



URINE STONES OF DIFFERENT CHEMICAL COMPOSITION OCCURRENCE DEPENDING ON THE LEVEL OF URICURIA

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Introduction. According to modern concepts one of the key links in the pathogenesis of urolithiasis is metabolic lithogenic disturbances. The study of the complex effect of many factors on the metabolism of urolithiasis patient is the basis of modern scientific research. We studied the frequency of various chemical urinary stones occurrence depending on various levels of uricuria. **Materials and methods.** Data from of 708 urolithiasis patients (303 men and 405 women) were analyzed. The results of blood and urine biochemical analysis and chemical composition of urinary stone were studied. The degree of uricuria was ranked by 10 intervals: from 0.4 to 14.8 mmol/day to assess the occurrence of different stones at various levels of uricuria. **Results.** The incidence of calculi consisting of uric acid also increases with increasing levels of uric acid in the urine. An increase in the level of uricuria above 3.11 mmol/day is observed to increase calcium-oxalate stones occurrence. Decrease in the prevalence of carbonatapatite and struvite stones observed at an increase of urine uric acid excretion. At high levels of uric acid excretion, we found uric acid and calcium oxalate stones most often. **Conclusion.** Control over the level of urinary acid excretion in urine is important in case of calcium-oxalate and uric acid urolithiasis.

Keywords: kidney stones; urolithiasis; uricuria.

ВСТРЕЧАЕМОСТЬ МОЧЕВЫХ КАМНЕЙ РАЗЛИЧНОГО ХИМИЧЕСКОГО СОСТАВА В ЗАВИСИМОСТИ ОТ УРОВНЯ УРИКУРИИ

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Введение. По современным представлениям одним из ключевых звеньев патогенеза мочекаменной болезни (МКБ) являются метаболические литогенные нарушения. Изучение комплексного влияния множества факторов на метаболизм пациента, страдающего МКБ, лежит в основе современных научных исследований патогенеза уролитиаза. В настоящей работе мы изучили частоту встречаемости мочевого камней различного химического состава при различных уровнях урикурии. **Материалы и методы.** Проанализированы данные обследования 708 пациентов (303 мужчины и 405 женщин), страдающих МКБ. В процессе работы изучены результаты биохимического анализа крови и суточной мочи, анализа химического состава мочевого конкрементов. Для оценки встречаемости камней различного химического состава при различных уровнях урикурии производили ранжирование степени урикурии на 10 интервалов: от 0,4 до 14,8 ммоль/сут. **Результаты.** При возрастании уровня мочевой кислоты в моче увеличивается и частота встречаемости конкрементов, состоящих из мочевой кислоты. Также при росте уровня урикурии выше 3,11 ммоль/сут отмечается стойкая тенденция к увеличению встречаемости кальций-оксалатных конкрементов. При увеличении уровня экскреции мочевой кислоты с мочой выше 3,11 ммоль/сут, напротив, отмечается снижение распространенности карбонатапатитных и струвитных камней. Наиболее часто при высоких уровнях экскреции мочевой кислоты встречаются мочекишлые и кальций-оксалатные конкременты. **Выводы.** Контроль за уровнем экскреции мочевой кислоты с мочой имеет принципиальное значение при кальций-оксалатном и мочекишлом уролитиазе.

Ключевые слова: мочекаменная болезнь; уролитиаз; урикурия; мочевые камни.

INTRODUCTION

Based on modern concepts, one of the key aspects in kidney stone disease (KSD) pathogenesis is metabolic lithogenic disorders. At the same time, the chemical composition of urinary stones and frequency of recurrence of urolithiasis are determined not only by metabolic disorders, but also by the degree of their severity and influence of other concomitant factors, such as body mass index, presence of concomitant diseases, age, and amount of proteins, fats, carbohydrates, and micro- and macronutrients consumed with food [1, 2].

Modern scientific research on the KSD pathogenesis was based on the study of the complex influence of many factors on the metabolism of patients with KSD. Numerous studies have shown that patients with uric acid urolithiasis, in comparison with patients with calcium oxalate urolithiasis, have a higher body mass index, uric acid levels in blood serum and daily urine, lower morning urine pH values, and characteristic changes in diet (increased consumption of carbohydrates and vitamin C with food) [1, 3–6]. KSD has age-related characteristics because patients with uric acid urolithiasis are older than patients with calcium oxalate and calcium phosphate stones [5].

