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State of phosphorus-calcium metabolism in young and old rats under conditions of experimental vitamin D hypervitaminosis at different altitudes and ways of its correction

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Abstract. This study aimed to systematically analyse and synthesise current scientific data on the mechanisms of Ca-P metabolism disorders under the combined influence of hypervitaminosis D, altitude hypoxia and age, as well as to justify effective corrective approaches. Scientific sources were analysed using comparative analysis, data synthesis, and information generalisation methods. The analysis conducted that the Ca-P metabolism regulation system is a complex network with vitamin D metabolism being central, where the balance between parathyroid hormone and FGF23 determines the stability of Ca and P levels in plasma. Analysis of scientific sources revealed characteristic age-related features of metabolic disorders. The data showed that in young organisms with high levels of bone remodelling, Ca/P imbalance can lead to a significant decrease in bone mineral density (by 12-18%), while in older organisms, data on the development of progressive osteomalacia and renal failure in the context of a decrease in functional reserves predominate. A review of studies on the effects of high-altitude hypoxia showed that it can cause a complex of disorders, including renal dysfunction (increase in creatinine to 0.81 ± 0.04 mg/dL), electrolyte imbalance (decrease in calcium to 8.1 ± 0.6 mg/dL with an increase in phosphorus to 7.1 ± 0.4 mg/dL) and adaptation of vitamin D metabolism, in particular through increased CYP27B1 expression. The conclusions obtained as a result of the analysis are of theoretical importance for the further development of scientifically based recommendations for the safe supplementation of vitamin D in patients of different age groups living in high-altitude regions

Keywords: parathyroid hormone; osteomalacia; high altitude hypoxia; age-related characteristics; renal failure

Introduction

Phosphorus-calcium metabolism is a central mechanism for ensuring the structural integrity of bone tissue, regulating neuromuscular conduction, and maintaining systemic metabolic balance. Blood calcium

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and phosphorus levels are controlled by a complex network of hormonal, enzymatic, and cellular mechanisms, among which the activity of vitamin D and its metabolites is substantial. Disruption of these mechanisms can lead to soft tissue calcification, nephropathy, cardiovascular dysfunction, osteoporosis and other pathological conditions, which makes the study of Ca-P homeostasis highly relevant from a medical and biological point of view. The analysis of age differences and the influence of external factors, such as hypoxia, which can modify the biological effects of vitamin D and change the course of hypervitaminosis depending on the altitude above sea level, is becoming increasingly relevant.

A contribution to the relationship between vitamin D, calcium and phosphates was made in a study by I.V. Kolosovych & I.V. Hanol [1], which showed that an imbalance of these components affects the course of acute pathological conditions. The study emphasised that changes in the levels of calcium, phosphates and active metabolites of vitamin D can be predictors of the severity of the inflammatory process. A comprehensive review by M. Sun *et al*. [2] showed that calcium-phosphate metabolism disorders are multifactorial in nature and are accompanied by profound changes in the cellular proteome and metabolome. The study emphasised that the changes identified affect signalling pathways, energy metabolism and stress responses. Their conclusions underscored the complexity of the body's systemic responses to Ca-P imbalance and the need for multifaceted analysis models. The importance of studying phosphorus-calcium metabolism disorders is also due to its key role in maintaining the structural integrity of bone tissue and systemic metabolic balance. As noted by B. Çaykara *et al*. [3], the relationship between vitamin D, calcium and phosphorus levels is fundamental to homeostasis, and any imbalance can have serious pathophysiological consequences.

D.D. Bikle [4] highlighted the latest insights into the metabolism and functions of vitamin D, particularly its role in regulating immune response, cell cycle, and intercellular interactions. The study emphasised that even small deviations in the levels of 25(OH)D and $1.25(OH)_2D$ can cause a systemic effect. The study by D. Bikle & S. Christakos [5] revealed new aspects of the skin's involvement in vitamin D metabolism, contributing to the research the role in overall mineral homeostasis. The study demonstrated that skin tissue can act as an autonomous endocrine organ capable of altering systemic calcium and phosphate concentrations. F. Saponaro *et al*. [6] emphasised enzymatic pathways of vitamin D metabolism, including the variability of Cytochrome P450 family 24 subfamily A member 1 (CYP24A1) and Cytochrome P450 family 27 subfamily B member 1 (CYP27B1) activity in different age groups. The article emphasises that changes in the enzymatic profile with age or under stressful conditions can contribute to the development of hypervitaminosis.

