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# CAUSES OF THE INCREASED CARDIOVASCULAR RISK IN CHRONIC KIDNEY DISEASE

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**Abstract.** The article is devoted to the problem of the increased cardiovascular risk in chronic kidney disease. It reviews the role of hypercalcemia, hyperphosphatemia, secondary hyperparathyroidism, fibroblast growth factor 23, Klotho, and dyslipidemia in the increased risk of cardiovascular events in chronic kidney disease, and discusses features of their correction.

**Keywords:** chronic kidney disease, cardiovascular risk, mineral and bone disorders, calcification of blood vessels, dyslipidemia.

## Background

Chronic kidney disease (CKD) is one of the most important health care problems. Given the global increase in the incidence of the leading causes of CKD, as, for example, diabetes, hypertension, and obesity, the widespread increase in number of patients with CKD has become a kind of "silent epidemic". Due to the long asymptomatic course of the disease, CKD usually requires a long period of time to declare itself, becoming an accidental "laboratory finding" when performing diagnostics on some other complaints of a patient. This is a joyless situation, because early detection of a kidney disease, based on proteinuria and/or reduction of glomerular filtration rate (GFR), may allow an early start of nephroprotective therapy aimed at slowing down progression of the disease. In recent years, more and more researchers were attracted to the question of the relationship between cardiovascular mortality and the functional status of kidneys.

For the total population aged 45-74 years, the decrease in GFR less than 60 ml/min is considered as an independent risk factor for the overall and cardiovascular-associated mortality, as well as for the acute myocardial infarction (Smirnov, 2005). According to the research conducted amongst 1,120,295 people of the U.S. adult population who had not undergone renal replacement therapy, the risk of death from any cause increased by 17% when GFR reached the level of 45-59 ml/min/1.73 $m^2$ of body-surface area, and with an estimated GFR less than 15 ml/min/1.73 $m^2$ there was observed almost 600% increase in death risk. The same results were obtained concerning the risk of all cardiovascular events: 43% of increase was observed with an estimated GFR of 45 to 59 ml/min/1.73 $m^2$ and 343% of increase – with GFR estimated less than 15 ml/min/1.73 $m^2$. In this study it was found that the decrease in GFR was significantly associated with an increased risk of death, cardiovascular events, regardless of known risk factors and the presence or absence of a history of cardiovascular disease. According to the NHANES II survey, an estimated GFR of less than 70 ml/min/1.73 $m^2$ was associated with a 68% increase in the risk of death from any cause and a 51% increase in the risk of death from cardiovascular causes, as compared with an estimated GFR of at least 90 ml/min/1.73 $m^2$ (Go, 2004). Another study, conducted in Hoorn (Denmark), showed that the risk of cardiovascular mortality among patients from 50 to 75 years old was increased by 26% as GFR reduced per 5 ml/min (Smirnov, 2005).

The development of acute coronary syndrome in persons with moderate decrease in GFR < 70 ml/min is associated with a higher incidence of mortality and re-infarction at 30-day and 180-day observations (Smirnov, 2005). The risk of sudden death is 100 times more common in patients with CKD compared with the general population (Stenvinkel, 2010). Despite recent advances in the technology of dialysis solutions and membranes, annual mortality in dialysis patients is more than 20% and cardiovascular mortality, on average, is 10-30 times higher than in the general population, with particularly high growth rates among young adults (Smirnov, 2005; Efstratiadis, 2007; Tomasello, 2008). In Russia, according to the Moscow registry of patients with end-stage kidney disease (ESRD), during the period of 1995-2000 the rates of mortality from cardiovascular causes in the group of dialysis patients was 45.5% and in the group of patients receiving treatment by the method of peritoneal dialysis it was 42.3% (Tomilina, 2003). In addition, cardiovascular complications remain the leading cause of death after successful kidney transplantation, accounting for 36% of mortality. In recipients with a functioning graft, coronary artery disease is diagnosed 15-20 times more often than in the general population, although after kidney transplantation a twofold reduction in the incidence of cardiovascular events is observed (Tomilina, 2003). What are the reasons for the increased risk of cardiovascular events in CKD?

## The role of mineral and bone disorders (MBD)

In 2009 the new guidelines for the diagnosis and treatment of mineral and bone disorders in chronic kidney disease were published (KDIGO CKD-MBD, 2009), where mineral metabolism disorders affecting bone and cardiovascular system, calcification of blood vessels and heart valves, making a significant contribution to the overall mortality of patients with CKD-MBD, are considered.

