HHS Public Access

Author manuscript

J Urol. Author manuscript; available in PMC 2018 May 01.

Published in final edited form as:

J Urol. 2018 May ; 199(5): 1262–1266. doi:10.1016/j.juro.2017.10.046.

Relative Supersaturation of 24-hour Urine and Likelihood of Kidney Stones

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Abstract

Purpose—Relative supersaturations of calcium oxalate, calcium phosphate, and uric acid are used clinically in kidney stone prevention. The magnitudes of association between relative supersaturation and stone risk require further quantification.

Materials and Methods—We performed a cross-sectional study using 24-hour urine collections from Nurses' Health Study I (NHS I), Nurses' Health Study II (NHS II), and Health Professional Follow-up Study (HPFS) cohorts to quantify the association between calcium oxalate, calcium phosphate, and uric acid relative supersaturations levels and likelihood of stone formation.

Results: Odds ratio—(OR) for being a stone former were 5.85 (3.40 to 10.04) in NHS I, 6.38 (3.72 to 11.0) in NHS II, and 6.95 (3.56 to 13.6) in HPFS for the highest category of calcium oxalate relative supersaturation compared with <1.0. The OR for being a stone former were 1.86 (0.94 to 3.71) in NHS I, 4.37 (2.68 to 7.10) in NHS II, and 3.59 (2.04 to 6.31) in HPFS for the highest category of calcium phosphate relative supersaturation compared with <1.0. For uric acid relative supersaturation, OR for being a stone former were 4.30 (2.34 to 7.90) in NHS I and 2.74 (1.71 to 4.40) in NHS II for the highest relative supersaturation category compared with <1.0. In HPFS, uric acid relative supersaturation was not significantly associated with likelihood of stone formation.

Conclusion—Likelihood of being a stone former increases with higher calcium oxalate and calcium phosphate relative supersaturation levels in men and women, and higher relative supersaturation levels of uric acid in women.

Introduction

Urine factors play a role in kidney stone formation. Independent contributions of 24-hour excretion of calcium, oxalate, citrate, uric acid, total urine volume, sodium, magnesium, phosphorus, and urine pH to stone risk have been reported.[1] Urine supersaturation levels of

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calcium oxalate (CaOx), calcium phosphate (CaP), and uric acid (UA) are used clinically in kidney stone management. Supersaturation of a compound is the concentration in solution above its solubility and drives crystallization.[2–4]

Supersaturation is not directly measured; it is calculated using an iterative computer program taking the physiochemical interactions of multiple factors (promoters and inhibitors) into account.[5] For example, urinary factors contributing to supersaturation of CaOx salts include calcium, oxalate, and volume, and inhibitors.[2] Urinary pH is important for UA and CaP.[2]

Cross-sectional studies have demonstrated higher supersaturation values for stone formers compared with non-stone formers.[3,6] Intuitively, higher levels of supersaturation should increase risk of stone formation; however, the magnitude of risk is not clear for different supersaturation levels. To quantify the magnitude of association of supersaturation level of CaOx, CaP, and UA and likelihood of being a stone former we analyzed 24-hour urine collections from 2,508 male and female stone formers, and 1,267 male and female controls from the Nurses' Health Study I (NHS I), Nurses' Health Study II (NHS II), and Health Professional Follow-up Study (HPFS) cohorts.

Methods

Study cohorts

The NHS I is comprised of 121,700 female nurses aged 30–55 years at study start in 1976. The NHS is comprised of 116,430 female nurses aged 25–42 years at study start in 1989. The HPFS is comprised of 51,529 male health professionals aged 40–75 at study start in 1986. Participants in these cohorts are followed every two years with questionnaires that collect disease and lifestyle information. Follow-up is greater than 90% of eligible person-time for each cohort.

Ascertainment of kidney stones

Biennial questionnaires for each cohort ask about a new diagnosis of kidney stones. Those self-reporting an incident kidney stone were mailed a supplemental questionnaire requesting information such as date of diagnosis. A validation study using medical records performed in the three cohorts confirmed self-report in ≥ 95% of cases.[7] Of these, stones contained at least 50% CaOx in 77% of 78 stone composition reports from NHS I, 79% of 243 stone composition reports from NHS II, and 86% of 148 stone composition reports from HPFS.[7] For this present study, we do not have stone composition reports for most participants, though it is expected that the majority of stones were CaOx.[8–11] Although it is likely that less than 10% of stones were 100% UA[10,11], we analyzed UA supersaturation for this study for completeness, but given the low percentage, these results should be interpreted with caution.

