The Association of Urolithiasis with Uricosuria, Uricemia, and their Combination

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ABSTRACT **Background:** There are conflicting data on the significance of hyperuricemia or hyperuricosuria in urolithiasis formation and on the need for medical treatment.

Objectives: To assess the significance of hyperuricemia or hyperuricosuria in urolithiasis formation, particularly when hyperuricemia occurs with normal uricosuria.

Methods: The electronic medical records of patients treated in Haifa and the Western Galilee district of Clalit Health Services, Israel, were retrospectively screened for diagnosis of nephrolithiasis or renal or urinary tract/bladder calculi between February 2014 and April 2019. The diagnosis was confirmed by ultrasonography or computed tomography. The study group included patients with one of these diagnoses. Patients in the control group did not have these diagnoses. The inclusion criterion for all patients was the presence of both serum and urinary uric acid levels.

Results: The study group included 359 patients and the control group 267. After adjustment by logistic regression, we found no significant differences in the prevalence of hyperuricosuria in the study group (14.8%) compared to the control group (9.7%), odds ratio (OR) 1.54 (95% confidence interval [95%CI] 0.74–3.2, P = 0.245). No significant differences between the groups were observed for hyperuricemia prevalence (45.4% vs. 55.1%, respectively, OR 0.82, 95%CI 0.54–1.25, P = 0.355), nor among those without hyperuricosuria (OR 0.83, 95%CI 0.52–1.33, P = 0.438) and after propensity score matching (OR 0.93, 95%CI 0.66–1.3, P = 0.655).

Conclusions: There were no significant differences in hyperuricemia or hyperuricosuria between the two groups of patients or in hyperuricemia among participants without hyperuricosuria.

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KEY WORDS: hyperuricemia, uric acid, urinary calculi, urinary stones, urolithiasis

Nephrolithiasis is associated with considerable morbidity and healthcare burden, including emergency room and ambulatory visits, hospitalizations, and invasive procedures due to renal colic episodes, urinary obstruction, and infections [1]. A history of nephrolithiasis is associated with an increased risk of chronic kidney disease such as end-stage kidney disease [2] and metabolic syndrome traits [3]. The prevalence of urolithiasis is 7.8–8.8% according to different surveys, including those using computed tomography screening [4]. Urinary stones are composed of calcium oxalate, calcium phosphate, and uric acid in approximately 70%, 20%, and 8% of patients, respectively [5].

Precipitating factors of uric acid stones are acidic urine pH, reduced urinary volume, and hyperuricosuria. Hyperuricosuria was reported in up to 63% of 167 patients with pure uric acid stones, but blood uric acid levels did not correlate significantly with uric acid excretion and urinary pH [6]. The frequency of uric acid stones, relative to other types of stones, is higher in diabetic, obese, hypertensive, inflammatory bowel disease, and gout patients and in congenital conditions, such as rare metabolic disorders and uric acid transporter mutations that elevate urinary uric acid levels. Acquired causes of hyperuricosuria include high dietary purine intake, increased purine metabolism associated with malignancy and chemotherapy, and hyperuricosuric medications. The prevention of uric acid stones may be achieved by diet adjustment and medical treatment. Dietary restriction of animal protein intake, as in the dietary approach to stop hypertension (DASH) diet, increases urine pH and citrate content and weight loss. It also reduces urinary uric acid excretion. Urinary alkalization by enteral medication, especially citrate tablets, is the most effective treatment of uric acid lithiasis. Some practitioners reserve uric acid reduction medical treatment for patients with gout or for those in whom alkalinization

may not be effective, such as patients with bowel disease or high urinary uric acid levels [7].

Urinary urate may precipitate calcium stones, the most frequent type of urolithiasis, through several mechanistic processes [8]. A prospective trial showed that uric acid lowering treatment by xanthine oxidase inhibitors reduced stones events in hyperuricosuric or hyperuricemic calcium stone formers [9]. Several placebo-controlled randomized trials demonstrated that citrate treatment reduced recurrent stone events in calcium stone formers with and without hypocitraturia [10]. Similarly, thiazide diuretics were found to be effective in the prevention of recurrent calcium stone, even in patients with normocalciuria [11].

