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Original Article

Fasting and 24-h urine pH in patients with urolithiasis using potassium citrate

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Abstract: Purpose: To evaluate the correlation between the pH readings in 24-h urine and the random fasting specimen in patients with urolithiasis using 2 methods. Methods: A total of 114 patients with urinary lithiasis using potassium citrate were prospectively analyzed. All patients collected 24-h urine and an additional sample, after nocturnal fasting, collected on the day they brought the 24-h sample at the lab. Two different methods (test strip and digital meter) were used to determine pH values. Results: The pH analysis using strips in the 24-h urine presented a mean value similar to the one obtained in the fasting sample (6.07 ± 0.74 vs. 6.02 ± 0.82, respectively; $P > 0.05$). The same behavior was seen considering the readings with a digital pH meter (5.8 ± 0.78 vs. 5.75 ± 0.83; $P > 0.05$). However, readings conducted in the same specimen with pH meter and test strip were dissonant ($P < 0.05$), suggesting that the colorimetric method is not reliable in the assessment of urinary pH in this population. Conclusion: pH assessment in a random urinary specimen proved as efficient as the 24-h urine standard method to monitor patients with kidney stones in the use of potassium citrate. Classical test strip analysis is not sensitive enough to evaluate the urine pH in this population and digital pH meter reading is preferred.

Keywords: 24-h urine, nephrolithiasis, potassium citrate, urinary pH, random urinary specimen

Introduction

Urinary Tract Lithiasis (UTL) is a frequent disorder in daily clinical practice, and the third most frequent disorder of the genitourinary system, with a global incidence of around 2 to 3% [1].

In most patients with recurrent lithiasis, the stones have a composition similar to the previous ones, suggesting that this process is also regulated by factors present in the urine [2]. Under normal conditions, urinary solutes are kept at balance by forces that tend towards solubilization or precipitation; stone formation would result from the predominance of the latter [3]. In the opinion of many authors, the unbalance between the promoter and inhibitor factors of crystallization would be affected by the physicochemical proprieties of the urine, such as pH, for instance [4].

Alterations in urinary pH represent an important isolated risk factor for nephrolithiasis since they can modify the solubility coefficient of the many urine components. Usually, patients who form struvite and calcium phosphate (PCa) stones have a more basic pH. On the other hand, in urine with acid pH, there is a greater predisposition to the precipitation of uric acid crystals [5]. Potassium citrate supplementation is one of the most utilized strategies to increase the urine solubility coefficient, preventing UTL in many conditions. Urinary pH monitoring is routinely performed to guide its dose adjustment [1, 3].

Classically, the analysis of the composition and the physicochemical properties of twenty-four-hour urine (24-hU) has been considered one of the most important auxiliary tools in the investigation and treatment of factors involved in the etiology of UTL. However, collecting this type of exam presents great practical difficulties, especially in pediatric patients. In addition to predisposing to errors, it is also cumbersome for the patient, demanding a high level of commitment. According to Hong *et al.*, the commitment of patients to 24-hU collection decreases from 94% to 79% when more than one collection was required [6].

Recent studies suggest that urinary pH obtained from an isolated sample of fasting urine (fU) could be as reliable as the 24-hU in the assessment of patients with UTL [7-9]. According to Grases *et al.,* the isolated fasting urine specimen would present a more reliable baseline pH than the 24-h sample, since it would be minimally affected by dietary factors [10]. However, such an opinion is not shared by other authors, who suggest that, while the 24-hU pH correlates to the fasting specimen in a large population, there is significant variability between those two parameters when evaluated individually [5].

To shed some light on such controversies, this study evaluated the relationship between the urinary pH obtained from 24-hU as compared to the random fasting urine specimen (fU), aiming at standardizing the ideal methodology to monitor urinary pH in patients with UTL who use potassium citrate.

Methods

Participants of the study

A total of 114 patients with kidney stones followed at the Metabolism in Nephrolithiasis Ambulatory were prospectively evaluated. All patients were older than 18 years, with a previously treated UTL confirmed by imaging, and in use of potassium citrate. Patients in use of antibiotics, with recurrent urinary tract infection (defined as three or more episodes/year) or with abnormal kidney function (Clearance < 60 ml/min) were excluded. Current medications and doses, metabolic diagnosis, associated diseases, personal history, and age, were also evaluated. Body Mass Index (BMI) was calculated based on weight and height. All patients signed the Informed Consent (IC). This study was previously approved by the Committee for Medical and Ethical Questions of São Paulo State University, under the protocol number: 4348/2012.

