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**L. Zub, A. Shkarutyak, I. Buzdugan, V. Vivsyannik**

# Malabsorption syndrome aggravates calcium homeostasis impairment in chronic kidney disease patients

Bukovinian State Medical University, Ukraine

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**Abstract.** *Recent data on the role of digestive pathology in the progression of chronic kidney disease (CKD) remain scarce. Calcium homeostasis plays an important role in the progression of renal pathology, especially in patients with malabsorption syndrome (MAS).*

*The research aimed to evaluate calcium homeostasis in CKD patients with MAS.*

*Methods. In this cross-sectional observational study, 99 CKD patients with MAS were enrolled. The patients were divided into 4 groups according to the CKD stage and the presence of MAS. Group I included 25 patients with CKD stages 1 and 2 without MAS; Group II consisted of 26 patients with CKD stages 1 and 2, and MAS; Group III (n = 23) and Group IV (n = 25) included patients with CKD stage 3 without and with MAS, respectively. According to the morphological study of in vivo biopsies of the small intestinal mucosa, mild and moderate morphological changes were observed among all patients. The levels of calcium, phosphorus, parathyroid hormone, osteocalcin, and calcitonin in the blood, as well as urinary calcium levels, were detected.*

*Results. Pathological changes in calcium metabolism were observed among CKD patients with MAS. The severity of calcium homeostasis disorders was more evident among patients with CKD stage 3 compared with stages 1 and 2. Urinary calcium levels were reduced in the patients of Groups III and IV. No changes were detected in phosphorus levels. Changes in parathyroid hormone and osteocalcin are caused primarily by combined renal pathology with impaired renal calcium absorption.*

*Conclusion. MAS in CKD patients leads to deep violations of calcium homeostasis resulting in rapid CKD progression and bone tissue violation.*

**Key words:** *malabsorption syndrome, chronic kidney disease, calcium.*

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**Л.О. Зуб, А.Є. Шкарутяк, І.О. Буздуган, В.В. Вівсянник**

# Синдром мальабсорбції як тригер фактор порушення гомеостазу кальцію у пацієнтів з хронічною хворобою нирок

Буковинський державний медичний університет

**Резюме.** *На сьогодні дані про роль факторів немікробної етіології, що формують поєднану патологію нирок та шлунково-кишкового тракту, залишаються малочисельними. Кальцієвий гомеостаз відіграє значну роль у прогресуванні ниркової патології, особливо у пацієнтів з хронічною хворобою нирок (ХХН) та синдромом мальабсорбції (СМА).*

*Метою дослідження було вивчення кальцієвого гомеостазу у хворих на ХХН з СМА.*

*Методи. До цього перехресного обсерваційного дослідженя було залучено 99 пацієнтів з ХХН та СМА. Залежно від стадіїї ХХН та наявності СМА, пацієнтів було розподілено на 4 групи: I група (n = 25) – ХХН-I-II ст. без СМА; II група (n = 26) ХХН-I-II ст. з СМА; III група (n = 23) – ХХН III ст. без СМА; IV група (n = 25)– ХХН III ст. з СМА. За даними морфологічного дослідження прижиттєвих біоптатів слизової оболонки тонкої кишки у всіх хворих спостерігалися морфологічні зміни легкого та середнього ступеня вираженості. У крові включених до дослідження пацієнтів визначали рівень кальцію, фосфору, паратгормону, остеокальцину та кальцитоніну. Рівень кальційурії досліджували у добовому аналізі сечі.*

*Результати. Патологоанатомічні зміни кальцієвого обміну спостерігалися у пацієнтів з СМА. Тяжкість порушень гомеостазу кальцію була більш вираженою у хворих на ХХН III стадії порівняно з I та II стадіями. Рівень добової кальційурії був статистично значущо знижений у III та IV групах. Змін рівня фосфору не виявлено. Зміни паратгормону та остеокальцину викликані, в першу чергу, поєднаною нирковою патологією з порушенням всмоктування кальцію нирками.*

*Висновок. МАС у хворих на ХХН призводить до глибоких порушень гомеостазу кальцію, що сприяє швидкому прогресуванню ХХН та порушенню кісткової тканини.*

**Ключові слова:** *синдром мальабсорбції, хронічна хвороба нирок, кальцій.*

**Introduction.** Nowadays, the great importance of metabolic disorders and chronic intestinal diseases in the formation of combined pathology of the kidneys and digestive organs has been proven [1-4]. However, there are no data on the role of factors of non-microbial etiology that form the combined pathology of the kidneys and digestive organs.