There are conflicting data on the significance of hyperuricemia or hyperuricosuria in the formation of urolithiasis of unknown composition and on the need of their medical treatment. In the clinical setting, where frequently the stone composition is unknown, it is not clear whether hyperuricosuria, hyperuricemia, or hyperuricemia coincident with normal uricosuria are risk factors for urolithiasis and whether these conditions should be treated to prevent stone formation. Considering the efficacy of the empiric treatment for calcium stones, regardless of the urinary findings, it may be assumed that uric acid lowering treatment may prevent stones formation even when their composition is not known or when uricosuria is normal.

We assessed the prevalence of hyperuricemia in patients with urolithiasis, compared to patients without, while adjusting for various relevant factors, including urinary composition, especially uricosuria. A finding of higher prevalence of hyperuricemia in patients with urolithiasis would support uricemia lowering treatment. This therapy might also be given to patients with normal uricosuria if hyperuricemia is also found to be more frequent among them.

PATIENTS AND METHODS

STUDY DESIGN AND PATIENT POPULATION

The electronic medical records of patients treated in Haifa and the Western Galilee district of Clalit Health Services, the largest healthcare organization in Israel, were retrospectively screened for diagnosis of nephrolithiasis or renal or urinary tract/bladder calculi between February 2014 and April 2019. The study group included patients with one of these diagnoses, and patients in the control group did not have any of these diagnoses. Diagnoses were confirmed according to the imaging (ultrasonography/computed tomography) provided in the medical records. Inclusion criterion for all patients was the presence of results of both serum and urinary uric acid levels. Ethics approval was waived by the local ethics committee of Clalit Health Services.

DEMOGRAPHIC AND CLINICAL VARIABLES

Demographic and clinical variables of the participants, which had been assessed in the past as part of a routine follow-up, as part of an investigation of stones disease, or because of other unknown causes were obtained from their medical and laboratory records and included age, sex, socioeconomic status, ethnicity, body mass index (BMI), presence of obesity, gout, malignancy, diabetes mellitus, psoriasis, serum sodium, calcium, phosphorus, uric acid, magnesium, creatinine, urea, glucose, pH and parathyroid hormone levels, urinary sodium, calcium, phosphorus, uric acid, magnesium, citrate, oxalate and pH levels, presence of positive urinary culture and treatment by citrate, allopurinol, calcium, thiazides, and vitamin D. Because the information on stone composition was too scant and there were too few patients with inflammatory bowel disease or alcohol abuse, we did not include these data in the analysis. There was no information on diet composition or fluid intake. None of the patients had one of the rare genetic disorders of metabolism or urate transporter or used febuxostat or uricosuric medications. The variables for each patient, which were included in the whole analysis, were recorded in the shortest time from the date of urinary uric acid measurement.

STATISTICAL ANALYSIS

The baseline characteristics of the two groups were compared by chi-square test for categorial variables and independent *t*-test or Mann-Whitney test, as appropriate, for continuous variables. The prevalence of hyperuricosuria (urinary uric acid > 750 mg% per day) was compared between the groups by univariable and multivariable logistic regression, adjusted to age, sex, ethnicity, socioeconomic status, BMI, presence of psoriasis or obesity, serum sodium, calcium, phosphorus, creatinine, urea, uric acid and glucose levels, urinary calcium and pH levels, treatment by citrate, allopurinol, calcium, thiazides, and vitamin D. The prevalence of hyperuricemia (serum uric acid > 6 mg%) was compared between the groups by logistic regression, adjusted to age, sex, ethnicity, socioeconomic status, BMI, presence of psoriasis or obesity, serum sodium, calcium, phosphorus, creatinine, urea and glucose levels, urinary calcium, uric acid and pH levels, treatment

by citrate, allopurinol, calcium, thiazides, and vitamin D. The same comparison was repeated, with adjustment to the same confounders, except of urinary uric acid, for patients with normal urinary uric acid level (≤ 750 mg/day). The variables taken for adjustment were those that are important factors influencing stone formation or uric acid levels, reflect the hydration status of the participants, or were significantly different between the groups. When the number of patients with missing confounders data was too large, these confounders were not included in the adjustment, because otherwise these patients would have been entirely excluded from the analysis. To overcome the differences between the groups, we ran a propensity matched analysis as a sensitivity analysis. The variables included in the propensity score were age, sex, ethnicity, socioeconomic status, BMI, presence of gout, diabetes mellitus, obesity, malignancy or psoriasis, serum sodium, calcium, phosphorus, creatinine, urea and glucose levels, urinary calcium and pH levels, presence of positive urinary culture and treatment by citrate, allopurinol, calcium, thiazides, and vitamin D. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA). For all analyses, $P < 0.05$ for the 2-tailed tests was considered statistically significant.

