Hypercalciuria is the main lithogenic pathometabolism in calcium nephrolithiasis which manifests with multilateral impairments of metabolic risk factors of recurrent development of kidney stone disease and different types of hypercalciuria. Causes of hypercalciuria can include impairments of gastrointestinal function, hormonal impairments and their imbalance in the regulation of bone tissue metabolism, impairments of vitamin D metabolism, congenital genetic pathologies and dietary factors.

There are distinguished 6 main types of hypercalciuria and different conditions, giving rise to hypercalciuria (oncology diseases and others).

For performing metaphylaxis of calcium oxalic nephrolithiasis, it is necessary to differentiate types of calcium oxalic nephrolithiasis and choice of adequate treatment. Our study pays attention to absorbent calcium oxalic nephrolithiasis of types I, II, III and IV, renal, resorptive HK and tubular acidosis. There are also presented schemes of metaphylaxis and results of 3-year metaphylaxis of calcium oxalic nephrolithiasis.

Key words: calcium oxalic nephrolithiasis, metaphylaxis, hypercalciuria, hyperparathyroidism, vitamin D.

Kidney stone disease (KSD) is a significant problem of state importance. People of all age groups are suffer, to a large extent young age categories. Unfortunately, last 10–15 years significant increase in morbidity are marked.

The most common form of USD are calcium oxalate and calcium phosphate urolithiasis. According to conducted statistical and clinical data in Europe calcium oxalate urolithiasis amounts to 82.5% of patients, calcium phosphate to 33% of patients. In Ukraine, this indicator is 65.4–70.2% and tending to increase, which is confirmed by the data of other industrially developed countries. Significant moment in progress of disease is tendency to recurring up to 50% and more percent during first 5 years. Consequently important area in treatment arise anti-relapse treatment – the metaphysics of calcium-oxalate nephrolithiasis.

Necessary constituents and conditions for the effective metaphylaxis are:

1. Dispensary observation of patient, which includes laboratory examination with the determination of the mineral composition of the stone, daily urinary and blood tests with determination of Ca, oxalate, uric acid, urine pH, phosphorus, magnesium, sodium, potassium, level of creatinine and ureas. Under certain conditions it’s necessary to determine blood level of parathormone and active form of vit-D (D-250H).

2. Conducting ultrasound diagnostic of the urinoexcretory system to determine the reoccurrence of the KSD (once in 3 months).


4. Control of transport of salts and their level in blood and urine (once in 6 months).

Clinical urine analysis, urine culture on bacteriuria and sensitivity to anti-infective drugs (if necessary, once in 2 months).

The main in metaphylaxis of calcium-oxalate nephrolithiasis are following: decrease in urine concentration of stone-forming salts, increase in urine of stone-forming inhibitors, correction of urine pH. Adhering to these conditions, it is possible to significantly reduce the number recurrence of stone formation.

The main course of metaphylaxis should be directed to correct hypercrystalline and hyperuricuria. Hypercalciuria – increase of daily excretion of calcium in the urine for women higher than 6.2 mmol/day and 7.5 mmol/day for men. It's important to note that hypercalciuria is not an independent disease, but is a metabolic complex which is characteristic for many diseases or conditions.

Hypercalciuria – the main lithogenic agent in recurrent calcium nephrolithiasis and is found in most patients with (KSD). High concentration of Calcium in the urine leads to supersaturation of urine with salts, it’s cause reduction of it’s inhibitory activity by complexation with anionic inhibitors of citrate and chondroitin sulfate, wich is causes hypercrystallization, formation of microliths and possible stone formation. Hypercalciuria has a lot of variety. In it’s basis a different pathogenetic mechanisms.

– Absorptive Hypercalciuria. It develops as a result of absorption abnormality (hyperabsorption) of calcium in the intestine.

1st type. Arise abnormality of reabsorption in the distal kidney tubules. It leads to hypercalciuria, urinary alkalinizing, abnormality of reabsorption of bicarbonates and of H+ ions.

To understand the meaning of metaphylaxis therapy, it is necessary to describe more profoundly and in detail the types of hypercalciuria. Absorbent hypercrystalluria – most commonly found in patients with calcium oxalate nephrolithiasis. It is based on an increase in absorption of calcium from the intestine (duodenum) as a result of high concentrations of Vit D, or excessive intake of...
products with high calcium content. Normally, it should not exceed 20% Ca from consumed food. An increase in the absorption of calcium leads to calcemia and, as a result, hypercalciciuria. At the same time, the level of parathormone remains in the norm.

There are 4 types of absorbent hypercalciciuria:

1. 1st type – Most rarely found (10–15%) and is the most serious. Practically not adjusted by a calcium diet. Practically not adjusted by a calcium diet. An important diagnostic test can be the determination of the ratio of calcium / creatinine in determining the excretion of calcium and creatinine (in urine) fasting. Absence of reduction of calciuria during calcium-free diet.