A. Papadopoulou *et al*. [7] detail the genetic mechanisms of hereditary disorders of calcium-phosphate metabolism. The study emphasised that mutations in transporters and enzymes can cause severe forms of metabolic disorders with early onset. Vitamin D is central in this regulatory network. According to N.A. Shaikh *et al*. [8], vitamin D has a complex effect not only on mineral absorption but also on the function of cell populations, particularly intestinal stem cells. However, the mechanisms by which vitamin D modulates the processes of proliferation, differentiation, and homeostasis in target organs remain unclear, especially in conditions of excess. The dissertation by A. Hossain [9] emphasised the role of vitamin D deficiency and excess as modified risk factors for the development of non-communicable diseases, including metabolic syndrome and cardiovascular pathologies. The study analysed in detail the mechanisms of Ca-P metabolism disorders in the context of the systemic inflammatory response. The final link in the calcium-phosphate metabolism regulation system was highlighted by M.L. Noonan [10] in an analysis of the role of Fibroblast growth factor 23 (FGF23) in the mechanisms of osteocyte oxygenation and biomineralization, especially in the context of chronic kidney disease. The study demonstrated that changes in the oxygen supply to bone tissue can radically alter the hormonal regulation of phosphate.

Thus, analysis of the accumulated data clearly demonstrates the complexity of the Ca-P homeostasis regulation system and its dependence on age and environmental factors. However, there are gaps in the research on this problem. There is conflicting and incomplete data on the characteristics of hypervitaminosis D in organisms of different ages. In addition, there are virtually no studies devoted to the effect of chronic hypoxia on the development and consequences of vitamin D toxicity. These shortcomings in existing works necessitate a targeted study of these aspects and form a specific scientific basis for conducting new experimental studies. The study aimed to analyse current theoretical data on changes in phosphorus-calcium metabolism in young and old rats under conditions of experimental vitamin D hypervitaminosis at different altitudes and to identify possible ways to correct these disorders. The study goals included: establishment of age-specific features of phosphorus-calcium metabolism under normoxic and hypoxic conditions, in particular, description of differences between young and old organisms, determination of variations in basic biochemical parameters, and characterisation of changes occurring in response to vitamin D excess; analysis of the complex of biochemical, hormonal and metabolic disorders induced by hypervitaminosis D in animals of different ages; assessment of the effectiveness of approaches to the correction of calcium-phosphate metabolism disorders.

As part of the preparation of the review, a multi-stage literature search was conducted in PubMed,

Scopus, Web of Science, and Google Scholar databases. At the initial stage, 512 publications were identified that matched a broad set of keywords related to phosphorus-calcium metabolism, vitamin D hypervitaminosis, age differences, and the effects of hypoxia. After removing duplicates, the number was reduced to 426 sources, which were screened by title and abstract. Further filtering based on inclusion criteria – the presence of primary experimental or generalised data on Ca-P metabolism regulation; analysis of the effects of hypervitaminosis D; comparison of young and old organisms; availability of data on hypoxia and high-altitude conditions; clear description of methodology – reduced the sample to 148 sources. Thirty-six publications that met the methodological quality requirements, contained transparently described statistical procedures, and had practical or theoretical significance for the formation of a conceptual model of Ca-P metabolism disorders were selected for the final stage.

The final selection included both experimental studies on rodents and animal models of different age groups, as well as systematic clinical observations of patients with Ca-P metabolism disorders, chronic kidney diseases, conditions associated with vitamin D deficiency or excess, as well as studies devoted to the adaptation of the body to mid-mountain and high-mountain conditions. The sample size in clinical and experimental studies ranged from 15-30 experimental animals to 250-600 individuals in population and cross-sectional studies. The main results included the assessment of hormonal markers (parathyroid hormone, calcitonin, FGF23), active metabolites of vitamin D, indicators of bone remodelling, functional state of the kidneys, and calcium and phosphorus levels. This systematic characterisation of sources ensured the representativeness of the review and formed a comprehensive theoretical basis for further analysis of the pathophysiological mechanisms and age-specific responses to vitamin D hypervitaminosis in normoxic and hypoxic conditions. The analysis had certain limitations, mainly due to the lack of experimental studies that simultaneously studied the combined effect of all three factors – hypervitaminosis D, altitude hypoxia, and age – on a single model. Most of the sources cited examined individual aspects of this problem, which complicates direct comparison of results and requires logical extrapolation of data.

Theoretical basis of Ca–P metabolism regulation

A systematic analysis of scientific literature synthesised a comprehensive overview of the mechanisms regulating phosphorus-calcium metabolism, including age-related characteristics, the effects of vitamin D toxicity, and conditions of altitude hypoxia. B. Zhang *et al*. [11] provided a fundamental concept of the systemic nature of changes, demonstrating profound age-related remodelling of ion profiles, including calcium and phosphorus, in various organs of mice. The "ion clocks of ageing" indicate a close relationship between mineral homeostasis disorders and general ageing processes. The specific mechanisms of these changes are revealed in studies devoted to individual organs. V.A. Areco *et al*. [12] described in detail the molecular architecture of intestinal calcium absorption, in which the transporters Transient Receptor Potential Vanilloid 6 (TRPV6), calbindin-D9k and PMCA1b is central, the expression of which is strictly controlled by calcitriol via the Vitamin D receptor (VDR). With age, the efficiency of this system may decrease, contributing to the development of hypocalcaemia.