RESULTS

A total of 359 patients were included in the study group and 267 in the control group. The characteristics of the participants are shown in Table 1. Stones were found in the kidneys or ureters and in some of the patients also in the urinary bladder. In eight patients the stones were just in the urinary bladder. Hyperuricosuria was found in 14.8% of the study group and in 9.7% of the control group ($P = 0.061$). After adjustment to the confounders, independent risk factors for hyperuricosuria were age, sex, BMI, urinary calcium, treatment by allopurinol and gout. The odds ratio (OR) for hyperuricosuria in the study group compared to the control group was 1.54 (95% confidence interval [95%CI] 0.74–3.2) but without significance ($P = 0.245$). Hyperuricemia was observed in 45.4% of the study-group patients and in 55.1% of the control-group ($P = 0.016$) [Figure 1]. After adjustment to the confounders, independent risk factors for hyperuricemia (total n=536) were sex, BMI, serum creatinine, urinary phosphorus, and treatment by allopurinol. Odds ratio for hyperuricemia in the study group compared to the control group was 0.82 (95%CI 0.54–1.25) without significance ($P = 0.355$). Among patients without hyperuricosuria, a higher percentage of hyperuricemia was found in the control group: 55.2%, compared to 42.2% in the study group. The OR was 0.59 (95%CI 0.42–0.83, $P = 0.02$) [Figure 2], but after adjustment, OR was 0.83 (95%CI 0.52–1.33, $P = 0.438$, total N=471) and after propensity matched analysis OR was 0.93 (95%CI 0.66–1.3, $P = 0.655$, n of each group = 157). Independent risk factors for hyperuricemia included sex, BMI, socioeconomic status, serum calcium and creatinine and urinary calcium and phosphorus.

DISCUSSION

The mean age of our study group was 55 years, which is slightly younger compared to the U.S. National Health and Nutrition Examination Survey data. That data showed that the highest prevalence of urolithiasis was between the ages of 60 and 69 years. Low socioeconomic status was more prevalent among our stones patients, and most were males, which is consistent with previous surveys [12]. The higher prevalence of males in the control group than in the general population may reflect the predominance of males among gout patients and the high prevalence of gout among the control participants (12.4%), which is higher than in the general population. For example, gout prevalence was reported to be 3.9% in the United States in 2007–2008, although it may have increased given the known tendency of increasing prevalence of gout over the years). The prevalence of hyperuricemia among both groups was higher than in the general population (21%) [13]. The presence of serum and urinary uric acid levels was the inclusion criterion for this study. These parameters, especially urinary uric acid, are not routinely evaluated unless there is an indication, such as history of gout. Therefore, the control group included patients with gout and hyperuricemia at a higher percentage than in the general population. The prevalence of gout in the study group was similar to previous reports among recurrent nephrolithiasis patients (8.6%) [14].

The mean urinary uric acid level of the study group was higher than in the control group, but after adjustment to the different variables, hyperuricosuria prevalence among the urinary-stones patients (14.8%) was not found to be significantly higher than in the control group. Greater prevalence of hyperuricosuria among kidney stones patients was also not observed in a previous cross-sectional study [15]. However, it was found to be much more prevalent among uric acid stone patients

