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ORIGINAL PAPER

Fasting versus 24-h urine pH in the evaluation of nephrolithiasis

Giovanna Capolongo · Khashayar Sakhaee · Charles Y. C. Pak · Naim M. Maalouf

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Abstract An abnormal urinary pH (UpH) represents an important risk factor for nephrolithiasis. In some stone formers, a fasting urine specimen is obtained instead of a 24-h urine collection for stone risk evaluation. We examined the relationship between 24-h and fasting UpH in non-stone forming individuals and stone formers with various etiologies and a wide range of urine pH to test the validity of fasting UpH. Data from 159 subjects was examined in this retrospective study. We included non-stone forming subjects and stone formers with hypercalciuria, distal renal tubular acidosis, idiopathic uric acid nephrolithiasis, or chronic diarrhea. Participants collected a 24-h urine followed by a 2-h fasting urine. For the entire cohort, a significant correlation was seen between fasting and 24-h UpH ($r^2 = 0.49$, $p < 0.001$). Fasting pH was significantly higher than 24-h UpH for the entire cohort (6.02 ± 0.63 vs. 5.89 ± 0.51; $p < 0.001$), and in the subgroups of non-stone formers and stone formers with hypercalciuria or distal renal tubular acidosis. Fasting UpH was >0.2 pH units different from 24-h UpH in 58% of participants. The difference between fasting and 24-h UpH did not correlate with net gastrointestinal alkali absorption or urine sulfate, suggesting that dietary factors alone cannot explain this difference in UpH. Fasting urine pH correlates moderately with 24-h urine pH in a large cohort of individuals. Significant variability between these two parameters is seen in individual patients, emphasizing the cardinal role of 24-h urine collection for evaluating UpH in nephrolithiasis.

Keywords Nephrolithiasis · Urine pH

G. Capolongo · K. Sakhaee · C. Y. C. Pak · N. M. Maalouf (✉)
Department of Internal Medicine, Center for Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8885, USA
e-mail: naim.maalouf@utsouthwestern.edu

Introduction

An abnormal urinary pH represents an important metabolic risk factor for nephrolithiasis [1]. A high urinary pH predisposes to the formation of calcium phosphate stones due to increased urinary saturation of calcium phosphate [2], and to the formation of struvite stones due to low phosphate solubility in the context of excessive ammonia production by urea-splitting organisms [3]. On the other hand, a low urinary pH predisposes to uric acid precipitation, and excessively low urine pH is a universal finding in idiopathic uric acid stone formers [4, 5]. Low urinary pH can also result from excessive gastrointestinal alkali loss such as diarrhea, and contributes to stone disease in patients with chronic diarrhea [6].

A 24-h urine collection is generally recommended to evaluate patients with recurrent nephrolithiasis to assess the underlying risk factors [7]. However, many patients do not undergo such an evaluation [8] either because of unwillingness, perceived complexity of such a collection, or concern with over- or under-collection of 24-h urine specimen. Some investigators have suggested the use of a spot urine or fasting urine as a substitute for 24-h urine collection [9]. While several studies have compared spot versus 24-h urine collection for determination of hypercalciuria [10–16], there is no data comparing urine pH in spot versus 24-h urine. In this report, we examine the relationship between fasting and 24-h urine pH in a group of subjects with a wide range of urine pH.

Materials and methods

Study participants

In this retrospective study, we reviewed data from kidney stone patients included in the University of Texas Southwestern Stone Registry who underwent a detailed ambulatory evaluation [7, 17] and from a group of non-stone forming subjects. All subjects provided informed consent. At the time of evaluation, none of the patients/subjects were taking any medications known to alter urine pH (such as potassium alkali, sodium bicarbonate or carbonic anhydrase inhibitors). Nephrolithiasis patients with the following metabolic conditions were selected: distal renal tubular acidosis (RTA), chronic diarrheal syndrome, idiopathic uric acid nephrolithiasis, and calcium oxalate stone formers with hypercalciuria. We selected a group of non-stone forming subjects as controls.