W.L. Miller & E.A. Imel [13] described in detail in their review the two-stage process of vitamin D metabolism, which is the basis for the regulation of calcium-phosphorus homeostasis. The authors emphasised that the first stage of 25-hydroxylation occurs in the liver with the formation of 25(OH)D, the main circulating marker of the body's supply. The second key stage, according to their data, occurs in the kidneys, where the enzyme CYP27B1 (1α-hydroxylase) converts 25(OH)D into the biologically active hormone calcitriol ($1.25(OH)_2D$), whose activity is hundreds of times higher. D. Bellavia *et al*. [14] investigated the molecular mechanisms of calcitriol action through its nuclear receptor (VDR). The study described how the calcitriol-VDR complex, forming a heterodimer with the retinoic acid receptor (RXR), binds to vitamin D response elements (VDRE) in deoxyribonucleic acid (DNA), regulating gene transcription. The study outlined the effects in target organs in detail: in the intestine, the genes for calcium channels TRPV6, calbindin-D9k and calcium-magnesium ATPase (PMCA1b) are induced, ensuring active calcium transport; calcium reabsorption increases in the kidneys; a dual role is noted in the bones, from being necessary for mineralisation to promoting resorption with the participation of parathyroid hormone (PTH) in calcium deficiency.

O.M. Gutiérrez *et al*. [15] investigated the feedback mechanisms in the regulation of calcitriol levels on the example of mice. The study determined that PTH is a potent stimulator of CYP27B1 expression in response to hypocalcaemia. In contrast, fibroblast growth factor-23 (FGF23), which is produced in bone during hyperphosphataemia, inhibits CYP27B1 and induces the expression of the inactivation enzyme CYP24A1. Thus, the PTH/FGF23 balance determines the rate of vitamin D metabolism and the stability of Ca and P levels. S. De Vincentis *et al*. [16], in a clinical study, substantiated the importance of the calcium-to-phosphorus ratio (Ca/P) in plasma as an integral indicator of the state of the mineral homeostasis system. The study demonstrated that changes in this ratio may be early markers of profound disturbances in the complex regulatory network involving vitamin D, PTH and FGF23, even before the onset of clinical symptoms. Thus, the results of these

studies have shaped the concept of the Ca-P metabolism regulation system as a complex network with a central integrated role of vitamin D metabolism.

Effects of hypervitaminosis D at the molecular and systemic levels

Hypervitaminosis D causes a rapid disruption of this finely tuned system. Experimental data from M. El-Boshy *et al*. [17] on rats documented the development of severe hypercalcaemia (12.4 ± 0.5 mg/dL) and hyperphosphataemia (7.9 ± 0.3 mg/dL) in the context of severe oxidative stress and inflammation. According to the analysis by M. Gurudatta [18], the endocrine profile of this condition includes a sharp suppression of parathyroid hormone secretion due to the activation of calcium-sensitive receptors (CaSR) and a compensatory increase in FGF23 levels aimed at reducing toxicity. However, as described by A. Nowacka *et al*. [19], the enzyme CYP24A1, which catalyses the inactivation of both calcitriol and 25(OH)D, are substantial in protecting against intoxication. Its activity increases sharply in hypervitaminosis in an attempt to restore balance. The biochemical consequence is not only calcification of soft tissues, but also a paradoxical disturbance of bone mineralisation, similar to osteomalacia, observed by D. Durup *et al*. [20] in female rats under conditions of deficiency (Table 1).

Table 1. Biochemical and molecular effects of hypervitaminosis D in rats (according to literature data)

Parameter	Control group (normal vitamin D levels)	Group with hypervitaminosis D	Effect
Serum calcium (mg/dL)	9.8 ± 0.3	12.4 ± 0.5	Hypercalcaemia
Serum phosphorus (mg/dL)	6.2 ± 0.2	7.9 ± 0.3	Hyperphosphataemia
Malondialdehyde in the liver (nmol/mg prot.)	1.8 ± 0.2	4.5 ± 0.3	Oxidative stress
TNF-α in the liver (pg/mL)	25.6 ± 2.1	68.3 ± 4.5	Systemic inflammation
Serum creatinine (mg/dL)*	0.52 ± 0.03	0.81 ± 0.04	Kidney dysfunction

Note: * – creatinine data are taken from a study of the effects of hypoxia, which also demonstrates similar mechanisms of renal damage during metabolic stress, which is relevant for the hypervitaminosis D model
Source: compiled by the authors based on M. El-Boshy et al. [17], M. Gurudatta [18], A. Nowacka *et al*. [19], D. Durup *et al*. [20]

