ISSN 1607-419X
ISSN 2411-8524 (Online)
УДК 616.61:616.1

Systemic disorders of inorganic phosphate exchange as a novel cluster of cardiovascular risk factors

V. A. Dobronravov

First Pavlov State Medical University of St. Petersburg, St Petersburg, Russia

Corresponding author:
Vladimir A. Dobronravov,
First Pavlov State Medical University of St Petersburg, Research Institute of Nephrology, 17 L. Tolstoy street, St Petersburg, 197022 Russia.
Phone: +7(812)234–66–56.
E-mail: dobronravov@nephrolog.ru

Received 01 November 2014;
accepted 10 November 2014.

Abstract

Recent studies have clearly linked higher serum inorganic phosphate (Pi) concentrations and an imbalance of Pi-regulation by kidney-bone-parathyroid endocrine systems to cardiovascular events and mortality. This association has been identified in patients with chronic kidney disease, as well as in general population. The editorial discusses the available clinical and experimental data linking the pathophysiology of phosphate exchange disorders and cardiovascular events.

Key words: inorganic phosphate, chronic kidney disease, cardiovascular diseases, cardiovascular risks

For citation: Dobronravov VA. Systemic disorders of inorganic phosphate exchange as a novel cluster of cardiovascular risk factors. Arterial Hypertension = Arterial'naya Gipertenziya. 2014;20(6):478–491.

Нарушения системного обмена неорганического фосфата как новый кластер кардиоваскулярных рисков

В. А. Добронравов

Государственное бюджетное образовательное учреждение высшего профессионального образования «Первый Санкт-Петербургский государственный медицинский университет имени академика И. П. Павлова» Министерства здравоохранения Российской Федерации, Санкт-Петербург, Россия

Контактная информация:
Добронравов Владимир Александрович, ГБОУ ВПО ПСПбГМУ им. И.П. Павлова Минздрава России, научно-исследовательский институт нефрологии, ул. Л. Толстого, д. 17, Санкт-Петербург, Россия, 197022.
Тел.: +7(812)234–66–56.
E-mail: dobronravov@nephrolog.ru

Статья поступила в редакцию 01.11.14 и принята к печати 10.11.14.

Резюме

Исследования последней декады показали отчетливую связь между уровнем неорганического фосфата (Pi) сыворотки крови, а также нарушением баланса эндокринных систем почек, паращитовидных желез и костей, регулирующих обмен Pi, с сердечно-сосудистыми событиями и смертностью. Данные связи продемонстрированы для пациентов с хронической болезнью почек и для общей популяции. В передовой статье обсуждаются клинические и экспериментальные данные, объединяющие патофизиологию нарушений обмена Pi и развитие изменений в сердечно-сосудистой системе.

Ключевые слова: неорганический фосфат, хроническая болезнь почек, изменения сердечно-сосудистой системы, сердечно-сосудистые риски

Для цитирования: Добронравов В.А. Нарушения системного обмена неорганического фосфата как новый кластер кардиоваскулярных рисков. Артериальная гипертензия. 2014;20(6):478–491.

Introduction

Available data provides the evidence of a bidirectional link between renal dysfunction and cardiovascular changes. On the one hand, the kidneys are the target organ in terms of traditional cardiovascular risk factors; on the other hand, the organ damage is one of the mechanisms of the development and progression of cardiovascular disease (CVD) [1–4]. These ideas have been recently implemented in clinical practice at the national and international levels, and chronic kidney disease (CKD) is recognized as an independent risk factor for cardiovascular mortality [2, 5]. Mechanisms for accelerated development and progression of changes in cardiovascular system are determined by a variety of alterations of excretory and non-excretory kidney functions leading to the occurrence of other (non-traditional) cardiovascular risk factors [6].

CKD is a condition associated with the altered mineral metabolism involving the retention of inorganic phosphate (Pi) as a key factor. Pi is an essential component of cell metabolism, and an increase in its tissue content has a wide range of negative biological effects [7–9]. Experimental and clinical models of reduction of glomerular filtration rate (GFR) are widely used to study systemic Pi imbalance, because the kidney is a major way of Pi elimination. Moreover, the kidneys play an important role in paracrine/endocrine regulation of Pi metabolism, being the major site for production of Pi metabolism regulating factors,

i. e. calcitriol and protein α-Klotho (Klotho). The organ changes developed at the backgprund of Pi imbalancewith or without renal dysfunction are phenotypically similar to premature aging, and might be considered for modeling, in particular, in studies of the effects on cardiovascular system.

Accumulation of Pi can occur even at mild initial decline in GFR, especially in case of excessive nutritional consumption and its endocrine regulation imbalance. Therefore, not only patients with renal diseases, but also individuals with initial GFR decline without overt signs of renal dysfunction are target population regarding this problem [1, 2]. Pi accumulation is characterized by long-term subclinical course and is not accompanied by an increase in blood Pi level until the end-stage renal failure onset. According to conventional concept, it due to the adaptation of phosphate-regulating systems, enhancement of the effects of phosphaturic factors (phosphotonines) on the kidneys, and the reduction in the intestinal absorption of this anion. In addition, adaptive regulation of the Pi balance in reduced urinary excretion is provided by its rapid transition from circulation to the bones and soft tissues, where it accumulates intracellularly and in the matrix. Hyperphosphatemia, on one side, represents a threatening reduction of urinary excretion, and on the other side, a decline in the Pi "buffer capacity" of peripheral tissues, that is usually observed in patients with evident vascular calcification and bone metabolism disorders.

Phosphate and cardiovascular risk

Increase in serum Pi is associated with clinical and subclinical manifestations of cardiovascular disease in patients with and without renal pathology: calcification of blood vessels and valves, myocardial hypertrophy, accelerated atherogenesis, cardiovascular morbidity and mortality. Vascular calcification is a very significant risk factor for cardiovascular events and mortality in patients with and without renal dysfunction [7–15]. Among individuals with CKD (non-hemodialysis patients), increased arterial stiffness, calcification of blood vessels and heart valves are associated with higher serum Pi levels [16–20]. In the Multi-Ethnic Study of Atherosclerosis, an increase in risk of coronary heart disease (CHD) by 21 % (p = 0,002) and of valvular calcification by 25–62 % was associated with the elevation of Pi concentration by 1 mg/dL in patients without clinical manifestations of CVD and moderate decrease in GFR [21].

Similar links were found in populations without renal disease in a number of large-scale studies, which involved the evaluation of the main cardiovascular risk and other contributing factors. In patients without obvious CKD, increased serum Pi level, even within the "normal laboratory reference range" (< 4,5 mg/dL) was an independent predictor of arterial wall thickening and vascular calcification [20]. In a prospective study of Coronary Artery Risk Development in Young Adults (CARDIA), there was a 52 % increase in the risk of coronary artery calcification in young patients with serum Pi levels more than 3.9 mg/dL after 15 years of follow-up (compared to 3.3 mg/dL) [22]. The National Health and Nutrition Examination Survey showed a 5-fold increase in risk of peripheral arteries stiffening, assessed by shoulder-ankle index, in patients with normal renal function and the highest circulating Pi level [23]. A recent meta-analysis (24 studies, n = 147 634) showed that elevated serum Pi level in patients without CKD or a significant decrease in GFR is associated with an increase in cardiovascular and total mortality [24]. Previously it had been demonstrated in patients with overt renal dysfunction (47 studies, n = 327 644) [25].

Left ventricular hypertrophy (LVH) is a significant and common risk factor for cardiovascular events and mortality in patients with and without CKD [26–29]. In dialysis patients, high serum Pi is associated with LVH [29, 30], and extracorporeal Pi elimination leads to its involution [31]. According to the recently published papers, there is a potential link between higher nutritional consumption of Pi and LVH in individuals without renal disease [32].

A number of studies demonstrate the relationship between the increase in Pi serum level and nonfatal cardiovascular events in individuals with and without kidney disease. In patients with predialysis and dialysis CKD stages and higher Pi concentrations, the incidence of cardiovascular events and hospitalization rate are higher. In a large study, involving dialysis patients (n > 54000), the risk of cardiovascular events increased progressively with the increasing Pi level (by 25 % in patients with Pi level within the top quintile) [33–35]. Similar connections were found in patients with predialysis CKD stages: an increase in Pi by 1 mg/dL was associated with the increased risk of acute myocardial infarction by 35 % (95 % confidence interval 9–66 %), in 3490 patients with CKD stages 3–4 (GFR < 45 ml/min), regardless of the traditional cardiovascular and renal risk factors [7].