The progressive loss of the nephron mass in CKD leads to decreased production of calcitriol (active form of vitamin D, 1,25-dihydroxyvitamin D) and development of imbalances in serum calcium and phosphorus levels. Epidemiological studies have revealed a direct correlation between serum level of calcium and phosphorus, and mortality in dialysis patients. Multifactorial hyperphosphatemia and hypercalcemia, that consequently develop, a compensatory increase of the fibroblast growth factor 23 (FGF23) level, resistance to parathyroid hormone (PTH) with subsequent reduction in activation threshold and expression level of receptors (VDR, Sa-SR, FGF-23/Klotho), along with other factors contributing excessive synthesis and secretion of PTH – all these events ultimately bring to the development of secondary hyperparathyroidism and various forms of renal osteodystrophy. These changes associated with CKD may extend beyond the previously established framework of disorders of mineral metabolism at the bone level.

**Vessel calcification**

Calcification of blood vessels is a frequent complication in patients with end-stage chronic renal failure (CRF), and since it contributes to high mortality rate among these patients, its pathogenesis, clinic and possible therapeutic effects determines the high interest of investigators and clinicians. Attention to the problem of vascular calcification can be noted since the first days of hemodialysis introduction. In 1976, by radiological study of patients with severe renal insufficiency a 30 % incidence of vascular calcification was shown in the age group of 15-30 years and more than 50% – in the age group of 40-50 years. Autopsy conducted in the period 1969 - 1977 also revealed extensive calcification of soft tissues and blood vessels in 50-80% of patients on hemodialysis (Efstratiadis, 2007).

Calcification of the coronary arteries is a common finding in dialysis patients, where its incidence is 2-5 times higher compared to patients with angiographically confirmed coronary heart disease but normal renal function. According to the study conducted by Goodman et al., in young patients on hemodialysis (mean age from 20 to 30 years) coronary calcification was observed in a greater proportion of cases and was associated with hyperphosphatemia. In another study, in patients undergoing hemodialysis (in age from 19 to 39 years) calcification of the coronary arteries was detected in more than 90% of cases (Efstratiadis, 2007).

Traditional risk factors vessel calcification include: age, male gender, diabetes mellitus, obesity, hypertension, smoking, stress, dyslipidemia, sedentary lifestyle. Facotrs associated with uremia include: duration of dialysis, anemia, hyperhomocysteinemia, mineral and bone disorders (including hyperphosphatemia, changes in the metabolism of vitamin D, hyperparathyroidism, elevated levels of FGF-23), dyselectrolytemia, oxidative stress, hypoalbuminemia, chronic inflammation, increased expression of osteogenic factors (nuclear binding factor alpha-1, runt-related transcription factor -2), decrease in the expression of fetuin (Volgina, 2012b; Scarpioni, 2010).

The risk factors for cardiovascular calcification in patients with CKD can be divided into 4 groups (Volgina, 2012b): genetic, clinical (age, diabetes mellitus, ischemic heart disease, the degree of decrease in renal function, duration of dialysis, pathology of bone tissue); biochemical (hyperphosphatemia, hypercalcemia, increased levels of FGF-23, hyperparathyroidism, osteogenic factors, oxidative stress, increased levels of aldosterone); medication (taking calcium-containing drugs, warfarin, high doses of vitamin D).

Elevation of calcium and phosphate serum concentration leads to the growth of apatite crystals both through passive precipitation and by activation of cellular and tissue mechanisms of calcification. High content of phosphorus in serum (> 6.5 mg/DL) is associated with increased risk of coronary disorder and sudden death (Volgina, 2012b; Milovanova, 2011). Under the influence of hyperphosphatemia and as a consequence of an increased flow of phosphate, vascular smooth muscle cells transform to osteosarcoma phenotype. Cells with osteoblastogenesis phenotype lose the ability to express contractile proteins, but initiate the expression of proteins that usually participate in bone metabolism (osteocalcin (OS), osteopontin (OPN), matrix GLA protein (MGP) and osteoprotegerin (OPG)). Appearance of intracellular matrix vesicles containing calcium and

phosphorus, mineralization of nuclei indicate eventual apoptosis of vascular smooth muscle cells. Assessment of the contribution of a certain risk factor in the development of cardiovascular complications is a difficult task because in most cases, each patient exhibits a combination of factors.