At the molecular level, hypervitaminosis D initiates a cascade of pathological events, the central links of which are powerful oxidative stress and systemic inflammation. Experimental data from M. El-Boshy *et al*. [17] in rats document a sharp increase in malondialdehyde (MDA) levels, a key marker of lipid peroxidation, from 1.8 ± 0.2 to 4.5 ± 0.3 nmol/mg protein in the liver. At the same time, there was a significant increase in the concentration of the pro-inflammatory cytokine tumour necrosis factor-alpha (TNF-α) from 25.6 ± 2.1 to 68.3 ± 4.5 pg/mL. These processes directly damage cell membranes and structures, initiating apoptosis, which confirms the close relationship between vitamin D toxicity, oxidative damage and immune dysregulation, as described in detail by C. Argano *et al*. [21]. A key pathophysiological consequence is soft tissue calcification, as excess $Ca^{2+}$and PO_4^{3-} ions in plasma lead to the formation of hydroxyapatite microcrystals in the walls of blood vessels, kidneys, heart and lungs, accompanied by structural and functional disorders. Renal damage is particularly pronounced, manifested by elevated urea and creatinine levels, as well as histological signs of tubular necrosis and interstitial fibrosis. The endocrine profile of this condition is characterised by a profound imbalance: a sharp suppression of parathyroid hormone secretion due to the activation of calcium-sensitive receptors (CaSR) is combined with a compensatory increase in fibroblast growth factor-23 (FGF23) levels aimed at reducing toxicity, as described by M. Gurudatta [18]. However, the effectiveness of this protective mechanism may be limited, especially in the context of a possible decrease in the expression of the Klotho co-receptor. The enzyme CYP24A1, which catalyses the inactivation of vitamin D metabolites, is substantial in the body's response to intoxication. A. Nowacka *et al*. [19] emphasise that its activity increases sharply in hypervitaminosis D, attempting to restore homeostasis by accelerating the breakdown of both calcitriol ($1,25(OH)_2D$) and its precursor 25(OH)D. A paradoxical but natural consequence is a negative effect on bone tissue. Excess vitamin D can lead to excessive stimulation of osteoclast differentiation and activity through a change in the Receptor Activator of Nuclear factor Kappa-B Ligand/Osteoprotegerin (RANKL/OPG) ratio, enhancing bone resorption, which can contribute to osteopenia. This is consistent with the data of D. Durup *et al*. [20], who observed the development of osteomalacia in female rats under conditions of hypophosphatemic hypovitaminosis, emphasising the critical significance of balanced levels of both vitamin D and phosphorus for maintaining healthy bone remodelling. Thus, hypervitaminosis D is a complex pathological condition that exceeds the scope of simple hypercalcaemia and includes the mutual reinforcement of hormonal imbalance, oxidative stress, systemic inflammation, calcification and functional damage to key organs.

Age-related features of Ca-P metabolism disorders

The most fundamental and systemic age-related changes in the regulation of phosphorus-calcium metabolism occur in the FGF23-Klotho axis, as confirmed by an

in-depth analysis in a review by S. Devi [22]. The study described in detail how Klotho, being an essential co-receptor for fibroblast growth factor-23 (FGF23), performs a key anti-ageing function. Its decreased expression with age is not only a marker but also a central driver of ageing, leading to the development of renal resistance to FGF23. S. Wang *et al*. [23] further contributed to the topic by demonstrating how a defective FGF23-Klotho axis directly contributes to chronic microinflammation and the progression of renal fibrosis, creating a cycle of damage. The study highlighted the renal link in this mechanism, clearly describing that the main physiological task of FGF23, which is produced by osteocytes, is to inhibit phosphate reabsorption in the proximal tubules of the kidneys by modulating sodium-phosphate cotransporters. Thus, age-related Klotho deficiency disrupts this negative feedback, promoting the accumulation of phosphate in the blood and the progression of hyperphosphatemia (Table 2).

Table 2. Synthesised age differences in the regulation of Ca-P metabolism

Parameter/System	Young organisms	Old organisms
Axis FGF23-Klotho	Adequate renal sensitivity to FGF23, high Klotho levels	Resistance to FGF23, a sharp decrease in Klotho, and hyperphosphataemia
Kidney function	High clearance, effective phosphaturia	Decreased glomerular filtration rate (GFR), impaired phosphate excretion
Intestinal absorption of Ca	Effective due to high expression of TRPV6 and calbindin	Possible reduction due to decreased expression of VDR and transport proteins
Systemic mineral balance	Stable ion profile	Deep remodelling of Ca and P content in organs
Musculoskeletal cross-flow	Synchronised remodelling, synergism	Imbalance, development of osteoporosis and sarcopenia

Source: compiled by the authors based on B. Zhang *et al*. [11], S. Devi [22], D.-X. Huang *et al.* [24], B. Kirk *et al*. [25]

This process is significantly exacerbated by the parallel age-related decline in renal functional reserve. Experimental data from D.-X. Huang *et al*. [24] on rats simulate this condition, demonstrating that under conditions of metabolic stress (readaptation after hypoxia), creatinine clearance drops sharply by 27%, reflecting a deterioration in glomerular filtration. The systemic nature of age-related remodelling of mineral homeostasis was demonstrated by B. Zhang *et al*. [11] in a study of ion mice. The study identified specific, organ-associated changes in the content of calcium, phosphorus and other ions, which made it possible to construct accurate "ion clocks of ageing". This indicates that Ca-P metabolism disorders are not an isolated phenomenon, but part of a profound systemic metabolic restructuring of the entire organism.

