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Violation of Mineral Metabolism and Vascular Remodeling in Chronic Kidney Disease (CKD)

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Abstract Violation of mineral metabolism and vascular remodeling in Chronic kidney disease (CKD) is one of the formidable and common complications of this condition. One of the main risk factors for remodeling is a violation of mineral metabolism, namely phosphorus-calcium. Abnormalities in the metabolism of calcium, phosphorus, parathyroid hormone (PTH) and vitamin D lead to ectopic, i.e. vascular or tissue calcification. To date, studies concerning ectopic calcification are of great interest to researchers, which is due to both the improvement of methods for detecting calcification and the sharp progression of its prevalence due to the pandemic of chronic non-communicable diseases, including CKD

Keywords: chronic kidney disease, vascular remodeling, ectopic calcification, acute and chronic cerebrovascular accident.

Introduction. Vascular remodeling is a change in the structure and function of blood vessels in response to the influence of pathological factors, which is the leading link in the defeat of the cardiovascular and cerebrovascular system in CKD. Remodeling of the vascular wall in CKD occurs under the influence of numerous cardiovascular risk factors, both traditional (arterial hypertension - hypertension, including isolated systolic hypertension, metabolic syndrome, smoking) and directly caused by kidney damage (proteinuria, anemia, violation of phosphorus–calcium metabolism, hyperhomocysteinemia) [2]. Remodeling of cerebral vessels in CKD contributes to the formation of cerebrovascular insufficiency, leading to acute and chronic disorders of cerebral circulation [Shishkova V.N., 2014; Yakhno N.N., 2005; Bajaj J.S., 2014]. One of the main risk factors for remodeling is a violation of mineral metabolism, namely phosphorus-calcium. Abnormalities in the metabolism of calcium, phosphorus, parathyroid hormone (PTH) and vitamin D lead to ectopic, i.e. vascular or tissue calcification. To date, studies concerning ectopic calcification are of great interest to researchers, which is due to both the improvement of methods for detecting calcification and the sharp progression of its prevalence due to the pandemic of chronic non-communicable diseases, including CKD [12]. The relationship between vascular calcification and kidney damage was described by Virchow in 1855 and in 1979 by Alfred [8] showed its high prevalence in patients with CKD. According to literature data, vascular calcification begins 10-20 years earlier in patients with CKD than in the general population. The prevalence of calcification at the predialysis stages reaches 80% [6], and at the initiation of dialysis -100% [10]. As renal insufficiency progresses, the excretory function of the kidneys decreases, i.e. the excretion of phosphorus in the urine. Hyperphosphatemia entails excessive production of PTH, which in turn compensatorily stimulates the release of Ca

(calcium) from bones and an increase in vitamin D synthesis. There are two types of vascular calcification: calcification of the intima of the arteries and calcification of the media. Calcification of intima, characterized by lipid accumulation, inflammation and apoptosis, is closely associated with atherosclerosis [1,3,4]. Mediacalcinosis develops independently of the presence of atherosclerosis and is characterized by diffuse calcification of the media, an increase in the number of collagen fibers with a relative decrease in the content of elastic fibers, which leads to arterioclerosis and increased stiffness of the vascular wall [1,4,7]. Calcification of arterial walls in patients with CKD occurs both at the intima level and in the middle layer of the arterial wall, independently or simultaneously [1, 3, 4-7].

Loss of elasticity of the walls of the arteries accelerates the pulse wave, and, as a result, disrupts the process of oxygenation in the capillary bed, increases systolic blood pressure. On the other hand, systemic inflammation, oxidative stress and unfavorable lipid profile in uremia, responsible for endothelial dysfunction and vascular intima damage, contribute to the formation of atherosclerotic plaques and acceleration of atherosclerosis processes. In conditions of hyperphosphatemia and an increased level of calcium-phosphorus product, calcium phosphate is deposited in atherosclerotic plaques, stenosis and thrombosis of blood vessels, which are realized in a heart attack and stroke. Thus, the processes of violation of calcium-phosphorus homeostasis lead to unfavorable outcomes of MCS-CKD: vascular pathology, increased overall mortality. Ultrasound is the only noninvasive imaging method capable of differentiating the layers of the arterial wall and localizing calcium deposits in it [9, 11].

