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Effect of quertine on electrolyte metabolism indicators in patients with urate nephrolithiasis comorbid with metabolic syndrome

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SUMMARY

The treatment of urate nephrolithiasis (UN) comorbid with metabolic syndrome (MS) is greatly interested in flavonoids, which are actively involved in purine, electrolyte, nitrogen, lipid, and carbohydrate metabolism. The aim of the study was to study the effect of quertine on electrolyte metabolism and excretion of stone-forming compounds in patients with UN comorbid with MS.

The indicators of stone-forming compounds excretion were studied by the values of inorganic phosphorus, ionized calcium, magnesium, sodium, and potassium in blood serum and urine. Urine pH was determined by test indicator strips.

Normalization of indicators of stone-forming compounds excretion under the influence of quertine, traditional therapy and drugs that correct metabolic processes, contributed to an increase of magnesium crystallization inhibitor in blood serum and urine. Besides, it is also important to increase daily diuresis and normalize urine pH, which contributed to the reduction of stone formation and recurrence of urolithiasis. It is important to prescribe quertine, traditional therapy and drugs that correct metabolic disorders, taking into account metabolic disorders, urinary pH and daily diuresis.

INTRODUCTION
Вступ

Urolithiasis is a polyetiological disease that ranks second in the structure of causes of death from a urological pathology [1]. An important function of the kidneys is to maintain electrolyte balance, especially that of ions such as sodium, potassium, calcium, phosphorus and others. In urate nephrolithiasis (UN), urinary sodium excretion can be both increased and decreased. Kidney damage leads to a decrease in sodium reabsorption to 80% and, accordingly, to an increase in its secretion. Damage to the glomeruli and reduction of glomerular filtration leads to sodium retention, accumulation of fluid in the body and increased

blood pressure [2]. Glomerular and tubular dysfunction results in hyperphosphatemia, moderate elevations in serum magnesium, and hypocalcemia. Deterioration of phosphorus-calcium metabolism contributes to increased levels of parathyroid hormone, which is supported by a decrease in ionized calcium due to phosphorus retention and progression of various forms of osteodystrophy [3]. The progression of renal failure against the background of UN, as well as the weakening of the adaptive reserves of the body, requires the search for the most physiological, complex-acting drugs that cause the least side effects [4]. The greatest interest in the treatment of UN comorbid with metabolic syndrome (MS) are flavonoids, which are actively involved in purine,electrolyte,nitrogen,lipid,and carbohydrate metabolism. One of the bioflavonoids is quertine, which has membrane-stabilizing, anti-inflammatory, antioxidant and nephroprotective activity [5].

The aim of the study is to investigate the effect of quertine on electrolyte metabolism and excretion of stone-forming compounds in patients with UN comorbid with MS.

MATERIALS AND METHODS
Матеріали і методи дослідження

The study enrolled 183 patients with UN and UN comorbid with MS. The patients were 54.93± 1.07 years of age. General clinical methods of blood and urine tests, X-ray methods, ultrasound, radioisotope and biochemical methods were used. Patients with UN comorbid with MS were divided into two groups. Main group patients (n=61) were prescribed 40 mg (1 pill) of quertine 3 times a day for 6 months and traditional therapy (riabal or no-spa, dexalgin, Uralit-U, water shock) and common drugs that correct metabolic disorders (atorvastatin, metformin, allopurinol, vitamin B6, magnesium oxide). Comparison group patients with UN comorbid with MS (n=63) were prescribed only traditional therapy and conventional drugs that correct metabolic disorders. Patients with UN (n = 59) of the control group received only traditional therapy. Data obtained from 40 healthy individuals were taken as normal. Excretion rates of stone-forming compounds were studied by the level of inorganic phosphorus, ionized calcium, magnesium, sodium and potassium in serum and urine. Urine pH was determined by test indicator strips. Daily diuresis was studied.

The concentration of inorganic phosphorus in daily urine was determined using the Cormay, Assent-200 Phosphorus kit (Poland). The levels of sodium, potassium and ionized calcium in the urine were determined with an electrolyte analyzer "E-Lyte Plus". Magnesium levels were determined with the Cormay, Assent-200, MG kit, Poland. Electrolyte metabolism in serum was assessed by the excretion of stone-forming compounds by phosphorus (PZ Cormay S.A., Poland), ionized calcium (PZ Cormay S.A., Poland), sodium and potassium (electrolyte concentration analyzer AEK-01 "Kver").

