

Calcium-oxalate nephrolithiasis and the bases of its metaphylaxis

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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).

3. Determining functional status of kidney using radioisotope rheography (once in 6 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

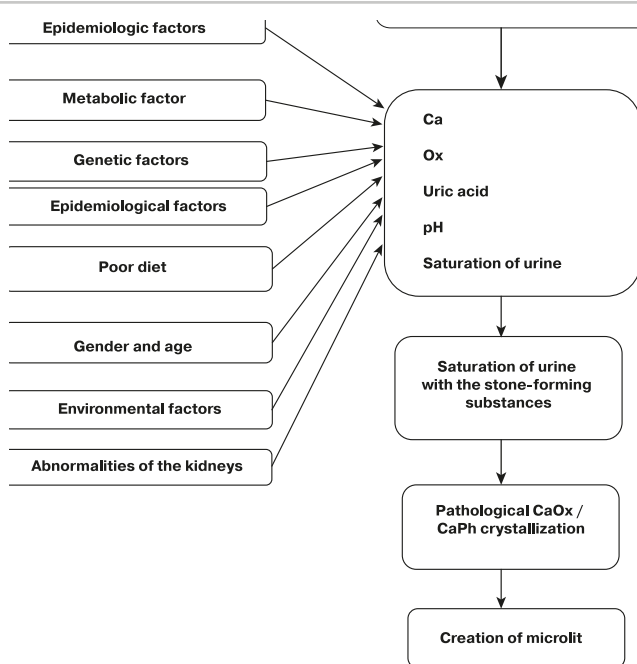


Fig. 1.

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 Ca-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 alkalizing, 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, to hypercalciuria. At the same time, the level of parathormone remains in the norm.

There are 4 types of absorbent hypercalciuria:

- 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 normalization 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.

- 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.

- 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 calciurium.

Renal hypercalciuria – 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 hypercalciuria is the high calcium level in the fasting urine at normal calcium levels in the blood. Increased urinary calcium excretion and high levels of parathyroid hormone make it possible to differentiate renal hypercalciuria from absorbent hypercalciuria of the first and second type.

Resorption hypercalciuria – 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, resorptive hypercalciuria appears as hypercalcemia and hypercalciuria. 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 assignment of thiazide diuretics (thiazide provocation) enhances reabsorption of calcium in the kidneys and exacerbates hypercalciuria, thereby facilitating diagnosis. The main method for correction of resorptive hypercalciuria 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 hypercalciuria. There are several types: 1; 2 and 4 types. Kidney tubule acidosis 1st type (distal acidosis) is most common in patients with kidney 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 (≈ 4500 mmol/l) is required for maintaining buffer capacity. In addition, the kidneys excrete an excess of acid after the decomposition of

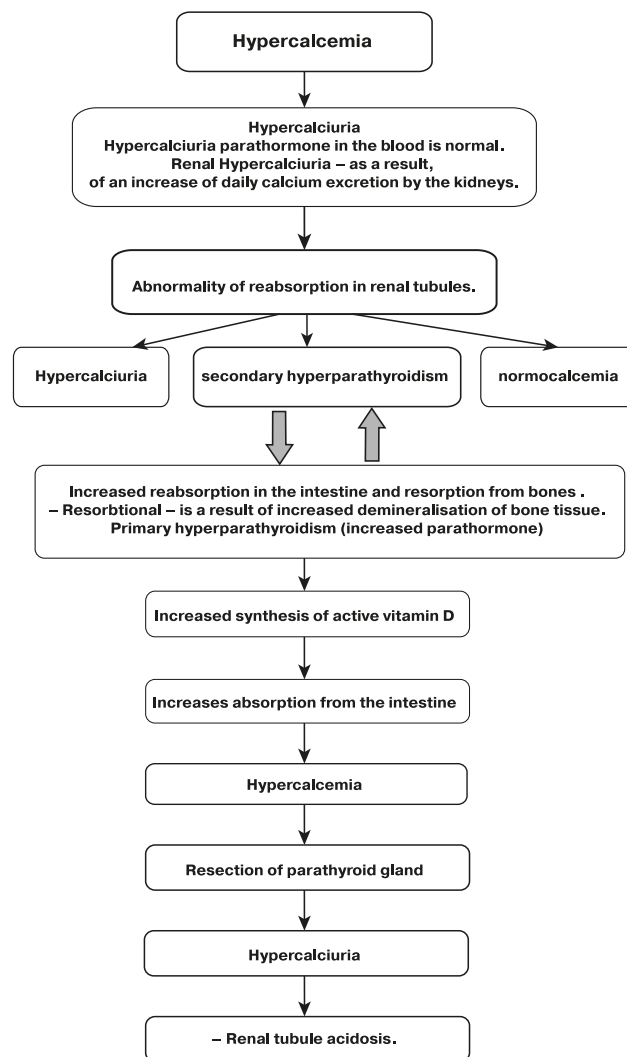


Fig. 2.

