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CHARACTERISTICS OF ALTERATIONS IN PHOSPHORUS-CALCIUM METABOLISM IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND ARTERIAL HYPERTENSION

Abstract

According to recent research, the number of patients with chronic kidney disease (CKD) — a significant cause of mortality — is increasing globally. Serious complications of CKD include disturbances in phosphorus-calcium metabolism and pathological changes in the cardiovascular system. Arterial hypertension is considered a primary risk factor for the progression of CKD and is present in 85–100% of patients with CKD. On one hand, declining renal function can contribute to the development of hypertension; on the other, arterial hypertension can mask the manifestations of the underlying disease. The objective of the study was to determine the interrelationships between serum phosphorus and calcium levels and urinary hydroxyproline levels in patients with various stages of CKD, depending on the presence of arterial

hypertension. The study included 76 patients with CKD (mean age 36.5 ± 12.8 years). By CKD stage, patients were divided into four groups: Stage I — 22 (29%), Stage II — 28 (37%), Stage IIIA — 14 (19%), and Stage IIIB — 12 (15%). By the presence of arterial hypertension, two groups were formed: Group A — 42 patients with hypertension (55%), and Group B — 34 patients without hypertension (45%). The study revealed alterations in phosphorus-calcium metabolism in patients with stages I–III CKD, characterized by a tendency toward elevated phosphorus and decreased calcium levels, as well as alterations in collagen metabolism markers in both groups. The urinary content of total hydroxyproline and its free fraction in patients with CKD — both with and without hypertension — was statistically significantly higher than in healthy individuals ($p < 0.05$). In Group A, the total hydroxyproline fraction was 38.8 ± 3.7 mg/day, and in Group B, 37.3 ± 5.4 mg/day; the free fraction was 6.86 ± 1.02 mg/day in Group A and 4.04 ± 0.47 mg/day in Group B. It was concluded that disturbances of phosphorus-calcium metabolism accompany CKD and are associated with increased urinary excretion of the free hydroxyproline fraction, while the presence of arterial hypertension is associated with more pronounced disturbances of mineral and collagen metabolism in patients with CKD.

Key words: phosphorus-calcium metabolism, chronic kidney disease, arterial hypertension, hydroxyproline, collagen metabolism, renal osteodystrophy.

Problem statement

According to recent studies, the number of patients with chronic kidney disease (CKD) is increasing worldwide, and CKD is one of the leading causes of patient death. Severe complications of CKD include disturbances of phosphorus-calcium metabolism (PCM) and cardiovascular complications. Substantial disturbances of mineral metabolism and of the calcium-regulating hormone system create conditions for an imbalance in bone-tissue remodeling already at the early stages of CKD. These complications lead to the formation of renal osteodystrophy, which substantially

reduces treatment efficacy and worsens the course of the underlying disease. The identification of early, informative markers of these disturbances therefore remains a relevant task of modern nephrology.

Analysis of recent research and publications

According to many authors, arterial hypertension (AH) develops in 85–100% of patients with CKD [1, 2]. A close correlation has been identified between the degree of AH and the severity of CKD and its mineral-metabolism complications. The role of the kidneys in regulating PCM is well known, owing to the synthesis of active vitamin D metabolites in the mitochondria of proximal tubular epithelial cells; therefore, renal osteodystrophy is a frequent manifestation of progressive loss of renal function. As CKD progresses, phosphate retention increases and hyperphosphatemia becomes persistent. A high phosphate concentration stimulates the synthesis of parathyroid hormone, leading to reduced calcitriol synthesis and hypocalcemia [3, 4]. AH is currently regarded as one of the most important risk factors for CKD progression, and cardiovascular complications are the most common causes of death in patients with CKD. AH, hyperphosphatemia, lipid metabolism disorders, and immune system impairment are considered the main factors of CKD progression. Thus, the data available to date indicate that kidney disease can lead to hypertension, and that a correlation exists between CKD stage and the presence and level of AH. At present, an increase in CKD incidence is observed, along with acceleration of fibroplastic and sclerotic processes in the kidneys and an increased frequency of treatment resistance [5, 6].