Similar figures were found in patients without evident chronic renal dysfunction [36–38]. In the Framingham Offspring Study, 3368 participants with GFR ≥ 60 ml/min at baseline, with no clinical signs of cardiovascular disease were followed-up. Pi level

> 3.5 mg/dl was associated with the increased risk of cardiovascular disease by 55% (compared to Pi level < 2.8 mg/dL) [37]. In the Cholesterol and Recurrent Events Study (CARE, n = 4159), patients with CHD, GFR > 60 mL/min and serum Pi > 4.0 mg/dl demonstrated higher risk of myocardial infarction, heart failure and death by 50, 43 and 27%, respectively, compared to the patients who Pi within the range 2.5–3.4 mg/dl [36, 39].

Along with Pi, calcium (Ca) plays a key role in vascular calcification, which is based on Ca mineral hydroxyapatite. Obviously, a number of studies showed a strong relation between calcification, cardiovascular dysfunction or mortality, on the one hand, and an increase in calcium levels (even within the normal range) and calcium-phosphate product. It was found both in dialysis patients [34, 40] and in general population [41]. Thus, in a cohort of patients with stable CHD without apparent kidney dysfunction increased calcium serum level up to the upper quartile was associated with the 2.4-fold increase in the relative mortality risk [41]. Although data on the possible impact of dietary calcium on cardiovascular mortality and morbidity are contradictory [42–45], the latest meta-analysis including 11 prospective studies (n = 757 304), showed that nutritional consumption of calcium in doses higher than 1 g/day is associated with the increased cardiovascular mortality [46]. Its an important counter plea for the widespread prescription of calcium supplements and requires more careful analysis of the potential risks of their widespread use, for example, for osteoporosis prevention [47].

Central aspects of the pathophysiology of cardiovascular disorders in impaired Pi metabolism: paracrine dysregulation

Impaired renal excretion of Pi is not accompanied by an increase in its blood concentration. Obviously, it results from the adaptive regulation of Pi, and bones and soft tissues play a buffering role. Among the latter, arterial wall is the most vulnerable part, and clinical manifestations of soft tissue calcification are the most widespread and severe in arteries. Importantly, the processes of calcification can occur at normal Ca and Pi plasma levels, remaining till terminal renal failure develops. The total pool of Pi increases in case of excessive intestinal absorption, renal retention or its release from the bones. Abrupt transition of Pi from blood to the tissues leads to a consistent local increase in its levels in the extra- and intracellular space. Na-Pi co-transporters type 3 — Pit-1 and Pit-2 — mediate the enhancement of Pi transport into cells in case of the expansion of systemic Pi pool. Extra- and intracellular increase in Pi concentration has potential "toxic" effects on cells and induces a number of intracellular signaling pathways leading to the formation of vascular calcification. On the other hand, Pi accumulation in the extracellular space in the presence of Ca stimulates formation of Ca-Pi inorganic complexes, which induce adverse cellular effects realized through the membrane and intracellular mechanisms [48–51]. Stimulation of smooth muscle cells (SMC) by Ca-Pi crystals is accompanied by an increase in intracellular calcium and leads to apoptosis activation. The Ca-Pi compounds are supposed to enter into the cell by endocytosis, and then they are transported to the lysosomes where in acid environment they disintegrate and release Ca ions into the cytosol and inducing apoptotic signaling pathways [52]. Extracellular Ca-Pi complexes can also affect a cell through the formation of Ca-Pi nanoparticles, mainly calciprotein particles (CPP) [52, 53]. The latter ones are the hydroxyapatite crystals $Ca_{10}(PO_4)_6(OH)_2$, connected with proteins (usually, with fetuin-A and albumin). CPP formation is a protective mechanism that does not prevent the formation of inorganic Ca-Pi complexes (hydroxyapatite and intermediate crystalls), but leads to the transformation of metastable crystal structures into colloid. Its interaction with the plasma membrane is much weaker. CPP are believed to induce the intracellular cascades by interacting with lipid bridges on cell surface [52].

Arterial calcification is the central pathogenetic feature associated with the systemic Pi retention and an increase in intracellular Ca and Pi. Transdifferentiation of SMC into cells with osteochondroblastic phenotypes the key process for arterial calcification development. It is characterized by the formation of bubbles containing hydroxyapatite Ca, fragments of collagen type 1 on the cell surface, excessive production of the matrix capable for rapid calcification, and impaired formation of natural inhibitors of mineralization (pyrophosphate, Klotho, fetuin-A, osteocalcin). The main mechanisms underlying SMC transdifferentiation include modification of the genetic cellular program induced by excess extra- and intracellular Pi levels, expression of transcription factors and genes typical for osteoblast/chondroblast cell lines (Msx1/2, Runx2, osterix, alkaline phosphatase, osteoprotegerin), and simultaneous reduction in gene expression of smooth muscle cell lines (smooth muscle α-actin, SM22α) [54–58]. As a result, SMC acquires osteohondroblastic phenotype that functionally is characterized by a significant increase in PI transport into the cell and its

export into the matrix. These phenotypic changes, apparently, are necessary for the vascular integrity, as the excessive intracellular Ca and Pi levels would lead to the massive apoptosis or necrobiosis of SMC. AS a retribution, protein and mineral Ca-Pi complexes accumulate in the ground substance leading to hemodynamic changes and clinical manifestations of arterial calcification.

The accumulation of Pi causes not only changes in SMC, but also a deeper breakup of vascular wall. In terms of basic biology, dysregulation of Pi metabolism is an impairment of key processes of cell activity induced by intracellular signaling pathways activated by an increase in interstitial and intracellular Pi levels. Dysregulation of signaling pathways of bone morphogenic proteins (BMP) and Wnt (Wingless/Integration), which are critical for the normal proliferation, plasticity, transdifferentiation and differentiation, migration and repair of different cell populations, plays the key role in these processes. Excessive activation or depression, as well as an imbalance in BMP and Wnt-signaling pathways play significant role in pathological processes in the tissues, first of all, the ones susceptible to Pi accumulation in the bones, cardiovascular system and kidneys [59–63].

Pi is a potent inducer of the canonical (beta-catenin dependent) and non-canonical Wnt-signaling pathways, as well as of closely associated BMP system. At initial stages of activation, BMP- and Wnt-signalling pathways are synergistic, as inducers of reprogramming of SMC "behavior", endothelial and mesenchymal progenitors due to the activation of transcription factors of osteogenic reorganization (cyclin D, MSX2, Runx2, AP-1) [61–63]. Calcification progression is a result of both the activation of Wnt- and BMP systems, and an imbalance between them. Sustained activation of BMP-signaling in case of Pi retention, decreased production of inhibitors, and partial Wnt suppression are the main features of the imbalance between the systems. These are due to the excessive production of natural inhibitors Wnt-, Dkk-1 (dikkorpf-1), sclerostin (SOST), soluble forms of Wnt-receptor (Frizzled). Interestingly, the increased production of Wnt inhibitors is one of the downregulation BMP2 signals, and is a compensating mechanism of the Wnt-signaling pathway [64]. Wnt-inhibitors are formed locally in the endothelium and other cell populations: platelets [65], kidney and osteocytes at early stages of CKD. This might be one of the mechanisms of a systemic Wnt inhibition [66]. The stable activity of BMP appears to be the major factor for the "forced" osteoblastic differentiation of SMC [67]. The simultaneous suppression of Wnt in case of Pi retention leads to additional adverse effects on cardiovascular cell populations. These include enhanced endothelial-mesenchymal transdifferentiation, SMC apoptosis, decreased differentiation and survival of SMC, endocardial and epicardial mesenchymaltransdi fferentiation, SMC apoptosis, impaired differentiation and integration of myocardial cell populations [60, 61, 68]. In turn, these phenotypic changes of vascular cells may lead to the SMC depopulation, fibroplastic changes in arterial wall and endocardium, calcification, instability of atherosclerotic plaques, and myocardial remodeling. Adverse effects of Wnt inhibition are confirmed by experimental and clinical observations. Thus, increased level of Wnt inhibitors is associated with clinical manifestations of atherosclerosis and calcification [69–71], and anti-Wnt-inhibitors antibodies prevent arterial calcification when intestinal Pi absorption is restricted [72].