Vascular calcification is a multistep process, at the initial stage involving differentiation of vascular mesenchymal cells to osteoblast-like cells. The main transcriptional activator of this differentiation process is Cbfα1/Runx2 (Volgina, 2012b; Zemchenkov, 2009; Efstratiadis, 2007). Other mechanisms of vascular calcification are related to the deficiency of inhibitors of ectopic osteochondromas mineralization, namely fibroblast growth factor 23 (FGF-23), Klotho, M-GLA-protein, OPN, OPG, fetuin-A.

FGF-23 is a protein with a molecular mass of 32 kDa and the half-life of 58 minutes, consisting of 251 amino acids, synthesized in osteoblasts and osteoclasts in response to hyperphosphatemia and calcitriol (Zemchenkov, 2009; Shutov, 2012). FGF23 selectively reduces the reabsorption of phosphorus in the kidneys, providing suppressive effect on the expression of co-transporters type IIa and IIc (NaPiIIa and NaPiIIc), in fact, being post-adolescent hormone, and reduces the intake of phosphate from the intestine by reducing the concentration of calcitriol (Dobronravov, 2011; Shutov, 2012). The effect of FGF23 is mediated via a receptor complex consisting of native FGF-receptor (FGF1c) and co-receptor Klotho, expressed in the kidney and PSG.

Klotho is a transmembrane β-glucuronidase with a molecular mass of 130 kDa, named after one of the three Greek goddesses of fate, spinning the thread of life and determining its duration. It was found that Klotho is involved in the mechanisms of aging, and its level decreases significantly with age (Scarpioni, 2010). Mice with knocked-out Klotho exhibit quick senescence, rapid development of atherosclerosis and calcification (Shutov, 2012). FGF23-defecient mice were also characterized by heavy calcification of blood vessels and soft tissues.

MGP (matrix γ-carboxyglutamate protein) is a 10 kDa protein, originally isolated from bone tissue, containing 5 γ-carboxyglutamic acid (GLA) residues. MGP inhibits activity of bone morphogenetic protein BMP-2, which is involved in bone transformation of vascular smooth muscle cells. MGP is co-localized with crystals of calcium and prevents their growth (Zemchenkov, 2009; Efstratiadis, 2007).

Fetuin-A is a crucial system inhibitor of calcification, functioning as a calcium-binding protein and being able to form a complex with GLA-protein. Fetuin-A is produced mainly in the liver and is secreted to the plasma at high levels. In fetuin-A knock-out mice, extended extraosseous calcification was observed under hypercalcaemic conditions (Zemchenkov, 2009; Efstratiadis, 2007). In patients with ESRD serum fetuin-A levels are significantly reduced. The systemic blood concentration of fetuin A decreases during inflammation in patients under dialysis, and correlates inversely with the level of C-reactive protein (Efstratiadis, 2007).

Osteoprotegerin (OPG) is a member of the tumor necrosis factor family, regulating the process of bone resorption mainly due to its ability to function as a trap for RANKL-receptor and to affect the activity of osteoclasts. OPG is produced by various tissues, including cardiovascular system, lungs, kidneys, and immune system. Experimentally it was proved that the OPG-null mice develop severe osteoporosis and calcification of the media of arteries. In patients under dialysis, the level of OPG significantly increased, in contrast to patients without renal dysfunction. Also it has been proved that serum OPG levels correlate with the severity of coronary calcification and represent an independent risk factor for progression of atherosclerosis (Zemchenkov, 2009; Milovanova, 2011; Efstratiadis, 2007). Osteopontin (OPN) is an acidic phosphoprotein that is expressed in mineralized tissues and inhibits the formation of hydroxyapatite.

Low levels of calcitriol are correlated with an increased risk of vascular calcification. The vascular smooth muscle cells have receptors for vitamin D (VDR) and 1-alpha-hydroxylase to 25-(OH)-vitamin D. Calcitriol enhances the expression of VDR, a well-known factor of proliferation and differentiation for vascular smooth muscle cells, and also induces the expression of local

inhibitor of calcification - ARF. Calcitriol can stimulate calcification of the vessels by increasing the ratio of RANKL/OPG (Zemchenkov, 2009).