One specific metabolic lithogenic disorder is not always characteristic for the formation of urinary calculi of one or another chemical composition [1]. For example, the formation of uric acid stones and mixed stones, which include uric acid, depends not only on the severity of uricuria. At the same time, patients with calcium oxalate or calcium phosphate urolithiasis have an increased serum uric acid concentration and/or in daily urine [1, 7]. The level of calcium excretion with daily urine can be within the reference values [1].

Thus, lithogenesis is influenced by many different factors that act jointly. To study the KSD pathogenesis, a comprehensive assessment of the metabolism of patients with KSD is required, as well as the study of the complex impact of all possible risk factors on the state of the body of a patient with urolithiasis.

In this work, we analyzed the incidence of urinary stones of various chemical compositions at different levels of uricuria.

MATERIALS AND METHODS

In the Lopatkin Research Institute of Urology and Interventional Radiology, a branch of the National

Medical Research Center of Radiology of the Ministry of Health of Russia, the survey data of 708 patients with KSD (303 men and 405 women) who received treatment in 2017–2019 were analyzed.

The study was conducted retrospectively. The results of the biochemical analysis of blood and daily urine and analysis of the chemical composition of urinary calculi were studied. The time interval between the analysis of the urinary stone composition and biochemical studies of blood and urine did not exceed 3 months.

Serum levels of total calcium, sodium, potassium, phosphorus, magnesium, chlorine, uric acid, creatinine, and urea were determined. In daily urine, the levels of excretion of total calcium, sodium, potassium, phosphorus, magnesium, chlorine, uric acid, creatinine, urea, oxalates, and citrates were determined. Biochemical studies of venous fasting blood serum samples and of daily urine samples were performed on an ADVIA 1200 autoanalyzer (Bayer-Siemens, Germany).

The chemical composition of urinary calculi was analyzed using infrared spectroscopy on a Nicolet iS10 apparatus (Thermo Scientific, USA) with a standard library of urinary calculi spectra provided by the equipment manufacturer. In case of the presence of a component constituting >50% of the total calculus composition in mixed urinary stones, the chemical composition of the stone was attributed to the group of calculi based on the predominant element (oxalate, uric acid, and phosphate from carbonate apatite or struvite).

The incidence of stones of different chemical compositions at different uricuria levels was ranked into 10 intervals, from 0.7 to 7.3 mmol/day (see Table).

Statistical analysis was performed using Pearson chi-squared test, which was able to determine the significance of the difference between the frequencies of detecting stones of different chemical compositions at different degrees of uricuria.

RESULTS AND DISCUSSION

Analysis of the data on the distribution of the incidence of uric acid stones (uric acid monohydrate, uric acid dihydrate) depending on the degree of uricuria showed that the incidence of uric acid calculi increases with an increase in uric acid level in urine (intervals of 2.4–3.1 and 3.87–7.3 mmol/day), (Fig. 1). The graph has a zigzag shape, and a periodic increase and de-

Ranges of uricuria degree distribution

Распределение степени урикурии на диапазоны

Range No	Degree of uricuria, mmol/day
Ur1	0.7–1.71
Ur2	1.8–2.1
Ur3	2.15–2.40
Ur4	2.41–2.77
Ur5	2.80–3.11
Ur6	3.2–3.4
Ur7	3.48–3.87
Ur8	3.9–4.3
Ur9	4.4–5.0
Ur10	5.1–7.3

crease in the incidence of uric acid stones with an increase in the degree of uricuria was observed. At the same time, when constructing an exponential trend line, a stable increase in the incidence of uric acid urolithiasis with an increase in uricuria degree is noted.

Published studies demonstrated that hyperuricuria is rare in patients with uric acid stones [8], which may be due to the low pH of urine, the main risk factor for uric acid stone formation [9]. At urine pH of 6.0, the solubility of uric acid is 600 mg/l. At urine pH < 5.5, uric acid crystals become relatively insoluble in urine [10].

However, if uric acid excretion in urine significantly exceeded the normal level, the risk of uric acid calculus formation increases regardless of urine pH [1].

The results confirm the well-known fact that the level of uric acid excretion in urine must be main-

tained within the reference values in patients with uric acid urolithiasis.

Figure 2 presents the incidence of calcium oxalate stones at different uricuria levels. With increase in uricuria level of >3.11 mmol/day, a persistent tendency was observed in an increase in the incidence of calcium oxalate calculi ($p < 0.05$).