Urine collection

All participants collected 24-h urine (24-hU) followed by one random fasting specimen (fU), collected at the moment they delivered the 24-h sample. The 24-hU collection began in the morning, disposing of the first micturition and collecting until the same time of the following day, keeping it in the refrigerator at 4°C until the moment of delivery. For standardization, the fU specimen was collected two hours after the end of the 24-h collection. To obtain more accuracy in the readings of the specimens, two different methods were employed to determine urinary pH: clinical analyses by test strip and digital pH meter reading.

Statistical analysis

Paired t-test was used for contrasts between the different collecting types and the methodologies applied. Variables concerning age and urinary volume utilized the T-test, with the variables expressed in averages and standard deviation, using the SAS software. Pearson's and Spearman's correlation tests were used to analyze the level of correlation between the 24-h urine and the random specimen, in parametric and non-parametric variables, with the SPSS software version 2.0.

The tools were compared by the Spearman correlation, rho coefficient (r^2) -1 to +1 and classified as [11]: - "very weak": .00-.19; - "weak": .20-.39; - "moderate": .40-.59; - "strong": .60-.79; - "very strong": .80-1.0.

The level of significance was 5% ($P < 0.05$).

Results

Population characteristics

The main data collected on the profile of the population studied are summarized in **Table 1**. Of the 114 subjects evaluated, 44 (39%) were men and 70 (61%) women, with mean age 51.11 ± 12.93 years; 52.91 ± 12.77 years for men and 49.96 ± 13 years for women ($P = 0.24$). The mean body mass index (BMI) was 28.71 ± 4.56 Kg/m^2. When subdivided according to gender, women were slightly more obese with 29.87 ± 5.14 Kg/m^2, as compared to 27 ± 2.82 Kg/m^2 for men ($P < 0.0003$). The total vol-

Table 1. Characteristics of the studied population

Variable	Men (44)	Women (70)	P
Age (years)	52.91 ± 12.77	49.96 ± 13	P = 0.2391
BMI (kg/m^2)	27 ± 2.82	29.87 ± 5.14	P < 0.0003
Volume of diuresis (ml)	1,920 ± 681.49	1,773 ± 680.25	P = 0.2659

Values in averages and standard deviation.

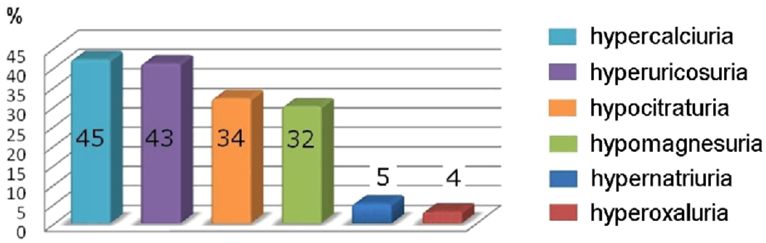

Figure 1. Main metabolic diagnosis found in the patients followed at the Metabolism in Nephrolithiasis Ambulatory.

Table 2. Average pH in 24-h urine and random fasting specimen, according to different assessment methods

Variable	24-h urine		Random fasting specimen	
	Test strip	pH meter	Test strip	pH meter
pH	6.07 ± 0.74 Aa	5.8 ± 0.78 Bb	6.02 ± 0.82 Aa	5.75 ± 0.83 Bb

Values are expressed as averages and standard deviations. Upper cases indicate a statistically significant difference between the different collections; lower cases indicate the differences between the different methodologies in the same type of collection (P < 0.02).

ume of diuresis obtained from the 24-hour collection was similar between men and women, with a total of 1,920 ± 681.49 mL and 1,773 ± 680.25 mL, respectively (P = 0.27).

The most frequent metabolic abnormalities diagnosed in this population were hypercalciuria, present in 45 patients (39.5%), followed by hyperuricosuria, diagnosed in 43 subjects (37.5%). Hypocitraturia was the third most prevalent diagnosis, with a total of 34 cases (30%), followed by hypomagnesuria in 32 (28%) patients. Hypernatruria was diagnosed in 5 cases (4.5%) and hyperoxaluria in 4 subjects (3.5%). It is important to emphasize that some patients might have had more than one metabolic diagnosis (**Figure 1**).

Correlation between the pH of 24-h urine (24-hU) and random fasting specimen (fU)

The comparative analysis of the pH between the 24-hU and fU specimens did not present a statistically significant difference when the same pH assessment method was considered (**Table 2**).