The role of PTH as a cause of medial calcification remains uncertain. In the study of G. Coen et al., it was demonstrated that higher levels of intact PTH in hemodialysis patients are correlated with greater calcification of the coronary arteries, and a low level iPTH was not associated with severity of coronary calcification (Go, 2004). According to other studies, it was found that low levels of PTH are associated with the development of calcification of blood vessels and soft tissues (Zemchenkov, 2009; Efstratiadis, 2007). These data indicate that vascular calcification in CKD and related adverse effects are not a passive process due to simple saturation of serum calcium and phosphate, but are an active process, in many aspects resembling osteogenesis occurring under the influence of the imbalance between promoters and inhibitors of calcification.

Anatomically one can distinguish four types of vascular deposition of calcium: atherosclerotic/fibrous calcification, medial calcification of the arteries, calcification of the heart valves and vascular calciphylaxis (Efstratiadis, 2007).

Arterial calcification is represented by two different models: the calcification of the inner lining (intima), closely associated with the atherosclerotic process, and the average shell - medial calcification, characterized by diffuse calcification of the media, especially at the level of the internal elastic lamina, which is often observed in patients on hemodialysis, especially at a young age, and not always accompanied by atherosclerosis.

Intimal calcification is usually associated with the development of acute complications as a result of occlusion of the vessel lumen on the background of the rupture of the plaque and the development of thrombotic complications. Mediasclerosis is generally asymptomatic, causing vessel reocclusion, however, it may lead to reduction of vascular elasticity, increase in stiffness clinically defined as elevated velocity of propagation of pulse wave, systolic blood pressure (pseudohypertension), hypertrophy of the left ventricle, impaired coronary perfusion and the development of heart failure (Volgina, 2012b; Zemchenkov, 2009; Efstratiadis, 2007).

In patients with uremia, calcification of the media is the predominant histological form, at least among younger patients. However, given the fact that chronic uremia occurs in atherogenic environment, often two types of calcification occur at the same time in the same patient (Volgina, 2012b; Efstratiadis, 2007). Calcification may involve the arteries of the forearm, leading to the difficulty in formation of arteriovenous fistula, wrists, hands, abdomen, lower extremities, pelvis, chest, and brain. Calcification of blood vessels can be so pronounced that it complicates the measurement of blood pressure, due to the lack of opportunities to pinch the vessels of the limb cuff (Volgina, 2012a).

Calciphylaxis or calciphilous uraemic arteriolopathy develops in 2-5% of patients with ESRD (Volgina, 2012b), especially in those receiving long-term dialysis therapies. It appears as severe ischemic skin lesions with formation of necrosis, resulting from calcification of the media of small skin and subcutaneous arterioles, and performs high mortality rates (up to 80%) (Zemchenkov, 2009; National Kidney Foundation, 2003). The established risk factors of calciphylaxis are: female gender, obesity, diabetes, malnutrition and hypoalbuminemia, hypotension, high level of serum calcium and phosphate, deficiency of protein C and S, hypercoagulation, local trauma, warfarin administration. The latter is an supressor of the vitamin K-dependent inhibitor of calcification (GLA-protein) (Zemchenkov, 2009).

The development of visceral calcification is associated with valvular heart disease (from 20 to 47% in patients on dialysis) (Volgina, 2012b), myocardium, kidneys, lungs and other organs. For many years, vascular calcification was considered to be the result of a passive process of deposition of hydroxyapatite crystals due to increased blood levels of calcium and phosphate and was associated with advanced age, atherosclerosis, and rare genetic diseases. However, more recent data support the concept of actively regulated cell-mediated process, reminiscent of mineralization of bone tissue (Volgina, 2012b; Zemchenkov, 2009; Efstratiadis, 2007).

It is important to diagnose mineral and bone disorders as soon as possible, based on laboratory dynamics of vitamin D, iPTH, levels of calcium, phosphate and FGF-23. Abnormalities

in laboratory parameters can occur early, asymptomatically, leading to severe complications. Taking this into account, KDIGO recommends to monitor the levels of calcium, phosphate, parathormone and alkaline phosphatase from as early as stage HBP (1C), and, in patients with CKD 3-5D, the frequency of observations should be based on the severity of the deviation, the rate of progression of CKD, and suggests making decisions regarding therapeutic strategies based on the whole set of indicators but not on single measurement (1C) (KDIGO 2009).

Electron-beam computed tomography (EBCT) and multislice spiral computed tomography (MSCT) are currently the most frequently used methods to assess calcification of the coronary arteries. EBCT is the gold standard for this purpose and is used in most studies on calcification of the heart in uremic patients. The limitation for wide use of EBCT is a relatively high cost and limited availability of this technique, in contrast to the use of MSCT, which is a more affordable method. A reasonable alternative to these methods, according to the KDIGO recommendations in patients with CKD stages 3-5D for detecting the presence or absence of calcification is the use of x-ray abdomen in lateral projection, and to detect the presence or absence of calcification of the valves echocardiography (KDIGO 2009).