Such aspects of lithogenesis can be explained by the initiation of epitaxy processes. Epitaxy is the growth of one crystal on the surface of another (heterogeneous nucleation). Epitaxy may be one of the possible mechanisms of calcium oxalate stone formation in patients with hyperuricuria. This is due to an increase in the uric acid excretion, which accelerates the precipitation of calcium oxalate crystals from a metastable solution [11]. The theory was proposed in 1975 by Coe et al. [12] who demonstrated in an *in vitro* experiment that stone formation was based on the precipitation of calcium oxalate

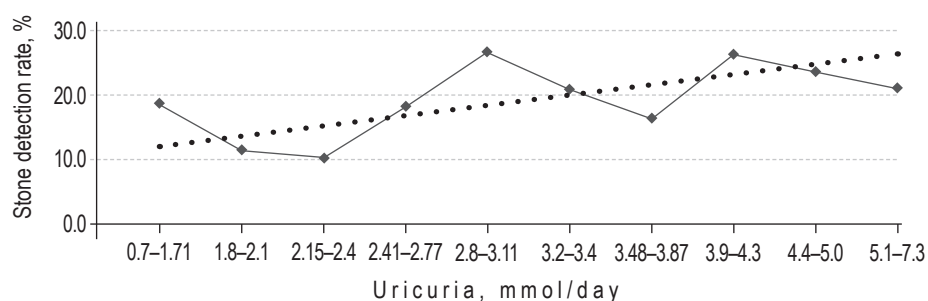


Fig. 1. The frequency of occurrence of urate urolithiasis (% of the total number of urinary stones) depending on the level of uricuria. The exponential trend line is indicated by a dotted line

Рис. 1. Частота встречаемости мочекаменного уролитиаза (процент от общего количества мочевых камней) в зависимости от уровня урикурии. Экспоненциальная линия тренда обозначена пунктиром

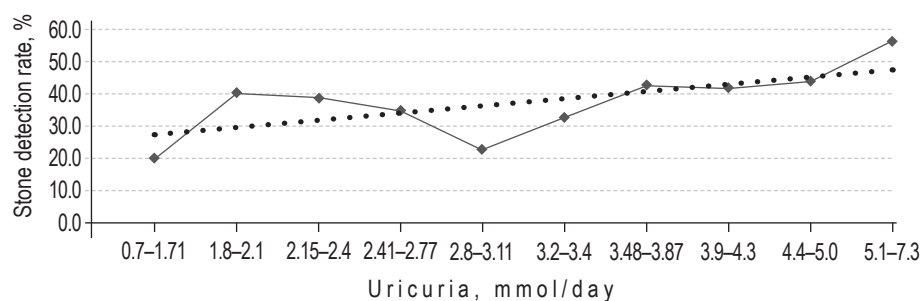


Fig. 2. The frequency of occurrence of calcium-oxalate urolithiasis (% of the total number of urinary stones) depending on the level of uricuria. The exponential trend line is indicated by a dotted line

Рис. 2. Частота встречаемости кальций-оксалатного уролитиаза (процент от общего количества мочевых камней) в зависимости от уровня урикурии. Экспоненциальная линия тренда обозначена пунктиром

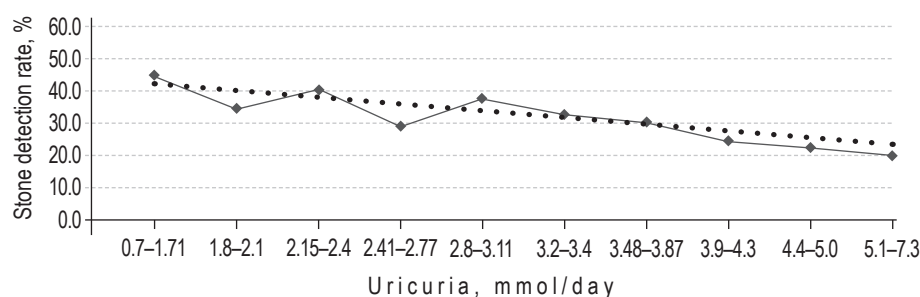


Fig. 3. The frequency of occurrence of carbonate-apatite urolithiasis (% of the total number of urinary stones) depending on the level of uricuria. The exponential trend line is indicated by a dotted line

Рис. 3. Частота встречаемости карбонататапатитного уролитиаза (процент от общего количества мочевых камней) в зависимости от уровня урикурии. Экспоненциальная линия тренда обозначена пунктиром

crystals at urine pH of 5.7 with the addition of crystalline sodium urate. Pak et al. [13] also described in detail the effect of sodium urate on the initiation of heterogeneous nucleation of calcium oxalate at urine pH of 5.7 and 6.7, and calcium phosphate at urine pH of 5.3, 5.7, and 6.7 *in vitro*. The effect of epitaxy on calcium stone formation has also been proven *in vivo*. A decrease in consumption of foods rich in purines or the administration of allopurinol to patients with calcium oxalate urolithiasis and hyperuricemia leads not only to a decrease in uric acid level in blood and urine, but also to a decrease in calcium oxalate crystal formation in urine [14].

