wave speed increase. It is manifested by increased systolic and pulse pressure and rapid left ventricle hypertrophy [Davies, 2005; London, 2000; Pletcher, 2004; Townsend, 2011; Wang, 2006]. Heart calcification is manifested mostly by coronary arteries and heart valves calcinosis. They result in mitral valve failure or stenosis, arrhythmias, congestive heart failure; however, diffuse myocardial calcification can develop [London, 2000; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO,2009].

Blood vessels calcification risk factors:

- Increased plasma levels of calcium and phosphorus
- $\text{Ca}^{2+} \times \text{P}^{5+}$ over $55 \text{ mg}^2/\text{dl}^2$ ($5,5 \text{ mmol}^2/\text{l}^2$)
- Elevated plasma level of iPTH
- Fetuin A protein deficiency

Blood vessels calcification compromises the formation of arterio-venous fistula and complicates kidney transplantation.

Arteries of forearm, wrists, hands, lower extremities, abdominal cavity, thoracic cavity, pelvis and brain can undergo calcification [Ermolenko, 2009; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003, Zemchencov, 2009].

Some patients develop severe vascular calcification so that the arteries can't be pressed by the cuff during blood pressure measurement [London, 2000; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; Townsend, 2011].

Electronic beam tomography is used to evaluate the calcium content in blood vessel walls [Davies, 2005; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO,2009; Wang, 2006].

The mechanisms of CKD-associated extra-osseous calcification are complicated and multifactorial. It has been demonstrated that VSMC and other vascular cells (pericytes, fibroblasts) can transform into osteoblast-like cells that produce hydroxy-apatite - the main mineral of bone tissue. In case of hyperphosphatemia smooth muscles of blood vessels accumulate phosphorus, express the genes of bone proteins and turn into areas of calcification [Nishimura, 2011; Shanahan,1994; Wang, 2006].

Parathyroid gland hypertrophy in CKD patients contributes to severity of cardiovascular complications. It participates in development of myocardial fibrosis. iPTH elevates Ca^{2+} loading in cells and enhances the atherosclerotic changes. It also activates fibroblasts and provides direct impact on myocardium through myocardial cells metabolism disorders [Nishimura, 2011; Wang, 2006].

Myocardial fibrosis, coronary calcification and valves calcification promote the development and progression of systolic dysfunction and congestive heart failure. Left ventricle hypertrophy and increased Ca^{2+} level in myocardial cells result in diastolic dysfunction. These disorders are the main cause of cardiovascular mortality in CKD patients [London, 2000; Lederer, 2011; Nishimura, 2011; Pletcher,2004; Wang, 2006].

Hypoxia-induced 1- α factor (HIF1- α) and vascular endothelium growth factor are the main mediator of osteogenesis – angiogenesis interaction. It is considered that these factors induce vascular calcification through angiogenous signaling [Wang, 2006].

The initial stage of arterial media calcification is associated with elastin degradation. Matrix metalloproteinases (MMP-2 and MMP-9) destroy elastin with formation of soluble elastin peptides. The latter bind to laminin-elastin receptors (ELR) on the surface of smooth muscles cells. Excessive expression of growth factor β (TGF- β) contributes to elastin destruction also. It is known that it enhances VSMC calcification rate and plays an important role in proliferation of osteoblasts. VSMC osteogenous transformation is activated by consecutive signaling of ELR, TGF- β , and mitogen-activated protein kinase. Calcification of media is associated with expression of several proteins related to osteogenesis: osteocalcin, osteopontin, matrix γ -GLA (carboxyglutamic acid) protein and osteoprotegerin [Isakova, 2008; KDIGO,2009; Wang, 2006; Zemchencov, 2009].

3.5.1 Relationship between osteogenesis and ectopic mineralization

The relationships between osteogenesis and blood vessels calcification has been established. New factors produced by kidneys and bone tissues have been identified recently. The morphogenetic proteins (FGF-23 and Klotho) regulate homeostasis of phosphates, vitamin D and bone tissue mineralization. The level FGF-23 (fibroblasts growth factor 23, produced mostly by osteocytes) is increased even at the pre-dialysis stage of CKD [Gutiérrez, 2009; Jean, 2009; Pande, 2006; Razzaque 2008, 2009; Zemchencov, 2009].

The role of circulating FGF-23 level increase at various CKD stages is being studied. It has been established that enhanced production of FGF-23 during CKD stages II-III contributes to adaptive increase of phosphorus excretion and decrease of calcitriol production [Boekel, 2008; Carpenter, 2005; Fang, 2001; Gutierrez, 2005, 2008; Kawata, 2007].

Later, when the CKD IV-V results in GFR decrease, the elevated FGF-23 level is not enough to prevent hyperphosphatemia and hyperparathyroidism. Prospective studies [Gutiérrez, 2009; Jean, 2009; Pande, 2006; Razzaque, 2009] demonstrate that elevated FGF-23 level in CKD patients at the stage of dialysis initiation is associated with mortality and vascular calcification independent of other risk factors or serum phosphorus and iPTH levels. Therefore, FGF-23 is the potential independent uremic toxin (Table 2).