Table 1. Characteristics of participants

Characteristics	Stones				*P*-value
	No		Yes		
	Mean ± SD/n	N	Mean ± SD/n	N	
Age in years	59.3 ± 16.3	267	55.0 ± 16.1	359	0.001
Male sex (%)	166 (62.2)	267	233 (64.9)	359	0.482
Body mass index kg/m2	28.4 ± 5.3	267	28.4 ± 5.3	359	0.949
Jewish ethnicity (%)	238 (89.1)	267	296 (82.5)	359	0.019
Socioeconomic status (%)					
Low	92 (34.5)	267	152 (42.3)	359	0.047
Middle	131 (49.1)		141 (39.3)		
High	44 (16.5)		66 (18.4)		
Serum sodium mEq/L	140.7 ± 2.8	267	140.8 ± 2.2	359	0.368
Serum magnesium mg/dl	2.02 ± 0.28	144	2.04 ± 0.21	181	0.506
Serum phosphorus mg/dl	3.5 ± 0.71	265	3.4 ± 0.62	359	0.027
Serum calcium mg/dl	9.47 ± 0.57	267	9.58 ± 0.42	358	0.015
Serum uric acid mg/dl	6.31 ± 1.8	267	5.93 ± 1.8	359	0.010
Serum creatinine mg/dl	1.21 ± 0.88	267	1.02 ± 0.56	359	0.01
Serum urea mg/dl	43.2 ± 28.2	267	37.3 ± 19.6	359	0.02
Serum glucose mg/dl	109.3 ± 33.4	267	107.3 ± 31.2	359	0.435
Plasma pH	7.39 ± 0.07	54	7.37 ± 0.07	47	0.164
Parathyroid hormone pg/ml	53.3 ± 76.9	147	35.1 ± 24.5	244	0.395
Urinary uric acid mg/dl	480.2 ± 233.7	267	540.0 ± 231.6	359	< 0.0001
Urinary calcium mg/dl	134.0 ± 107.6	204	176.9 ± 114.8	229	< 0.0001
Urinary magnesium mg/dl	99.7 ± 38.2	41	108.0 ± 52.5	140	0.424
Urinary phosphorus mg/dl	677.1 ± 348.9	157	751.0 ± 342.4	294	0.009
Urinary sodium meq/dl	155.2 ± 95.5	88	173.1 ± 86.8	139	0.072
Urinary citrate mg/dl	487.9 ± 299.7	49	506.6 ± 337.4	244	0.888
Urinary oxalate mg/dl	26.4 ± 10.3	55	29.9 ± 18.4	245	0.706
Urinary pH	6.1 ± 0.64	238	6.1 ± 0.68	301	0.725
Positive urinary culture (%)	38 (15.3)	196	52 (15.2)	342	0.997
Citrate tablets (%)	7 (2.6)	267	39 (10.9)	359	< 0.0001
Allopurinol (%)	94 (35.2)	267	88 (24.5)	359	0.004
Calcium tablets (%)	150 (56.2)	267	162 (45.1)	359	0.006
Thiazides (%)	81 (30.3)	267	83 (23.1)	359	0.042
Vitamin D tablets (%)	190 (71.2)	267	226 (63.0)	359	0.031
Gout (%)	33 (12.4)	267	25 (7.0)	359	0.021
Obesity (%)	112 (41.9)	267	134 (37.3)	359	0.242
Psoriasis (%)	13 (4.9)	267	10 (2.8)	359	0.171
Malignancy (%)	73 (27.3)	267	77 (21.4)	359	0.088
Diabetes mellitus (%)	98 (36.7)	267	113 (31.5)	359	0.171

SD = standard deviation

Figure 1. Unadjusted prevalence of serum uric acid (UA) level > 6 mg% and urinary uric acid (UUA) level > 750 mg/d among patients without urolithiasis (control group) and in patients with urolithiasis (study group)

#*P* = 0.061
**P* = 0.017

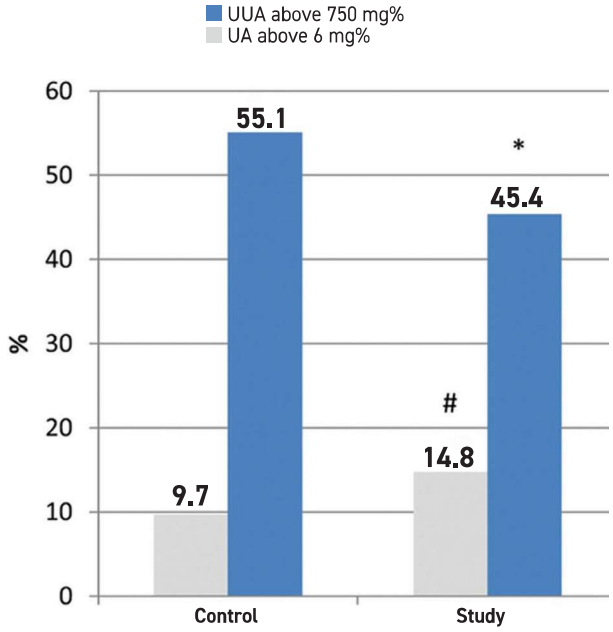
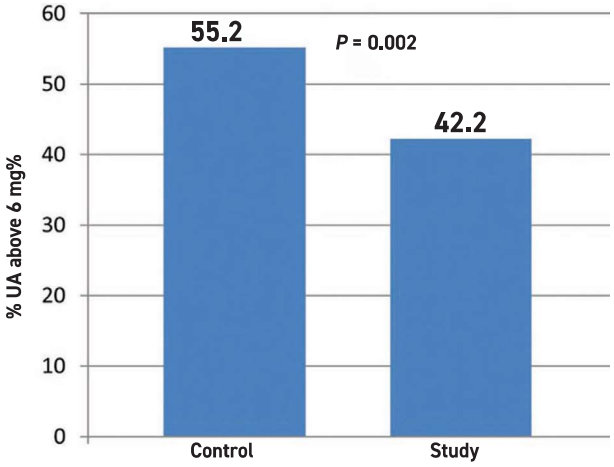