The following criteria were applied for each group: non-stone forming controls: subjects without a personal history of kidney stones. Hypercalciuric calcium oxalate stone formers: Stone formers with documented calcium oxalate stone (>70% calcium oxalate in composition on stone analysis) and urinary calcium >200 mg/day on a diet restricted in calcium and sodium content (400 mg and 100 mmol/day, respectively). Distal RTA: Patients with nephrolithiasis and either complete distal RTA (evidence of systemic metabolic acidosis), or the incomplete form with normal serum electrolytes but defective urinary acidification following ammonium chloride load. Chronic diarrhea: Patients with nephrolithiasis and different gastrointestinal diseases including ulcerative colitis, Crohn's disease, and gastric or intestinal resection. Idiopathic uric acid nephrolithiasis: Patients with uric acid stones (on stone analysis) and a 24-h urinary pH < 5.5 in the absence of diarrhea or high intake of animal protein.

Data collection and measurements

After consuming a diet restricted in calcium and sodium content (400 mg and 100 mmol/day, respectively) for 1 week, all participants had a 24-h urine collection, followed by a 2-h urine collection after an overnight fast. Urine was kept refrigerated during the 24-h and 2-h collection periods and measurements were conducted at the end of the collection period. The 24-h urine was analyzed for stone risk parameters including total volume, creatinine, calcium, oxalate, uric acid, citrate, magnesium, sodium, potassium, phosphate and pH; urine sulfate and chloride were available on a subset of patients. Measurements on fasting urine included total volume, creatinine, calcium and pH. Urine pH was measured by pH electrode. Other measurements were performed as previously described [7]. Net gastrointestinal alkali absorption (NGIA) was calculated by the method of Oh [18].

Statistical analyses

Demographic and biochemical parameters for each group of participants are presented as mean ± standard deviation, and were compared with those of the non-stone forming group using the Student *t* test. Paired two-tailed *t* test was used to compare the 24-h urine pH and the fasting urine pH in the overall sample and within each subgroup. Pearson correlation coefficient was used to assess the degree of correlation between 24-h and fasting urine pH. The absolute difference between 24-h and fasting urine pH (ΔpH) was calculated for each participant, and the proportion of subjects with ΔpH above two different cutoffs (0.2 and 0.4) is presented for each group. Pearson correlation coefficient was used to assess the degree of correlation between ΔpH and NGIA and urine sulfate.

Results

Demographic and biochemical characteristics

A total of 159 stone and non-stone formers were included in this study. The demographic characteristics are illustrated in Table 1 for individual groups of patients. The mean age for the overall population was 45 years, with patients in the distal RTA and hypercalciuric CaOx stone forming groups significantly younger than non-stone formers. The mean body mass index (BMI) in the idiopathic uric acid nephrolithiasis patients was in the obese range, while the 4 other groups had a mean BMI in the overweight range. Creatinine clearance was lower in the distal RTA and chronic diarrhea groups.

Relationship between 24-h and fasting urine pH

For the entire cohort, there was a significant correlation between fasting and 24-h urine pH ($r^2 = 0.49$, $p < 0.001$) (Fig. 1). The idiopathic uric acid nephrolithiasis group had the lowest mean 24-h urine pH (5.25 ± 0.16) and fasting urine pH (5.35 ± 0.36), while the mean 24-h urine pH (6.49 ± 0.28) and fasting urine pH (6.67 ± 0.37) were highest in the distal RTA group (all significantly different from corresponding values for the non-stone forming group, $p < 0.001$) (Fig. 2). In the chronic diarrhea group, mean 24-h and fasting urine pH were significantly lower than the non-stone forming group, while there were no significant differences in 24-h and fasting urine pH between the hypercalciuric calcium oxalate stone formers and non-stone forming groups (Fig. 2).