Systemic changes in endocrine phosphate-regulating factors and cardiovascular risk

The system of phosphate metabolism and pool regulation includes at least three closely related endocrine systems of kidneys, parathyroid gland and bones, and parathyroid hormone (PTH), FGF23/klotho and calcitriol are the main "players" (Fig. 1) [73]. CKD and persistent positive Pi balance lead to regular changes in the main phosphate-regulating systems: reduced production of calcitriol and α-Klotho in renal tubular epithelium, increased PTH secretion by parathyroid glands and enhanced production of FGF23 by osteocytes. In turn, changes associated with imbalanced endocrine Pi-regulating systems involved in the control of Pi metabolism, can lead to direct and/or indirect cardiovascular effects. These effects are discussed below, and are summarized in Figure 2.

Calcitriol

Vitamin D receptor-mediated (VDR) pleiotropic effects of calcitriol on cardiovascular system has been described elsewhere, and the decrease in vitamin D level in CKD is one of the key factors of accelerated progression of cardiovascular diseases [74–77]. VDR gene knockout, reduction or blockade of calcitriol synthesis results in hypertension and myocardial hypertrophy [77], and increased systemic renin activity and elevated angiotensin II level [78]. High doses of VDR-activators stimulate matrix calcification and low doses lead to its reduction. This is due to the VDR-mediated activation of Runx2 and osteocalcin gene expression, which determine SMC

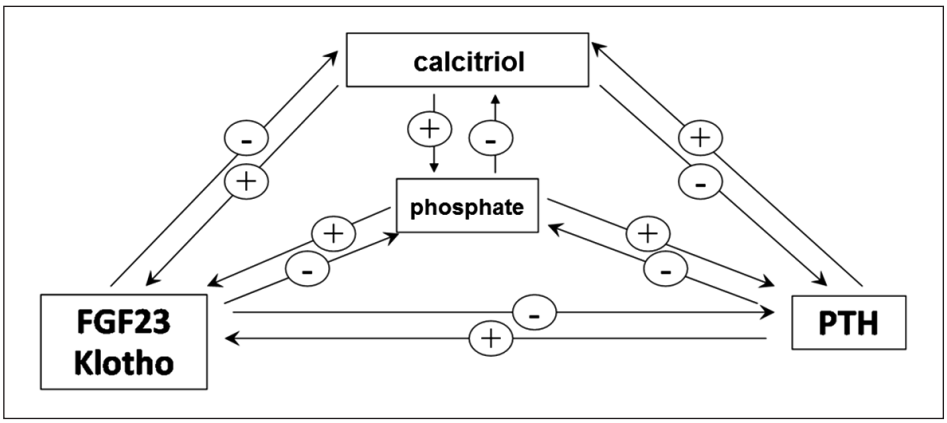
transdifferentiation into osteochondroblastic cell lines [79, 80]. Numerous clinical studies have shown a link between decreased level of 25 (OH)D_3-calcitriol precursor- and cardiovascular changes: hypertension, myocardial function, cardiovascular morbidity and mortality in patients without renal disease [81–86].

Downward regulated activation of genes involved in cellular processes plays the key role in cellular and molecular mechanisms of the favorable cardiovascular effects. These effects are related to the negative calcitriol-mediated regulation of renin-angiotensin-aldosterone system and the improvement of endothelial function, decreased expression of NF-kB, oxidative stress, inflammation, and increased NO production [87].

Parathyroid hormone

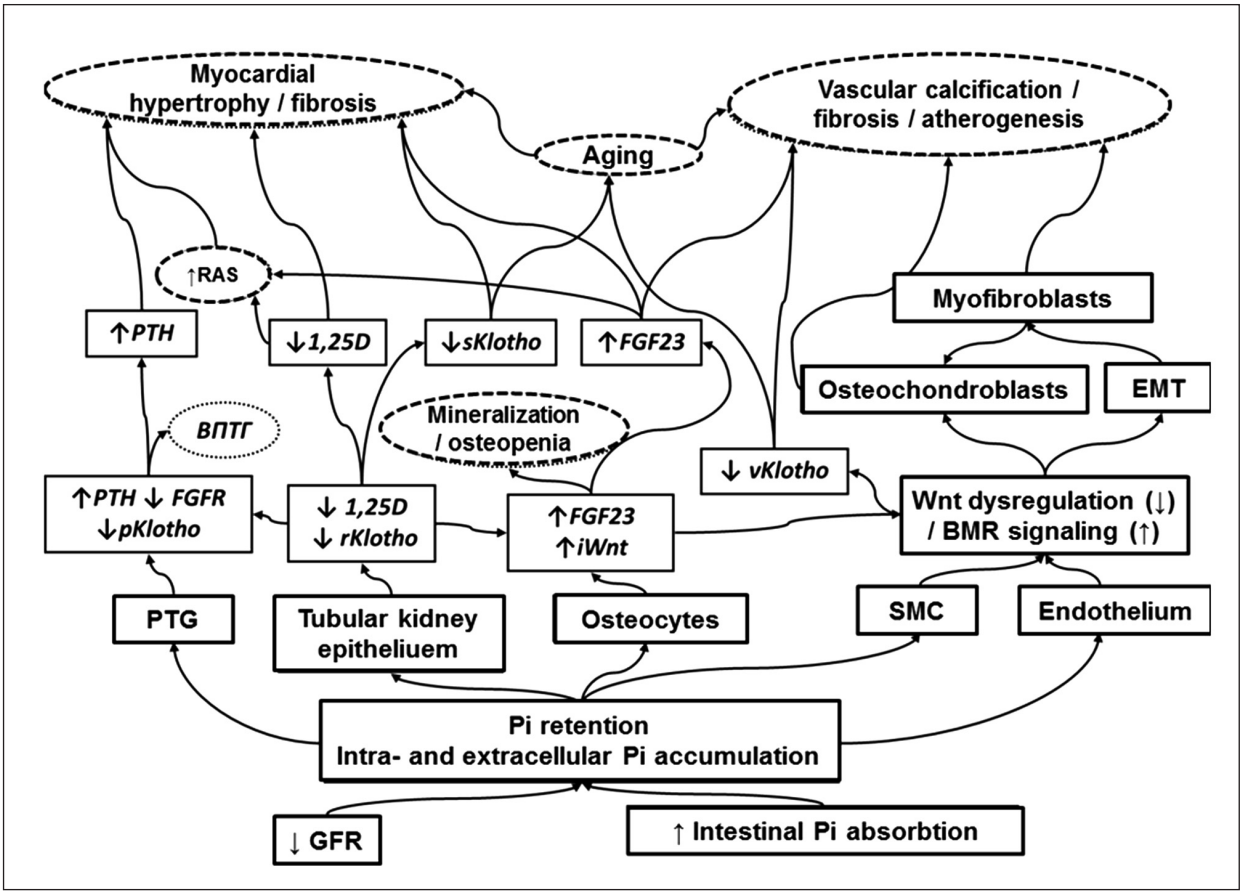
PTH is supposed to play role in the pathophysiology of cardiovascular disease, as its receptors are present in SMC, endothelium, and cardiomyocytes [88]. Although possible molecular mechanisms remain unstudied, they are believed to be associated with the activation of intracellular signaling pathways (cyclic adenosine monophosphate, AMP; phospholipases, protein kinases A and C, ERK — extracellular signal-regulated kinase; an increase in intracellular Ca level), that are involved in the development of cardiomyocyte hypertrophy, hypertension, atherosclerosis and vascular calcification [89]. This link is highly probable, as patients with primary and secondary hyperparathyroidism show similar phenotype of cardiovascular disorders — vascular and valvular calcification, endothelial dysfunction and increased cardiovascular morbidity and mortality [90, 91]. It is noteworthy that the risk persists in people with increased PTH within the normal range but without hyperparathyroidism, and regardless of renal function [92, 93]. Recent studies have demonstrated arterial calcification and rigidity reduction, after secondary hyperparathyroidism was eliminated by allosteric activation of the calcium-sensing receptor (CaSR) in dialysis patients [94]. However, it can be assumed that the relationship between PTH and cardiovascular changes are largely mediated by other factors that both regulate PTH production and have independent cardiovascular effects. In particular, PTH production refers to the tertiary response of the phosphate regulatory systems, because it is strictly controlled by calcitriol and FGF23/Klotho axis

Figure 1. A simple diagram of the feedback interaction of three major endocrine systems regulating phosphate metabolism [73]