2. 2nd type – Most common. It’s possible to diagnose in the outpatient department. Mandatory condition is calcium-free diet during 3 days, it leads to significant decrease or normalization of calciuria. This diagnostic test we widely used in the metaphylaxis of calcium-oxalate nephrolithiasis taking into account the necessary physiological norm of calcium 800–1200 g per day.

3. 3rd type – sparingly type (5–8%). It is based on the loss of phosphates in the kidneys as a result of enzymatic deficiency and hypophosphatemia. Reduced phosphates in the blood activates Vitamin D, which stimulates absorption of phosphorus in the intestine, as well as calcium hyperabsorption in parallel, therefore this type is absorbent indirectly due to loss of phosphorus in urine and hyperproduction of Vit D-3. It based on ideopathic hyperproduction of Vit D-3 and excessive absorption of calcium from the intestine, which stimulates calciuria.

Renal hypercalciciuria – occurs as a result of a abnormality of calcium reabsorption in the renal tubules, increased levels of calcium in the urine and the emergence of secondary hyperparathyroidism, while the level of calcium in the blood remains normal, since its loss with the urine is compensated by increased reabsorption of calcium from the intestine and resorption of bone marrow tissue. The main metabolic mark of renal hypercalciciuria is the high calcium level in the fasting urine at normal calcium levels in the blood. Increased urinary calcium excretion and high levels of parathormone and active form of Vit D (D-250H) in the blood. Increased urinary calcium excretion and high levels of parathyroid hormone make it possible to differentiate renal hypercalciciuria from absorbent hypercalciciuria of the first and second type.

Resorption hypercalciciuria – most commonly found in the complex with primary hyperparathyroidism. Lithogenic syndrome occurs due to loss of calcium during resorption of bone tissue. Primary hyperparathyroidism is the cause of stone formation in 5% of cases. Increased secretion of parathormone in adenoma of parathyroid glands directs the reabsorption of calcium from bones and increase the synthesis of active form of Vit D-3, which contributes to increased absorption of calcium from the intestine in 5% of cases.

In most patients, resptive hypercalciciuria appears as hypercalcemia and hypercalciciuria. The normal level of calcium in the blood at high concentrations of parathormone in the blood may be, which makes it difficult to diagnose. Output is – the asignment of thiazide diuretics (thiazide provocation) enhances reabsorption of calcium in the kidneys and exacerbates hypercalciciuria, thereby facilitating diagnosis. The main method for correction of resptive hypercalciciuria is resection of parathyroid glands. As alternative therapies use – analogues of Vit D-3 and calcium.

Kidney tubule acidosis – clinical syndrome associated with metabolic oxidation as a result of abnormality of excretion hydrogen ions in the renal tubules and acidification of urine, which leads to hypercalciciuria. There are several types: 1; 2 and 4 types. Kidney tubule acidosis 1st type (distal acidosis) is most common in patients with kedi- stone disease. Acid-alkaline balance is maintained by the kidneys using several mechanisms, including distal and proximal nephrons.

Bicarbonates are free to be filtered by glomeruli and in the process of renal reabsorption, almost all of the filtered bicarbonate (≥1500 mmol/l) is required for maintaining buffer capacity. In addition, the kidneys excrete an excess of acid after the decomposition of carbohydrates, fats, proteins. Against this background, the kidneys lose the opportunity to reabsorb bicarbonates and extrude into urine ions of H+, which causes metabolic acidosis. Reabsorption in the tubules decreases and, as a result, hypercalciciuria, as well as increased alkalinity of the urine and a decrease in the number of citrates.

An important factor for the successful metaphylaxis of calcium-oxalate nephrolithiasis is the differential diagnosis of hypercalciciuria, since the choice of adequate antirecurrent treatment depends on this.

Basics of differential diagnosis of hypercalciciuria.

Methods of examination of a patient with hypercalciciuria:

- Biochemical blood tests with identification of creatinine, urea, calcium, uric acid, phosphorus, magnesium, sodium, potassium.
- Biochemical parameters of daily urine with the identification of the level of excretion of calcium, uric acid, phosphorus, oxalates, citrate, sodium, potassium, creatinine.
- Determine the pH of urine diurnal diuresis.
- Urine culture to the flora and identify sensitivity to antibiotics.
- Determine the mineral (chemical) composition of the removed stone.
- According to the indications – determine the level of parathormone and active form of Vit D (D-250H) in the blood.
- To conduct special tests for differential diagnostics of hypercalciciuria (examination of calcium excretion after low calcium samples, calcium loading, thiazide provocation).