Table 1 Demographic and biochemical characteristics of study groups

	Non-stone formers ($n = 20$)	Hypercalciuric CaOx stone formers ($n = 37$)	Distal RTA ($n = 41$)	Chronic diarrhea ($n = 33$)	Idiopathic UA nephrolithiasis ($n = 28$)
Age (years)	48.4 ± 12.6	41 ± 11.2*	39.0 ± 13.2*	48.2 ± 15.0	52.3 ± 11.4
Height (cm)	165 ± 14	173 ± 8	168 ± 9	171 ± 11	178 ± 9**
Weight (kg)	70.5 ± 18.9	84.1 ± 17.0**	76.0 ± 18.1	79.4 ± 18.0	96.9 ± 18.8**
BMI (kg/m^2)	25.7 ± 5.3	28.1 ± 5.1	26.8 ± 6.2	27.1 ± 6.8	30.7 ± 6.6*
Creatinine clearance (ml/min)	110 ± 23	125 ± 28	94 ± 32*	92 ± 35*	120 ± 30
NGIA (mEq/day)	27 ± 20 ($n = 20$)	30 ± 28 ($n = 23$)	24 ± 28 ($n = 21$)	−14 ± 26** ($n = 17$)	11 ± 25* ($n = 16$)
24-h urine sulfate (mEq/day)	36 ± 8 ($n = 20$)	52 ± 20** ($n = 33$)	32 ± 14 ($n = 39$)	29 ± 14 ($n = 28$)	54 ± 15** ($n = 28$)

CaOx calcium oxalate, *RTA* renal tubular acidosis, *UA* uric acid, *NGIA* net gastrointestinal alkali absorption

* $p < 0.05$ versus non-stone formers

** $p < 0.005$ versus non-stone formers

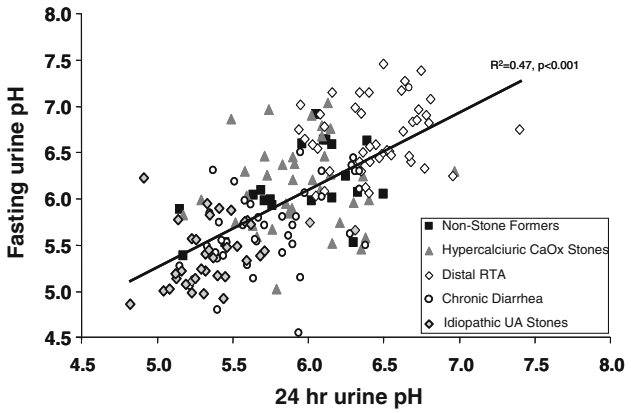

Fig. 1 Scatter plot of fasting versus 24-h urine pH in the overall study population. *CaOx* calcium oxalate, *RTA* renal tubular acidosis, *UA* uric acid

Mean fasting urine pH was significantly higher than 24-h urine pH for the entire group of subjects (6.02 ± 0.63 vs. 5.89 ± 0.51; $p < 0.001$) and in the distal RTA (6.67 ± 0.37 vs. 6.49 ± 0.28; $p = 0.007$), hypercalciuric calcium oxalate stone formers (6.15 ± 0.47 vs. 5.94 ± 0.35, $p = 0.031$) and non-stone forming (6.14 ± 0.42 vs. 5.93 ± 0.38; $p = 0.036$) groups. On the other hand, there was no significant difference between fasting and 24-h urine pH in the chronic diarrhea (5.57 ± 0.42 vs. 5.60 ± 0.24; $p = 0.67$) and the idiopathic uric acid nephrolithiasis (5.35 ± 0.36 vs. 5.25 ± 0.24; $p = 0.18$) groups (Fig. 2).

Absolute difference between fasting and 24-h urine pH

The absolute difference between fasting and 24-h urine pH (ΔpH) was calculated for each subject. Table 2 details the proportion of patients in whom ΔpH is >0.4 or >0.2. In the overall group, the majority of subjects (58%) had ΔpH > 0.2 and 40% had ΔpH > 0.4. A larger proportion of subjects in the non-stone forming and hypercalciuric calcium oxalate stone forming groups had ΔpH >0.4 and >0.2, compared to the proportion of participants from the chronic diarrhea and idiopathic uric acid nephrolithiasis groups.

Since dietary factors would be expected to impact 24-h urine pH more than fasting urine pH, we examined whether urinary markers of acid–base intake/absorption could explain the difference between 24-h and fasting urine pH. ΔpH did not correlate with urine sulfate ($r^2 = 0.003$) (Fig. 3a), nor with NGIA ($r^2 = 0.0005$) (Fig. 3b) in the subgroup of subjects in whom data on urine sulfate ($N = 148$) and NGIA calculation ($N = 97$) were available.