The purpose of our study was to study the violation of mineral metabolism and the degree of calcification of brachiocephalic arteries in patients with CKD.

Objective:

1. Examination of patients with CKD (complaints, anamnesis morbi, vitae, general examination, neurological status,laboratory diagnostic methods: determination of Ca and P in serum), duplex scanning of brachiocephalic vessels.

2. To study the available algorithms and methods of laboratory and instrumental diagnostics of CKD patients with neurological complications in healthcare practice.

3. Introduction of early diagnosis of mineral metabolism disorders in patients with CKD to prevent vascular remodeling and calcification.

Materials and methods of research:

Under our supervision were 101 patients diagnosed with CKD who received inpatient treatment and planned hemodialysis in the department of TSTP on the basis of the multidisciplinary clinic of the Center for the development of professional qualifications of medical workers. CKD was diagnosed based on the KDIGO (Kidney Disease: Improving Global Outcomes) criteria developed in 2002 [6]. Of these, 61 (60.3%) are men, and 40 (39.6%) are women. The average age of all patients was 46.2±15.01 years, while the average age of men was 42.2±12 years, the average age of women was 39.3±11.5 years. The control group included 50 practically healthy people (average age – 41.3 years (20-66 years)), of which 23 men (46.0%), 27 women (54.0%).

According to the Classification of ICD 10 (N18), all patients are divided into 3 groups:

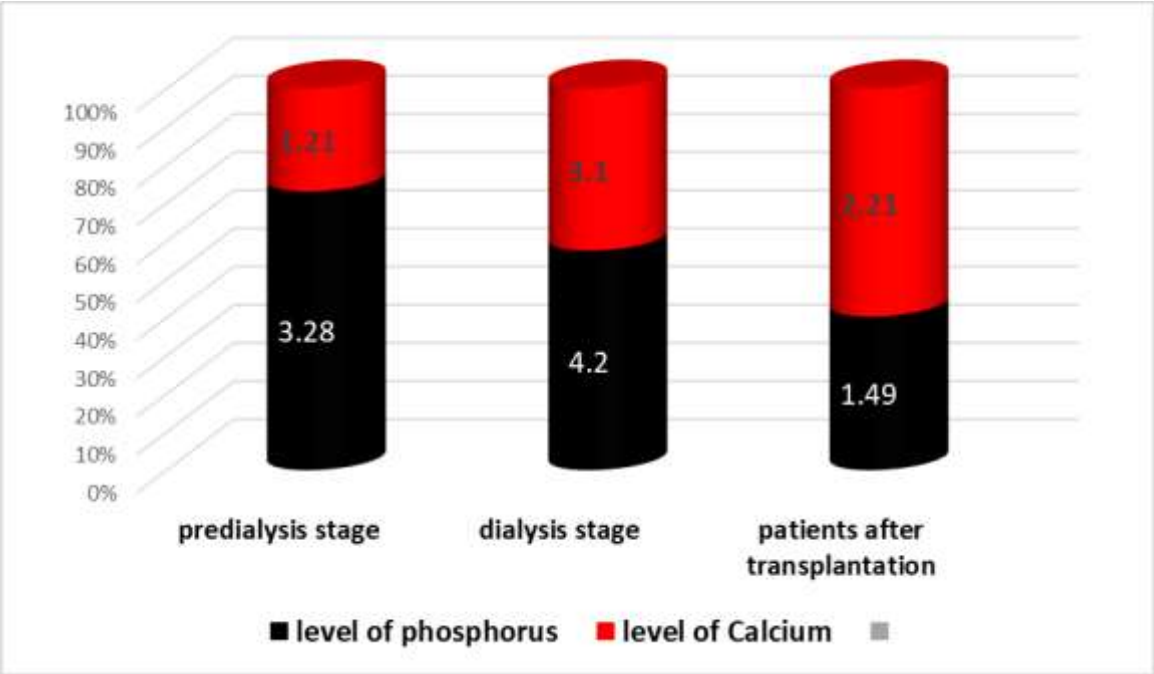
1.Predialysis patients (N18.1 N18.2 N18.3 N18.4) – 28 patients (28%). The average age was 56.1±12.1