Urine collections

There were two cycles of 24-hour urine collections from participants with a history of kidney stones and participants randomly selected as controls. Cycle one was from 1994 to 1999 and consisted of one 24-hour urine collection from stone formers and controls.

Participants were included if they were aged 70 or younger in HPFS or 65 or younger in NHS I.[1,12] Participants were excluded if they had a history of cancer or cardiovascular disease.[1,12] Cycle two was in 2003 and consisted of additional stone formers and controls who were asked to perform two 24-hour urine collections. The participation and completion rates for all three cohorts have been previously described.[1] Participants older than 75 years and those with history of cancer (other than non-melanoma skin cancer) were excluded from the collection.

Urine collections were performed using the Mission Pharmacal (San Antonio, TX) system. Participants were sent a urine collection kit and samples were returned to Mission Pharmacal using a FedEx mailer.

Supersaturation calculation

The measurements of individual components contributing to the calculation of supersaturation, including total urine volume, calcium, oxalate, phosphorus, pH, and uric acid, have been previously described.[1] To assess reproducibility, blinded split samples were sent and for all of the measured factors the coefficients of variation were less than 10%.[1] Relative supersaturation (RS) was calculated using supersaturation from the EQUIL2 program.[5] Different laboratories have different approaches for manipulating and presenting supersaturation data as a RS or other modified supersaturation.

Statistical Analysis

Participants whose 24-hour creatinine was in the top or bottom 1% were excluded to remove possible over or under collections. Data from each cohort were analyzed separately. Baseline characteristics and urine values for cases and controls were compared using t-tests for normally distributed variables and Wilcoxon-rank sum tests for non-normally distributed variables. Logistic regression was performed to calculate odds ratio of being a stone former after adjusting for age. For each cohort, the primary analysis used participants with at least one 24-hour urine collection. A secondary analysis used participants with two 24-hour urine collections; the arithmetic mean of each factor was used. Categories for RS of CaOx, CaP, and UA were chosen based on clinically reasonable increments. For UA RS, a stratified analysis was performed examining for effect modification by age, using age cut point 65 years for NHSI and HPFS, and age 55 years for NHSII. Analyses were done using SAS 9.4 (SAS Institute Inc., Cary, NC). The research protocol for this study was approved by the institutional review board of Brigham and Women’s Hospital.

Results

There were 1354 NHS I, 1276 NHS II, and 1145 HPFS participants who completed at least one urine collection. There were no substantial differences in characteristics between the HPFS participants who collected urine and those who did not, but the body mass index (BMI) for controls who provided a sample was 2.2 kg/m^2 lower in NHS I and 1.6 kg/m^2 lower in NHS II.[1] There were no meaningful differences in dietary intake of calcium, sodium, and animal protein between participants who collected urine and those who did not.[1]

The characteristics of the cases and controls for each cohort are provided in Table 1. Compared with controls, cases were older in NHS I but younger in NHSII and HPFS. Mean BMI was higher for cases compared with controls for NHS I and NHS II. More cases had a family history of kidney stones compared with controls for NHS II and HPFS. Median times from initial kidney stone diagnosis to 24-hour urine collection were 5.8 years for NHS1, 3.9 years for NHSII, and 5.0 years for HPFS.

Mean values for 24-hour urine factors by case status are presented in Table 2. Compared with controls, cases had significantly higher mean RS of CaOx and CaP in all three cohorts (Table 2). NHS I and II cases had significantly higher RS of UA than controls (Table 2). Cases also had lower total urinary volume, potassium and pH, and higher calcium and oxalate in all three cohorts (Table 2).

For a single urine collection in all three cohorts, the likelihood of being a stone former was higher with higher CaOx RS (Table 3). In NHS I and NHS II, the odds ratio for being a stone former were 5.85 (95% CI 3.40 to 10.04) and 6.38 (95% CI 3.72 to 11.0), respectively, for the highest category of RS of 3.0 or greater compared with the lowest category of <1.0 (Table 3). In HPFS, the odds ratio of being a stone former was 6.95 (95% CI 3.56 to 13.6) for RS of CaOx of 4.0 or greater compared with <1.0 (Table 3). When two urine collections were analyzed, a similar pattern was seen (Supplementary Tables 1, 2, 3). Results were similar in an analysis stratifying at age for all three cohorts.