Note: Pluse marks activating effect, minus shows inhibiting effect. According to the novel concepts, there are three major Pi regulating endocrine factors ("classic") produced in the kidneys, bones and parathyroid glands (PTG): calcitriol, fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH), respectively. Their interaction include positive and negative feedback. Pi retention reduces anabolism and catabolism of calcitriol in renal tubular epithelium, and PTH and FGF23 stimulation. Calcitriol (synonyms: vitamin D, D-hormone dihydroxycalciferol) is produced in tubular epithelium, its interaction with VDR (receptor Vitamin D — Vitamin D Receptor) leads to an increased expression of sodium phosphate co-transporter genes (NPT2a in the kidney and NPT2b in the intestine) and stimulates renal and intestinal absorption of Pi; in parathyroid glands, it negatively regulates gene expression of PTH and calcium-sensitive receptor (CaSR); calcitriol upregulates the expression of the Klotho gene. PTH is a phosphotonine, which inhibits Pi reabsorption by the kidneys due to the NPT2a internalization in the epithelial cells of proximal tubule; It stimulates calcitriol production and Klotho in the kidney and of FGF23 — in osteocytes. FGF23 is synthesized by bone cells and stimulates phosphaturia, regulates the expression of the sodium-phosphate transporter (NPT2a, NPT2c) in the proximal nephron; modulates the activity of enzymes Cyp24a1 and Cyp27b1, leading to the increased catabolism and reduced anabolism of calcitriol, a lower genomic control of PTH synthesis and a decreased intestinal Pi absorption. Co-expression of FGF receptor (FGFR) and co-receptor of transmembrane protein Klotho on the cell membrane mark target organs of FGF23. The last one binds to FGFR and to a C-terminal portion of FGF23 leading to the conversion of the canonical FGFR into specific high affinity receptors.

Figure 2. The relationship and effects of major processes related to paracrine and endocrine dysregulation of inorganic phosphate metabolism



Note: Pi — inorganic phosphate; GFR — glomerular filtration rate; SMC — smooth muscle cells; PTG — parathyroid gland; pKlotho — Klotho in the parathyroid glands; rKlotho — renal pool of Klotho; vKlotho — vascular pool of Klotho; sKlotho — circulating Klotho; Wnt — signaling pathway Wingless/integration; iWnt — endogenous inhibitors of Wnt; BMP — bone morphogenetic proteins; FGF23 — fibroblast growth factor 23; FGFR — fibroblast growth factor 23 receptor; PTH — parathyroid hormone; 1,25D — calcitriol; SHPT — secondary hyperparathyroidism; EMT — endothelial and mesenchymal transdifferentiation; RAS — renin-angiotensin system; Up Arrow — activation/increase; Down Arrow — inhibition/reduction.

(Fig. 1). Furthermore, PTH level increase results from the activation of mineralcorticoid receptor, and might be a symptom of aldosteronism, that is common in CVD, and CKD [95].

FGF23 and Klotho

The marked increase in FGF23 and reduced level of its co-receptor Klotho are typical signs of the persistent positive Pi balance in patients with renal dysfunction. Interestingly, besides GFR decline, other predictors of FGF23 increase include traditional cardiovascular risk factors, e. g. age, smoking, obesity, hypertension, diabetes mellitus, and inflammation [96–98]. Clinical observations suggest a link between FGF23 blood level and cardiovascular risk in CKD [98–102]. The growing body of evidence proves the role of FGF23 as a cardiovascular risk factor in general population. Recent studies have shown that even a moderate increase in FGF23 is associated with the major adverse events in patients without significant renal dysfunction [103, 104]. Ärnlöv J. et al. showed that the increase in FGF23 level may be considered as a cardiovascular risk factor in population, independent of traditional risk factors and other determinants of calcium-phosphate metabolism, myocardial mass and arterial wall remodeling in patients without significant GFR reduction [104, 105]. Progression of myocardial hypertrophy and dysfunction is indicative of the increased risk associated with elevated FGF23 level [106, 107]. Thus, higher levels of FGF23 was independently associated with LVH in a large cohort of CKD patients of different race [108]. Clinical data suggest a direct link between the FGF23 level and left ventricular myocardial mass and ejection fraction, independent of the kidney function and other indicators of phosphate metabolism [109]. LVH progression in patients with stable blood pressure directly correlates with the ratio "FGF23/Klotho" [110].

A three-year prospective observational study showed a 4.5-fold increase in risk of decompensated heart failure and/or cardiac death in CKD patients with FGF23 level within the third tertile, compared to patients with FGF23 values within the first tertile [111].

A number of experimental models helps our understanding of the possible mechanisms of cardiac effects of FGF23. In a cardiomyocyte cell culture, FGF23 leads to typical molecular events inherent in the development of cardiac hypertrophy, activation of atrial and brain natriuretic peptide synthesis, imbalance in α and β myosin heavy chains, possibly, as a result of the reactivation of fetal genetic programs [108, 112, 113]. In vivo experiments demonstrated that myocardial effects of FGF23 are mediated by its canonical receptor and activation of a calcineurin-NFAT-associated signaling pathway, and are independent of the Klotho presence [112]. These data suggest that the dramatic increase in FGF23 blood level can lead to an imbalance in paracrine regulation of myocardium involving other FGF (FGF2, FGF16, FGF21). This occurs due to competitive binding to canonical FGFR receptors type 1, although the details of this interaction are unknown [114]. Increase in FGF23 level is strongly related to atherosclerotic events occurrence — myocardial infarction, amputation, stroke in patients with severe renal dysfunction [115, 116]. Few studies showed an impairment of endothelial function in elderly individuals without CKD with increased circulating FGF23 level [121], although its association with the development of atherosclerosis and arterial calcification is not so obvious in case of unapparent renal dysfunction [117–120].

The phenotypes of experimental models of knockout or reduced expression of the gene Klotho (Klotho — in Greek mythology, Moira, spinning the thread of life), are characterized by accelerated aging and premature death, and homeostatic changes are similar to progressive metabolic Pi disorders in CKD patients — hyperphosphatemia, increased FGF23, hyperparathyroidism, osteopenia, and vascular calcification [122, 123]. Systemic cardiovascular effects of the receptor interaction between FGF23 and Klotho may be mediated by renin-angiotensin system activation due to the reduction in calcitriol synthesis and angiotensin-convertase 2 gene suppressing [124].

Osteocytes are the main site of FGF23 production, while protein Klotho is synthesized mainly in renal tubules, parathyroid gland and choroid plexus [125]. At the same time both proteins and matrix ribonucleic acid are expressed in arterial wall, and FGF23 has been also detected in the myocardium [126, 127]. Local reduction in the expression of both proteins was observed in progressive renal dysfunction and arterial calcification [128, 129]. FGF23 receptors type 1 and 3 were also found in the vascular wall [126]. Based on these data, a significant role of the receptor interaction between FGF23 and Klotho for the physiology and pathology of cardiovascular system was suggested, although the significance of their local expression in cardiovascular system is not yet understood. An increased activity of Klotho by supplementation or by genetic manipulation significantly suppresses vascular calcification in experimental CKD models [129]. The coexpression of FGF23 and Klotho was predominantly found in calcified plaques in coronary arteries [126, 127], suggesting a dual role of FGF23 and Klotho in the development of vascular calcification. On the one hand, their primary deficit (genetic, CKD) promotes arterial calcification, on the other hand, the low ability of cells in the calcification site to produce FGF23 and Klotho might be a contributing factor for the progression of existing vascular calcification. The circulating form of α-Klotho protein is produced by alternative splicing of the α-Klotho transcript or by release of the extracellular domain of membrane-bound α-Klotho [130]. Unlike this one acting as a FGF23 co-receptor, the circulating form of α-Klotho functions as a hormonal factor and likely plays a significant role in the prevention of aging, oxidative stress, modulation of ion transport and Wnt-signaling [62]. Vascular effects of Klotho include inhibition of SMC reprogramming induced by high Pi level [128]. Moreover, Klotho is known to be a modulator of inflammatory effects [129] in the endothelium and GMC [131, 132]. The circulating form of Klotho can decrease oxidative processes FoxO through activation and increased expression of superoxide dismutase [133], and is apparently involved in the process of endothelial integration and function [134, 135]. The interrelation between Klotho and life span might be mediated by the inhibition of the signaling pathways of insulin/IGF-1 [136], and TGF-β upon binding to the type 2 receptor [137]. This might have a systemic impact involving the development of interstitial fibrosis, vascular and myocardial fibroplastic changes. In the myocardium, Klotho is expressed only in the sinoatrial node, and is considered to be involved in its functional integration [138]. Sinoatrial node dysfunction and dysrhythmia might be the reason of high incidence of sudden death in Klotho animals [138], as well as cause atrial fibrillation in clinics [139]. The available experimental data suggest that Klotho might significantly weaken the FGF23-induced