There are 2 types of Klotho protein – trans-membraneous and extra-cellular (secreted). It is produced and secreted by the cells of proximal renal tubules; the trans-membraneous protein is also produced by the parathyroid gland cells [Makoto, 2009; Sitara, 2006].

Makoto K demonstrated that trans-membraneous Klotho protein is a co-receptor of FGF-23 and therefore contributes to regulation of phosphorus, calcium and vitamin D turnover. Extra-cellular part of Klotho protein that is secreted to systemic circulation acts as an endocrine factor and encodes multiple growth factors, including insulin-like growth factor 1 and Wnt [Makoto, 2009].

In CKD patients the expression rate of Klotho protein is decreased; therefore, it is considered to be the factor of renal protection. It is obvious that phosphorus turnover regulation is an important link of CKD pathogenesis. Early correction of hyperphosphatemia by influencing the endocrine interactions of the bones-kidneys-parathyroid glands axis mediated by Klotho and FGF-23 improves the quality of life in CKD patients [Boekel, 2008; Carpenter, 2005; Fang, 2001; Gutiérrez, 2005, 2008, 2009; Jean, 2009; Kawata, 2007; Pande, 2006; Razzaque 2008, 2009]. In CKD patients the FGF-23 serum level elevation precedes hyperphosphatemia; therefore, resistance to FGF-23 can be one of the early signs of CKD-related metabolic disorders. It is

considered that development of resistance to FGF-23 is associated with decreased renal expression of Klotho protein. Therefore, low rate of renal expression of Klotho protein can be a prediction of poor long-term outcome in dialysis patients [Makoto , 2009].

Authors	Study results
Razzaque M.S. [NDT 2009; 24(1): 4-7]	Meta-analysis (10 studies). Most CKD patients demonstrated FGF-23 elevation prior to phosphorus level increase. In dialysis patients low level of trans-membraneous Klotho expression in renal cells was associated with poor cardiovascular prognosis
Gutierrez O.M. <i>N Engl J Med</i> 2008; 359(6): 584 - 592	10 044 CKD patients, stage V. FGF-23 plasma level increase at initial stage of dialysis was associated with a dose-related 1-year lethality increase. Lethality hazard ratio (OR = 5.7) was higher compared to hazard ratio for high phosphorus levels (OR = 1.2).
Jean G et al <i>NDT</i> 2009; 24(9); 2618-2620	219 CKD stage V patients. FGF-23 level elevation (median 2740 RU/ml) at initial stages of dialysis was associated with cardiovascular lethality not related to risk factors and plasma phosphorus levels
Gutierrez O.M. <i>Circulation</i> . 2009; 119(19): 2545-2552	162 CKD stage III-IV. Multivariate regressive analysis demonstrated correlation of serum FGF-23 elevation and left ventricle infarction (11% annual increase) or risk of coronaries calcification (2.4 fold increase)

Table 2. Relationship between elevated FGF-23 plasma level and poor CKD prognosis (results of prospective studies)

FGF-23 level decreases along with the decline of hyperphosphatemia; therefore, low phosphate diet and phosphate binders seems to be an appropriate treatment strategy beginning from early CKD stages. These measures prevent the cardiovascular complications and secondary hyperparathyroidism in CKD patients. CKD patients demonstrate fasting FGF-23 level elevation, even without hyperphosphatemia and hypocalcemia. It is not clear yet, which CKD stage is associated with initial FGF-23 serum level increase; however, it is considered that FGF-23 hyper-production precedes plasma phosphorus and iPTH levels increase [Gutiérrez,2009; Pande , 2006; Razzaque 2008, 2009].

In most clinical studies plasma phosphorus, calcium, FGF-23 and iPTH levels were measured in fasting conditions. However, at early CKD stages without hyperphosphatemia and hypocalcemia plasma FGF-23 and iPTH levels are increased after meals. Urine excretion rate of phosphorus increase after meals was found in 13 CKD patients with normal fasting phosphorus and calcium levels and in 21 healthy volunteers despite normal plasma levels of phosphorus and FGF-23. Increased postprandial urine excretion of calcium was found in both groups; in CKD patients it was associated with significant calcium level decrease and elevation of iPTH plasma level. Therefore, FGF-23 does not impact the postprandial phosphaturia both in healthy volunteers and in CKD patients; however, CKD patients developed postprandial transient calciuria associated with relative hypocalcemia. This effect might reflect early stages of secondary hyperparathyroidism development [Craver ,2007; Razzaque ,2008].

Recent studies demonstrate poor value of fasting iPTH evaluation in early diagnosing of secondary hyperparathyroidism; while assessment of FGF-23 plasma level (both fasting and postprandial) might be used as a sensitive screening test for secondary hyperparathyroidism development [Pande ,2006; Razzaque ,2009].

FGF-23 Elisa kit is used to evaluate FGF-23 serum level. Anti-Klotho polyclonal antibodies are used to evaluate Klotho levels in serum, spinal fluid, and urine. FGF-23/Klotho ratio in proximal renal tubules is assessed by immune-histochemical analysis [Gutiérrez,2009; Razzaque ,2009].