For CaP, the likelihood of being a stone former was higher with higher RS category in all three cohorts (Table 3). The odds ratios for being a stone former were 1.86 (95% CI 0.94 to 3.71) for NHS I, 4.37 (95% CI 2.68 to 7.10) for NHS II, and 3.59 (95% CI 2.04 to 6.31) for HPFS for the highest RS category compared with <1.0 (Table 3). The pattern was similar for the two urine collections (Supplementary Tables 1, 2, 3).

The likelihood of being a stone former was also higher with higher RS of UA for NHS I and NHS II (Table 3) but was not statistically significant for HPFS (Table 3). The odds ratios for being a stone former were 4.30 (95% CI 2.34 to 7.90) for NHS I and 2.74 (95% CI 1.71 to 4.40) for NHS II highest RS category of 4.0 or greater compared with <1.0 (Table 3). A similar pattern was seen for the two urine collections (Supplementary Tables 1, 2, 3).

For all three cohorts, there was moderate correlation between RS of CaOx and CaP (Spearman r=0.51–0.55) and between CaOx and UA (Spearman r=0.36–0.45).

Discussion

Relative supersaturation appears to be a useful measure of risk of stone formation. There was higher likelihood of being a stone former with higher RS of CaOx and CaP in all three cohorts in this study. There was higher likelihood of being stone former for higher UA RS in both female cohorts though not in the male cohort.

A previous study noted that high supersaturations were associated with higher likelihood of being a stone former. In a cross-sectional analysis of 24-hour urine from 123 male workers in Tennessee, odds of being a stone former was higher in the highest tertile of CaOx

supersaturation index but there was no statistical difference in the middle tertile.[6] Of 40 stone formers, stone composition reports were available for 13 and 92% of stones were CaOx. The results of our study emphasize the importance of understanding that risk of stone formation increases continuously with increasing CaOx and CaP RS levels in both men and women. Risk was already significantly higher at RS levels that fall within the 'normal' reference range of less than 2.0. When other urinary factors were analyzed, including the individual factors that contribute to the calculation of the RS of CaOx and CaP, risk of stone formation similarly increased continuously, starting within the previously considered 'normal' range.[1] The results of the current study again challenge previous beliefs of what has been considered 'normal' vs 'abnormal' for RS of CaOx and CaP.

For UA RS, results differed between the female and male cohorts. For NHS I and II, there was higher risk of being a stone former with increasing RS level and risk was higher even within the 'normal' range. In HPFS, risk of being a stone former was flat and nonsignificant across the levels of RS. This difference by sex held true for participants with two 24-hour urine collections. There is no clear reason for this difference between the sexes; however, previous studies have found age and sex variations in stone risk for some urinary components.[1] Previous studies have examined the change in stone composition by age and sex.[11] In our study, we did not find that results varied by age in any of the three cohorts.

It is also important to note that interpretation of the RS results from this study requires caution as we do not have stone composition reports for each stone former. Given that CaOx is the most common stone type[8,9] and that most first time stones are CaOx,[10] it is likely that most stones in our study were CaOx. Furthermore, in a validation study of stone formers in these cohorts using medical records, 77% of NHS I, 79% of NHS II, and 85% of HPFS stones were at least 50% calcium stones.[7]

Knowledge of stone composition is important because supersaturations of CaOx, CaP, and UA have been shown to closely reflect the stone composition of these stone types.[3] Circumstances where the correlation weakens include conditions of low or high urine volume.[13] Given that CaOx is likely the predominant stone type in our study,[7] we expect that the magnitudes of association for CaOx RS to be most reliable.

We found a moderate correlation between the values for CaOx and CaP RS. Some of the same factors that contribute to CaOx RS also contribute to CaP, such as calcium, citrate, and urine volume. In addition to any true association, the point estimate for the likelihood of stone formation by CaP RS could be partly attributable to the correlation with CaOx RS. There was also a moderate correlation between CaOx and UA RS. A portion of the finding in the female cohorts may be attributable to the moderate correlation between these two RS. However, additional study of UA RS with known stone type is needed to provide further understanding of the association of UA RS level and likelihood of being a stone former.

There are limitations to this study. We do not have stone composition reports on the vast majority of stone formers. Due to our study design, the age distribution of our sample did not include participants under the age of 30 and included few over the age of 70. In these younger and older age groups there may be differences in stone composition, which would

not be reflected in our results. We did not have data on stone recurrence and thus are unable to distinguish between incident stone former and recurrent stone formers. Generalizability of results may be limited as there were few non-white participants. Is important to note that the 24-hour urine collection does not capture temporary spikes in supersaturation, such as post-prandial or in the early morning hours.[14] In addition, RS is a calculated number using multiple different measured variables. There is biologic variability as well as possible errors in the collection and measurement of the factors that contribute to the RS calculation, and RS is not the only factor that influences stone formation. However, the coefficients of variation for the measurements were all low and participants with extreme 24-hour urinary creatinine levels were excluded to reduce error associated with over- and under-collection, so the error should have been minimized. Finally, urine collections in the cases were performed after a stone event so it possible that changes in behavior, such as fluid intake, could have attenuated the magnitude of the associations.