2. Patients on planned hemodialysis (N18.5) – 30 patients (30%). The average age was 53.1±13.3

3. Patients after kidney transplantation (Z94.0) – 43 patients (43%). The average age was 34.8±9.3

All patients were assessed for serum levels of P (phosphorus), Ca (calcium) and PTH (parathyroid hormone), as well as duplex scanning of brachiocephalic vessels.

Results of the study: The level of P (phosphorus), Ca (calcium) and PTH (parathyroid hormone) depending on the stage of the disease (average arif)



In the group of patients at the predialysis stage of CKD, the average phosphorus level was 3.28±0.81 (norm 0.87-1.45); the Ca level was 1.21±0.74 (2.25-2.75); the parathyroid hormone level was 96.5±1.64. Due to a decrease in the number of functioning nephrons and a decrease in GFR <60 ml/min, secretory kidney function decreases and hyperphosphatemia was observed in patients at this stage. In response to hyperphosphatemia by osteoblasts and osteocytes, the production of the hormone phosphotanin FGF23 increases, which suppresses the synthesis of calcitriol, it in turn reduces the absorption of Ca, resulting in hypocalcemia in patients at this stage. A decrease in calcium levels increases the production of PTH and, as a consequence, leads to hyperplasia of the parathyroid glands.

In the group of patients undergoing programmed hemodialysis, the phosphorus level was 4.2± 1.7; Ca 3.1±1.8: PTH 250±2.7. At this stage, almost all patients had hyperphosphatemia. Hyperproduction of PTH stimulates the release of calcium from the bone, bringing the blood calcium level to normal or increased. The PTH level remains elevated.

In patients after transplantation, the average serum P level was 1.49±0.54; calcium level was 2.21±0.88; PTH level was 70.65±2.54. Which indicates a gradual restoration of mineral dysfunction.

Systemic disorder of mineral metabolism leads to a number of complications from the bone (as a result of the leaching of calcium from the bones) and cardiovascular systems (due to the deposition of calcium phosphates on the heart valves and on the walls of blood vessels). The already existing violation of lipid metabolism and the presence of atherosclerosis further aggravates this condition. Ca phosphates are deposited on the atherosclerotic plaque, leading to the development of a complicated type 5 plaque, which leads to vascular stenosis and the development of complications.

Results of ultrasound examination of blood vessels in groups of patients with CKD and the control group:

Arteries	parameter	CKD 1-4 (dialysis patients) (n=28)	Stage 5d CKD. (patients on programmed hemodialysis) (n=30)	CKD (post-transplant condition) n=43
CCA (COMMON CAROTID ARTERY)	**Diameter**	5,85±0,344	4,423±0,591	4,423±0,591
	Vps	94,286±1,013	91,233±2,417	91,233±2,417
	Ved	24,321±1,09	20,96±2,157	20,96±2,157
	IR	0,734±0,017	0,761±0,029	0,761±0,029
	Thickness of the intima media complex	1,039±0,142	1,27±0,215	1,27±0,215
	The presence of calcification	21%(6)	36,6% (11)	16% (7)
ICA (Internal carotid artery)	**Diameter**	4,268±0,279	4,03±0,36	4,03±0,36
	Vps	64,071±1,438	63,1±2,325	63,1±2,325
	Ved	24,217±1,137	22,6±3,155	22,6±3,155
	IR	1,029±304	0,74±0,114	0,74±0,114
	Thickness of the intima media complex	1,05±0,143	1,2±0,271	1,2±0,271
	The presence of calcification	39%(11)	43,3%(13)	18,6%(8)
ECA (external carotid artery)	**Diameter**	3,88±0,141	3,867±0,135	3,867±0,135
	Vps	81,143±0,744	80,767±1,251	81,143±0,744
	Ved	15,536±1,201	15,067±1,337	15,536±1,201
	IR	0,827±0,031	0,80±0,017	0,827±0,031
	Thickness of the intima media complex	1,096±0,19	1,103±0,201	1,096±0,19
	The presence of calcification	28%(8)	40%(12)	13,9%(6)
VA (VERTEBRAL ARTERY)	**Diameter**	3,88±0,141	2,82±0,35	3,88±0,141
	Vps	81,143±0,744	45,133±1,137	81,143±0,744