The bone manifestations of this complex of disorders were analysed from a different perspective in the context of bone-muscle cross-talk, analysed in detail by B. Kirk *et al*. [25]. The study emphasised the inextricable link between the progression of osteoporosis and sarcopenia (loss of muscle mass) through common hormonal and metabolic pathways, such as the Insulin like growth factor (IGF-1), vitamin D and chronic inflammation, which simultaneously affect bone mineral density and skeletal muscle function. This concept complements the traditional view of age-related changes in bone, which is based on a comparison of different models. A study by T. Li *et al*. [26] on growing broiler chickens demonstrates that a young organism dependent on intensive bone formation is extremely sensitive to Ca/P imbalance in the diet. Calcium or phosphorus deficiency led to sharp fluctuations in alkaline phosphatase (ALP) activity and a significant decrease in bone mineral density (by 12-18%) and bone strength (by 15-22%). In contrast, the model of hypophosphatemic hypovitaminosis D in sexually mature female rats, created by D. Durup *et al*. [20], caused the development of true osteomalacia and disruption of the mineralisation of already formed osteoid. This indicates that in adult and elderly organisms, the main problem is not the speed as the quality of remodelling, which deteriorates due to resource deficiency and hormonal resistance. A clinical study by S. Jiampochaman *et al*. [27] among elderly patients with renal insufficiency confirms the practical aspect of these changes, demonstrating the need for individual vitamin D dosing due to the reduced effectiveness of standard regimens associated with decreased renal conversion and tissue sensitivity.

Thus, the most significant age-related difference is not simply a different rate of remodelling, but a fundamental change in the state of regulatory systems. In young organisms, Ca/P imbalance mainly affects the kinetics of active bone mineralisation. In older organisms, the progression of osteomalacia and osteoporosis in the context of resistance syndrome caused by a decrease in Klotho, renal dysfunction and systemic metabolic remodelling, which creates a pathophysiological basis for a more severe course of conditions associated with hypervitaminosis D or hypoxia.

The effect of high-altitude hypoxia on oxygenation, renal function and metabolism

The effects of altitude hypoxia exert a complex and potent modulatory influence on phosphorus-calcium homeostasis, often acting as a catalyst or amplifier of disturbances initiated by other factors,

notably hypervitaminosis D. Systematic reviews by L.M. Palubiski *et al*. [28] and S.-Y. Wang *et al*. [29] described this effect, classifying it according to duration and severity. They emphasised that although acute hypoxia can cause transient changes in renal haemodynamics, chronic hypoxia leads to persistent and often irreversible disorders such as renal vascular remodelling, hyperfiltration with subsequent decline in glomerular function, and tubulointerstitial damage. These changes directly affect the ability of the kidneys to perform their role in mineral homeostasis to effectively filter and reabsorb electrolytes, particularly phosphates.

Experimental data from C. Yan *et al*. [30] on rats exposed to chronic hypoxia quantitatively confirm the specific nature of these disorders. They recorded the development of a characteristic electrolyte imbalance: stable hypocalcaemia (decrease in serum calcium to 8.1 ± 0.6 mg/dL) and hyperphosphataemia (increase in phosphorus to 7.1 ± 0.4 mg/dL). This profile (low Ca, high P) is a key pathogenetic factor, as it creates favourable conditions for FGF23 secretion by osteocytes and leads to further imbalance in the regulatory system. The adaptation of vitamin D metabolism to oxygen-deficient conditions demonstrates a compensatory response. A study by X. Chen *et al*. [31] on high-altitude rodents revealed increased expression of the CYP27B1 (1α-hydroxylase) gene in the kidneys. This was interpreted as an attempt by the body to increase the synthesis of active calcitriol ($1.25(OH)_2D$) to counteract hypocalcaemia by enhancing intestinal calcium absorption. However, in the case of excessive doses of vitamin D, this adaptation can become pathological, leading to uncontrolled generation of calcitriol and an increase in its toxic effects.

The key intracellular integrator of all responses to hypoxia is the hypoxia-inducible factor (HIF) system. G. Almanzar *et al*. [32] described in detail how the stabilisation of HIF-1α under conditions of oxygen deficiency triggers a large-scale reorganisation of cellular metabolism, directing it towards anaerobic glycolysis, and modulates numerous signalling pathways associated with angiogenesis, inflammation and cell survival. Regarding Ca-P metabolism, HIF can directly interact with the signalling pathways involved in its regulation. It is believed that there is cross-regulation between HIF and vitamin D receptor signalling. HIF can influence the transcription of VDR target genes or modulate the stability of the receptor. In addition, hypoxia through HIF activation can suppress the expression of NaPi-IIa and NaPi-IIc, the main transporters responsible for phosphate reabsorption in the renal tubules. This mechanism may explain hyperphosphataemia regardless of FGF23 levels. Studies also show that hypoxia can exacerbate oxidative stress and systemic inflammation, which in turn suppresses Klotho expression in the kidneys, as described by S.-Y. Wang *et al*. [29]. Thus, hypoxia creates a triple blow to phosphate homeostasis: through direct renal effects (inhibition of transporters), through increased resistance to FGF23 (decreased Klotho), and through modulation of vitamin D metabolism (increased CYP27B1). This complex interaction significantly increases the risk of developing severe Ca-P metabolism disorders, especially in combination with other pathological conditions, such as hypervitaminosis D, and necessitates the development of special corrective strategies for high-altitude conditions.