Therefore, in CKD patients phosphorus and calcium turnover disorders with hyperphosphatemia, vascular calcification, left ventricle hypertrophy are also mediated by newly discovered regulation mechanisms - Klotho and FGF-23. These effects are important risk factors of cardiovascular complications that are the cause of significant lethality rate in such patients.

3.5.2 Ectopic mineralization inhibitors

Calcification inhibitors deficiency is an important factor of arterial calcification development.

Matrix γ -Carboxyglutamic Acid Protein – MGP is a protein produced in bone tissue. It blocks the osteo-chondrocytous trans-differentiation of vascular smooth muscles cells into osteoblast-like cells. MGP also prevents the formation of crystallization areas in vascular tunica media and atherosclerotic plaques. It regulates the synthesis of skeletal matrix [Craver, 2007; London, 2000; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; Zemchencov,2009].

Osteopontin – acidic protein that is being expressed in arterial calcification areas. It activates osteoblasts and inhibits hydroxyl-apatite formation. Osteopontin enters the crystallization loci and inhibits their formation [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; Zemchencov,2009].

Osteoprotegerin – is expressed in atherosclerotic plaques and tunica media calcification loci. Osteoprotegerin inhibits the process of osteoclasts differentiation and the activity of bone alkaline phosphatase isoenzyme. Therefore, it hampers the process of tunica media and atherosclerotic plaques [Zemchencov,2009].

Protein α_2 Heremans-Schmid (Phetuin) – is a calcium-binding protein mostly produced in liver. Uremia is associated with significant decrease of this protein's level. Experimental studies demonstrated that phetuin A binding results in vascular calcification. It is stored in smooth muscles and prevents their transformation into osteoblast-like cells [Zemchencov,2009].

Pyrophosphates suppress the osteo-chondrogenous trans-differentiation of vascular smooth muscles cells and formation of hydroxyl-apatite crystals. They are synthesized from nucleotide-triphosphates; the synthesis process is mediated by nucleotide-pyrophosphatase. In CKD patients the levels of nucleotide-pyrophosphatase and pyrophosphates carrier in tunica media are decreased. IGF-1 and N3 fatty acids inhibit the differentiation of vascular smooth muscles cells into osteoblast-like cells and tunica media calcification also [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; Zemchencov,2009].

3.5.3 Ectopic mineralization stimulators

Hyper-phosphatemia causes the induction of osteoblastic differentiation factors - Cbfa1/Runx2, osteocalcin and sodium-dependent phosphate co-transporter type III – Pit-1.

Pit-1 expression is stimulated by high levels of extra-cellular calcium. Matrix vesicles and bone matrix proteins are secreted into the peri-vascular space; further they are subject to mineralization [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO,2009; Zemchencov,2009].

3.6 Uremic toxins

Uremic toxins cause the expression of Cbfa1/Runx2, osteopontin, bone AP isoenzyme and osteoprotegrin independently of phosphorus levels. They enhance the secretion of bone morphogenesis protein (BMP-2) by vascular smooth muscles cells and stimulate their mineralization. As renal failure progresses, new factors are added to arterial calcification process [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO,2009; Moe , 2003; Sitara, 2003].

3.7 Oxidation stress and inflammation

Uremic intoxication is associated with oxidation stress and systemic inflammation. The latter one jeopardizes oxidation stress, typical for uremia. Formation of oxidants contributes to high oxidation rate of lipoproteins that enhance the transformation of vascular smooth muscle cells into osteoblast-like ones. VSMC osteoblastic transformation is stimulated by glucocorticosteroids, leptin and hyperglycemia [KDIGO,2009].

3.8 Vitamin D metabolism disorders

Vitamin D has been reported to contribute to regulation of VSMC activity and metabolism. Vascular smooth muscle cells express 1α -hydroxylase to convert $25(\text{OH})\text{D}_3$ into $1,25(\text{OH})_2\text{D}_3$; they also express vitamin D receptors (VDR). Calcitriol stimulates the VDR expression on smooth muscle cells. VDR is the factor of smooth muscles proliferation and differentiation. Depending on plasma levels, calcitriol can both stimulate and inhibit the proliferation of vascular smooth muscles cells. Calcitriol levels 10^{-7} - 10^{-10} M stimulates vascular calcification in a dose-dependent way by increasing the ratio "nuclear factor receptor activator/osteoprotegrin".

In CKD experimental models calcitriol analogues (paricalcitol and doxercalciferol) caused lesser vascular calcification compared to similar doses of calcitriol. Unlike calcitriol, paricalcitol didn't cause any increase of Cbfa1/Runx2 and osteocalcin expression rate. Doses of calcitriol and its analogues used in doses sufficient for iPTH hyper-production suppression prevented vascular calcification; however, higher doses of the drugs stimulated calcification [Craver ,2007; Finch,2010; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; Zemchencov, 2009].

Study with 520 CKD patients (median follow-up 21 years) with mean GFR 30 ml/min/1,73 m² demonstrated that calcitriol treatment was associated with lethality rate decrease. Similar study demonstrated comparable results [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003].