	Ved	15,536±1,201	14,567±1,501	15,536±1,201
	IR	0,827±0,031	1,054±0,174	0,827±0,031
	Thickness of the intima media complex	1,096±0,19	1,107±0,238	1,096±0,19
	The presence of calcification	42%(12)	50%(15)	25,5%(11)

Vps – peak systolic blood flow rate; Ved – final diastolic blood flow rate;
IR – Resistance index; ТКИМ – Thickness of the intima media complex

When analyzing the data of ultrasound examination of brachiocephalic vessels, significant calcification of the vessels of patients with CKD was revealed. Type V atherosclerotic plaque (type V: unclassifiable due to severe calcification forming an acoustic shadow.) in the group of patients who receive programmed hemodialysis was detected in the OSA in 50% (15), in the ICA in 43%(13), in the NSA in 40%(12) and in the PA in 36.6(11) cases. In the group of patients who are in the predialysis period of CKD, plaques with calcification were in the OCA in 30% (10), in the ICA in 28% (8), in the NSA in 21% (6), PA 36.6% (11).

Calcified plaques were also detected in the group of patients after transplantation, despite the younger age of patients in this group in the CCA of 23.2%(10), ICA of 10%(11), ECA of 10%(11), VA in 16.2%(7).

TCIM was increased (<0.9) in all study groups, but the highest indicators were in the group of patients who are on routine hemodialysis (CCA 1.27±0.215; ICA 1.2±0.271; ECA 1.103±0.201; PA 1.107±0.238 p <0.001). Regression analysis was performed to identify risk factors affecting carotid artery TKIM. At the same time, TKIM was chosen as a dependent variable, and as an independent variable, factors that could potentially affect the development of complicated calcified plaque are: age, duration of the disease, phosphorus, calcium, cystatin C levels. When assessing risk factors potentially affecting TKIM, the influence of patients' age (p <0.001), serum phosphorus level (p <0.001), duration of the disease (p <0.003) (R2=0.33; F=41.09; p <0.001) was revealed.

Correlations were also calculated in the group of patients undergoing hemodialysis: a significantly significant medium-strength correlation was revealed between the age of patients and the diameter of the CCA (r=-0.7813 P <0.0001) as well as a significantly significant strong correlation between the level of phosphorus and TCIM (r=0.7967 P <0.0001)

Conclusions:

Patients with CKD have all the risk factors for the development of atherosclerosis of blood vessels (arterial hypertension, impaired lipid metabolism, anemia, the effect of uremic toxins).Violation of mineral metabolism depending on the stage of CKD (hyperphosphatemia, hypocalcemia, increased PTH levels) exacerbates this condition with the development of vascular calcification. Our research proves that the violation of mineral metabolism in direct and indirect ways affects vascular remodeling and thereby causes the development of formidable complications from the nervous system. Statistically significant correlations between the levels of phosphorus, calcium and the diameter of the WASP were revealed. When assessing risk factors potentially affecting TKIM, the influence of patients' age (p<0.001), serum phosphorus level (p<0.001), duration of the disease (p<0.003) (R2=0.33; F=41.09; p<0.001) was revealed. It is safe to note that impaired mineral metabolism and vascular remodeling are prognostic predictors of the development of cerebrovascular complications in patients with CKD . As a result, early detection and treatment of mineral metabolism can prevent complications from the nervous system, improve the quality and life expectancy of renal patients.

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