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## Is hyperuricosuria really a risk factor for calcium oxalate stone formation?

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### Keywords:

calcium oxalate, hyperuricosuria, urolithiasis, recurrence rate, renal stone disease

### Ключові слова:

оксалат кальція, гіперурикозурія, уролітіаз, частота рецидивування, сечокам'яна хвороба

### SUMMARY

In the seventies of the last century the term hyperuricosuric calcium oxalate (CaOx) urolithiasis has been coined. Allopurinol significantly decreased the recurrence in CaOx stone formers. Nevertheless, the role of hyperuricosuria has been questioned. Other mechanisms could have decreased the risk for recurrence. The underlying mechanisms are not clear. All these studies have been performed with only a limited number of patients. We studied n=2,480 consecutive patients with CaOx stones. For stone analysis, x-ray diffraction was used. The following parameters were examined in all patients: age, sex, body mass index (BMI), arterial blood pressure, stone episodes, diabetes mellitus; blood: creatinine, glucose, uric acid, calcium, sodium and potassium; urine: pH, volume, calcium, uric acid, citrate, ammonia and urea. According to the uric acid excretion (UAE), patients were divided into two groups: 1. UAE > 4 mmol/d (hyperuricosuria), 2. UAE ≤ 4 mmol/d (normouricosuria). We observed significant correlations between UAE and sex, age, BMI, blood pressure, serum values of creatinine, sodium, urine volume, urine levels of calcium, citrate, urea and ammonia as well as serum calcium. No significant correlations were seen to the stone frequency (number of stone episodes), serum potassium and urine pH. In group 1 (n=741), there were 87.2% male and 12.8% female patients; in group 2 (n=1,739), the ratio was 60.6:39.4%. In the hyperuricosuric group, there were significantly more males than in the normouricosuric collective. Hyperuricosuric subjects had a higher BMI, higher blood levels of uric acid and glucose, a higher diuresis, a higher excretion of calcium, urea and ammonium, but a lower excretion of citrate than normouricosuric patients. All the other parameters did not show any significant differences. Especially the number of stone episodes was not different. We concluded that hyperuricosuria went along with many other risk factors for CaOx stone formation, but was not associated with an increased risk for recurrence. Therefore, UAE is not a prognostic marker in CaOx urolithiasis. It is unlikely that hyperuricosuria is a real risk factor for CaOx stone formation and hyperuricosuric CaOx urolithiasis is an own entity.

### РЕФЕРАТ

Чи є гіперурикозурія ризик фактором формування кальцієво-оксалатних конкрементів? Штромайєр В.Л., Врубель-Тенцер Б. Термін «гіперурикозурична кальцієво-оксалатна сечокам'яна хвороба» було створено у