Therefore, recent studies demonstrated that in CKD patients high doses of calcitriol and its analogues can stimulate vascular calcification, while their moderate doses provide a protective effect through type I collagen and promoter gene core-binding factor- α 1 (Cbfa1)

production inhibition. Collagen type I is the basis for calcium deposits, while Cbfa1 stimulates the production of type I collagen [Finch,2010; Moe , 2003; Sitara ,2003].

3.9 Clinical manifestations of soft tissues calcification

Metastatic calcification is found in patients with secondary hyperparathyroidism and with adynamic skeletal diseases susceptible to hypercalcemia due to inability of bone tissue to accept surplus calcium. Hyperphosphatemia with elevated $\text{Ca}^{2+} \times \text{P}^{5+}$ index ($>55 \text{ mg}^2/\text{dl}^2$ or $4,5\text{--}5,5 \text{ mmol}^2/\text{l}^2$), dialysis-associated alkalosis and local tissue damage promote formation of calcium phosphate deposits in soft tissues [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO,2009; Zemchencov,2009].

Soft tissues and vascular calcifications contain hydroxyl-apatite crystals with Ca: Mg: P ratio similar to bone; amorphous micro-crystals of calcium, magnesium and phosphates ($\text{CaMg}_3(\text{PO}_4)_2$) are found in muscles, heart and lungs. It is considered that the variability of calcification depends on local tissue factors - hydrogen ions, magnesium, calcium and phosphorus levels. Formation of hydroxy-apatite crystals is associated with significant fibrosis; while formation of amorphous crystals doesn't result in fibrosis [Ermolenko, 2009; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003].

Formation of phosphorus and calcium salts deposits in skin results in severe itching that is resolved only after parathyroidectomy [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003, KDIGO,2009; Zemchencov,2009].

Skin calcification. Calcium salts deposits in skin are associated with formation of maculae and vesicles containing solid structures. Calcium salts crystals can be found at biopsy. After subtotal parathyroidectomy skin deposits of calcium salts undergo regression; therefore, secondary hyperparathyroidism is the leading factor of skin calcification [Craver, 2007; Zemchencov, 2009].

Formation of skin ulcers and tissue necrosis (calciphylaxis). This syndrome was described by Seyle in 1962; the author named it calciphylaxia. Recently, most authors prefer the name calcifying uremic arteriopathy. This clinical syndrome is characterized by progressing skin ischemia, affecting fingers of hands and feet, hips and ankles. It develops in patients receiving dialysis on a regular basis for 10 years and more. It is less frequent in patients receiving peritoneal dialysis. The syndrome is characterized by vascular calcification and sub-periosteum bone resorption. Painful erythematous subcutaneous vesicles or blue maculae are followed by ulceration or necrosis. Reynaud's syndrome can precede the affection of fingers of hands and feet. Ulcers develop slowly (for several months) or fast (within several weeks). Concomitant infections can result in fatal sepsis [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003, KDIGO,2009; Zemchencov,2009].

The treatment strategy is not established yet. Local treatment is ineffective; in most patients subtotal parathyroidectomy resulted in calciphylaxia regression, however, in some patients skin lesions persisted or even progressed.

Mineral metabolism disorders with secondary hyperparathyroidism and vascular calcification, local tissue lesions, obesity (especially in white females), vitamin C deficiency predispose to development of this syndrome. Vitamin C deficiency in CKD patients was reported to result in hyper coagulation; therefore vascular occlusions and tissue necrosis

occur. However, administration of warfarin results in progression of skin lesions in these patients. Local tissue lesions at insulin, heparin or dextran administration sites are usual locations of ulceration or skin necrosis [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO,2009].

Calcification of eyes. Conjunctiva and corneal calcium deposits associated with vascular inflammation result in “red eyes” syndrome. This transient process recurs as new conjunctiva calcium deposits are formed [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003].

Conjunctiva deposits of calcium salts can be symptoms-free. In such cases they are found during ophthalmologic examination. Calcium salts deposits are represented by white plaques or small dot-like deposits on lateral or medial segments of the conjunctiva. They are also found on cornea or lateral/medial segments of eye border (band-like keratopathy). Calcium deposits in eye blood vessels result in local pH increase due to CO₂ loss through the conjunctiva surface [Zemchencov,2009].

Visceral calcification. Usually calcium salts deposits are found in lungs, stomach, heart, skeletal muscles and kidneys. Usually calcifications can't be determined by standard X-ray; however, they are found during isotope scanning with ^{99m}Tc - pyrophosphate. Calcifications of lungs and heart can result in severe or fatal complications. Cases of pulmonary calcifications resulting in severe pulmonary fibrosis, pulmonary hypertension and left ventricle hypertrophy have been reported. Heart and lungs calcifications are one of the main causes of morbidity and mortality in dialysis patients [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003 , Zemchencov, 2009; Huang Chou-Long, 2010].

High level of dietary vitamin C that is being metabolized into oxalates can result in calcium oxalate deposits formation in soft tissues, heart, mitral and aortal valves, resulting in cardiomyopathy and fatal heart failure [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003;KDIGO,2009].