There is also an opinion that uric acid is able to inactivate stone formation inhibitors, which prevent calcium oxalate salt formation in urine. Studies proved that uric acid reduces the activity of one of the inhibitors of lithogenesis, mucopolysaccharides in urine [15], which leads to the initiation of calcium oxalate stone formation processes.

Thus, in patients with calcium oxalate urolithiasis, along with the control of the level of calcium and oxalate excretion in urine, the degree of uricuria must be adjusted when the uric acid concentration in urine exceeds 3.11 mmol/day.

Analysis of the occurrence of carbonate apatite stones at different levels of uricuria showed that the incidence of carbonate apatite stones decreases with an increase in uric acid excretion level in urine (Fig. 3). Similar to calcium oxalate calculi, the graph has a zigzag pattern. At the same time, the exponential trend line clearly showed the tendency of a decrease in the incidence of carbonate apatite stones with an increase in the degree of uricuria. When uric acid excretion is >3.11 mmol/day, an inverse relationship was observed between the incidence of carbonate apatite stones and degree of uricuria ($p < 0.05$).

Carbonate apatite calculi can be referred to as infectious stones [16, 17]. The formation of calcium phosphate calculi can be caused by concomitant diseases, such as primary hyperparathyroidism and renal tubular acidosis [16]. High urinary pH and hypercalciuria are common in these diseases [18].

The results showed that the incidence of struvite stones correlated statistically significantly with the severity of the degree of uricuria (Fig. 4). A decrease in the prevalence of struvite calculi was noted with increase in uric acid excretion >3.4 mmol/day ($p < 0.05$).

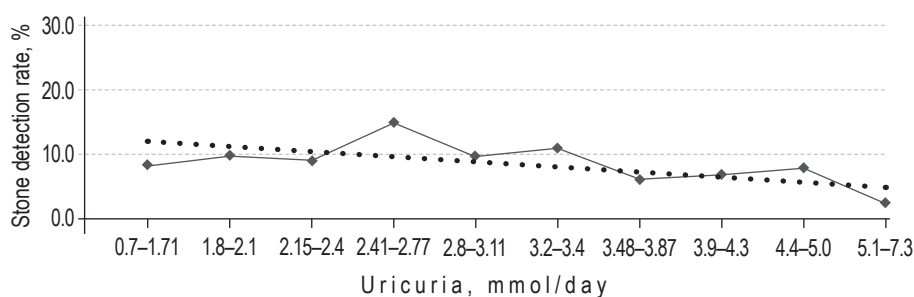


Fig. 4. The frequency of struvite stones (in % of the total number of urinary stones) depending on the level of uricuria. The exponential trend line is indicated by a dotted line

Рис. 4. Частота встречаемости струвитных камней (процент от общего количества мочевых камней) в зависимости от уровня урикурии. Экспоненциальная линия тренда обозначена пунктиром

According to contemporary concepts, the etiological factor in the genesis of struvite calculi is urease-producing microflora [16]. Some experts note that despite the presence of an obvious cause of stone formation, assessment of the metabolism of stone-forming substances in this category of patients is necessary [1, 19–21]. It is believed that metabolic lithogenic disorders can increase the activity of crystal adhesion to damaged urothelium and, thus, accelerate lithogenesis [19]. It also should be emphasized that in the presence of mixed struvite and carbonate apatite stones, lithogenic disorders are diagnosed much more often than in cases of pure struvite stones [19].

CONCLUSION

The analysis of dependence of the incidence of urinary stones of various chemical compositions on the degree of uricuria showed that uric acid and calcium oxalate calculi are most often detected with uric acid excretion >3.11 mmol/day. In this regard, control of uric acid excretion in the urine is of fundamental importance for adequate metaphylaxis in calcium oxalate and uric acid urolithiasis.

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