Pic. 2.
Low calcium test: for 3 days a diet – to exclude milk, kefir, yogurt, cheese, bran, coffee, cocoa, chocolate, bean, sour cream, nuts, feta, mustard, oatmeal, tomatoes, salad, spinach.

Daily urine collection is conducted, salt transport with hypercalciuric parameters is less than 6.25 and 6.30 mmol/day – to diagnose an absorptive hypercalciuria of type II.

To confirm the absorption hypercalciuria, we proposed a load of calcium: calcium gluconate 0.5g × 3 times a day (daily dose is 150 mg) for 3 days. In the case of hypercalciuria increased above 6.25 mL/day, we confirm the absorptive type of hypercalciuria.

Thiazide test: in hypertensive samples of parathyroid hormone, hypercalciuria and hyperuricemia (primary hyperparathyroidism): thiazide diuretics (hydrochlorothiazide 50 mg × 2 times/day) or chlorothalidone 50 mg × 2 g/day or triorthotiazide 4 mg 1 g/day.

To perform special tests for differential diagnostics of hypercalciuria (examination of calcium excretion after low-calcium tests, calcium load, thiazide provocation).

Low-calcium test: 3-day diet – to exclude milk, kefir, yogurt, cheese, bran, coffee, cocoa, chocolate, legumes, sour cream, nuts, pistachios, mustard, oatmeal, tomatoes, lettuce, spinach.

Collection of daily urine is conducted; transport of salts with hypercalciuric parameters is less than 6.25 and 6.30 mL/day – we diagnose the absorptive hypercalciuria of type II.

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Low-calcium test: for 3 days a diet – to exclude milk, kefir, yogurt, cheese, bran, coffee, cocoa, chocolate, legumes, sour cream, nuts, feta, mustard, oatmeal, tomatoes, lettuce, spinach.

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To perform special tests for differential diagnostics of hypercalciuria (examination of calcium excretion after low-calcium tests, calcium load, thiazide provocation).

**Table 1**

<table>
<thead>
<tr>
<th>Types of hypercalciuria</th>
<th>Pathogenesis</th>
<th>Laboratory signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I type</td>
<td>Significant absorption of Ca from the gastrointestinal tract</td>
<td>Hypercalciuria is preserved against the background of low-calcium diet</td>
</tr>
<tr>
<td>II type</td>
<td>Insignificantly increased absorption of Ca from the gastrointestinal tract</td>
<td>Hypercalciuria disappears after intervention of low-calcium diet</td>
</tr>
<tr>
<td>III type</td>
<td>Loss of phosphorus in urine, activation of vitamin D</td>
<td>Hypophosphatemia, hyperphosphaturia against this background – hypercalciemia – hypercalciuria</td>
</tr>
<tr>
<td>IV type</td>
<td>Idiopathic hyperproduction of vitamin D-3</td>
<td>High concentration of vitamin D-3 in blood, hypercalciemia, hypercalciuria, low level of parathyroid hormone</td>
</tr>
<tr>
<td>Renal</td>
<td>Impairment of reabsorption of calcium in the renal canals, hypercalciuria, secondary hyperparathyroidism – increased intestinal reabsorption of calcium</td>
<td>Normocalciemia, high level of parathyroid hormone, high hypercalciuria – on empty stomach</td>
</tr>
<tr>
<td>Resorptive</td>
<td>Primary hyperparathyroidism, resorption of Ca from bones, increased synthesis of vitamin D</td>
<td>Increased level of parathyroid hormone in blood serum, hypercalciemia</td>
</tr>
<tr>
<td>Renal tubular acidosis, type I</td>
<td>Moderate reabsorption of calcium in the real canals due to chronic acidosis</td>
<td>Hypercalciemia, hypercalciuria, hyperphosphaturia</td>
</tr>
</tbody>
</table>

Paricalcitol is an analogue of vitamin D, calcimimetics – cinacalcet.

The objective: to improve results of anti-relapsing treatment of patients with calcium oxalate nephrolithiasis by studying pathogenetic aspects of hypercalciuria, to develop differential diagnostics of types of hypercalciuria, to determine main directions of scientific-based metaphylaxis.

**MATERIALS AND METHODS**

The study included 100 patients with calcium oxalate nephrolithiasis. The base of the study and treatment was the Clinic of kidney stone disease of the State Institution «Institute of Urology of National Academy of Medical Sciences of Ukraine».

Sex of patients: 67 – male, 33 – female. Average age of patients – 38.5 years.

For removal of concrements from the upper urinary tracts, there was used percutaneous nephrolithotripsy (67 patients – 67%), extracorporeal lithotripsy for 13 patients, contact ureterolithotripsy for 12 patients (12%), open surgical interventions for 8 patients (8%).