Peri-articular calcification. Calcium salts deposits formation in peri-articular space results in limited mobility and tendovaginitis. Affected joints contain transparent synovial with normal viscosity and cell counts [Darry ,2008; Masuyama,2006; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003;KDIGO,2009]. This acute condition is called calcifying peri-arthritis. Uric acid salts are also found in the peri-articular tissues (secondary gout). This condition is often associated with chondro-calcinosis. Pseudo-gout is diagnosed when pyro-phosphate crystals are found in synovial cells. The study including 135 dialysis patients demonstrated the increase of peri-articular calcification rate from 9 to 42% from dialysis year 1 to dialysis year 8 [Zemchencov,2009].

Some dialysis patients develop large tumor-like formations in the peri-articular regions. They contain encapsulated lime fluid and soft calcium-based substance. Usually these formations are painless; however, their size can limit the mobility of the joint. Tumor-like calcium deposits can regress if serum phosphorus is adequately controlled by phosphorus binders or after subtotal parathyroidectomy [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; Zemchencov,2009].

4. Prevention and treatment of CKD associated phosphorus and calcium metabolism disorders

4.1 Diet and phosphate binders

Low phosphate diet and/or phosphate binders are considered to be an important therapeutic approach targeted to prevent life-threatening complications in CKD patients. According to K/DOQI Practical Clinical Recommendations, daily phosphorus uptake should be limited to 800-1000 mg (adjusted by requirement in protein) in CKD III-IV patients with serum phosphorus level over 4.6 mg/dl (1.49 mmol/l) and over 5.5 mg/dl (1.78 mmol/l) in dialysis patients or in patients with plasma iPTH level exceeding normal limits established for corresponding CKD stages [Craver, 2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003]. If dietary phosphorus limitations are insufficient to control phosphorus and iPTH levels, phosphate binders are recommended [Moore, 2010; Wang, 2006]. Long-term administration of calcium-based phosphate binders can result in hypercalcemia. Calcium carbonate - associated hypercalcemia is found 3.5 fold more frequent compared to calcium acetate associated hypercalcemia because calcium carbonate interacts with phosphorus at pH 5.0, when its dissolution rate is decreased [Ketteler, 2011; Zemchencov, 2009]. Calcium - based phosphate binders decrease the serum phosphorus level effectively and can be used for initial phosphate-binding treatment. Total daily dose of elementary dietary calcium should be within 1.5 g/day [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003]. Calcium based phosphate binders should not be used in dialysis patients with hypercalcemia (adjusted total serum calcium level over 10.2 mg/dl or 2.54 mmol/l) and in patients with plasma PTH level under 130 pg/ml (14.4 pmol/l) as measured by 2 consequent analyses [Craver, 2007; Moore, 2010; KDIGO, 2009]. Calcium-free phosphate binders should be used in these patients. At present, sevelamer hydrochloride (renagel) is widely used in clinical setting for binding of dietary phosphates. Renagel is synthetic calcium- and hydroxyl-aluminum free drug. It is not absorbed in gastro-intestinal tract. The drug decreases plasma levels of iPTH, phosphorus and Ca×P index; it also corrects the dyslipidemia [Craver, 2007; KDIGO, 2009]. The drug administration does not result in calciemia, therefore its combinations with active vitamin D analogues are safe. Renagel is effective for control of vascular and soft tissues calcification. Renagel is indicated for to patients with elevated serum phosphorus level and total adjusted calcium level over 5.5 and 10.2 mg/dl, respectively, and iPTH level decrease under 130 pg/ml and metastatic calcification [Craver, 2007; KDIGO, 2009]. Long-term Renagel administration can result in decrease of furosemide's diuretic effect and hypochloremic acidosis associated with bicarbonates loss [Craver, 2007; Block, 2010; Reddy, 2009]. Table 3 represents the pattern of sevelamer hydrochloride dosage choice based on serum phosphorus level.

Serum phosphorus level	Sevelamer hydrochloride dosage (800 mg tablets)
6-7,5 mg/dl (1,94-2,42 mmol/l)	1 tablet × 3 times per day
> 7,5 mg/dl (2,42 mmol/l)	2 tablets × 3 times per day

Table 3. Sevelamer hydrochloride dosage choice based on serum phosphorus level

Equivalent doses of sevelamer hydrochloride (calculated in mg/kg) are used for transfer from calcium-based phosphate binders. Sevelamer hydrochloride dosage is 800 tablet per

one meal [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO,2009]. In USA and Europe lactane (Fosrenol) carbonate is used for phosphate binding in gastro-intestinal tract. 500, 750 and 1000 mg Fosrenol tablets are available. Treatment course continues until normal phosphorus level is reached (1.13 - 1.78 mmol/l; 3.5 - 5.5 mg/dl). Maximum daily dosage - 3750 mg (for short-term treatment - 5-7 days). However, lactane is subject to partial absorption and can accumulate in bone tissue [Craver ,2007; Moore, 2010]. At present sevelamer carbonate and Zerenex phosphate binder, containing inorganic iron compounds are being studied. Preliminary data indicate similar efficacy to calcium salts [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; Volgina, 2004].