The traditional pH analysis in the 24-h urine using the test strip presented an average pH of 6.07 ± 0.74, a value that is very similar to the 6.02 ± 0.82 obtained from the isolated specimen (P > 0.05). Likewise, considering the reading from the digital pH meter, the mean pH was 5.8 ± 0.78 and 5.75 ± 0.83, for 24-hU and fU, respectively (P > 0.05).

A positive correlation between the values of urinary pH (obtained from either the test strip or the digital pH meter) was observed for both collection forms (r^2 = 0.267, P < 0.000; r^2 = 0.366, P < 0.000, respectively) (**Figure 2**).

Discussion

Urinary tract lithiasis (UTL) is a highly prevalent disease all over the world, affecting mainly young people. A great amount of the socio-economic burden caused by urolithiasis is consequent to the fact that it affects people in their most productive phase, between the third and fifth decades, with ages ranging from 39.0 to 52.9 years [1].

We noted a predominance of UTL in females, with 1.59 women for each man, the mean age being 51.1 years. In line with our findings, recent evidence has shown the rise in kidney stone disease prevalence among females, and continued research is warranted to determine causation [12]. This trend also occurs in the scenario of kidney stone needing intervention (surgical or shockwave), which has recently showed a female predominance [13, 14].

It is well known that urinary volume is an important factor in the etiopathogenesis of kidney stones. For this reason, patients with UTL are advised to increase fluid intake to obtain daily urinary volumes of around two liters, in an

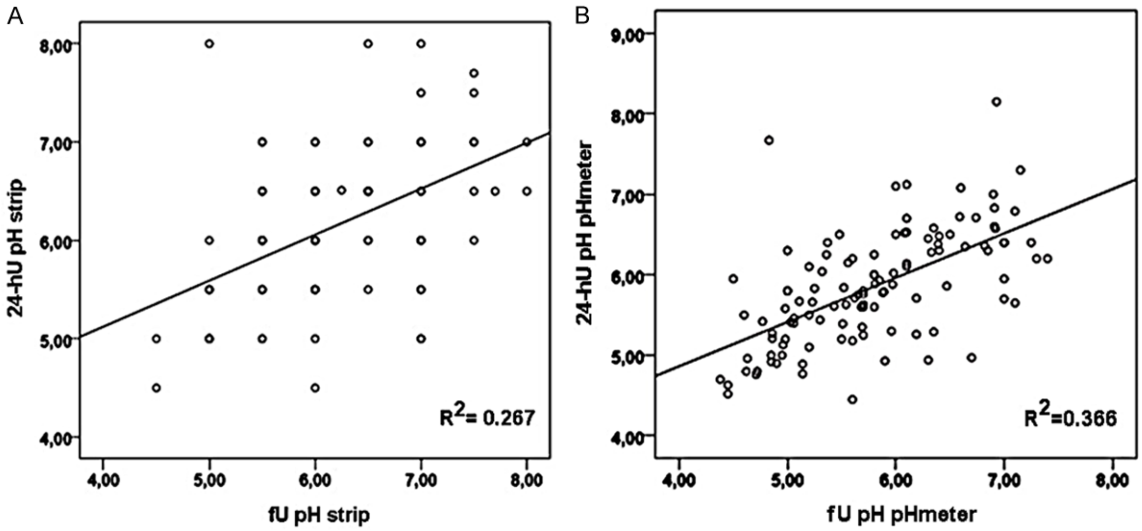

Figure 2. Scatter plot of the pH values obtained from (A) test strip readings in 24 hours urine (24-h pH strip) and (B) digital pH meter reading in the 24-hU pH meter, compared to the random specimen (fU pH) on strip and pH meter, respectively.

attempt to decrease the risk of new stone formation [8, 9]. In our study we noted that only 7.01% of patients had less than 1,000 mL diuresis in 24-h; the average volume for each patient being around 1,675 mL per day. Although it may seem satisfactory, this volume is still below the recommended, especially if we consider these patients have known stone formers under treatment.

Hypercalciuria is one of the main metabolic diagnoses, having multifactorial etiology and being responsible for more than 50% of the adult cases of lithiasis and around 53 to 75% in children [10]. In our study, increased urinary calcium was the most frequently seen metabolic abnormality, present in 39.5% of patients, followed by hyperuricosuria, diagnosed in 37.5% cases. This proportion was similar to the results obtained by Del Valle and Miján Ortiz, where hypercalciuria was also the predominant metabolic abnormality, followed by hyperuricosuria [15, 16].