Objective of the article

To determine the interrelationships between serum phosphorus and calcium levels and the levels of various hydroxyproline fractions in the urine in patients with different stages of CKD, depending on the presence of arterial hypertension.

Presentation of the main material

Materials and methods. The study enrolled 76 patients with CKD aged 22–60 years; the mean age was 36.5 ± 12.8 years. Among those examined were 48 women (63%) and 28 men (37%). Based on CKD stage, patients were divided into four groups: Stage I — 22 (29%), Stage II — 28 (37%), Stage IIIA — 14 (19%), and Stage IIIB — 12 (15%). Based on the presence of AH, two groups were formed: Group A — 42 patients with hypertension (55%), and Group B — 34 patients without AH (45%).

The diagnosis of CKD was established taking into account complaints, medical history, and the results of clinical and laboratory examinations in accordance with the requirements of Order No. 593 of the Ministry of Health of Ukraine dated 02.12.2004 (as amended by Order No. 384 of the Ministry of Health of Ukraine dated 24.05.2012), the KDIGO 2012 criteria, and the recommendations of the National Kidney Foundation (NKF-K/DOQI, USA). Patients with glomerulonephritis, pyelonephritis, and diabetic kidney disease were included in the observation.

The CKD stage was determined by the glomerular filtration rate (GFR): a value ≥ 90 mL/min corresponded to Stage I, 60–89 mL/min to Stage II, 45–59 mL/min to Stage IIIA, and 30–44 mL/min to Stage IIIB. Persons over 60 years of age, women in menopause, and patients with concomitant somatic pathology were not included in the study. The control group comprised 15 practically healthy individuals matched by age and sex to the main group.

Serum phosphorus concentration was determined by a biochemical photometric method using the "Human" kit, and calcium by a biochemical photometric o-cresolphthalein method using the "Human" kit. The total, free, and bound hydroxyproline fractions in urine were determined by the method of P. N. Sharaev as modified by L. A. Utevska. Statistical analysis was performed using the Statistica for Windows software package, version 6.0; differences were considered statistically significant at $p < 0.05$.

Results. The analysis showed that the levels of total and bound hydroxyproline in the urine of patients with CKD did not demonstrate a clear dependence on the stage

of the disease (Table 1). At the same time, the content of the free hydroxyproline fraction was statistically significantly higher in patients with CKD than in the control group ($p < 0.05$). Comparison of hydroxyproline parameters in patients with Stage I and Stage II CKD revealed no statistically significant differences, which may be associated with the preservation of the body's compensatory capacity at the early stages of the disease. Upon transition to Stage III, statistically significant differences in the corresponding parameters were observed compared with Stage II ($p < 0.05$). Patients with CKD also showed alterations in phosphorus-calcium metabolism, characterized by a tendency toward elevated phosphorus and decreased calcium levels.

Table 1

Hydroxyprolinuria parameters depending on CKD stage (mg/day)

Observation group	**Phosphorus, mmol/L**	**Calcium, mmol/L**	**Total hydroxyproline**	**Free hydroxyproline**	**Bound hydroxyproline**
Stage I CKD	1.15 ± 0.04	2.34 ± 0.03	39.5 ± 4.5	4.1 ± 0.4	34.2 ± 4.2
Stage II CKD	1.66 ± 0.16	2.36 ± 0.1	32.9 ± 3.6	4.5 ± 0.7	27.1 ± 3.1
Stage IIIA CKD	1.84 ± 0.12	2.07 ± 0.1	40.1 ± 4.9	6.5 ± 0.9 *1, *2	30.7 ± 4.1
Stage IIIB CKD	1.86 ± 0.13	2.09 ± 0.1	41.4 ± 4.3	7.2 ± 0.8 *1, *2	31.4 ± 3.8
Control group	1.48 ± 0.3	2.31 ± 0.1	26.8 ± 2.5	2.3 ± 0.3	22.65 ± 2.8

Note: *1 — statistically significant difference compared with Stage I CKD; *2 — statistically significant difference compared with Stage II CKD; ^{n} — statistically significant difference compared with the control group.

Source: developed by the author based on the study results.