These results contribute to clinical practice as RS is often used as a target for stone prevention and management. Without RS, it can be difficult to assess overall likelihood of stone formation for an individual who has day-to-day variations in the components of supersaturation. Relative supersaturation can also be used to assess the impact of an intervention when components of the supersaturation increase or decrease with dietary and therapeutic modifications. These results demonstrate that the likelihood of stone formation increases with higher RS levels of CaOx and CaP in men and women, and higher RS levels of UA in women and this increase begins at levels below the currently accepted ‘normal’ values.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of funding: From the National Institutes of Health grant numbers DK59583, DK73381, T32DK00752730, F32DK111056, K24DK091417, UM1CA186107, R01CA67262, UM1CA176726, UM1 CA167552, and CA50385

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Table 1

Characteristics of participants in the 24-hour urine collection study by cohort and case status.

Variable	NHS I Case (N=947)	NHS I Control (N=407)	NHS II Case (N=833)	NHS II Control (N=443)	HPFS Case (N=728)	HPFS Control (N=417)
Age	66.5 (7.8)[b]	65.5 (5.7)	48.4 (6.2)[a]	51.0 (5.1)	63.4 (8.8)[a]	64.6 (6.3)
Weight, kg	73.4 (15.6)[a]	69.7 (14.5)	74.8 (18.3)[b]	72.3 (17.1)	83.5 (12.3)	84.0 (13.2)
Body mass index (kg/m)	27.4 (5.7)[a]	25.8 (5.1)	27.8 (6.6)[a]	26.6 (6.0)	26.2 (3.6)	26.2 (3.6)
Family history (%)	NA	NA	31.5%[a]	14.5%	20.6%[a]	13.0%

HPFS, Health Professionals Follow-up Study; NHS I, Nurses' Health Study Cohort; NHS II, Nurses' Health Study II; NA, not available

Values are means (SD) except where otherwise noted

[a] $p \leq 0.01$ for case compared with control within the cohort

[b] $p < 0.05$ for case compared with control within the cohort

Table 2

Values of 24-hour urine relative supersaturation and individual factors by cohort and case status.

Variable	NHS I Case (N=947)	NHS I Control (N=407)	NHS II Case (N=833)	NHS II Control (N=443)	HPFS Case (N=728)	HPFS Control (N=417)
Calcium Oxalate RS, median (25%, 75%)	1.54 (1.00, 2.30)[a]	1.10 (0.69, 1.60)	1.64 (1.06, 2.46)[a]	1.03 (0.69, 1.60)	1.97 (1.26, 2.87)[a]	1.37 (0.82, 2.16)
Calcium phosphate RS, median (25%, 75%)	0.98 (0.43, 1.86)[a]	0.82 (0.40, 1.48)	1.43 (0.73, 2.59)[a]	0.99 (0.52, 1.71)	1.09 (0.59, 1.95)[a]	0.79 (0.42, 1.48)
Uric acid RS, median (25%, 75%)	1.26 (0.50, 2.46)[a]	0.85 (0.34, 1.72)	1.51 (0.60, 2.90)[a]	1.04 (0.43, 2.12)	2.08 (1.08, 3.42)	1.93 (0.83, 3.46)
Creatinine, mg	1047 (229)	1030 (217)	1211 (260)	1207 (252)	1673 (370)[c]	1606 (373)
Calcium, mg	198 (109)[b]	183 (94)	218 (100)[a]	187 (87)	212 (111)[a]	170 (91)
Oxalate, mg	30.0 (11.3)[a]	27.7 (10.0)	28.5 (11.4)[a]	25.8 (8.5)	41.3 (13.2)[c]	39.1 (14.7)
Uric acid, mg	444 (162)	446 (154)	516 (160)	506 (158)	606 (237)[b]	638 (214)
Citrate, mg	607 (313)[a]	670 (298)	713 (314)[a]	791 (290)	685 (312)	714 (301)
Potassium, mEq	58.7 (21.0)[a]	62.9 (21.2)	52.7 (19.8)[a]	58.6 (20.3)	74.9 (24.5)[c]	78.8 (26.0)
Sodium, meq	142 (60)	136 (56)	153 (63)	151 (64)	186 (70)[b]	177 (71)
Magnesium, mg	98 (41)[c]	106 (39)	97 (36)[b]	103 (39)	125 (45)	122 (42)
Phosphorus, mg	757 (246)	740 (240)	857 (274)	826 (278)	1090 (334)[a]	1025 (300)
PH	5.96 (0.53)[a]	6.07 (0.48)	6.01 (0.47)[b]	6.07 (0.46)	5.83 (0.46)[b]	5.90 (0.47)
Total Volume, L	1.7 (0.7)[a]	2.0 (0.8)	1.6 (0.7)[a]	1.9 (0.8)	1.6 (0.6)[a]	1.8 (0.7)