Discussion

An abnormal urine pH is a well-described risk factor for kidney stone formation, and measurement of urine pH is essential in the evaluation of patients with nephrolithiasis. This is the first study to examine the relationship between fasting and 24-h urine pH in a systematic fashion. In 159 subjects, we found a significant correlation between fasting and 24-h urine pH for the entire cohort ($p < 0.001$). However, fasting pH was >0.2 pH units different from 24-h urine pH in 58% of participants.

Urine pH is a key risk factor for uric acid [4, 5], calcium phosphate [2], and struvite stones [3], and is frequently acidic from increased net GI alkali loss [6]. High urine pH is also associated with a greater likelihood of transformation from calcium oxalate to calcium phosphate stones [19, 20]. Hence pH measurement is indicated during the initial evaluation and follow-up of patients with nephrolithiasis on therapy. A spot and/or fasting urine sample has been suggested as a viable alternative to a 24-h urine

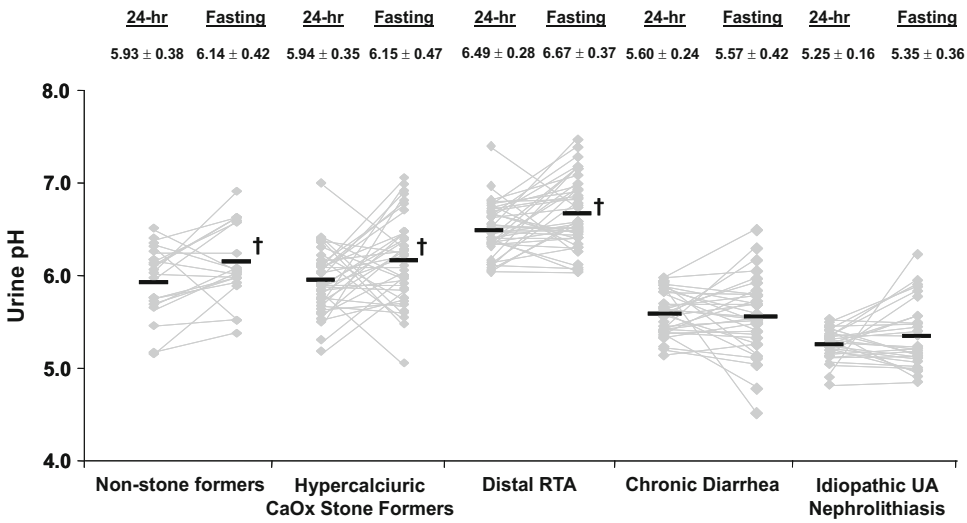

Fig. 2 Relationship between fasting and 24-h urine pH in individual study groups. $^{\dagger}p < 0.05$ by paired *t* test for fasting versus 24-h urine pH within group. *CaOx* calcium oxalate, *RTA* renal tubular acidosis, *UA* uric acid

Table 2 Proportion of patients at different cut-offs for the absolute difference between fasting and 24-hr urine pH (Δ pH)

	Overall ($n = 159$) (%)	Non-stone formers ($n = 20$) (%)	Hypercalciuric CaOx stone formers ($n = 37$) (%)	Distal RTA ($n = 41$) (%)	Chronic diarrhea ($n = 33$) (%)	Idiopathic UA nephrolithiasis ($n = 28$) (%)
Δ pH > 0.4	40	50	62	40	30	22
Δ pH > 0.2	58	75	73	54	46	47

CaOx calcium oxalate, *RTA* distal renal tubular acidosis, *UA* uric acid

sample for the estimation of calcium [9, 10, 12], phosphorus [10] and protein excretion [21]. Some investigators have also used fasting urine pH rather than 24-h urine pH in the evaluation of kidney stone formers [22–24]. Our results suggest that relying on a fasting urine sample for pH assessment is not adequate for individual patients due to the significant variability in comparison with 24-h urine samples.