сімдесятих роках минулого сторіччя. Терапія алопуринолом суттєво знизила частоту рецидивів. Також є інші механізми для зниження частоти рецидивів. Але ці механізми не остаточно вивчені. Усі ці дослідження проводились лише з обмеженою кількістю пацієнтів. Було вивчено дані 2480 пацієнтів з кальцієво-оксалатною сечокам'яною хворобою. Аналіз каменів проводився за методом рентгенівської дифракції. Було враховано наступні параметри пацієнтів: вік, стать, індекс маси тіла, артеріальний тиск, кількість епізодів хвороби, наявність цукрового діабету, аналіз крові (креатинін, глюкоза, сечова кислота, калій, натрій, кальцій), аналіз сечі (рН, об'єм, кальцій, сечова кислота, аммоній та сечовина). Пацієнтів було розділено на дві групи за рівнем виділення сечової кислоти: 1. Гіперурикозурія ( $>4$  ммоль/д), 2. Нормоурикозурія ( $\leq 4$  ммоль/д). Ми спостерігали певні кореляції між рівнем виділення сечової кислоти та статтю, віком, індексом маси тіла, артеріальним тиском, рівнями креатиніну, кальцію та натрію у крові, об'ємом сечі, рівнями кальцію, цитрату, амоніаку. Значних кореляцій між рівнями калію, рН сечі та частотою епізодів хвороби не спостерігалось. У першій групі (n=741) було 87,2% чоловіків та 12,8% жінок, співвідношення у другій групі (n=1739) було 60,6% до 39,4%. У гіперурикозуричній групі було значно більше чоловіків, аніж у нормоурикозуричній. Пацієнти з гіперурикозурією мали вищий індекс маси тіла, підвищений артеріальний тиск, підвищені рівні сечової кислоти та глюкози, більший діурез, підвищене виділення кальцію, сечовини та амонію у сечі. У нормоурикозуричних пацієнтів спостерігалось знижене виділення цитрату. Суттєвих різниць в інших параметрах не спостерігалось, особливо це стосується кількості епізодів хвороби. Нами було зроблено висновок, що гіперурикозурія супроводжується багатьма іншими факторами ризику для формування кальцієво-оксалатних каменів, але не асоціюється з підвищеним ризиком рецидивів. Таким чином, рівень екскреції сечової кислоти не є прогностичним маркером кальцієво-оксалатної сечокам'яної хвороби. Також є малоймовірним припущення, що гіперурикозурія є справжнім фактором ризику формування кальцієво-оксалатних каменів та виділення гіперурикозуричного кальцієво-оксалатного уrolітіазу у самостійну групу.

## INTRODUCTION

More than seventy years ago, Smith and coworkers described hyperuricosuria in calcium stone formers (Smith et al., 1969). Since that time, several other authors reported hyperuricosuria as a risk factor for calcium oxalate (CaOx) stone formation and coined the term hyperuricosuric calcium urolithiasis (Coe, 1978; Pak et al., 1980). Experimental studies revealed heterogenous nucleation (Pak and Arnold, 1975), removing inhibitors (Pak et al., 1977), and salting out (Grover et al., 1993) as potential mechanisms of action. Consequently, hyperuricosuric CaOx stone formers (CaOxSF) were treated with allopurinol and alkaline citrate (Coe y Raisen, 1973; Pak and Peterson, 1986). In one randomized prospective study, it has been shown that that allopurinol could decrease the recurrence rate in hyperuricosuric CaOxSF (Ettinger et al., 1986). Nevertheless, the role of hyperuricosuria has been questioned only several years later by the same working group (Ettinger, 1989). Possibly, other mechanisms than lowering uric acid excretion (UAE) were responsible for the decreased recurrence rate. The role of hyperuricosuria as a risk factor for calcium stone disease has been questioned later by Curhan and coworkers as they found that the risk of being a stone former decreased with increasing UAE in men (Curhan et al., 2001). In a recent review the role of hyperuricosuria has been challenged again (Moe y Xu, 2018). One problem is that all studies on hyperuricosuric CaOxSF have been performed with only a limited number of patients. Therefore, we examined the role of

hyperuricosuria in large series of CaOxSF with complete metabolic evaluation.

## MATERIALS AND METHODS

A total of 2,480 consecutive patients with CaOx stones treated in the Department of Urology and Paediatric Urology at the Regiomed-Klinikum Coburg, Germany were studied. Patients with primary hyperparathyroidism, hyperoxaluria and distal renal tubular acidosis were excluded.

Stone analysis was performed via polarization microscopy and x-ray diffraction.

A detailed history including age, sex, the number of stone episodes and the presence of diabetes mellitus was recorded. Arterial blood pressure (RR) was measured according to the recommendations of the World Hypertension League sitting after 5 minutes at rest. the body mass index (BMI) was assessed as well.

The following biochemical parameters were determined in all patients: urine pH profiles on three consecutive days in the morning (fasting), noon (postprandial) and evening (postprandial). For urine pH measurements, dipsticks, which allowed pH measuring in 0.1 steps (Madaus GmbH, Cologne, Germany), were used. The mean urinary pH was calculated in every patient.