The results were statistically processed with the software Statistica 13. 04 (StatSoft Inc., license No. JPZ804I382130ARCN10-J). The results were considered statistically significant at a value of $p<0.05$.

RESULTS AND DISCUSSION
Результати та їх обговорення

The study revealed that in the pre-treatment period, the level of potassium in the blood of patients (Table 1) of the main group (6.51±0.19 mmol/l) and the comparison group (6.17±0.32 mmol/l) was probably more than that in normal (4.59± 0.08 mmol/l) and control (6.51±0.19 mmol/l) groups. After 7 days, in patients with UN + MS of both comparison and groups, potassium was probably decreasing relating to the initial values, and on the 14th day, respectively, reached 4.72±0.10 mmol/l ($p<0.05$) and 4.96±0.13 mmol/l ($p<0.05$), moderately exceeding normal values. During the treatment, in the main group patients with UN + MS who received quertine, after 2 and 6 months, the rate decreased and was probably less (4.31± 0.09 mmol/l, $p<0.05$) than both before treatment and relating to the comparison group patients (4.92±0.10 mmol/l).

At the beginning of treatment, blood sodium levels in patients of all groups were probably higher than normal (134.77±1.25 mmol/l), which was observed up to 2 months of the study. After 3–6 months, the rate in patients of the main group (134.71± 1.72 mmol/l) was equal to normal and was probably lower than in patients of the comparison group (142.13±0.89 mmol/l).

Before treatment, ionized serum calcium (table 1) in all patients with UN was probably less than normal (1.21±0.01 mmol/l), and in patients of the main group (0.85±0.03 mmol/l), it was also probably less than that in the control and comparison groups (0.96±0.02 mmol/l). During follow-up on days 7 and 14 and after 2 months, the level of ionized serum calcium in patients of all groups was probably higher than before treatment and moderately lower than normal. At the end of the study, after 3–6 months in patients of the main group (1.21±0.02 mmol/l) and the comparison group (1.22±0.02 mmol/l) the indicator was equal

TABLE 1. Indicators of electrolyte metabolism of serum in patients with UN

Indicator	Normal n=40	Groups of patients	Pretreatment n=44	7th day follow up n=43	14th day follow-up n=38	60th day follow-up n=39	3-6 months follow-up n=30
Potassium, mmol/l	4.59±0.08	UN	5.02±0.19	4.59±0.08 p>0.05	4.52±0.12 p<0.05	4.82±0.12 p>0.05	4.43±0.19 p<0.05
		UN+MS	6.17±0.32* p_1<0.05	4.91±0.19 p<0.05	4.72±0.10 p<0.05	4.92±0.08 p<0.05	4.92±0.10 p<0.05;p_1<0.05
		UN+MS+ quertine	6,51±0,19* p_1<0,05	4,87±0,13 p<0,05	4,96±0,13 p<0,05	5,23±0,15* p<0,05	4,31±0,09# p <0,05
Sodium, mmol/l	134.77±1.2	UN	156.85±2.89*	143.6±0.8* p<0.05	143.2±0.9* p<0.05	144.12±1.54* p<0.05	139.3±1.6* p<0.05
		UN+MS	165,1±3,4* p_1<0,05	145,5±0,8* p<0,05;p_1<0,05	144,0±0,58* p<0,05	144,47±1,09* p<0,05	142,1±0,8* p<0,05
		UN+MS+ quertine	171.6±3.4* p_1<0.05	147.2±0.8* p<0.05;p_1<0.05	143.3±0.7* p<0.05	146.0±0.69* p<0.05;p_1<0.05	134.7±1.7# p<0.05;p_1<0.05
Ionized Calcium, mmol/l	1.21±0.01	UN	1.04±0.03*	1.15±0.01 p<0.05	1.15±0.01 p<0.05	1.16±0.01 p<0.05	1.05±0.01* p<0.05
		UN+MS	0.96±0.02*	1.19±0.01 p<0.05	1.15±0.02 p<0.05	1.17±0.01 p<0.05	1.22±0.02 p<0.05;p_1<0.05
		UN+MS+ quertine	0,85±0,03*# p_1<0,05	1,15±0,02 p<0,05	1,14±0,02 p<0,05	1,17±0,01 p<0,05	1,21±0,02 p<0,05;p_1<0,05
Inorganic phosphorus, mmol/l	1.33±0.66	UN	1.86±0.08*	1.69±0.10* p>0.05	1.78±0.25* p>0.05	1.64±0.12* p>0.05	1.68±0.07* p>0.05
		UN+MS	2.02±0.10* p_1<0.05	1.97±0.12* p>0.05;p_1<0.05	2.13±0.13* p>0.05;p_1<0.05	1.71±0.08* p<0.05	1.63±0.11* p<0.05
		UN+MS+ quertine	2.16±0.12* p_1<0.05	2.13±0.13* p>0.05;p_1<0.05	1.56±0.17*# p<0.05;p_1<0.05	1.62±0.10* p<0.05	1.32±0.10# p<0.05;p_1<0.05
Magnesium, mmol/l	0.86±0.02	UN	0.83±0.02	0.78±0.02 p>0.05	0.81±0.02 p>0.05	0.76±0.02* p>0.05	0.65±0.01* p<0.05
		UN+MS	0.72±0.01* p_1<0.05	0.79±0.02* p<0.05	0.80±0.02* p<0.05	0.82±0.02 p<0.05	1.06±0.02* p<0.05;p_1<0.05
		UN+MS+ quertine	0.71±0.01* p_1<0.05	0.81±0.02 p<0.05	0.84±0.02 p<0.05	0.85±0.02 p<0.05	1.30±0.05*# p<0.05;p_1<0.05