unfavourable functional vascular effects [140]. There is an association between Klotho deficiency and hypertension-independent cardiac hypertrophy [108], and the severity of coronary artery disease [127]. An increase in the systemic or intramyocardial production of FGF23 may be a direct mediator of this process, since both intramyocardial and systemic administration of FGF23 resulted in left ventricular hypertrophy development in CKD model. At the same time, the blockade of FGFR was associated with the reduction of hypertrophy severity without change in blood pressure [108]. Klotho was suggested to affect directly cardiomyocytes. In particular, this journal issue presents an experimental study that demonstrated a FGF23-independent link between decrease in renal level of Klotho and cardiac hypertrophy progression [141]. Klotho-mediated exocytosis of voltage-dependent cation channels TRPC6 (transient receptor potential channel 6) in cardiomyocytes can be one of potential mechanisms of this relation [142]. Moreover, recently published experimental data suggest a complex impact of the imbalance in circulating Klotho and FGF23 on myocardial remodeling by inhibiting fibroplastic changes and hypertrophy mediated by TGF-β1, angiotensin II, and Pi increase [143], and by reduction of stress-induced cardiomyocyte apoptosis [144]. Hereditary Klotho deficiency may play a significant role in aging, including cardiovascular changes, mediated by interaction with Wnt [62]. In contrast, administration of exogenous Klotho blocks these processes in endothelial cells [145] and fibroblasts in experimental animals [131, 146]. There is a bidirectional regulation between Wnt and Klotho: Wnt stimulates the formation of Klotho, while Klotho inhibits Wnt, binding to various ligands of the signaling pathway [62, 131]. These data suggest that Wnt suppression, along with renal dysfunction, is an essential factor in reducing vascular Klotho level and induction of cell aging within the cardiovascular system [147, 148].

Conclusions

Thus, available clinical and experimental data indicate that the changes in inorganic Pi metabolism are associated with the development and progression of cardiovascular changes. The main and closely related mechanisms of the unfavourable cardiovascular effects of Pi include the intra- and extracellular formation of inorganic Pi-containing complexes; an imbalance in molecules involved in paracrine and endocrine regulation of Pi. Modification of phosphate metabolism can be a potential way for cardiovascular prevention.

Financing

This work was supported by the Russian Foundation for Basic Fundamental Research (project № 13–04–01886).

Conflict of interest

The author declares no conflict of interest.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD -MBD Work Group.KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease — Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009;113: S1-S130.

2. Smirnov AV, Shilov EM, Dobronravov VA et al. National guidelines. Chronic kidney disease: principles of screening, diagnostic, prophylaxis and approaches to treatment. Nephrologia. 2012;16(1):89–115. In Russian.

3. Smirnov AV, Dobronravov VA, Kaukov IG. The problem of chronic kidney disease in contemporary medicine. Arterial'naya Gipertenziya = Arterial Hypertension. 2006;12 (3):185–193. In Russian.

4. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS et al. Chronic Kidney Disease Prognosis Consortium. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int. 2011;80(1):93–104.

5. Perk J, De Backer G, Gohlke H et al. European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33(13):1635–1701.

6. Smirnov AV, Dobronravov VA, Kaukov IG. The cardiorenal continuum: pathogenetic grounds of the preventive nephrology. Nephrologia. 2005;9(3):7–15. In Russian.

7. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol. 2005;16 (2):520–528.

8. McGovern AP, de Lusignan S, van Vlymen J, Liyanage H, Tomson CR, Gallagher H et al. Serum phosphate as a risk factor for cardiovascular events in people with and without chronic kidney disease: a large community based cohort study. PLoS One. 2013;8(9):e74996.

9. Kendrick J, Kestenbaum B, Chonchol M. Phosphate and cardiovascular disease. Adv Chronic Kidney Dis. 2011;18(2):113–119.

10. Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension. 1999;33(5):1111–1117.

11. Hollander M, Hak AE, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A. Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam Study. Stroke. 2003;34(10):2367–2372.

12. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2008;358 (13):1336–1345.

13. Olson JC, Edmundowicz D, Becker DJ, Kuller LH, Orchard TJ. Coronary calcium in adults with type 1 diabetes: a stronger correlate of clinical coronary artery disease in men than in women. Diabetes. 2000;49(9):1571–1578.

14. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant. 2003;18(9):1731–1740.

15. Klassen PS, Lowrie EG, Reddan DN, DeLong ER, Coladonato JA, Szczech LA et al. Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. J Am Med Assoc. 2002;287(12):1548–1555.

16. Hunt JL, Fairman R, Mitchell ME, Carpenter JP, Golden M, Khalapyan T. Bone formation in carotid plaques: a clinicopathological study. Stroke. 2002;33 (5):1214–1219.

17. Edmonds ME, Morrison N, Laws JW, Watkins PJ. Medial arterial calcification and diabetic neuropathy. Br Med J (Clin Res Ed). 1982;284(6320):928–930.

18. Micheletti RG, Fishbein GA, Currier JS, Fishbein MC. Monckeberg sclerosis revisited: a clarification of the histologic definition of Monckeberg sclerosis. Arch Pathol Lab Med. 2008;132(1):43–47.

19. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342(20):1478–1483.

20. Ix JH, De Boer IH, Peralta CA, Adeney KL, Duprez DA, Jenny NS et al. Serum phosphorus concentrations and arterial stiffness among individuals with normal kidney function to moderate kidney disease in MESA. Clin J Am Soc Nephrol. 2009;4(3):609–615.

21. Adeney KL, Siscovick DS, Ix JH, Seliger SL, Shlipak MG, Jenny NS et al. Association of serum phosphate with vascular and valvular calcification in moderate CKD. J Am Soc Nephrol. 2009;20(2):381–387.

22. Foley RN, Collins AJ, Herzog CA, Ishani A, Kalra PA. Serum phosphorus levels associate with coronary atherosclerosis in young adults. J Am Soc Nephrol. 2009;20 (2):397–404.

23. Kendrick J, Ix JH, Targher G, Smits G, Chonchol M. Relation of serum phosphorus levels to ankle brachial pressure index (from the Third National Health and Nutrition Examination Survey). Am J Cardiol. 2010;106 (4):564–568.

24. Li JW, Xu C, Fan Y, Wang Y, Xiao YB. Can serum levels of alkaline phosphatase and phosphate predict cardiovascular diseases and total mortality in individuals with preserved renal function? A systemic review and meta-analysis. PLoS One. 2014;9(7): e102276.

25. Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. J Am Med Assoc. 2011;305(11):1119–1127.

26. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322(22):1561–1566.

27. Park M, Hsu CY, Li Y et al. Chronic Renal Insufficiency Cohort (CRIC) Study Group Associations between kidney function and subclinical cardiac abnormalities in CKD. J Am Soc Nephrol. 2012;23(10):1725–1734.

28. Levin A. Clinical epidemiology of cardiovascular disease in chronic kidney disease prior to dialysis. Semin Dial. 2003;16(2):101–105.

29. Strozecki P, Adamowicz A, Nartowicz E, Odrowaz-Sypniewska G, Wiodarczyk Z, Manitius J. Parathormone, calcium, phosphorus, and left ventricular structure and function in normotensive hemodialysis patients. Ren Fail 2001;23(1):115–126.

30. Galetta F, Cupisti A, Franzoni F, Morelli E, Caprioli R, Rindi P et al. Changes in heart rate variability in chronic uremic patients during ultrafiltration and hemodialysis. Blood Purif. 2001;19(4):395–400.

31. Culleton BF, Walsh M, Karenbach SW, Mortis G, Scott-Douglas N, Quinn RR et al. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. J Am Med Assoc. 2007;298(11):1291–1299.

32. Yamamoto KT, Robinson-Cohen C, de Oliveira MC, Kostina A, Nettleton JA, Ix JH et al. Dietary phosphorus is associated with greater left ventricular mass. Kidney Int. 2013;83(4):707–714.

33. Slinin Y, Foley RN, Collins AJ. Calcium, phosphorus, parathyroid hormone and cardiovascular disease in hemodialysis patients. The USRDS waves 1,3 and 4 study. J Am Soc Nephrol. 2005;16(6):1788–1793.

34. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in hemodialysis patients. J Am Soc Nephrol. 2004;15(8):2208–2218.

35. Chonchol M, Dale R, Schrier RW, Estacio R. Serum phosphorus and cardiovascular mortality in type 2 diabetes. Am J Med. 2009;122(4):380–386.

36. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. Circulation. 2005;112(17):2627–2633.