Malabsorption syndrome (MAS) combines all types of pathology caused by indigestion or absorption. Among the huge range of diseases with impaired intestinal absorption syndrome, the most common in therapeutic practice is lactase deficiency, exudative enteropathy, food allergy, Crohn's disease, nonspecific ulcerative colitis, and helminthic invasion, chronic pancreatitis [5, 6]. So far, there are little data on the role of factors of non-microbial etiology, that form a combined pathology of the kidneys and gastrointestinal tract. There is no well-developed program for early diagnosis, prevention of development and progression of this pathology [7-9].

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Calcium homeostasis plays a crucial role in the progression of chronic kidney disease (CKD) [10-13], especially in patients with MAS [14-17].

**This study aimed** to examine the calcium homeostasis in patients with CKD and MAS.

**Patients and methods.** A total of 99 CKD patients with MAS were included in this cross-sectional observational study. All patients were treated in the Department of Nephrology of the Chernivtsi Regional Clinical Hospital. There were 88 women and 11 men aged 52.5 ± 8.5 years. Also, 20 healthy individuals of the appropriate age were examined. In most of the examined patients, the cause of malabsorption syndrome was chronic pancreatitis [2]; 2 patients had nonspecific ulcerative colitis; 1 patient had Crohn's disease. The CKD causes included tubulointerstitial nephritis and dysmetabolic nephropathy. The patients were divided into 4 groups according to the CKD stage and the presence of MAS. Group I included 25 patients with CKD stages 1 and 2 without MAS; Group II consisted of 26 patients with CKD stages 1 and 2, and MAS; Group III (n = 23) and Group IV (n = 25) included patients with CKD stage 3 without and with MAS, respectively.

The iегвн was conducted in accordance with the ethical principles of the Declaration of Helsinki revised in 2008. All patients provided an informed written concept to participate in the study. The study protocol was

approved by the Local Ethics Commission of Bukovinian State Medical University.

Inclusion criteria were: patients with CKD and MAS, age of patients from 18 to 65 years, glomerular filtration rate (GFR) > 30 ml/min/1.73 $m^2$.

Exclusion criteria were: chronic glomerulonephritis or other immune-mediated kidney diseases, systemic connective tissue disease, neoplasm, tuberculosis, and refusal to participate in the study.

In addition to routine clinical and laboratory data (hemoglobin (Hb), glucose, albumin, urine tests, GFR, ultrasound), blood calcium and phosphorus levels were determined using standard kits in a certified laboratory of the regional clinical hospital. Moreover, the levels of parathyroid hormone and calcitonin were studied by enzyme-linked immunosorbent assay using standard kits from «CIS Bio International» (France). The level of non-collagenous osteocalcin protein, which is a marker of osteoporosis and plays an important role in the formation of the organic matrix of bone tissue was determined to evaluate the activity of osteoporosis and bone loss. Enzyme-linked immunosorbent assay using the standard kit from Roche Diagnostics (Switzerland) was applied to study the level of osteocalcin in the serum.

The diagnosis of MAS was confirmed by in vivo biopsies of the small intestinal mucosa; mild and moderate morphological changes were observed among the enrolled patients. Crypt deepening, decreased small intestinal villus height, (without atrophy), the change in the length of villi and crypt depth correlation, the increase in the number of lymphohistiocytic and plasma cells in the plate, and change in enterocytes were typical morphological signs of the moderate severity of the process.

Statistical analysis was done with NCSS 2007 package program. The data was presented as mean (M) and standard deviation (SD); the Student t-test was used to compare the differences between the groups. The results were considered significant if the p-value <0.05.

**Results.** The study showed that calcium and parathormone levels in CKD patients with MAS had significantly severe disorders compared with those without MAS (Table 1). Urinary calcium levels were significantly reduced among patients of Groups III and IV ($p < 0.05$), which was associated with decreasing in GFR. Phosphate, osteocalcin and calcitonin levels did not differ between the studied groups.