In patients receiving peritoneal dialysis phosphorus elimination rate can be increased by replacement of cellulose acetate membranes by poly-sulfone membranes or by switching to hemodiafiltration with higher phosphorus clearance compared to dialysis. Enhanced blood flow in the hemodialysis apparatus results in increased creatinine clearance; however, it does not change the phosphorus elimination rate. On the other hand, dialysis prolongation (transfer from 3 times per week regimen to daily dialysis) results in 30% decrease of the pre-dialysis serum phosphorus level and enables reduction of phosphate binders administration frequency [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003]. In patients receiving peritoneal dialysis frequent exchange of dialysis solution in peritoneal cavity results in higher creatinine and phosphorus clearance. Total adjusted plasma calcium level should be maintained within normal limits (8.4 - 9.5 mg/dl or 2.1 - 2.37 mmol/l) [1]. In dialysis patients receiving calcium-based phosphate binders and active vitamin D metabolites dose reduction or drug withdrawal is recommended when the total adjusted calcium serum level exceeds 10.2 mg/dl (2.54 mmol/l). Dosages should be suspended until total adjusted serum calcium level returns to normal. If these measures are ineffective, dialysis fluid with low calcium level (1.5 - 2.9 mEq/l) should be used for 3-4 weeks. Phosphorus-calcium ratio should be kept under 55 mg²/dl². This can be achieved through serum phosphorus level maintenance within the target limits [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003, Volgina, 2004].

Hyperphosphatemia control enables FGF-23 level decrease in CKD patients. Elevated FGF-23 serum level is associated with higher mortality rate in patients with terminal CKD. The possibility of using neutralizing antibodies for excessive FGF-23 production control is under discussion. However, the clinical benefit of this method is not clear yet [Yamazaki ,2008].

Hypocalcemia treatment should include oral calcium salts - e.g., calcium carbonate and/or vitamin D active metabolites [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003].

4.2 Vitamin D active metabolites

When iPTH plasma level exceeds the target limits established for corresponding CKD stage and the 25(OH)D₃ level is under 30 ng/ml, treatment with vitamin D₂ should be initiated. It is considered, that at early CKD stages ergocalciferol is safer compared to calciferol [Craver, 2007; Moore,2010; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003, Volgina, 2004]. Dose adjustment should be based on the rate of 25(OH)D₃ deficiency. If the 25(OH)D₃ level is

under 15 ng/ml (37 nmol/l), 50 000 IU/week × 4 weeks ergocalciferol dosage regimen should be used; later the 50 000 IU/month × 4 months regimen is used. If 25(OH)D₃ serum level is 20-30 ng/ml (50-75 nmol/l), 50 000 IU × 1 month treatment regimen should be used for 6 months [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO,2009]. Treatment with vitamin D is recommended for patients with pre-dialysis stages of CKD with a normal 25(OH)D₃ levels (over 30 ng/ml or 75 nmol/l) and decreased plasma level of as adjusted total calcium, elevated serum iPTH level and normal serum phosphorus level. Active vitamin D metabolites (calcitriol, alpha-calcidol or doxercalciferol) are more effective for iPTH synthesis and secretion suppression [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO,2009; Volgina, 2004]. Lower initial dosages are recommended (see Table 4).

iPTH plasma level, pg/ml [pmol/l]	Serum level		Calcitriol or alpha- calcidol, orally	Doxercalciferol, orally
	Ca, mg/dl [mmol/l]	P, mg/dl [mmol/l]		
> 70 [7,7] (CKD III) or > 110 [12,1] (CKD IV)	< 9,5 [2,37]	< 4,6 [1,49]	0,25 mcg/day	2,5 mcg 3 times per week

Table 4. Serum iPTH, adjusted total calcium and phosphorus levels requiring vitamin D active metabolites. Initial doses for patients with CKD stages III - IV

Calcitriol dosage should be within 0.5 mcg/day, except for cases, when the adjusted total calcium level increase is under 0.2-0.3 mg/dl/month. [Craver ,2007; Moore,2010; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003 KDIGO, 2009;]. Treatment with active vitamin D metabolites should be conducted only in patients with adjusted total calcium serum level under 9.5 mg/dl (2.37 mmol/l) and serum phosphorus level under 4,6 mg/dl (1.49 mmol/l) [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO,2009; Zemchencov,2009]. Patients receiving hemodialysis or peritoneal dialysis with serum iPTH level over 300 pg/ml (33.0 pmol/l) should receive active vitamin D metabolites (e.g., calcitriol, alpha-calciferol, paricalcitol, doxercalciferol, see Table 5) in order to decrease serum iPTH level up to target level 130–300 pg/ml (14,4–33,0 pmol/l) [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003, KDIGO,2009; Volgina, 2004].