Note: p<0.05 – pretreatment reliability; * – reliability relating to the norm; p_1 – reliability to control group patients (UN); # – reliability to comparison group patients (UN+MS).

to normal values and was probably higher than before treatment and in the control group (1.05± 0.01 mmol/l).

Inorganic blood phosphorus in patients with UN of all groups exceeded normal (1.33±0.66 mmol/l; p<0.05) values. During the entire treatment period up to 3–6 months in all patients, the value was probably higher than normal and lower than at the beginning of treatment. In the main group patients (1,32±0,10 mmol/l), who received quertine, the level of inorganic phosphorus in the blood at the end of the study was normal and was probably lower than that in the patients of the control (1.68± 0.07 mmol/l) and the comparison (1.63±0.05 mmol/l) groups.

The level of serum magnesium (see table 1) as an inhibitor of stone formation in control group patients with UN (0.83±0.02 mmol/l) did not differ statistically from normal (0.86±0.02 mmol/l). Blood counts in patients of the main group (0.71± 0.01 mmol/l) and the comparison group (0.72± 0.01 mmol/l) were probably lower than normal in the control group. On the 7th, 14th day and 2 months' follow-up, the magnesium level in the main group patients increased and did not differ from the norm and by the 6th month follow-up, it became (1.30±0.05 mmol/l; p<0.05) probably higher than that in the comparison group (1.06± 0.02 mmol/l) and the control group (0.65± 0.01 mmol/l).

Having studied the level of stone-forming compounds and inhibitors of crystallization in the urine (table 2) in patients with UN, it was found

TABLE 2. The level of excretion of stone-forming compounds and inhibitors of crystallization in the urine in patients with UN of the main, control, and comparison groups

Indicator	Normal	Groups of patients	Pretreatment	14 days after	1.5-6 months after
Ionized calcium, mmol/day	2.41±0.27	UN	2.54±0.15	3.02±0.25* p<0.05	3.13±0.20* p<0.05
		UN+MS	2.64±0.27*	2.60±0.19* p>0.05	2.43±0.25 p<0.05;p1<0.05
		UN+MS+ quertine	3.30±0.15*# p_1<0.05	2.71±0.27* p<0.05	2.55±0.26# p<0.05;p_1<0.05
Inorganic phosphorus, mmol/day	30.41±5.13	UN	33.59±4.05	35.48±2.99 p>0.05	41.01±3.89* p<0.05
		UN+MS	41.20±1.90	30.07±3.30 p<0.05	35.82±2.59 p<0.05
		UN+MS+ quertine	40.30±2.28*# p_1<0.05	28.17±1.95*# p<0.05;p_1<0.05	30.47±2.14# p<0.05
Sodium, mmol/day	183.09±4.21	UN	266.90±16.24*	246.36±17.59* p>0.05	287.95±12.21* p>0.05
		UN+MS	280,50±15,19*	256,25±14,21* p<0,05	254,16±11,69* p<0,05;p_1<0,05
		UN+MS+ quertine	261.79±12.01* p_1<0.05	219.60±13.56* p<0.05;p_1<0.05	222.62±6.87*# p<0.05;p_1<0.05
Calcium, mmol/day	59.69±2.83	UN	66.83±3.41	62.09±4.83 p>0.05	64.66±3.97 p>0.05
		UN+MS	64.44±1.72*	60.87±4.37 p<0.05	57.10±3.77 p<0.05
		UN+MS+ quertine	82.90±4.09*# p_1<0.05	64.14±2.91 p>0.05	58.90±2.63 p<0.05
Magnesium, mmol/day	4.71±0.36	UN	3.79±0.35*	3.60±0.39* p>0.05	4.00±0.37 p>0.05;p_1<0.05
		UN+MS	4.79±0.47*	4.69±0.59 p>0.05	4.97±0.66 p>0.05
		UN+MS+ quertine	3.17±0.38*# p_1<0.05	4.46±0.62 p<0.05	5.32±0.39* p<0.05
Urine pH	6.66±0.04	UN	5.02±0.08*	4.96±0.07* p>0.05	5.50±0.11* p>0.05
		UN+MS	4.51±0.08*#	4.62±0.06* p>0.05	6.04±0.08* p<0.05
		UN+MS+ quertine	4.32±0.04* p_1<0.05	5.03±0.06* p<0.05	6.74±0.05# p<0.05;p_1<0.05