37. Dhingra R, Sullivan LM, Fox CS, Wang TJ, D'Agostino RB Sr, Gaziano JM et al. Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. Arch Intern Med. 2007;167(9):879–885.

38. Foley RN, Collins AJ, Ishani A, Kalra PA. Calcium-phosphate levels and cardiovascular disease in community-swelling adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J. 2008;156(3):556–563.

39. Hruska K, Mathew S, Lund R, Fang Y, Sugatani T. Cardiovascular risk factors in chronic kidney

disease: does phosphate qualify? Kidney Int Suppl. 2011;79 (121): S9-S13.

40. Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J et al. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2008;52(3):519–530.

41. Grandi NC, Brenner H, Hahmann H et al. Calcium, phosphate and the risk of cardiovascular events and all-cause mortality in a population with stable coronary heart disease. Heart. 2012;98(12):926–933.

42. Van Hemelrijck M, Michaelsson K, Linseisen J, Rohrmann S. Calcium intake and serum concentration in relation to risk of cardiovascular death in NHANES III. PLoS One. 2013;8(4): e61037.

43. Li K, Kaaks R, Linseisen J, Rohrmann S. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC — Heidelberg). Heart. 2012;98(12):920–925.

44. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. Br Med J. 2010;341: e3691.

45. Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R et al. Vascular events in healthy older women receiving calcium supplementation: randomized controlled trial. Br Med J. 2008;336(7638):262–266.

46. Wang X, Chen H, Ouyang Y, Liu J, Zhao G, Bao W et al. Dietary calcium intake and mortality risk from cardiovascular disease and all causes: a meta-analysis of prospective cohort studies. BMC Med. 2014;12(1):158.

47. Bolland MJ, Grey A, Reid IR. Calcium supplements and cardiovascular risk: 5 years on. Ther Adv Drug Saf. 2013;4(5):199–210.

48. Sage AP, Lu J, Tintut Y, Demer LL. Hyperphosphatemia-induced nanocrystals upregulate the expression of bone morphogenetic protein-2 and osteopontin genes in mouse smooth muscle cells in vitro. Kidney Int. 2011;79 (4):414–422.

49. Villa-Bellosta R, Sorribas V. Phosphonoformic acid prevents vascular smooth muscle cell calcification by inhibiting calcium-phosphate deposition. Arterioscler Thromb Vasc Biol. 2009;29(5):761–766.

50. Ewence AE, Bootman M, Roderick HL, Skepper JN, McCarthy G, Epple M et al. Calcium phosphate crystals induce cell death in human vascular smooth muscle cells: a potential mechanism in atherosclerotic plaque destabilization. Circ Res. 2008;103(5): e28-e34.

51. Khoshniat S, Bourgine A, Julien M, Petit M, Pilet P, Rouillon T et al. Phosphate-dependent stimulation of MGP and OPN expression in osteoblasts via the ERK1/2 pathway is modulated by calcium. Bone. 2010;48 (4):894–902.

52. Kuro-o M. Klotho, phosphate and FGF-23 in ageing and disturbed mineral metabolism. Nat Rev Nephrol. 2013;9 (11):650–660.

53. Smith ER, Ford ML, Tomlinson LA, Rajkumar C, McMahon LP, Holt SG. Phosphorylated fetuin-A-containing calciprotein particles are associated with aortic stiffness and a procalcific milieu in patients with pre-dialysis CKD. Nephrol Dial Transplant. 2012;27(5):1957–1966.

54. Steitz SA, Speer MY, Curinga G, Yang HY, Haynes P, Aebersold R et al. Smooth muscle cell phenotypic transition associated with calcification: up-regulation of Cbfa1 and down-regulation of smooth muscle lineage markers. Circ Res. 2001;89(12):1147–1154.

55. Speer MY, Li X, Hiremath PG, Giachelli CM. Runx2/Cbfa1. but not loss of myocardin, is required for smooth muscle cell lineage reprogramming toward osteochondrogenesis. J Cell Biochem. 2010;110(4):935–947.

56. Shioi ANY, Jono S, Koyama H, Hosoi M, Morii H. Beta-glycerophosphate accelerates calcification in cultured bovine vascular smooth muscle cells. Arterioscler Throm Vasc Biol. 1995;15 (11):2003–2009.

57. Chen NX, O'Neill KD, Duan D, Moe SM. Phosphorus and uremic serum up-regulate osteopontin expression in vascular smooth muscle cells. Kidney Int. 2002;62(5):1724–1731.

58. Mathew S, Tustison KS, Sugatani T, Chaudhary LR, Rifas L, Hruska KA. The mechanism of phosphorus as a cardiovascular risk factor in CKD. J Am Soc Nephrol. 2008;19(6):1092–1105.

59. Gittenberger-de Groot AC, Winter EM, Bartelings MM, Goumans MJ, DeRuiter MC, Poelmann RE. The arterial and cardiac epicardium in development, disease and repair. Differentiation. 2012;84(1):41–53.

60. Von Gise A, Pu WT. Endocardial and epicardial epithelial to mesenchymal transitions in heart development and disease. Circ Res. 2012;110(12):1628–1645.

61. Mill C, George SJ. Wnt signalling in smooth muscle cells and its role in cardiovascular disorders. Cardiovasc Res. 2012;95(2):233–240.

62. Liu H, Fergusson MM, Castilho RM, Liu J, Cao L, Chen J. Augmented Wnt signaling in a mammalian model of accelerated aging. Science. 2007;317(5839):803–806.

63. Kawakami T, Ren S, Duffield JS. Wnt signalling in kidney diseases: dual roles in renal injury and repair. J Pathol. 2013;229(2):221–231.

64. Kamiya N, Kobayashi T, Mochida Y, Yu PB, Yamauchi M, Kronenberg HM et al. Wnt inhibitors Dkk1 and Sost are downstream targets of BMP signaling through the type IA receptor (BMPRIA) in osteoblasts. J Bone Miner Res. 2010;25(2):200–210.

65. Ueland T, Otterdal K, Lekva T, Halvorsen B, Gabrielsen A, Sandberg WJ et al. Dickkopf-1 enhances in flammatory interaction between platelets and endothelial cells and shows increased expression in atherosclerosis. Arterioscler Thromb Vasc Biol. 2009;29(8):1228–1234.

66. Sabbagh Y, Graciolli FG, O'Brien S, Tang W, dos Reis LM, Ryan S et al. Repression of osteocyte Wnt/β-catenin signaling is an early event in the progression of renal osteodystrophy. J Bone Miner Res. 2012;27(8):1757–1772.

67. Li X, Yang HY, Giachelli CM. BMP-2 promotes phosphate uptake, phenotypic modulation, and calcification of human vascular smooth muscle cells. Atherosclerosis. 2008;199(2):271–277.

68. Cheng SL, Shao JS, Behrmann A, Krchma K, Towler DA. Dkk1 and MSX2-Wnt7b signaling reciprocally regulate the endothelial-mesenchymal transition in aortic endothelial cells. Arterioscler Thromb Vasc Biol. 2013;33 (7):1679–1689.

69. Askevold ET, Gullestad L, Aakhus S, Ranheim T, Tønnessen T, Solberg OG et al. Secreted Wnt modulators in symptomatic aortic stenosis. J Am Heart Assoc. 2012;1(6): e002261.

70. Garcia-Martín A, Reyes-Garcia R, García-Fontana B, Morales-Santana S, Coto-Montes A, Muñoz-Garach M et al. Relationship of Dickkopf1 (DKK1) with Cardiovascular Disease and Bone Metabolism in Caucasian Type 2 Diabetes Mellitus. PLoS One. 2014;9(11): e111703.

71. Wang L, Hu XB, Zhang W, Wu LD, Liu YS, Hu B et al. Dickkopf-1 as a novel predictor is associated with risk stratification by GRACE risk scores for predictive value in patients with acute coronary syndrome: a retrospective research. PLoS One. 2013;8(1): e54731.

72. Fang Y, Ginsberg C, Seifert M, Agapova O, Sugatani T, Register TC et al. CKD-Induced Wingless/Integration1 Inhibitors and Phosphorus Cause the CKD -Mineral and Bone Disorder. J Am Soc Nephrol. 2014;25(8):1760–1773.

73. Dobronravov VA. Modern view on the pathogenesis of the secondary hyperparathyreosis: the role of fibroblast growth factor and Klotho. Nephrologia. 2011;15(4):11–20. In Russian.

74. Smirnov AV, Volkov MM, Dobronravov VA. C ardioprotective effects of D-hormone in patients with chronic kidney disease: literature review and personal data. Nephrologia. 2009;13(1):30–38. In Russian.