In patients receiving peritoneal dialysis oral calcitriol or doxercalciferol dosages are 0.5-1.0 and 2.5-5.0 mcg 2-3 times per week, respectively [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003;KDIGO,2009]. Alternative regimen of oral calcitriol is 0.25 mcg daily [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003; KDIGO,2009]. During the initial stage of active vitamin D metabolites or during the dosage increase period serum phosphorus and calcium levels should be monitored each 2 weeks throughout the first month; monthly monitoring is recommended later [Craver ,2007; National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003;KDIGO,2009].

iPTH, pg/ml [pmol/l]	Ca, mg/dl [mmol/l]	P, mg/dl [mmol/l]	Ca-P	Calcitriol	Paricalcitol	Doxecalciferol
300-600 [33-66]	< 9,5 [2,37]	< 5,5 [1,78]	< 55	0,5-1,5 mcg, i/v 0,5-1,5 mcg orally	2,0-5,0 mcg, i/v	5 mcg, orally 2 mcg, i/v
600-1000 [66-110]	< 9,5 [2,37]	< 5,5 [1,78]	< 55	1,0-3,0 mcg, i/v 1,0-4,0 mcg, orally	6,0-10,0 mcg, i/v	5-10 mcg, orally 2-4 mcg, i/v
> 1000 [110]	<10 [2,5]	< 5,5 [1,78]	< 55	3,0-5,0 mcg, i/v 3,0-7,0 mcg, orally	10,0-15,0 mcg, i/v	10-20 mcg, orally 4-8 mcg, i/v

Table 5. Recommended initial doses of active vitamin D metabolites – based on iPTH, phosphorus and calcium serum levels and Ca×P index in patients receiving dialysis

In most patients effective suppression of iPTH secretion results in recovery of parathyroid glands hyperplasia [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003]. High concentrations of 1,25(OH)₂D₃ stimulate apoptosis of parathyroid gland cells [Craver ,2007; Moore,2010]. This effect is used for “drug parathyroidectomy”, when 1,25(OH)₂D₃ is injected into the hyperplastic parathyroid glands [National kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003, Volgina, 2004]. Paricalcitol, or 1,25(OH)₂D₂ is effective for iPTH suppression. Paricalcitol is selective active vitamin D metabolite with modified lateral chain (D2) and A ring (19-nor). Paricalcitol (Zemplar) selectively induces VDR (S-VDRA) gene expression in parathyroid glands, suppresses iPTH secretion without activation of intestinal VDR. The drug has no effect on bone resorption, therefore, it causes hypercalcemia less frequently compared to non-selective active vitamin D metabolites. Unlike calcimimetics, paricalcitol possesses significant pleiotropic effects that provide the decrease of cardiovascular complications risk and inhibit CKD progress (anti-proteinuria effect). The anti-proteinuria effect of paricalcitol has been demonstrated in 3 double blind randomized placebo-controlled studies enrolling 220 patients with CKD III-IV and hyperparathyroidism [Ermolenko, 2009]. By the end of week 24, proteinuria level decrease was demonstrated in 51% of patients receiving paricalcitol and in 25% of patients from placebo group (p = 0.004). PTH level 30% decrease was found in 91% of patients receiving paricalcitol compared to 13% of patients in placebo group (p<0,001). Decreased level of intact PTH <110 pg/ml was found in 75% of patients from paricalcitol group and in 12% of patients from placebo group [KDIGO,2009]. Our study that enrolled 50 CKD III-IV patients with systemic diseases (35 patients – lupus erythematosus, 15 patients – different types of vasculites) had similar results. Patients were randomized in 2 groups; calcitriol 0.35 mcg/day was used in Group 1, paricalcitol 1 mcg/day – in Group 2. Prior to treatment, proteinuria levels were 1.2 +/- 0.6 g/day in Group 1 and 1.3 +/- 0.4 in Group 2; iPTH levels were 75 +/- 17.4 pg/ml and 80 +/- 16.6 pg/ml, respectively. Calcinosi/s/atherosclerosis of carotids was found in 27.3% of patients in Group 1 and in 33.3% of patients in Group 2. Calcitriol and paricalcitol were generally well tolerated. As a result, iPTH plasma levels reached normal levels after 3 months of treatment

in patients with elevated iPTH levels at baseline. In patients receiving paricalcitol, proteinuria level decrease occurred faster ($p < 0.05$) and the arterial hypertension decrease by the end of Month 3 was more pronounced ($p < 0.01$) compared to patients receiving calcitriol. In 4 of 12 patients from Group 2 with diagnosed atherosclerosis/calcinosis, no episodes of hypercalcemia or signs of atherosclerosis/calcinosis were reported. Hypercalcemia episodes were reported in 27.3% of patients receiving calcitriol; progressing of atherosclerosis/calcinosis diagnosed at baseline was reported in 3 patients [Milovanova, 2011].