HPFS, Health Professionals Follow-up Study; NHS I, Nurses' Health Study Cohort; NHS II, Nurses' Health Study II, RS, Relative Supersaturation (calculated using EQUIL2)

Data presented as mean (SD), except where noted

[a] $p \leq 0.001$ for case compared with control within the cohort

[b] $p < 0.05$ for case compared with control within the cohort

[c] $p \leq 0.01$ for case compared with control within the cohort

Table 3

Age-adjusted odds ratio for being a stone former according to category of 24-hour relative supersaturation for a single urine collection within NHS I, NHSII, and HPFS

Calcium Oxalate RS	NHS I Cases	NHS I Controls	OR (CI)	NHS II Cases	NHS II Controls	OR (CI)	HPFS Cases	HPFS Controls	OR (CI)
<1.0	236	181	1.0 (ref)	184	209	1.0 (ref)	112	141	1.0 (ref)
1.0–1.9	395	165	1.89 (1.45 to 2.47)	324	172	2.10 (1.60 to 2.76)	258	155	2.09 (1.52 to 2.87)
2.0–2.9	197	43	3.83 (2.60 to 5.65)	200	44	4.72 (3.21 to 6.94)	197	80	3.04 (2.11 to 4.36)
3.0+ (or 3.0– 3.9)	119	18	5.85 (3.40 to 10.0)	125	18	6.38 (3.72 to 11.0)	92	29	3.91 (2.40 to 6.36)
4.0+	-	-		-	-		69	12	6.95 (3.56 to 13.6)
P trend			<0.001			<0.001			<0.001
Calcium Phosphate RS									
<1.0	479	238	1.0 (ref)	285	222	1.0 (ref)	330	250	1.0 (ref)
1.0–1.9	247	107	1.15 (0.88 to 1.52)	256	137	1.36 (1.03 to 1.80)	223	106	1.56 (1.17 to 2.08)
2.0–2.9	120	37	1.61 (1.08 to 2.41)	142	62	1.57 (1.10 to 2.24)	96	45	1.56 (1.06 to 2.32)
3.0–3.9 (or 3.0+)	61	14	2.19 (1.20 to 3.99)	150	22	4.37 (2.68 to 7.10)	79	16	3.59 (2.04 to 6.31)
4.0+	40	11	1.86 (0.94 to 3.71)	-	-		-	-	
P trend			<0.001			<0.001			<0.001
Uric Acid RS									
<1.0	414	225	1.0 (ref)	322	217	1.0 (ref)	158	118	1.0 (ref)
1.0–1.9	198	103	1.09 (0.82 to 1.46)	188	106	1.12 (0.83 to 1.51)	196	98	1.47 (1.04 to 2.07)
2.0–2.9	162	44	2.11 (1.45 to 3.06)	125	63	1.26 (0.88 to 1.80)	138	72	1.40 (0.96 to 2.03)
3.0–3.9	80	22	2.16 (1.31 to 3.57)	91	31	1.91 (1.22 to 2.99)	104	55	1.36 (0.91 to 2.04)
4.0+	93	13	4.30 (2.34 to 7.90)	107	26	2.74 (1.71 to 4.40)	132	74	1.25 (0.86 to 1.82)

Calcium Oxalate RS	NHS I Cases	NHS I Controls	OR (CI)	NHS II Cases	NHS II Controls	OR (CI)	HPFS Cases	HPFS Controls	OR (CI)
P trend			<0.001			<0.001			0.16

OR, odds ratio; CI, confidence interval; NHSI, Nurses' Health Study I; NHSII, Nurses' Health Study II; HPFS, Health Professionals Follow-up Study; **RS, relative supersaturation**