Note: p<0,05 – pretreatment reliability; * – reliability relating to the norm; p_1 – reliability to control group patients (UN); # – reliability to comparison group patients (UN+MS).

that the level of ionized calcium is probably higher than normal (2.41±0.27 mmol/l), both in patients of the comparison (2.64±0.27 mmol/l; p<0.05) and the main (3.30±0.15 mmol/l; p<0.05) groups. In addition, in the main group patients receiving quertine, the content of ionized calcium in the urine was significantly higher (3.30±0.15 mmol/l) relating to the control group and the comparison group. During treatment, the level of this indicator in the control group probably increased and after 6 months reached 3.13±0.20 mmol/l; p<0.05. The concentration of ionized calcium in the urine of patients with UN gradually normalized and in the comparison group reached 2.43±0.25 mmol/l (p<0.05). In the main group patients, it was (2.55± 0.26 mmol/l (p<0.05), which is less than in the control group of patients (3.13±0.20 mmol/l).

Inorganic phosphorus count in the urine of patients with UN of the main group (40.30± 2.28 mmol/l; p<0.05) in the pre-treatment period was probably higher than normal (30.41± 5.13 mmol/l) and in the control group of patients

(33.30±4.05 mmol/l). The index of the control group during the whole observation period increased compared to the norm, and after 6 months reached 41.01±3.89 mmol/l ($p<0.05$). On the contrary, in the main group patients receiving quertine, the level of inorganic phosphorus in the urine normalized and after 6 months it was 30.47±2.14 mmol/l and became significantly less than in the control and comparison groups (35.82±2.59 mmol/l).

The urine sodium level in patients with UN of all groups before treatment and after 14 days and 6 months was probably higher than normal (183.09± 4.21 mmol/l).

After 14 days, the sodium count in the main group patients decreased (219.60±13.56 mmol/l; $p<0.05$), remaining above normal, and was probably higher than in the control group patients (256.25± 14.21 mmol/l). At the end of the study, 6 months after, the sodium count in patients of the main group (219.60±13.56 mmol/l; $p<0.05$) remained at the previous level, keeping probably less than in the control (287.95±12, 21 mmol/l) and comparison groups (254.16±11.69 mmol/l).

While studying the level of calcium in the urine, it was found that before treatment in patients of the comparison (64.44±1.72 mmol/l; $p<0.05$) and the main group (82.90±10.09 mmol/l; $p<0.05$) groups, it was probably higher than in healthy individuals (59.69±2.83 mmol/l). Besides, in the main group, the indicator was probably higher than the level of sodium in the urine taken from patients of the comparison and control groups. On the 14th day, the indicator level slightly decreased in patients of all groups, and 6 months after it was close to normal.

Urine magnesium, as an inhibitor of stone formation (table 2), in patients with UN of the main group before treatment was probably lower (3.17±0.38 mmol/l; $p<0.05$) than normal (4, 71± 0.36 mmol/l). In the control group, patients with UN (3.79±0.35 mmol/l) and the comparison group (4.79±0.47 mmol/l), the level of urine magnesium had no statistical differences. After 14 days, in the main group patients, the indicator increased (4.46±0.62 mmol/l; $p<0.05$), compared with the initial values, and after 6 months it probably exceeded both normal and initial urine magnesium values.