**Correction of mineral and bone disorders**

Monitoring of serum phosphate is an important therapeutic task. Dietary restriction of phosphate is often insufficient to maintain serum phosphorus concentrations within the required range and, under dialysis treatment, the restriction of protein food consumption can cause protein-energy malnutrition. In this case, phosphodiesterase drugs can be helpful, reducing the absorption of phosphorus. These drugs may differ in regimes of medication, individual tolerance, calcium load, and price. The purpose of calcium drugs administration is associated with an increased incidence of hypercalcemia and metastatic calcification, especially during concomitant therapy with active metabolites of vitamin D. According to prospective studies, even an application of standard doses is accompanied by an increase in the index of calcification of the coronary arteries (Volgina, 2012a). The alternative is the use of sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, aluminium hydroxide. By binding of nutritional phosphate, sevelamer improves clinical outcomes and performs lipid-lowering effect due to the sorbent characteristics. In the Renagel In New Dialysis (RIND) study, the use of sevelamer appeared more effective in preventing progressive calcification compared with calcium containing drugs (Zemchenkov, 2009; Zemchenkov, 2011). A prospective randomized Treat-to-Goal (TTG) trail revealed a higher incidence of hypercalcemia, as well as increased index of calcification of the coronary arteries and aorta, in patients receiving calcium carbonate compared to individuals receiving sevelamer. In addition, in patients receiving calcium supplementation a significant decrease in mineral density of the thoracic vertebrae was observed. Another prospective randomized study of the Dialysis Clinical Outcomes Revisited (DCOR) showed no difference in the risk of death between patients older than 65 years receiving calcium containing drug or sevelamer (Volgina, 2012; Zemchenkov, 2009). In patients on hemodialysis it is also possible to diminish calcium load by maintaining the concentration of calcium in dialysate at 1.25-1.5 mmol/l. In some cases, improving the efficiency of dialysis therapy (increasing dialysis time/frequency of sessions) can help to eliminate hyperphosphatemia.

Another therapeutic approach related to the prevention/delay of calcification is the control of PTH levels by administration of vitamin D analogues or a combination of calcimimetics and calcitriol. Activation of VDR has an U-shaped effect on calcification: excessively high or low serum levels of calcitriol enhance calcification, and optimal level reduces its risk by inhibiting the production of collagen type 1 (Zemchenkov, 2009; Milovanova, 2011; Shylo, 2012). Vitamin D is widely used for the correction of MBD and quite effective in reducing PTH levels, however, application of non-selective VDR activators is associated with hypercalcemia and hyperphosphatemia due to the increased intestinal absorption of the phosphate, which is correlated with the risk of calcification of the cardiovascular system. Studies have shown that ectopic calcification was detected in 60 % of patients with CKD treating with active metabolites of vitamin D (Scarpioni, 2010). Of selective VDR activators, it is paricalcitol that was able to effectively

reduce the level of PTH in experiments on rats being 10 times less active than calcitriol in its ability to stimulate absorption of calcium from the intestines and mobilization of calcium from bones (Shylo, 2012), or induce expression of Cbfα1/Runx2 and osteocalcin. It exhibits positive influence on cardiovascular system and have pleiotropy effects of VDR activation, mainly by suppressing the activity of the RAAS, as evidenced by the rapidly developing left ventricular hypertrophy and activation of the RAAS in mice with deregulated VDR gene function. Published in 2010, the ADVANCE trail demonstrated decreased rates of progression of vascular calcification under treatment with cinacalcet in combination with low doses of vitamin D. In addition, cinacalcet treatment displayed a strong tendency to decrease the progression of cardiovascular calcification in combination with a significant reduction in the serum levels of PTH, calcium and phosphate (Volgina, 2012a).

Application of sodium thiosulfate solution is also seemed to be a promising approach, as it induces the expression of cystathionine C-LiAZ and increases the production of $H_2S$ by smooth muscle cells of blood vessels. It was found that the hydrogen sulfide decreases deposition of calcium in the extracellular matrix and inhibits the activity of genes involved in osteoblast transformation of smooth muscle cells. It has been affirmed that a reduction in local production of hydrogen sulfide, through inhibition of cystathionine C-LiAZ, leads to increased osteoblastic transformation and mineralization. The low activity of this enzyme, and therefore the reduction of the $H_2S$ level in the plasma were detected in patients with CKD receiving dialysis. Experimentally it was found that $H_2S$ reduces vascular calcification induced by vitamin D in rats (Zavaczki, 2011).