75. Nigwekar SU, Thadhani R. Vitamin D receptor activation: cardiovascular and renal implications. Kidney Int Suppl (2011). 2013;3 5):427–430.

76. Li YC. Vitamin D: roles in renal and cardiovascular protection. Curr Opin Nephrol Hypertens. 2012;21(1): 72–79.

77. Weishaar RE, Kim SN, Saunders DE, Simspon RU. Involvement of vitamin D3 with cardiovascular function. III. Effects on physical and morphological properties. Am J Physiol. 1990;258(1 Pt. 1): E134-E142.

78. Xiang W, Kong J, Chen S, Cao LP, Qiao G, Zheng W et al. Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. Am J Physiol Endocrinol Metab. 2005;288 (1):125–132.

79. Mathew S, Lund RJ, Chaudhary LR, Geurs T, Hruska KA. Vitamin D receptor activators can protect against vascular calcification. J Am Soc Nephrol. 2008;19 (8):1509–1519.

80. Mizobuchi M, Finch JL, Martin DR, Ststopolsky E. Differential effects of vitamin D receptor activators on vascular calcification in uremic rats. Kidney Int. 2007;72 (6):709–715.

81. Kokot F, Pietrek J, Srokowska S, Wartenberg W, Kuska J, Jedrychowska M et al. 25-hydroxyvitamin D in patients with essential hypertension. Clin Nephrol. 1981;16 (4):188–192.

82. Burgaz A, Orsini N, Larsson SC, Wolk A. Blood 25-hydroxyvitamin D concentration and hypertension: a meta-analysis. J Hypertens. 2011;29(4):636–645.

83. Pilz S, Marz W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. J Clin Endocrinol Metab. 2008;93(10):3927–3935.

84. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008;117(4):503–511.

85. Pilz S, Iodice S, Zittermann A, Grant WB, Grandini S. Vitamin D status and mortality risk in CKD: a meta-analysis of prospective studies. Am J Kidney Dis. 2011;58(3):374–382.

86. Drechsler C, Verduijn M, Pilz S, Dekker FW, Krediet RT, Ritz E et al. Vitamin D status and clinical outcomes in incident dialysis patients: results from the NECOSAD study. Nephrol Dial Transplant. 2011;26 (3):1024–1032.

87. Abu el Maaty MA, Gad MZ. Vitamin D deficiency and cardiovascular disease: potential mechanisms and novel perspectives. J Nutr Sci Vitaminol (Tokyo). 2013;59 (6):479–488.

88. Clemens TL, Cormier S, Eichinger A, Endlich K, Fiaschi-Taesch N, Fischer E et al. Parathyroid hormone-related protein and its receptors: nuclear functions and roles in the renal and cardiovascular systems, the placental trophoblasts and the pancreatic islets. Br J Pharmacol. 2001;134(6):1113–1136.

89. Goettsch C, Iwata H, Aikawa E. Parathyroid hormone: critical bridge between bone metabolism and cardiovascular disease. Arterioscler Thromb Vasc Biol. 2014;34(7):1333–1335.

90. Macfarlane DP, Yu N, Leese GP. Subclinical and asymptomatic parathyroid disease: implications of emerging data. Lancet Diabetes Endocrinol. 2013;1(4):329–340.

91. Bosworth C, Sachs MC, Duprez D, Hoofnagle AN, Ix JH, Jacobs DR Jr et al. Parathyroid hormone and arterial dysfunction in the multi-ethnic study of atherosclerosis. Clin Endocrinol (Oxf). 2013;79(3):429–436.

92. Hagström E, Hellman P, Larsson TE, Ingelsson E, Berglund L, Sundström J et al. Plasma parathyroid hormone and the risk of cardiovascular mortality in the community. Circulation. 2009;119(21):2765–2771.

93. Hagström E, Michaëlsson K, Melhus H, Hansen T, Ahlström H, Johansson L et al. Plasma-parathyroid hormone is associated with subclinical and clinical atherosclerotic disease in 2 community-based cohorts. Arterioscler Thromb Vasc Biol. 2014;34(7):1567–1573.

94. Nakayama K, Nakao K, Takatori Y, Inoue J, Kojo S, Akagi S et al. Long-term effect of cinacalcet hydrochloride on abdominal aortic calcification in patients on hemodialysis with secondary hyperparathyroidism. Int J Nephrol Renovasc Dis. 2013;7:25–33.

95. Tomaschitz A, Ritz E, Pieske B, Rus-Machan J, Kienreich K, Verheyen N et al. Aldosterone and parathyroid hormone interactions as mediators of metabolic and cardiovascular disease. Metabolism. 2014;63(1):20–31.

96. Gutierrez OM, Wolf M, Taylor EN. Fibroblast growth factor 23, cardiovascular disease risk factors, and phosphorus intake in the Health Professionals Follow -up Study. Clin J Am Soc Nephrol. 2011;6(12):2871–2878.

97. Manghat P, Fraser WD, Wierzbicki AS, Fogelman I, Goldsmith DJ, Hampson G. Fibroblast growth factor-23 is associated with C-reactive protein, serum phosphate and bone mineral density in chronic kidney disease. Osteoporos Int. 2010;21(11):1853–1861.

98. Isakova T, Xie H, Yang W et al. Chronic Renal Insufficiency Cohort (CRIC) Study Group: fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. J Am Med Assoc. 2011;305 23):2432–2439.

99. Fliser D, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Lingenhel A et al. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: The Mild to Moderate Kidney Disease (MMKD) Study. J Am Soc Nephrol. 2007;18(9):2600–2608.

100. Wolf M, Molnar MZ, Amaral AP, Czira ME, Rudas A, Ujszaszi A et al. Elevated fibroblast growth factor 23 is a risk factor for kidney transplant loss and mortality. J Am Soc Nephrol. 2011;22(5):956–966.

101. Gutiérrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008;359(6):584–592.

102. Lundberg S, Qureshi AR, Olivecrona S, Gunnarsson I, Jacobson SH, Larsson TE. FGF23, albuminuria, and disease progression in patients with chronic IgA nephropathy. Clin J Am Soc Nephrol. 2012;7(5):727–734.

103. Ix JH, Katz R, Kestenbaum BR, de Boer IH, Chonchol M, Mukamal KJ et al. Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: CHS (Cardiovascular Health Study). J Am Coll Cardiol. 2012;60(3):200–207.

104. Ärnlöv J, Carlsson AC, Sundström J, Ingelsson E, Larsson A, Lind L et al. Higher fibroblast growth factor-23 increases the risk of all-cause and cardiovascular mortality in the community. Kidney Int. 2013;83(1):160–166.

105. Ärnlöv J, Carlsson AC, Sundström J, Ingelsson E, Larsson A, Lind L et al. Serum FGF23 and Risk of Cardiovascular Events in Relation to Mineral Metabolism and Cardiovascular Pathology. Clin J Am Soc Nephrol. 2013;8(5):781–786.

106. Jovanovich A, Ix JH, Gottdiener J, McFann K, Katz R, Kestenbaum B et al. Fibroblast growth factor 23, left ventricular mass, and left ventricular hypertrophy in community-dwelling older adults. Atherosclerosis. 2013;231 (1):114–119.

107. Scialla JJ, Xie H, Rahman M, Anderson AH, Isakova T, Ojo A et al. Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Fibroblast growth factor-23 and cardiovascular events in CKD. J Am Soc Nephrol. 2014;25 (2):349–360.

108. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T et al. FGF23 induces left ventricular hypertrophy. J Clin Invest. 2011;121(11):4393–4408.

109. Shibata K, Fujita S, Morita H, Okamoto Y, Sohmiya K, Hoshiga M et al. Association between circulating fibroblast growth factor 23, α-Klotho, and the left ventricular ejection fraction and left ventricular mass in cardiology inpatients. PLoS One. 2013;8(9): e73184.

110. Seifert ME, de Las Fuentes L, Ginsberg C, Rothstein M, Dietzen DJ, Cheng SC et al. Left ventricular mass progression despite stable blood pressure and kidney function in stage 3 chronic kidney disease. Am J Nephrol. 2014;39(5):392–399.

111. Seiler S, Rogacev KS, Roth HJ, Shafein P, Emrich I, Neuhaus S et al. Associations of FGF-23 and sKlotho with cardiovascular outcomes among patients with CKD stages 2–4. Clin J Am Soc Nephrol. 2014;9(6):1049–1058.

112. Molkentin JD, Lu J, Antos C, Markham B, Richardson J, Robbins J et al. A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. Cell. 1998;93(2):215–228.