Blood was drawn to measure creatinine (Jaffé reaction, Dade Behring Marburg, Germany), potassium (atomic absorption), calcium (indirect ion sensitive electrode), glucose (postprandial; hexokinase-glucose-6-phosphohate dehydrogenase method, Flex™ Siemens Healthcare Diagnostics Newark, DE, USA) and uric acid (modified uricase method, Dade

Behring Marburg, Germany). A 24 h-urine specimen was collected to determine the excretion of citrate (citrate lyase method, Boehringer Mannheim, Germany), creatinine (Jaffé reaction, Dade Behring Marburg, Germany), calcium (indirect ion sensitive electrode), uric acid (modified uricase method, Dade Behring Marburg, Germany), ammonia (modified glutamate dehydrogenase method using NADPH, test kit Ammonia Flex™, Dade Int., Newark, DE, USA) and urea (urease-glutamate dehydrogenase, Dade Behring Marburg, Germany) as markers for protein intake.

According to the UAE patients were divided into two groups: 1.  $\text{UAE} > 4 \text{ mmol/d}$  (hyperuricosuria), 2.  $\text{UAE} \leq 4 \text{ mmol/d}$  (normouricosuria).

For statistical analysis, means and standard deviations were calculated. Significant differences ( $p < 0.05$ ) were assessed by Student's t-test in case of Gaussian distribution and equal variance, otherwise the non-parametric Mann-Whitney test was used. Furthermore, correlations were calculated (Spearman r).

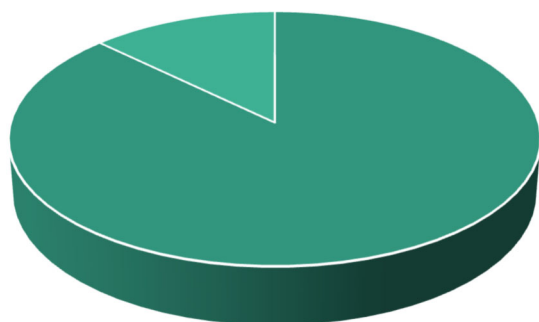
For these analyses, the programme Prism 9 (GraphPad Software, San Diego, CA, USA) was used. Calculations were performed on a personal computer.

## RESULTS AND DISCUSSION

The study population ( $n=2,480$ ) consisted of 1,949 males (78.6%) and 531 females (21.4%). There were 347 patients with diabetes mellitus (14.0%).

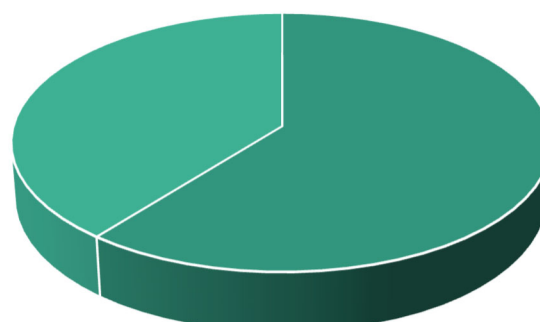
We observed significant correlations between UAE and sex, age, BMI, blood pressure, serum values of creatinine, sodium, urine volume, urine levels of calcium, citrate, urea and ammonia ( $p < 0.0001$ ) as well as serum calcium ( $p=0.023$ ). No significant correlations were seen to the stone frequency (number of stone episodes), serum potassium and urine pH.

In group 1 ( $n=741$ ; 29.9%), there were 87.2% male and 12.8% female patients; in group 2 ( $n=1,739$ ; 70.1%), the ratio was 60.6:39.4% (Fig.).



■ Males ■ Females

a



■ Males ■ Females

b

**Sex distribution in hyperuricosuric (a) and normouricosuric CaOxSF (b)**

In the hyperuricosuric group, there were significantly ( $p < 0.0001$ ) more males than in the normouricosuric collective. Hyperuricosuric subjects had a higher BMI (Table 1), higher blood levels of uric acid and glucose (Table 2), a higher diuresis, a higher excretion of calcium, urea and ammonium, but a lower excretion of citrate than normouricosuric patients (Table 3). All the other parameters did not show any significant differences. Especially the number of stone episodes was not different.