Paricalcitol is manufactured as 1, 2 and 4 mcg capsules or 1 ml (5 mcg) ampoules. Capsules are indicated for treatment and prophylaxis of secondary hyperparathyroidism associated with CKD III, IV and V; ampoules are indicated to patients with CKD V. In patients receiving peritoneal dialysis, the drug should be administered through slow intravenous injections (minimum duration - 30 seconds) in order to minimize the infusion-associated pains. Recommended initial dose of paricalcitol is 0.04 - 0.1 mcg/kg. Paricalcitol dose choice depends on baseline iPTH level: initial dose (mcg) = iPTH (pg/ml)/80. The drug is administered as bolus injections; within at least 1 day after dialysis. Paricalcitol capsules are administered once per day, every day or 3 times per week [KDIGO,2009]. The results of 3 prospective randomized multicenter studies demonstrate that paricalcitol effectively suppresses iPTH secretion, decreases the activity of bone AP isoenzyme and decreases the plasma level of osteocalcin. These effects are indicative of bone resorption rate decrease [Moore, 2010].

In patients with CKD III-IV with iPTH plasma level over 70 pg/ml (7.7 pmol/l) and 110 pg/ml (12.1 pmol/l) receiving low phosphorus diet, paricalcitol, calcitriol, alpha-calcidol or doxercalciferol are recommended for treatment and prophylaxis of bone disease (see Table 5) [KDIGO,2009]. In patients with CKD V and iPTH plasma level over 300 pg/ml (33.0 pmol/l) with renal osteodystrophy paricalcitol, calcitriol, doxercalciferol and alpha-calcidol are recommended to suppress the excessive iPTH secretion and normalize the elevated metabolic profile of bone tissue [Craver, 2007;KDIGO,2009; Slinin,2005].

5. Summary

Phosphorus metabolism disorders play an important role in CKD pathogenesis. Therefore, early control of hyperphosphatemia is required to improve the quality of life in CKD patients. Numerous cohort studies have shown associations between disorders of mineral metabolism, cardiovascular disease and mortality. These observational studies have broadened the focus of CKD-related mineral and bone disorders to include cardiovascular disease (which is the leading cause of death in patients at all stages of CKD). All three of these processes (abnormal mineral metabolism, abnormal bone and extra skeletal calcification) are closely interrelated and together make a major contribution to the morbidity and mortality of patients with CKD. Mechanisms of CKD-associated extra-osseal calcification are complicated and multi-factorial. Recently, new mediators of osteogenesis-angiogenesis interactions have been identified - they are hypoxia - induced factor 1- α (HIF1- α) and vascular endothelium growth factor (VEGF). These factors induce vascular calcification through angiogenous signaling. New factors produced by kidneys and bone tissue have been identified. They are morphogenetic proteins (FGF-23 and Klotho) that contribute to phosphorus and vitamin D turnover and bone mineralization regulation. It has been suggested that resistance to FGF-23 is one of the early manifestations of CKD-associated metabolic disorders. This effect is mediated through decreased renal expression

of Klotho. It has been reported that calcitriol and paricalcitol increase the rate of Klotho expression in kidneys. The possibility to use anti-FGF neutralizing antibodies to control FGF-23 hyperproduction is under discussion. However, further studies are required to evaluate their effects related to the system of complicated interactions between bone tissue, kidneys and parathyroid glands.

5.1 Recommendations for further research

Further research is needed to determine the reference values of corrected total serum calcium levels, depending on age, sex and race of patients with CKD and dialysis patients. Also, research is needed to determine the adequate calcium intake, the timing of the therapy with calcium and used calcium supplement drugs.

Very interesting is the new vitamin D metabolites testing, which are less likely to cause hypercalcemia. The ideal aim of such trials is to reduce serum IPTG levels with an insignificant change in serum calcium concentration. It would be useful to evaluate the relationship between serum IPTG levels and histological stage of hyperparathyroid bone disease in relation to the degree of renal failure progression.

Regulation of the IPTG level is a complex task. Need to find an acceptable balance between adequate levels of IPTG, accompanied by no bone lesions, and prevention of accelerated calcinosis / atherosclerosis

It is needed to carry out long-term studies evaluating the efficacy, side effects and impact on morbidity and mortality of various phosphate-binding drugs. Although the recently completed studies have demonstrated the benefits of sevelamer compared with calcium phosphate binders in prevention of aortic and coronary artery calcification progression in patients with CKD stage 4, research evaluating a positive impact on cardiovascular morbidity and mortality in dialysis patients is needed.

The next perspectives of controlled clinical trials in nephrology are associated primarily with the cooperation of medical, educational and scientific centers, including online, on the basis of professional social organizations. This interaction can intensify the integration of nephrologists in international clinical research, to organize the original clinical research on common standards (Good Clinical Practice, Good Research Practice), involving the maximum number of nephrology, outpatient and inpatient treatment centers.

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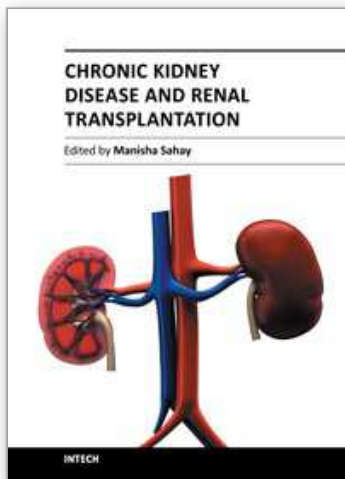
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