Hypocitraturia was the third most frequent metabolic diagnosis (30%) found in our study, different from the findings by other authors, where it was the most often found diagnosis [17]. In a study previously conducted by our group with 182 stone-former patients, hypocitraturia was the second most prevalent metabolic abnormality, diagnosed in 37.3% of cases [18].

Primary hyperoxaluria is a relatively rare abnormality, found in approximately 1% of people submitted to metabolic investigation [15]. In our study, hyperoxaluria was diagnosed in only 4.5% of the cases, consequent to problems with routine measurements of this metabolite in our center. Hypomagnesuria was diagnosed in 28% of the patients included in our study. This prevalence was very similar to the one seen in a previous study conducted by our group, where this metabolic abnormality was found in 21% of the cases [18].

Due to its important role in regulating the physicochemical properties of urine, the urinary pH has been considered a key parameter in the assessment of patients with nephrolithiasis [4, 19]. Abnormal urinary pH in itself is an important risk factor for the formation of UTL [5]. In our study, double reading the urinary pH (using the colorimetric method and digital pH meter) had the intention of checking the accuracy of the test strip reading; a well-known method in our setting due to availability and low cost.

Our results confirmed the findings by Kwong *et al.,* who demonstrated that the analysis of urinary pH with pH meter and test strip were significantly different from one another, some of the differences observed being clinically relevant [20]. This fact suggests that, although the classical strip analysis may be used with relative safety in the routine determination of urinary pH, it is not sensitive enough for the assessment of urinary pH in lithiasis patients [19].

Even though the 24-hour urine is still considered the gold standard in the evaluation of UTL patients, according to Sëric *et al.,* the fasting specimen might be used as a reliable parameter to evaluate the risk and recommend preventive measurements against the formation of urinary stones [21]. In our study, we did not find significant difference between the urinary pH obtained from the 24-h urine (24-hU) from the random fasting specimen (fU), regardless of the analysis method used (digital pH meter: $5.8 \pm 0.78 \times 5.75 \pm 0.83$; P = 0.497; test strip: $6.07 \pm 0.74 \times 6.02 \pm 0.82$; P = 0.521, respectively). Additionally, a positive correlation was found between the pH readings conducted in the different modalities of urine collection as depicted in **Figure 2** ($P < 0.0001$). Once the correlation was considered weak, the classic strip test analysis cannot be recommended over the pH meter before bigger sample studies can further explore the correlation power observed between the different modalities of urine collection. Therefore, while pH assessment in random fasting urine sample is an efficient method for monitoring urinary pH, the classic strip test analysis is not as sensitive as the pH meter.

Our results diverge from those found by Capolongo *et al.* who suggest that it is not adequate to base urinary pH on random specimen instead of 24-h specimen due to significant variation observed by the authors between the two samples analyzed by them [5]. According to the authors, diurnal variation of urinary pH would be partially related to the excretion of post-prandial bicarbonate by the gastric parietal cells to prevent cell alkalinization concurrent with acid secretion.

This hypothesis also suggests that urine would be more alkaline in the morning than overnight, this being related to the variation of respiratory patterns during sleep, called "morning alkaline tide" [22]. This was not observed in our patients, where fasting urine pH was consonant to the 24-h urine pH, regardless of the method used for pH reading. On the other hand, fomenting additional studies on the issue, the significant correlations between both collection forms were rather weak ($r^2 = 0.267$, $P < 0.000$; $r^2 = 0.366$, $P < 0.000$, respectively).

Fat is also a known calculi risk factor [23]. The observed difference in BMI between men and women might represent variations in our population and might not be clinically significant once both men and women are clinically classified as overweight (BMI range 25-29.9), **Table 1**.

To warrant applicability of current study results we chose to evaluate patients with kidney stones under potassium citrate treatment, which are used to routinely perform 24-hour urine collection to guide dose adjustment. Supporting improvements in clinical practice, pH assessment in a random urinary specimen proved as efficient as the 24-h urine standard method.

Though prospective, the current study is limited to patients under potassium citrate treatment. Future studies should confirm our results in patients with no medication use. Also, urolithiasis control should be confirmed in a randomized study using urine pH in random fasting versus standard 24-h urine specimen.

Conclusion

The pH assessment in random fasting urine specimens proved to be as efficient as the standard method in monitoring renal lithiasis patients in the use of potassium citrate. Nevertheless, though used with relative safety in routine urinary pH monitoring, the classical test strip analysis is not sensitive enough to evaluate the urine pH in this population and digital pH meter reading is preferred.

Disclosure of conflict of interest

None.

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