Our results showed that hyperuricosuria correlated with many metabolic parameters and stone

risk factors in CaOx stone formers. 29.9% of our CaOxSF were hyperuricosuric. Similar numbers have been reported already previously (Arowojolu and Goldfarb, 2014; Coe, 1978). Hyperuricosuria was associated with age, male sex and higher BMI. This in accordance with previous reports (Del Valle et al., 2012; Otto et al., 2017; Wang et al., 2018). Hyperuricosuric SF also showed a higher 24-h urine volume, ammonia, and urea excretion. These findings go along with a study on the composition of 24-h urine in diabetic and non-diabetic stone formers (Hartman et al., 2015).

**TABLE 1.** General parameters (means +/- standard deviations) om hyperuricosuic (group 1) and normouricosuric (group 2) CaOxSF

	<b>Group 1</b>	<b>Group 2</b>
Age (years)	49.7±12.7	53.7±15.4
BMI (kg <sup>2</sup> )	30.1±5.7*	27.8±4.9
Diab. mellitus (%)	14.4	13.9
Stone episodes (n)	1.8±1.4	1.8±1.2
BP sys (mm Hg)	138±15	136±15
BP dia (mm Hg)	83±8	81±8

*Significant differences: \* p<0.0001.*

**TABLE 2. Blood** parameters (means +/- standard deviations) om hyperuricosuic (group 1) and normouricosuric (group 2) CaOxSF

	<b>Group 1</b>	<b>Group 2</b>
Creatinine (mg/dl)	1.1±0.3	1.0±0.3
Sodium (mmol/l)	140±6	140±4
Potassium (mmol/l)	4.1±0.4	4.1±0.4
Calcium (mmol/l)	4.7±0.3	4.7±0.3
Uric acid (mg/dl)	5.2±1.0*	2.8±0.8
Glucose (mg/dl)	125±42*	118±40

*Significant differences: \* p<0.0001.*

**TABLE 3.** Urine parameters (means +/- standard deviations) om hyperuricosuic (group 1) and normouricosuric (group 2) CaOxSF

	<b>Group 1</b>	<b>Group 2</b>
pH	6.1±0.4	6.2±0.4
Volume (l/d)	3.0±1.4*	2.5±1.3
Calcium (mmol/d)	6.8±3.3*	5.1±2.9
Uric acid (mmol/d)	5.2±1.1	5.2±1.1
Citrate (mmol/d)	2.5±1.6*	2.8±0.8
Urea (mmol/d)	490±142*	304±119
Ammonia (mmol/d)	57±37*	38±39

*Significant differences: \* p<0.0001.*

## CONCLUSION

All these findings demonstrate that UAE is not an independent risk factor for CaOx stone formation. Conclusively, there was no correlation to the stone frequency and no association with an increased risk for recurrence. The number of stone episodes was comparable between hyperuricosuric and normouricosuric CaOxSF. Therefore, UAE is not a prognostic marker in CaOx urolithiasis. It is questionable whether hyperuricosuria is a real risk factor for CaOx stone formation. Our conclusions which are drawn from a large series of CaOxSF confirm the assumptions previously drawn from theoretical considerations and smaller clinical series (Ettinger, 1989). Although a linear relationship between uric acid excretion and the stone risk index  $FRP_{CaOx}$  has been demonstrated (Pak et al., 1977; Pak et al., 1978), this did not result in higher real world stone formation as the stone frequency did not

correlate with the UAE highlighting again that surrogate parameters as stone risk indices to not necessarily reflect the real stone events.

## STATEMENTS AND DECLARATIONS

The authors have no competing interests to declare that are relevant to the content of this article. The authors did not receive support from any organization for the submitted work.

This is an observational study. According to the laws in Germany, a vote of an Ethic Committee is not required as it is a retrospective study based on completely anonymized data that cannot be traced back to individual patients. It was exempt from the Regiomed-Kliniken Institutional Review board as it used only de-identified patient data.

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