Before treatment, urinary acidity in patients of all groups was probably higher ($p<0.05$) than in healthy individuals (6.66±0.04). Urine acidity remained significantly higher than normal during the entire treatment period in patients with UN of the control and comparison groups. In the main group patients with UN who received quertine, the acidity of urine on the 14th day was higher than normal, and after 6 months of follow-up (6.74± 0.05 mmol/l), the rate was less than in the control and comparison groups and was practically equal to normal.

Thus, at the end of observation (6 months afterwards) in the main group patients with UN who received quertine, the indicators of electrolyte metabolism in blood serum returned to normal. Normalization of excretion rates of stone-forming compounds due to the use of quertine against the background of traditional therapy contributed to an increase in the content of magnesium crystallization inhibitor in serum and urine. After 6 months of follow-up, inhibitors of crystallization in serum and urine in the main group patients were probably higher than in patients of the comparison group and healthy individuals. Urinary acidity in the main group of patients with UN after 6 months of observation was less (6.74±0.05 mmol/l) than in the control and comparison groups and was almost equal to normal.

CONCLUSIONS
Висновки

1. In all patients with UN, pre-treatment levels of K, Na, P in serum and urine were probably higher than normal. Due to the treatment, after 6 months, the level of electrolyte metabolism in the blood and urine of the main group patients probably decreased, compared with normal values and indicators of the comparison group.

2. Ionized blood calcium values before treatment in patients of the main group was probably lower (0.85±0.03 mmol/l; $p<0.05$) than in healthy individuals (1.21±0.01 mmol/l), and, on the contrary, in urine it was probably higher (3,30± 0,15 mmol/day) than normal (2,41±0,27 mmol/day). After 6 months of treatment, in the main group patients, the level of ionized blood calcium (1.21± 0.02 mmol/l, $p<0.05$) was normal and became significantly higher than in the control group. In urine, the level of this indicator in the main group probably decreased (2.55±0.26 mmol/day) compared to the norm, but was lower compared to the control group (3.13±0.20 mmol/day), $p<0.05$).

3. At the beginning of treatment, the inhibitor of blood magnesium crystallization (0.71± 0.01 mmol/l) and urine (3.17±0.38 mmol/day) in the main group patients was probably lower than normal. After 6 months of treatment, in the main group patients who received quertine, magnesium levels (1.30±0.05 mmol/l, $p<0.05$) increased, having become equal to the norm and significantly higher than in the control group. Urine magnesium values in the main group patients (5.32± 0.39 mmol/day, $p<0.05$) by the 6th month got

probably higher than in the control group (4.0± 0.37 mmol/ext.) and at the beginning of treatment.

4. Before treatment, urinary acidity in patients with UN of all groups was probably higher than in healthy individuals (6.66±0.04). After 6 months of treatment, in the main group patients, the acidity of urine decreased (6.74±0.05) and equated with the norm, becoming probably lower than in the comparison (6.04±0.08) and control (5.50±0.11) groups.

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РЕФЕРАТ

Вплив квертину на показники електролітного обміну у хворих на уратний нефролітіаз коморбідного з метаболічним синдромом

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Найбільший інтерес у плані лікування уратного нефролітіазу (УН) коморбідного з метаболічним синдромом (МС) представляють флавоноїди, що беруть активну участь у пуриновому, електролітному, азотистому, ліпідному, вуглеводному обміні. Метою дослідження було вивчення впливу квертину на електролітний обмін та екскрецію камнеутворювальних з'єднань хворих УН коморбідний з МС.

Показники екскреції камнеутворювальних сполук вивчали за рівнем фосфору неорганічного, іонізованого кальцію, магнію, натрію і калію в сироватці крові та сечі, pH сечі визначали за тестом індикаторними смужками. Нормалізація показників екскреції камнеутворювальних сполук під впливом квертину, традиційної терапії та лікарських засобів, що коригують метаболічні процеси, сприяла збільшенню вмісту інгібітору кристалізації магнію в сироватці крові та сечі. Крім того, важливо також збільшення добового діурезу та нормалізація pH сечі, що сприяло зменшенню каменеутворення та рецидивів сечокам'яної хвороби. Важливо призначати квертин, традиційну терапію та лікарські засоби, що коригують метаболічні порушення з урахуванням метаболічних розладів, рівня pH сечі та добового діурезу.

Ключові слова: уратний нефролітіаз, метаболічний синдром, показники електролітного обміну, квертин.