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, hypercalciuria, 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 hypercalciuria, since the choice of adequate antirecurrent treatment depends on this.

Basics of differential diagnosis of hypercalciuria.

Methods of examination of a patient with hypercalciuria:

- 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 hypercalciuria (examination of calcium excretion after low calcium samples, calcium loading, thiazide provocation).

Types of hypercalciuria

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

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

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

To confirm the absorption hypercalciuria, we proposed a load of calcium: calcium gluconate 0.5×3 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 absorption type of hypercalciuria.

Thiazide test: in hypertensive samples of parathyroid hormone, hypercalciuria and hyperuricemia (primary hyperparathyroidism): thiazide diuretics (hydrochlorothiazide 50 mg × 2 g/day) or chlorthalidone 50 mg × 2 g/day or trichlortiazide 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, bryndza, cottage cheese, coffee, cacao, 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 absorbent hypercalciuria of type II.

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Due to determination of the level of calcium in blood and urine with marked hypercalcemia, a resorptive form of hypercalciuria is diagnosed. In the treatment plan – resection of the parathyroid gland.

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.

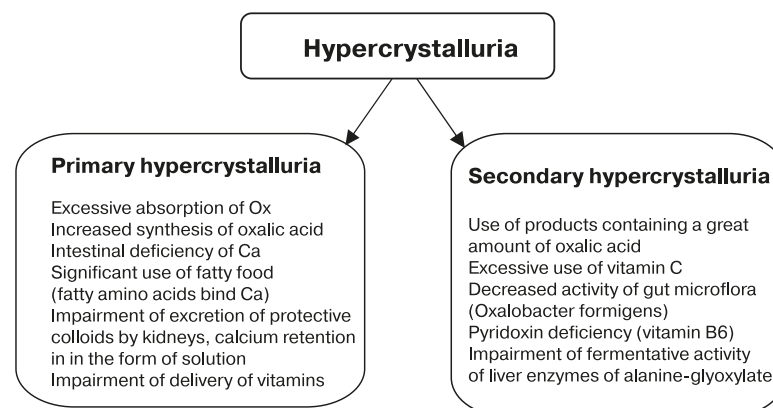
MATERIALS AND METHODS

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:



Pic. 3. Cause and effect in formation of calcium oxalate nephrolithiasis

Differential diagnostics of hypercalciuria of urine during day (transport of salts)

| Type of hypercalciuria | Calcium excretion in low-calcium diet | Calcium (mg) – creatinine (g) ratio on empty stomach (N ≤ 0.11) | Number of patients n=100 |
|------------------------------------|--|---|--------------------------|
| Absorbent hypercalciuria, type I | > 6.2 mmol/day – female > 7.5 mmol/day – male | ≤ 0.11 | n=10 (10%) |
| Absorbent hypercalciuria, type II | 2.5-6.2 mmol/day – female 2.5 – 7.5 mmol/day – male | ≤ 0.11 | n=60 (60%) |
| Absorbent hypercalciuria, III type | > 6.2 mmol/day – female > 7.5 mmol/day – male | ≥ 0.11 | n=5 (5%) |
| Renal hypercalciuria | > 6.2 mmol/day – female > 7.5 mmol/day – male | ≥ 0.11 | n=13 (13%) |
| Resorptive hypercalciuria | > 6.2 mmol/day – female > 7.5 mmol/day – male | ≥ 0.11 | n=3 (3%) |
| Renal tubular acidosis | > 6.2 mmol/day – female > 7.5 mmol/day – male | ≤ 0.11 | n=10 (10%) |

Table 3

Results of the metaphylactic therapy with calcium oxalate nephrolithiasis (follow-up by 3 years)

| Type of hypercalciuria Total n = 45 | Treatment | Results |
|--|--|--|
| I group: AH – 1 st type n=10; renal HK n=11; renal KA n=10; included from II group n=14 | Thiazide diuretics Trichlormethiazide (25–50 mg/L) | n=42 (98%) course without backset |
| II group: absorbent n=56; HK – II type (60–14) | Low-calcium diet | n=48 (86%) course of kidney stone disease without backset |

1. Calcium oxalate dehydrate (weddelite) – 23 patients.
2. Calcium oxalate monohydrate (whewellite) – 33 patients.
3. Mixed composition (whewellite + weddelite) – 17 patients.
– (whewellite + weddelite + uric acid) – 13 patients;
– (calcium phosphate + calcium oxalate) – 16 patients.

Metaphylactic therapy is associated with the result of differential diagnostics.

Thiazide diuretics: indapamide 2.5 mg/day, hydrochlorothiazide 25 mg/day, orthophosphates are indicated for hypercalciuria:

1. Absorbent type – 10 patients.
2. Renal hypercalciuria – 11 patients.
3. Renal tubular acidosis – 10 patients.

Result – 31 (31%) patients, low-calcium diet in absorbent hypercalciuria of type II in 60 (60%) patients. In the cases of instability of hypercalciuria, there are possible variants of translation of certain number of patients for intake of thiazide diuretics, citrate mixture.