A structured analysis of the literature identified promising corrective approaches that act at different levels of pathogenesis. The fundamental strategy is to optimise the dietary calcium-to-phosphorus ratio, the effectiveness of which in supporting bone mineralisation has been demonstrated by T. Li *et al*. [26]. Among pharmacological methods, substances aimed at restoring the balance of the FGF23-Klotho axis stand out. B.-H. Liu *et al*. [33] demonstrated that fucoidan improves Ca-P metabolism disorders and bone abnormalities in rats with a model of chronic kidney disease, precisely through modulation of this axis. Another approach is to combat oxidative stress with antioxidants, the effectiveness of which is substantiated by data from M. El-Boshy *et al*. [17] on a significant increase in lipid peroxidation markers in hypervitaminosis D. Non-pharmacological interventions are substantial. J. Zhang & Z.-B. Cao [34] provided convincing evidence that regular exercise is an effective way to improve vitamin D status and tissue sensitivity to it. The general principles of renoprotection and gradual adaptation to hypoxic conditions, described in the reviews by S.-Y. Wang *et al*. [29], form the basis for a physiological approach to the prevention of mineral metabolism disorders in high altitude conditions.

The obtained results can be used to analyse the complex nature of phosphorus-calcium metabolism disorders under the combined effects of hypervitaminosis D and altitude hypoxia, considering the age factor. The synergistic effect between these factors requires in-depth consideration of molecular and physiological mechanisms. The study by W.R. Beck *et al*. [35] demonstrates the complex effect of hypoxia on bone tissue, which is consistent with the data obtained on mineralisation disorders. The use of network analysis revealed specific changes in bone microarchitecture under conditions of simulated altitude training, confirming the significance of structural changes in bone when analysing Ca-P metabolism disorders. It has been established that hypoxia can modulate bone remodelling processes by altering the balance between mineralisation and resorption, which explains the age-related differences in susceptibility to Ca-P homeostasis disorders. O. Melnyk *et al*. [36] revealed the integral nature of the body's responses to hypoxic stress, confirming the data obtained on the systemic effects of hypoxia. A close relationship between the state of the neuro-endocrine-immune complex and metabolomic

indicators under conditions of acute stress has been proven, which is consistent with the identified disturbances in hormonal regulation. Specific markers of metabolic disorders that correlate with individual resistance to hypoxia were identified, emphasising the need for an individual approach to assessing the effects of hypoxic exposure. E. Sivertsson *et al*. [37] demonstrated a new mechanism of intrarenal hypoxia development, which complements the data obtained on renal disorders. The study demonstrated that thyroid hormones can induce intrarenal hypoxia by enhancing oxygen metabolism, which may be an additional factor in kidney damage in conditions of endocrine regulation disorders. This mechanism is substantial for research on the relationship between different hormonal systems in hypoxia.

The study by Y. Du *et al*. [38] reveals the molecular mechanisms of renal damage under hypoxia, confirming the data obtained on renal function disorders. Impaired uric acid excretion and changes in desmin expression in podocytes have been established, which is consistent with the identified signs of renal dysfunction. A decrease in Na+-K+-ATPase activity was detected, indicating impaired energy metabolism in renal cells and explaining the development of renal dysfunction under conditions of high-altitude hypoxia. D. Chang *et al*. [39] demonstrate the effectiveness of corrective interventions under conditions of hypoxia, confirming the promise of the developed corrective approaches. The protective role of L-carnitine in the reproductive system under hypoxic stress has been proven, indicating the promise of using metabolic correctors. A positive effect on the hormonal profile and spermatogenesis indicators has been found, confirming the possibility of correcting hypoxic damage. The study by M.M. Soliman *et al*. [40] provides substantial data on oxidative stress in high altitude conditions, which is consistent with the results obtained on oxidative stress in hypervitaminosis D. An increase in lipid peroxidation markers and changes in antioxidant protection were found, confirming the role of oxidative stress in the pathogenesis of hypoxic lesions. Histochemical studies have confirmed the presence of structural changes in various organs, which explains the systemic nature of lesions when hypoxia and hypervitaminosis D are combined. A.E. Ahmed *et al*. [41] demonstrated peculiarities of metabolic disorders in high-altitude populations, which complements the data obtained on age characteristics. The prevalence of metabolic syndrome and its components among high-altitude residents was analysed, confirming the relevance of considering the age factor. Age and gender characteristics of lipid metabolism disorders and cardiometabolic risks were established, which is relevant for the development of prevention strategies.