According to mineral composition, which was determined by X-ray structural analysis and infrared spectroscopy, removed concrements were the following:

![Image](https://via.placeholder.com/150)

**Pic. 3. Cause and effect in formation of calcium oxalate nephrolithiasis**
Results of the metaphylactic therapy with calcium oxalate nephrolithiasis (follow-up by 3 years)

<table>
<thead>
<tr>
<th>Type of hypercalciuria</th>
<th>Calcium excretion in low-calcium diet</th>
<th>Calcium (mg) – creatinine (g) ratio on empty stomach (N ≤ 0.11)</th>
<th>Number of patients n=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbent hypercalciuria, type I</td>
<td>&gt; 6.2 mmol/day – female &gt; 7.5 mmol/day – male</td>
<td>≤ 0.11</td>
<td>n=10 (10%)</td>
</tr>
<tr>
<td>Absorbent hypercalciuria, type II</td>
<td>2.5–6.2 mmol/day – female 2.5 – 7.5 mmol/day – male</td>
<td>≤ 0.11</td>
<td>n=60 (60%)</td>
</tr>
<tr>
<td>Absorbent hypercalciuria, type III</td>
<td>&gt; 6.2 mmol/day – female &gt; 7.5 mmol/day – male</td>
<td>≥ 0.11</td>
<td>n=5 (5%)</td>
</tr>
<tr>
<td>Renal hypercalciuria</td>
<td>&gt; 6.2 mmol/day – female &gt; 7.5 mmol/day – male</td>
<td>≥ 0.11</td>
<td>n=13 (13%)</td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
<td>&gt; 6.2 mmol/day – female &gt; 7.5 mmol/day – male</td>
<td>≤ 0.11</td>
<td>n=10 (10%)</td>
</tr>
</tbody>
</table>

Absorbent hypercalciuria of type III was diagnosed in 3 patients for hypercalciuria. The patients were referred for further examination and treatment by an endocrinologist.

Absorbent hypercalciuria of type I was diagnosed in 31 (31%) patients. Metaphylactic therapy includes orthophosphates – dipyridamole (sodium phosphate).

In the cases of moderate absorbent AH, treatment of hypercalciuria of type II requires low-calcium diet but it is necessary to include physiological needs of body in calcium from bones (osteoporosis, muscle pain, seizures). In this cases calcium gluconate 1.0 g, 2–3 months, which leads to correction at the level of uric acid.

Summary:

1. Calcium oxalate dehydrate (weddelite) – 23 patients.
2. Calcium oxalate monohydrate (whewellite) – 33 patients.
4. Calcium oxalate dehydrate (weddelite) – 16 patients.
5. Calcium phosphates – dipyridamole (sodium phosphate).

The therapy was performed in the form of quarter courses with the break in 1 month with intake of Pyridoxine (vitamin B6) – 40 mg/day. Pyridoxine is metabolized by the liver with the formation of active metabolites and protects from the formation of aldehyde and excessive amount of oxalic acid.

Due to constant intake of thiazide diuretics during the first year of treatment, 4 (4%) of patients had hypokalemia. Quarter therapy with month break gives an opportunity in restoration of the level of potassium in blood without intake of potassium citrate.

In performing thiazide metaphylaxis, it was found an increase of active metabolites and protects from the formation of aldehyde and excessive amount of oxalic acid.

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Гіперкальційурія є основним літогенним порушенням обміну ре- човин за наявності кальцієвого нефролітіазу, що проявляється багатогранними порушеннями метаболічних факторів ризику ре- щивого розвитку сечокам'яної хвороби і різними видами гіпер- кальційурії.

Причинами гіперкальційурії можуть бути порушення функції пищеварительного тракта, почергові гормональні нарушения і їх дисбаланс в регуляції метаболізма костної ткани, порушення об- мена вітаміна D, врожденних генних патологій і алиментарних факторів.

Розрізняють 6 основних видів гіперкальційурії і різних станів, що спричиняють виникнення гіперкальційурії (онко- каліноборозонь і др.).

Для проведення метафілактики кальційоксалатного нефроліті- аза необхідно четко диференціювати види гіперкальційурії і вибрати адекватне лікування. У даному дослідженні удосконалено визначення аборбтивної гіперкальційурії I, II, III та IV типів, рез- нальної, резорбтивної Гк і каналцевого ацидозу, представлений схеми метафілактики і результати трирічної метафілактики кальційоксалатного нефролітіазу.

Ключові слова: кальцій-оксалатний нефролітіаз, метафілак- тика, гіперкальційурія, гіперпаратиреоз, вітамін D.

CONCLUSION
So, hypercalciur is the most common pathometabolism in patients with kidney stone disease. Impairments have polymeric character and require a differential approach for detecting a type of hypercalciuria that gives an opportunity to approve metaphylaxis, to perform a control correction of lithogenic impairments and to decrease a risk in backset stone formation during a long period of treatment.