**Disorders of lipid metabolism**

Abnormality of lipid profile in CKD patients, as well as in the general population, is an independent risk factor for coronary atherosclerosis and is found at GFR lower than 50 ml/min (Tomilina, 2003; Scarpioni, 2010). In patients with CKD, the most frequently observed disorders of lipid metabolism are hypertriglyceridemia, elevated concentrations of LDL, VLDL, decreased HDL, but significant changes in total cholesterol are usually not detected (Tomilina, 2003). Dyslipidemia in CKD has a multifactorial nature, different mechanisms of its development are currently known, including proteinuria, decreased lipoprotein-lipase activity and trigliceridos associated with changes in insulin balance, as well as secondary hyperparathyroidism. In addition, ESRD occurs when the deficiency of calcitriol leads to disruption of atherogenesis-inhibitory processes (Tomilina, 2003; Scarpioni, 2010). Achieving an optimal level of lipid profile in patients with CKD gives an advantage in view of reduced cardiovascular risk and prevention of renal dysfunction based on pleotropic effects of statins, namely anti-inflammatory, antiproliferative activity, ability to decrease expression of endothelial adhesion molecules, markers of oxidative stress, and proinflammatory factors. Given the clinical benefits of statins in primary and secondary prevention of cardiovascular events in a population of patients without CKD, similar advantages can be assumed in patients with renal dysfunction (Scarpioni, 2010).

Two major trials have been conducted on the use of statins in patients on hemodialysis – 4D (Die Deutsche Diabetes Dialyse Study) and AURORA. In 4D study 1,255 patients with diabetes receiving dialysis were treated with 20 mg of atorvastatin or placebo. Despite effective reduction in LDL within 4 weeks, this study showed no significant reduction in mortality from cardiac causes. In patients receiving statins, the risk of death from cardiovascular events was reduced by 18%, but not with relation to cerebrovascular events and total mortality. In addition, an unexpectedly higher level of death from stroke was observed. A negative result of 4D trial was a surprise. The study showed a low incidence of side effects of atorvastatin at a dose of 20 mg per day in patients with CKD, with no cases of rhabdomyolysis or hepatic. In 4D the majority of deaths were due to sudden death, not associated with coronary heart disease, i.e., atherosclerosis, showing no potential protective role of statins. The number of deaths associated with cardiovascular events was 35% (Scarpioni, 2010). The AURORA trial involved 2,776 patients aged 50-80 years, receiving hemodialysis, randomly devided into two groups – those receiving rosuvastatin at a dose of 10 mg/day, or placebo. The average period of observation was 3.8 years, during which, despite the decrease of LDL by 43 % in

the group receiving the treatment compared with 1.9% decrease in the placebo group, rosuvastatin did not reduce deaths from cardiovascular causes.

Both studies, AURORA and 4 D, showed no successful effect of statin therapy in patients undergoing hemodialysis. The authors of these trials suggested that cardiovascular events in patients on dialysis differ from the general population and proceed in a completely "different scenario", in which atherosclerosis plays a minor role (Scarpioni, 2010). The SHARP study has shown that patients with impaired kidney function are suitable for treatment with statins in order to reduce the cardiovascular risk. The combination of ezetimibe and simvastatin in predialytic patients reduced the risk of cardiovascular events by 16%.

**Conclusion**

Thus, at present, the scientific interest to the problems of CKD complications has shifted to disorders of mineral and bone metabolism and connection of MBD with the development of cardiovascular impairments and possible impacts on potentially modifiable risk factors for these complications. Assessment of the contribution of each of the risk factors to the development of cardiovascular complications is challenging because in most cases a patient presents a combination of factors. In order to influence the risk of caridovascular events in patients with CKD it is necessary to affect all the modifiable risk factors.

Taking into account the data from prospective studies showing that increased levels of FGF-23 at the start of dialysis in patients with CKD are associated with mortality and vascular calcification independently of established risk factors and iPTH level (Volgina, 2012a), targeting of FGF-23 could be a promising therapeutic aproach and could improve the prognosis for patients with CKD.

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