A study by L. Jie *et al*. [42] on a rat model with comorbid osteoarthritis and osteoporosis demonstrated that the alkaloid palmatine can effectively influence bone tissue metabolism disorders by modulating the intestinal microflora and host metabolism. This highlights the potential role of prebiotics, probiotics, or metabolically active compounds in correcting Ca-P metabolism disorders, especially when they are associated with systemic inflammation and metabolic syndrome, which often accompany ageing. Similar approaches that aim to restore intestinal homeostasis may improve mineral absorption and tissue sensitivity to vitamin D. Insulin-like growth factor-1 can be integral in restoring renal function and bone metabolism. As noted by J.M.D. Tocados *et al*. [43], IGF-1 has pleiotropic effects in renal diseases, including anti-fibrotic and anti-apoptotic actions and involvement in the regulation of phosphate homeostasis. Therefore, strategies aimed at supporting or modulating the IGF-1 pathway are useful for protecting the kidneys from damage caused by both hypercalcaemia in hypervitaminosis D and ischaemia under conditions of hypoxia, thereby indirectly improving the regulation of Ca-P metabolism. When considering correction of the FGF23-Klotho axis, it is necessary to address the latest insights into the regulation of FGF23. S. Dastghaib *et al*. [44] emphasised the complex regulation of FGF23 expression and secretion, which depends not only on phosphate levels, but also on inflammatory cytokines, iron and oxidative stress. This creates opportunities for indirect influence on FGF23 through control of these factors, for example, with antioxidants or anti-cytokine therapy, which is relevant in hypervitaminosis D, accompanied by powerful oxidative stress. A fundamental aspect of any vitamin D-related correction remains its receptor (VDR). The molecular mechanisms of vitamin D3 action via VDR in different tissues are described in detail by V. Morsanuto [45]. Determination of the tissue-specific modulation of VDR-dependent pathways contributes to the development of selective vitamin D receptor modulators that would have protective effects on bones and kidneys, minimising the risk of soft tissue calcification during the correction of hypovitaminosis or excess. The potential role of vitamin D3 as a protector against hypoxic damage is noteworthy, as it can be substantial for patients in high altitudes. A study by C. Dai *et al*. [46] showed that vitamin D3 reduces hypoxia-induced lung damage by suppressing the complement system, coagulation, and autophagy pathways. This suggests that adequate (but not excessive) vitamin D levels are a substantial factor in resistance to hypoxic stress, particularly for protecting the vascular endothelium and preventing microvascular complications that exacerbate Ca-P metabolism disorders. Integrating the results of these studies formed a comprehensive pathogenetic model. The combination of hypervitaminosis D and hypoxia leads to a synergistic increase in Ca-P metabolism disorders through several interrelated mechanisms. Hypoxia-induced renal dysfunction limits phosphate excretion, exacerbating hyperphosphataemia.

Adaptation of vitamin D metabolism in the form of increased CYP27B1 expression under conditions of substrate excess leads to hypercalcitriolaemia. Age-related features determine the direction of organ damage – from calcification to osteomalacia.

Conclusions

Based on a systematic analysis of the literature, Ca-P metabolism is defined as a complex integrated network in which vitamin D metabolism is central. The key mechanism for maintaining homeostasis is the dynamic balance between parathyroid hormone (a stimulator of calcitriol synthesis) and FGF23 (its inhibitor), and the Ca/P ratio in blood plasma can serve as an integral indicator of the state of the system. A review of experimental data shows that hypervitaminosis D leads to a complex pathological condition characterised not only by pronounced hypercalcaemia and hyperphosphataemia, but also by severe oxidative stress, systemic inflammation, suppression of PTH secretion, compensatory increase in FGF23, and activation of the CYP24A1 inactivation enzyme. This leads to a high risk of soft tissue calcification and paradoxical bone mineralisation disorders.

The age factor determines fundamental changes in the reactivity of the Ca-P exchange system. The most substantial link is the age-related decrease in the expression of the Klotho co-receptor, which leads to renal resistance to FGF23, progression of hyperphosphataemia, renal dysfunction and impaired bone-muscle cross-flow. In young organisms, disorders prevail in the kinetics of bone formation, while in older organisms, they prevail in remodelling, leading to osteomalacia and osteoporosis. Altitude hypoxia acts as a substantial modulator that exacerbates Ca-P homeostasis disorders through a range of mechanisms: it causes a characteristic electrolyte imbalance (hypocalcaemia and hyperphosphataemia), contributes to renal dysfunction, inhibits Klotho expression, modulates the activity of renal phosphate transporters, and increases CYP27B1 expression. The latter, in conditions of excess vitamin D intake, can contribute to uncontrolled calcitriol synthesis. This synthesis suggests a synergistic effect between hypervitaminosis D, hypoxia, and ageing. This synergy may be realised through the mutual reinforcement of the following links: renal dysfunction under hypoxia limits phosphate excretion, exacerbating hyperphosphataemia from vitamin D, and increased CYP27B1 expression under hypoxia contributes to excessive calcitriol formation. Age-related Klotho deficiency and decreased functional reserves create the basis for a more severe course of such combined lesions.

A review of the literature indicates the promise of multi-level approaches to correction, including optimisation of the dietary Ca/P ratio, use of substances to modulate the FGF23-Klotho axis and combat oxidative stress, use of non-pharmacological methods (physical exercise), as well as strategies for renoprotection and adaptation to hypoxia. Some studies also highlight the potential role of modulation of the microbiome, the IGF-1 pathway, selective VDR modulators, and adequate vitamin D levels in protecting against hypoxic damage. Prospects for further research include experimental verification of the synergy of factors in a single model, study of the molecular mechanisms of cross-interaction between HIF and VDR pathways, as well as preclinical and clinical evaluation of comprehensive corrective approaches.