113. Komuro I, Yazaki Y. Control of cardiac gene expression by mechanical stress. Annu Rev Physiol. 1993;55:55–75.

114. Itoh N, Ohta H. Pathophysiological roles of FGF signaling in the heart. Front Physiol. 2013;4:247.

115. Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, Smits G et al. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. J Am Soc Nephrol. 2011;22(10):1913–1922.

116. Seiler S, Reichart B, Roth D, Seibert E, Fliser D, Heine GH et al. FGF-23 and future cardiovascular events in patients with chronic kidney disease before initiation of dialysis treatment. Nephrol Dial Transplant. 2010;25 (12):3983–3989.

117. Parker BD, Schurgers LJ, Brandenburg VM, Christenson RH, Vermeer C, Ketteler M et al. The associations of fibroblast growth factor 23 and uncarboxylated matrix Gla protein with mortality in coronary artery disease: the Heart and Soul Study. Ann Intern Med. 2010;152(10):640–648.

118. Taylor EN, Rimm EB, Stampfer MJ, Curhan GC. Plasma fibroblast growth factor 23, parathyroid hormone, phosphorus, and risk of coronary heart disease. Am Heart J. 2011;161(5):956–962.

119. Srivaths PR, Goldstein SL, Silverstein DM, Krishna-murthy R, Brewer ED. Elevated FGF 23 and phosphorus are associated with coronary calcification in hemodialysis patients. Pediatr Nephrol. 2011;26(6):945–991.

120. Roos M, Lutz J, Salmhofer H, Luppa P, Knauss A, Braun S et al. Relation between plasma fibroblast growth factor-23, serum fetuin-A levels and coronary artery calcification evaluated by multislice computed tomography in patients with normal kidney function. Clin Endocrinol (Oxf). 2008;68(4):660–665.

121. Mirza MA, Larsson A, Lind L, Larsson TE. Circulating fibroblast growth factor-23 is associated with vascular dysfunction in the community. Atherosclerosis. 2009;205(2):385–390.

122. Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T et al. Mutation of the mouse Klotho gene leads to a syndrome resembling ageing. Nature. 1997;390 (6655):45–51.

123. Kuro-o M. Phosphate and klotho. Kidney Int. 2011;79(121): S20-S23.

124. Dai B, David V, Martin A, Huang J, Li H, Jiao Y et al. A comparative transcriptome analysis identifying FGF23 regulated genes in the kidney of a mouse CKD model. PLoS One. 2012;7(9): e44161.

125. Lim K, Lu T.S, Molostvov G, Lee C, Lam FT, Zehnder D et al. Vascular Klotho deficiency potentiates the development of human artery calcification and mediates resistance to fibroblast growth factor 23. Circulation. 2012;125(18):2243–2255.

126. Van Venrooij NA, Pereira RC, Tintut Y, Fishbein MC, Tumber N, Demer LL et al. FGF23 protein expression in coronary arteries is associated with impaired kidney function. Nephrol Dial Transplant. 2014;29(8):1525–1532.

127. Navarro-González JF, Donate-Correa J, Muros de Fuentes M, Pérez-Hernández H, Martínez-Sanz R, Mora-Fernández C. Reduced Klotho is associated with the presence and severity of coronary artery disease. Heart. 2014;100 (1):34–40.

128. Hu MC, Shi M, Zhang J, Quiñones H, Griffith C, Kuro-o M et al. Klotho deficiency causes vascular calcification in chronic kidney disease. J Am Soc Nephrol. 2011;22(1):124–136.

129. Zhao Y, Banerjee S, Dey N, LeJeune WS, Sarkar PS, Brobey R et al. Klotho depletion contributes to increased inflammation in kidney of the db/db mouse model of diabetes via RelA (serine)536 phosphorylation. Diabetes. 2011;60(7):1907–1916.

130. Hu MC, Kuro-o M, Moe OW. Secreted klotho and chronic kidney disease. Adv Exp Med Biol. 2012;728:126–157.

131. De Oliveira RM. Klotho RNAi induces premature senescence of human cells via a p53/p21 dependent pathway. FEBS Lett. 2006;580(24):5753–5758.

132. Nakano-Kurimoto R, Ikeda K, Uraoka M, Nakagawa Y, Yutaka K, Koide M et al. Replicative senescence of vascular smooth muscle cells enhances the calcification through initiating the osteoblastic transition. Am J Physiol Heart Circ Physiol. 2009;297(5):1673–1684.

133. Kuroo M. Klotho as a regulator of oxidative stress and senescence. Biol Chem. 2008;389(3):233–241.

134. Kusaba T, Okigawa M, Matui A, Murakami M, Ishikawa K, Kimura T et al. Klotho is associated with VEGF receptor-2 and the transient receptor potential canonical-1 Ca2+ channel to maintain endothelial integrity. Proc Natl Acad Sci USA. 2010;107(45):19308–19313.

135. Nagai R, Saito Y, Ohyama Y, Aizawa H, Suga T, Nakamura T et al. Endothelial dysfunction in the klotho mouse and downregulation of klotho gene expression in various animal models of vascular and metabolic diseases. Cell Mol Life Sci. 2000;57(5):738–746.

136. Kurosu H, Yamamoto M, Clark JD, Pastor JV, Nandi A, Gurnani P et al. Suppression of aging in mice by the hormone Klotho. Science. 2005;309(5742):1829–1833.

137. Doi S, Zou Y, Togao O, Pastor JV, John GB, Wang L et al. Klotho inhibits transforming growth factor-beta1 (TGF-beta1) signaling and suppresses renal fibrosis and cancer metastasis in mice. J Biol Chem. 2011;286 (10):8655–8665.

138. Takeshita K, Fujimori T, Kurotaki Y, Honjo H, Tsujikawa H, Yasui K et al. Sinoatrial node dysfunction and early unexpected death of mice with a defect of klotho gene expression. Circulation. 2004;109(14):1776–1782.

139. Nowak A, Friedrich B, Artunc F, Serra AL, Breidthardt T, Twerenbold R et al. Prognostic value and link to atrial fibrillation of soluble Klotho and FGF23 in hemodialysis patients. PLoS One. 2014;9(7): e100688.

140. Six I, Okazaki H, Gross P, Cagnard J, Boudot C, Maizel J et al. Direct, acute effects of Klotho and FGF23 on vascular smooth muscle and endothelium. PLoS One. 2014;9 (4): e93423.

141. Bogdanova EO, Beresneva ON, Semenova NY et al. Renal αklotho expression is associated with myocardial hypertrophy in spontaneously hypertensive rats (experimental study). Arterial'naya Gipertenziya = Arterial Hypertension. 2014;20(6): [In press]. In Russian.

142. Xie J, Cha SK, An SW, Kuro-o M, Birnbaumer L, Huang CL. Cardioprotection by Klotho through down-regulation of TRPC6 channels in the mouse heart. Nat Commun. 2012;3:1238.

143. Hu MC, Shi M, Cho HJ, Adams-Huet B, Paek J, Hill K et al. Klotho and phosphate are modulators of pathologic uremic cardiac remodeling. J Am Soc Nephrol. 2015;26(6):1290–302.

144. Song S, Gao P, Xiao H, Xu Y, Si LY. Klotho suppresses cardiomyocyte apoptosis in mice with stress-induced cardiac injury via downregulation of endoplasmic reticulum stress. PLoS One. 2013;8(12): e82968.

145. Maekawa Y, Ohishi M, Ikushima M, Yamamoto K, Yasuda O, Oguro R et al. Klotho protein diminishes endothelial apoptosis and senescence via a mitogen-activated kinase pathway. Geriatr Gerontol Int. 2011;11 (4):510–516.

147. Liu F, Wu S, Ren H, Gu J. Klotho suppresses RIG-I-mediated senescence -associated inflammation. Nat Cell Biol. 2011;13(3):254–262.

148. Fang Y, Ginsberg C, Sugatani T, Monier-Faugere MC, Malluche H, Hruska KA. Early chronic kidney disease — mineral bone disorder stimulates vascular calcification. Kidney Int. 2014;85(1):142–150.

149. Kim HR, Nam BY, Kim DW, Kang MW, Han JH, Lee MJ et al. Circulating α-klotho levels in CKD and relationship to progression. Am J Kidney Dis. 2013;61 (6):899–909.

Author information:

Vladimir A. Dobronravov, MD, PhD, DSc, Professor, Deputy Director, Research Institution for Nephrology, First Pavlov State Medical University of St. Petersburg.