*Table 1*

**Calcium, phosphate and osteoporosis-related hormones in CKD patients according to the presence of MAS**

| Indexes | The patients' groups | | | | |
|---|---|---|---|---|---|
| | Healthy (n = 20) | Group I (n = 25) | Group II (n = 26) | Group III (n = 23) | Group IV (n = 25) |
| Blood calcium (mmol/l) | 2.20 ± 0.6 | 2.25 ± 0.05 | 1.85 ± 0.02*# | 1.82 ± 0.01* | 1.80 ± 0.03* |
| Urine calcium (mmol/day) | 4.25 ± 2.34 | 3.95 ± 1.37 | 4.01 ± 1.98 | 1.04 ± 0.9* | 0.97 ± 0.88* |
| Phosphorus (mmol/l) | 0.81 ± 0.99 | 0.81 ± 0.04 | 0.82 ± 0.33 | 0.88 ± 0.21 | 0.93 ± 0.11 |
| Osteocalcin (ng/l) | 25.4 ± 61.98 | 72.23 ± 4.28 | 73.03 ± 1.11 | 78.87 ± 1.16 | 98.23 ± 0.14*# |
| Parathyroid hormone (pg/ml) | 9.85 ± 6.94 | 45.38 ± 10.11 | 59.52 ± 9.23 | 51.99 ± 8.65 | 91.56 ± 9.11*# |
| Calcitonin (pg/ml) | 7.22 ± 11.91 | 8.68 ± 2.12 | 8.02 ± 2.34 | 7.99 ± 3.02 | 8.71 ± 2.86 |

Notes: * - p-values < 0.05 in comparison with the healthy control;
# - p-values < 0.05 in comparison between the studied groups.

It should also be noted that patients with morphologically severe changes in the intestinal mucosa had lower calcium levels (Table 2).

*Table 2*

**Comparative characteristics of calcium and phosphate indicators depending on the severity of morphological lesions**

| Indicators | The severity of morphological lesion complexity | |
|---|---|---|
| | Mild | Moderate |
| Calcium (mmol/l) | 2.22 ± 0.05 | 2.16 ± 0.04 |
| Phosphorus (mmol/l) | 1.45 ± 0.05 | 1.20 ± 0.04 |

**Discussion.** The previous studies have reported an important role of calcium homeostasis in CKD progression[1-4] and pointed out its significant disorders in patients with digestive disorders [12-14]. The present study aimed to investigate blood calcium and phosphorus levels, concentrations of calcium-regulating hormones, and urinary calcium in patients with early-stage CKD depending on the presence of MAS.

Our results showed that the CKD patients with MAS had significant changes in calcium metabolism compared with the patients without MAS. The severity of these disorders was higher among the patients with CKD stage 3 compared with those with CKD stages 1-2. No changes in serum phosphate levels were found in any of the patient groups. Changes in parathyroid hormone and osteocalcin with some manifestations of osteoporosis, which were confirmed radiologically, in our opinion, are primarily due to combined renal pathology with impaired renal calcium absorption. The obtained results have been demonstrated by other authors in patients with pancreatitis and other gastrointestinal disorders [10, 11, 14, 15]. Calcium levels in daily urine were reduced among Groups III and IV patients, while blood concentrations of calcitonin and phosphorus did not change in all examined CKD patients, which contradicts some published studies [15-17]. In our opinion, it could be associated with calcium and active vitamin D prescription in patients with CKD stage 3.

Moreover, in the present study, we demonstrated a significant decrease in serum calcium levels in CKD patients with severe morphological changes in the intestinal mucosa. It should be noted, that there was no overt morphological lesion of the intestine since MAS was the result of chronic pancreatitis in almost all examined patients [7-9].

The present study has several limitations. First, the cross-sectional observational design of the study and a relatively small sample size limits the causal relationship between the results. Second, we were not able to analyze the prescribing medicaments that might clarify the lack of difference in the studied indicators.

**Conclusions.** Pathological changes in calcium metabolism were observed in patients with CKD and MAS. The severity of these disorders was higher in patients with CKD stage 3. Changes in parathyroid hormone and osteocalcin with some manifestations of osteoporosis, in our opinion, are primarily associated with combined renal pathology with impaired absorption of calcium by the kidneys. MAS in CKD patients is serious comorbidity that requires further large-scale studies.

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**Author Contributions:**

***L. Zub:*** provided the conception and design of the study;

***A. Shkarutyak:*** provided acquisition of data, analysis, and interpretation of the data, drafted the article, revised and final approval to be submitted;

***I. Buzdugan:*** supplied the acquisition of data, and drafting of the manuscript; supplied the study design, analysis and interpretation;

***V.Vivsyannik:*** provided the critically manuscript revision and gave final approval of the manuscript final version.

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