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Conflict of Interest

None.

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Эксперименталдык D витамини гипервитаминозу шартында ар кандай бийиктиктерде жана анын түзөтүү жолдору аркылуу жаш жана кары чычкандардагы фосфор-кальций метаболизминин абалы

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Аннотация. Бул изилдөөнүн максаты – гипервитаминоз D, бийиктиктеги гипоксия жана куракты айкалышкан таасири астында кальций-фосфор алмашуунун бузулуу механизмдери боюнча учурдагы илимий маалыматтарды системалуу талдоо жана синтездоо, ошондой эле натыйжалуу түзөтүү ыкмаларын негиздөө болду. Илимий булактар салыштырма талдоо, маалыматтарды синтездоо жана маалыматты жалпылоо ыкмалары менен талданды. Талдоо көрсөткөндөй, Ca-P метаболизмин жөнгө салуу системасы – бул татаал тармак, анын борборунда D витаминин метаболизми турат, ал эми паратирин гормону менен FGF23 ортосундагы тең салмактуулук плазмадагы Ca жана P деңгээлин туруктуу кармап турууга жооптуу. Илимий булактарды талдоо метаболикалык бузулуулардын куракка байланыштуу мүнөздүү өзгөчөлүктөрүн аныктады. Маалыматтар сөөк ремоделирлөө деңгээли жогору болгон жаш организмдерде Ca/P теңсиздиги сөөк минералдык тыгыздыгынын 12-18 %га кыскарышына алып келерин көрсөттү, ал эми карыган организмдерде функционалдык резервдердин азайышы шартында прогрессивдүү остеомаляция жана бөйрөк жетишсиздигинин өнүгүшү тууралуу маалыматтар үстөмдүк кылат. Жогорку бийиктиктеги гипоксиянын таасири боюнча жүргүзүлгөн изилдөөлөрдүн обзору анын бөйрөк функциясынын бузулушун (креатининдин 0,81 ± 0,04 мг/длге чейин жогорулашы), электролиттердин теңсиздиги (кальцийдин 8,1 ± 0,6 мг/длге чейин төмөндөшү жана фосфордун 7,1 ± 0,4 мг/длге чейин жогорулашы) жана D витаминин метаболизминин адаптациясы, өзгөчө CYP27B1 экспрессиясынын жогорулашы аркылуу. Анализдин жыйынтыгында алынган корутундулар жогорку тоолуу аймактарда жашаган ар кандай курактагы бейтаптарга D витаминин коопсуз кошумча берүү боюнча илимий негизделген сунуштарды мындан ары иштеп чыгууда теориялык мааниге ээ

Негизги сөздөр: паратирин гормон; остеомаляция; жогорку бийиктиктеги гипоксия; куракка байланыштуу өзгөчөлүктөр; бөйрөк жетишсиздиги

Состояние фосфоро-кальциевого обмена у молодых и старых крыс в условиях экспериментального гипервитаминоза витамина D на разных высотах и способы его коррекции

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Аннотация. Целью данного исследования было систематическое анализирование и обобщение современных научных данных о механизмах нарушений кальций-фосфорного обмена под комбинированным воздействием гипервитаминоза D, высотной гипоксии и возраста, а также обоснование эффективных корректирующих подходов. Научные источники были проанализированы с использованием методов сравнительного анализа, синтеза данных и обобщения информации. Проведенный анализ показал, что система регуляции метаболизма Ca-P представляет собой сложную сеть, в центре которой находится метаболизм витамина D, где баланс между паратиреоидным гормоном и FGF23 определяет стабильность уровней Ca и P в плазме. Анализ научных источников выявил характерные возрастные особенности нарушений метаболизма. Данные показали, что у молодых организмов с высоким уровнем ремоделирования костей дисбаланс Ca/P может привести к значительному снижению минеральной плотности костей (на 12-18 %), тогда как у пожилых организмов преобладают данные о развитии прогрессирующей остеомаляции и почечной недостаточности на фоне снижения функциональных резервов. Обзор исследований по влиянию высокогорной гипоксии показал, что она может вызывать комплекс нарушений, в том числе почечную дисфункцию (повышение креатинина до 0,81 ± 0,04 мг/дл), электролитного дисбаланса (снижение кальция до 8,1 ± 0,6 мг/дл при повышении фосфора до 7,1 ± 0,4 мг/дл) и адаптации метаболизма витамина D, в частности, за счет повышения экспрессии CYP27B1. Выводы, полученные в результате анализа, имеют теоретическое значение для дальнейшей разработки научно обоснованных рекомендаций по безопасному добавлению витамина D в рацион пациентов разных возрастных групп, проживающих в высокогорных регионах

Ключевые слова: паратиреоидный гормон; остеомаляция; высокогорная гипоксия; возрастные особенности; почечная недостаточность