A number of studies have confirmed the finding of a diurnal variation in urine pH in healthy subjects with fluctuations over a wide range (urine pH between 4.5 and 8.5) [25]. This has been in part related to transient post-prandial bicarbonate extrusion by the gastric parietal cells to prevent cellular alkalinization concomitantly with acid secretion [26]. Furthermore, urine in healthy individuals is generally more alkaline in the morning than at night, a phenomenon described nearly a century ago by Leathes [27] who coined the term "morning alkaline tide" and related to variation in respiratory patterns during sleep. Our finding of a significantly higher fasting than 24-h urine pH in the majority of subjects is in accordance with this phenomenon.

The relationship between fasting and 24-h urine pH was somewhat different in the 2 groups of patients with low urine pH (chronic diarrhea and idiopathic uric acid nephrolithiasis). In these two groups, urine pH was similar in fasting and 24-h samples, unlike the three other groups in whom fasting urine pH was significantly higher than 24-h urine pH. These findings are also compatible with previous studies showing that calcium oxalate stone formers exhibit similar diurnal fluctuations in urine pH compared with non-stone forming controls, while uric acid stone formers have persistently low urine pH [28]. A possible explanation for the similar pH between fasting and 24-h urine in patients with chronic diarrhea could be due to defective gastrointestinal alkali absorption from bowel disease. The factor(s) that alter circadian variation in uric acid stone formers are currently unknown, but may be related to renal or gastrointestinal abnormalities [29].

Intake of animal protein lowers urine pH through generation of protons during the metabolism of sulfur-containing aminoacids [30], while alkali-rich food can raise urine pH. Dietary factors would be expected to impact pH in a 24-h urine sample more than in fasting urine. In this study, the contribution of animal protein intake (estimated by 24-h urine sulfate) and alkali-rich foods (estimated by NGIA), did not appear to explain the differences between fasting and 24-h urine pH (Fig. 3).

Conclusion

In conclusion, this study suggests that while 24-h urine pH correlates with fasting urine pH in a large population of stone and non-stone formers, there is a significant variability between these two parameters in individual patients. This

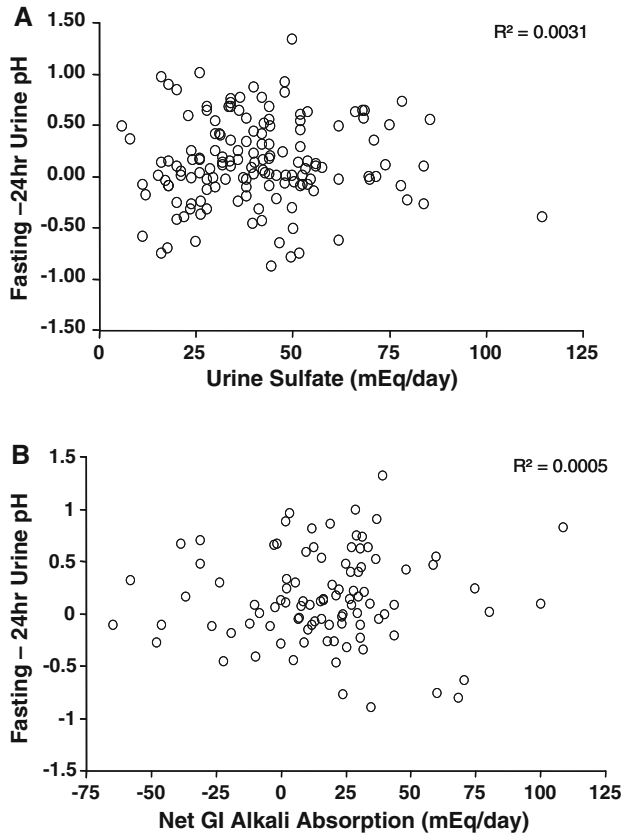

Fig. 3 Lack of relationship between dietary markers of acid–base intake/absorption and the difference between fasting and 24-h urine pH. **a** Relationship between urine sulfate and the difference between fasting and 24-h urine pH. **b** Relationship between net gastrointestinal (GI) alkali absorption and the difference between fasting and 24-h urine pH

variability emphasizes the cardinal role of 24-h urine collection in the evaluation of urinary pH in patients with nephrolithiasis. The difference between fasting and 24-h urine pH is not exclusively due to dietary factors and deserves further investigation.

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