When comparing patients by the presence of AH, alterations in collagen metabolism markers were established in both groups. The total content of hydroxyproline in the urine of patients with CKD — both with and without hypertension — was statistically significantly higher than in healthy individuals ($p <$

0.05). In Group A (CKD with AH), the total hydroxyproline fraction was 38.8 ± 3.7 mg/day, whereas in Group B (CKD without AH) it was 37.3 ± 5.4 mg/day. The free fraction also exceeded control values: 6.86 ± 1.02 mg/day in Group A and 4.04 ± 0.47 mg/day in Group B. The level of the bound hydroxyproline fraction in patients with AH was slightly lower than in patients without AH; this difference was not statistically significant, although the parameter in both groups exceeded the control value ($p < 0.05$). Phosphorus-calcium metabolism parameters also differed depending on the presence of AH (Table 2).

Table 2

Serum phosphorus and calcium and urinary hydroxyproline fractions in patients with CKD with and without AH

Parameter	**Control group**	**CKD with AH**	**CKD without AH**
Phosphorus, mmol/L	1.48 ± 0.03	1.59 ± 0.07	1.24 ± 0.09
Calcium, mmol/L	2.31 ± 0.1	2.2 ± 0.06	2.36 ± 0.06
Total hydroxyproline, mg/day	26.8 ± 2.5	38.8 ± 3.7	37.3 ± 5.4
Free hydroxyproline, mg/day	2.3 ± 0.3	6.86 ± 1.02 *	4.04 ± 0.47
Bound hydroxyproline, mg/day	22.65 ± 2.8	32.01 ± 3.6 ^{n}	33.3 ± 5.3 ^{n}

Note: * — statistically significant difference between groups; ^{n} — statistically significant difference compared with the control group.

Source: developed by the author based on the study results.

Discussion. The analysis performed did not demonstrate an unambiguous relationship between CKD stage and the levels of individual hydroxyproline fractions, except for the bound fraction. This may be explained by the interdependence of collagen synthesis and degradation. The content of bound hydroxyproline reflects the

activity of collagen formation and the intensity of fibrillogenesis; the mean values of this parameter tended to exceed control levels. Thus, nephrosclerotic changes in CKD may be accompanied by a simultaneous intensification of collagen degradation, fibrillogenesis, and synthesis [7].

The kidneys play an important role in the regulation of phosphorus-calcium metabolism, in particular by participating in the synthesis of the active vitamin D metabolite calcitriol in the mitochondria of proximal tubular epithelial cells. In CKD, hypocalcemia may develop as a result of decreased calcium absorption in the small intestine due to calcitriol deficiency [8]. When the filtration capacity of the kidneys deteriorates, the filtration and excretion of inorganic phosphate decrease. Hyperphosphatemia stimulates the secretion of parathyroid hormone, under the action of which resorption cavities form in bone tissue and collagen fibers change [7]. Thus, the progression of CKD combined with AH may deepen disturbances of phosphorus-calcium metabolism and collagen metabolism, which is consistent with the results obtained.

Connective tissue is a complex multicomponent system whose functional properties depend on the ordered interaction of the biopolymers of the extracellular matrix. Hydroxyproline is one of the characteristic amino acids of collagen and is used as a marker of its catabolism. CKD is typically characterized by sclerotic changes in renal tissue, in which connective tissue replaces the normal structures of glomeruli, tubules, stroma, and vessels [9, 10]. Progression of CKD against the background of AH may be accompanied by deterioration of collagen metabolism, and substantial changes in hydroxyproline parameters may reflect the deepening of structural disturbances of the renal stroma and parenchyma [11, 12]. To date, clear target values for mineral metabolism and collagen metabolism parameters have not been defined; the study is aimed at improving diagnosis and introducing pathogenetically substantiated approaches to the correction of mineral metabolism disorders and the prevention of sclerotic renal changes in patients with CKD.

Conclusions

1. Disturbances of phosphorus-calcium metabolism accompany CKD and are combined with increased urinary excretion of the free hydroxyproline fraction in the examined patients.

2. The presence of arterial hypertension is associated with more pronounced disturbances of mineral metabolism and collagen metabolism in patients with CKD. This manifests as higher serum phosphorus and lower serum calcium levels, and elevated levels of total and free urinary hydroxyproline in patients with AH compared with patients without AH.

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