Figure 2. Unadjusted prevalence of serum uric acid (UA) level > 6 mg% among patients without hyperuricosuria and without urolithiasis (control group) or with urolithiasis (study group)



(63%) [6] and among calcium stone patients (40%) [16]. In addition, urolithiasis was more prevalent among gouty patients as their urinary uric acid level increased [17].

There were some significant differences in serum parameters between the groups in our study, including uric acid levels, but these differences were too small to have clinical significance. Hyperuricemia was less frequent in the study group than in the control group, although not significantly, after adjustment for confounders. In a large previous study, no significant association was found between increasing serum uric-acid and urolithiasis [18]. In contrast, other studies did find an association between hyperuricemia and nephrolithiasis [17,19,20]. Male gender was found to be a significant risk factor for hyperuricemia in our study as in a previous study [14].

After adjustment for confounders and propensity score matching, we found no significant difference between hyperuricemia prevalence in participants of either group without hyperuricosuria. There is no information in previous studies on this subpopulation.

There are some limitations to our study. Since it is a retrospective epidemiological study, patient treatment included medications that might influence metabolic variables and stone formation. In addition, information on the stones composition was available for only a small minority of the patients and thus this information was not included. Nevertheless, this lack of data is common in real-world clinical situations. There was no information on the diet of the participants, nor on their fluid intake. The presence of uric acid levels in the serum and urine was an inclusion criterion; however, these parameters are not routinely evaluated. In addition, due to the relatively low prevalence of stones, the study was not a cohort study that could assess the prevalence of urolithiasis among hyperuricemic or hyperuricosuric patients. This limitation introduced bias that caused relatively frequent hyperuricemia in our study population.

The strengths of this study include the meticulous confirmation of the presence or absence of urolithiasis in the imaging of patients in the study and control groups and the detailed data of the different variables that were collected, including the relevant urinary parameters and treatments, for which multivariable adjustment was made.

CONCLUSIONS

We did not find significant differences in hyperuricemia or hyperuricosuria between patients with urolithiasis whose composition is unknown and those without urolithiasis. We also did not find differences in hyperuricemia between participants of both groups without hyperuricosuria. Further studies, including cohort prospective studies are required to observe the rate of urinary stones among patients with hyperuricemia and with or without hyperuricosuria,

and to observe the efficacy of treatment of hyperuricemia or hyperuricosuria in these different conditions.

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Capsule

Antigenicity and receptor affinity of SARS-CoV-2 BA.2.86 spike

A severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron subvariant, BA.2.86, has emerged and spread to numerous countries worldwide, raising alarm because its spike protein contains 34 additional mutations compared with its BA.2 predecessor. **Wang** et al. examined its antigenicity using human sera and monoclonal antibodies (mAbs). Reassuringly, BA.2.86 was no more resistant to human sera than the currently dominant XBB.1.5 and EG.5.1, indicating that the new subvariant would not have a growth advantage in this regard. Importantly, sera from people who had XBB breakthrough infection exhibited robust neutralizing activity against all viruses tested, suggesting that upcoming XBB.1.5 monovalent vaccines could confer added protection. Although BA.2.86 showed greater resistance to mAbs to subdomain 1 (SD1) and receptor-binding domain (RBD) class 2 and 3 epitopes, it was more sensitive to mAbs to class 1 and 4/1 epitopes in the 'inner face' of the RBD that is exposed only when this domain is in the 'up' position. The authors also identified six new spike mutations that mediate antibody resistance, including E554K that threatens SD1 mAbs in clinical development. The BA.2.86 spike also had a remarkably high receptor affinity. The ultimate trajectory of this new SARS-CoV-2 variant will soon be revealed by continuing surveillance, but its worldwide spread is worrisome.

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