Resorptive hypercalciuria was diagnosed in 3 patients for hypercalciuria. The patients were referred for further examination and treatment by an endocrinologist.

Absorbent hypercalciuria of type III was diagnosed in 5 (5%) patients. Metaphylactic therapy included orthophosphates – dipyrnidamole (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 × 3 times/day is assigned; thiazide diuretics, control of calcium.

Complex metaphylactic therapy includes increased diuresis up to 2 L, antibacterial, anti-inflammatory therapy, bacterial urine test, normalization of urine pH.

Metaphylaxis is performing all the time, in courses under follow-up by a doctor every 3 months in the first year, in the further in 6–12 months.

In the process of examination, we made a focus on two main groups of the metaphylactic therapy.

1st group: includes patients who took thiazide diuretics:

- AH – type I – 10 patients
- RH – 11 patients
- Renal tubular acidosis – 10 patients

} total number of patients
– 45 (31 patients + 14
patients, who were
included from the II group

2nd group:

AH – II – 60 patients who were prescribed low-calcium diet. Then, by a control method, 14 patients showed significant fluctuations of calciuria at the level of 7.04+/-0.421 mmol/L.

I–II groups covered 91% patients.

The scheme of the metaphylactic therapy with thiazide diuretics:

Thiazide diuretics trichlormethiazide (4 mg/day)

Canephron – H – 2 pills × 3 times/day

Water-intake regime – 2.5 L

Anti-inflammatory therapy – according to indications

} 3 months

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 in the level of uric acid – hyperuricuria and hyperuricemia (up to 24.4±5.2% and 17.6±2.44%). Given uric acid is a promoter of crystallization of salts, responsible for stone-formation, it is recommended to take allopurinol 100 mg × 3 times/day during 2–3 months, which leads to correction at the level of uric acid.

Control examination was performed in the first year every 3 months and, then, every 6 months.

RESULTS

Proposed differential diagnostics of types of hypercalciuria gives an opportunity to perform scientific-based metaphylaxis of the most widespread type of nephrolithiasis with its high efficiency (>90%). It can be common used in urology.

Кальций-оксалатный нефролитиаз и основы его метафилактики

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Гиперкальциурия является основным литогенным нарушением обмена веществ при кальциевом нефролитиазе, проявляется многогранными нарушениями метаболических факторов риска рецидивного развития мочекаменной болезни и различными видами гиперкальциурии.

Причинами гиперкальциурии могут быть нарушения функции пищеварительного тракта, почек, гормональные нарушения и их дисбаланс в регуляции метаболизма костной ткани, нарушения обмена витамина D, врожденных генных патологий и алиментарных факторов.

Различают 6 основных видов гиперкальциурии и различных состояний, способствующих возникновению гиперкальциурии (онкозаболевания и др.).

Для проведения метафилактики кальцийоксалатного нефролитиаза необходимо четко дифференцировать виды гиперкальциурии и выбор адекватного лечения. В данном исследовании уделено внимание абсорбтивной гиперкальциурии I, II, III и IV типов, ренальной, резорбтивной ГК и канальцевому ацидозу, представлены схемы метафилактики и результаты трехлетней метафилактики кальцийоксалатного нефролитиаза.

Ключевые слова: кальций-оксалатный нефролитиаз, метафилактика, гиперкальциурия, гиперпаратиреоз, витамин D.

CONCLUSION

So, hypercalciuria is the most common pathometabolism in patients with kidney stone disease. Impairments have polymorphic 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.

Кальций-оксалатный нефролитиаз та основи його метафілактики

Д.В. Черненко, В.В. Черненко, Н.І. Желтовська, В.І. Савчук

Гіперкальціурія є основним літогенним порушенням обміну речовин за наявності кальцієвого нефролітіаза, що проявляється багатогранными порушеннями метаболических факторів ризику рецидивного розвитку сечокам'яної хвороби і різними видами гіперкальціурії.

Причинами гіперкальціурії можуть бути порушення функції травного тракту, нирок, гормональні порушення та їхній дисбаланс у регуляції метаболізму кісткової тканини, порушення обміну вітаміну D, вроджених генних патологій та аліментарних чинників. Розрізняють 6 основних видів гіперкальціурії і різних станів, що спричиняють виникнення гіперкальціурії (онкозахворювання тощо).

Для проведення метафілактики кальційоксалатного нефролітіаза необхідно чітко диференціювати види гіперкальціурії і вибір адекватного лікування. У даному дослідженні приділено увагу абсорбтивній гіперкальціурії I, II, III та IV типів, ренальній, резорбтивній ГК і канальцевому ацидозі, представлені схеми метафілактики і результати трирічної метафілактики кальційоксалатного нефролітіаза.

Ключові слова: кальцій-оксалатний нефролітіаз, метафілактика, гіперкальціурія, гіперпаратиреоз, вітамін D.

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