Nomogram to predict uric acid kidney stones based on patient's age, BMI and 24-hour urine profiles: A multicentre validation

Fabio Cesar Miranda Torricelli, MD;[*] Robert Brown, MD;[†] Fernanda C.G. Berto, MD;[*] Sarah Tarplin, MD;[†] Miguel Srougi, MD;[*] Eduardo Mazzucchi, MD;[*] Manoj Monga, MD[†]

[*]Department of Urology, University of Sao Paulo Medical School, Sao Paulo, Brazil; [†]Department of Urology, The Cleveland Clinic, Cleveland, OH

Cite as: *Can Urol Assoc J* 2015;9(3-4):E178-82. http://dx.doi.org/10.5489/cuaj.2682
Published online April 13, 2015.

Abstract

Introduction: We performed a multicentre validation of a nomogram to predict uric acid kidney stones in two populations.
Methods: We reviewed the kidney stone database of two institutions, searching for patients with kidney stones who had stone composition analysis and 24-hour urine collection from January 2010 to December 2013. A nomogram to predict uric acid kidneys stones based on patient age, body mass index (BMI), and 24-hour urine collection was tested. Receiver-operating curves (ROC) were performed.
Results: We identified 445 patients, 355 from Cleveland, United States, and 90 from Sao Paulo, Brazil. Uric acid stone formers were 7.9% and 8.9%, respectively. Uric acid patients had a significantly higher age and BMI, as well as significant lower urinary calcium than calcium stone formers in both populations. Uric acid had significantly higher total points when scored according to the nomogram. ROC curves showed an area under the curve of 0.8 for Cleveland and 0.92 for Sao Paulo. The cutoff value that provided the highest sensitivity and specificity was 179 points and 192 for Cleveland and Sao Paulo, respectively. Using 180 points as a cutoff provided a sensitivity and specificity of 87.5% and 68% for Cleveland, and 100% and 42% for Sao Paulo. Higher cutoffs were associated with higher specificity. The main limitation of this study is that only patients from high volume hospitals with uric acid or calcium stones were included.
Conclusion: Predicting uric acid kidneys stone based on a nomogram, which includes only demographic data and 24-hour urine parameters, is feasible with a high degree of accuracy.

Introduction

Uric acid kidney stones affect less than 10% of kidney stone formers,[1] however correctly identifying these patients has great impact on medical practice, as alkalization therapy may be an effective treatment and may avoid more invasive procedures.[2] Currently, several conditions have been linked to uric acid kidney stones, such as obesity, high blood pressure, diabetes, and low urinary pH.[3-5] Furthermore, 24-hour urine analyses have demonstrated that uric acid stone formers have a higher excretion of urinary sodium and a lower excretion of urinary calcium and oxalate when compared to calcium stone formers.[6]

Imaging exams are also helpful when trying to distinguish between uric acid and calcium stones. Single- and dual-energy computed tomography (CT) scans have demonstrated promising results;[7] however, protocols for imaging acquisition and interpretation are not available in most of hospitals yet, thus preventing widespread use of this technology.

Considering only demographic data and 24-hour urine profiles from kidney stone formers, a nomogram was built to predict uric acid kidney stones.[6] This nomogram can guide medical decisions using select variables and minimizing the need for CT imaging, with its inherent cost and radiation exposure, as the nomogram does not include stone density (Hounsfield Units).

We performed an external validation of a nomogram developed to predict uric acid kidney stones in two populations from different countries.

Methods

Study design

After receiving Institutional Review Board approval, we retrospectively reviewed the kidney stone databases of two institutions, one from Cleveland, Ohio, United States, and other from Sao Paulo, Brazil. We searched for patients with kidney stones who had stone composition analysis and 24-hour urine collection within 6 months of each other from January 2010 to December 2013. Patients who were part of the initial construct of the nomogram[6] were excluded from this study. Kidney stones were obtained from surgical procedures for stone removal or after spontaneous passage. Stone composition was defined as uric acid or calcium stones based on its predominance (>50%). Patients with no uric acid or calcium stones (i.e., cystine and struvite) were excluded. Patients were also excluded if they were <18 years old or if they were taking allopurinol, potassium citrate, loop diuretics, or thiazides.

We recorded demographic data, including age and body mass index (BMI), whereas 24-hour urine parameters included sodium, calcium, oxalate, and uric acid. For each patient, these six variables were applied to a previous published nomogram (Fig. 1),[6] which has the capability of predicting uric acid over calcium stones. When using the nomogram, one should locate their patient's age and draw a line straight up to find the corresponding points score. This should be repeated for the rest of the components, and then the final score is calculated and plotted on the total points scale. The total points for each patient were recorded in this study. Urinary pH was also recorded, although it was not applied to the nomogram, as our prior study demonstrated that pH did not contribute significantly to the predictive value of the nomogram.[6]

For each population, patients were divided in two groups: uric acid versus calcium stones and then compared for demographic data, urinary parameters, and total points. Thereafter, nomogram sensitivity, specificity, and accuracy were tested.

Statistical analysis

Results were expressed in proportion, mean, and standard deviation. The Mann-Whitney test and Student's T test were used to compare the variables between the groups. Receiver-operating curves (ROC) were done to assess nomogram sensitivity, specificity, and accuracy; and then to find useful cutoffs. Accuracy was measured by the area under the ROC curve (an area of 1 represented a perfect test; whereas an area of 0.5 represented a worthless test). Statistical analysis was performed with SPSS version 20.0 (SPSS Inc., Chicago, IL) and the significance level was set at $p < 0.05$.

Results

There were 445 patients identified (355 from Cleveland and 90 from Sao Paulo). Uric acid stone formers comprised 7.9% and 8.9% in each population, respectively. Uric acid patients had a significantly higher age in both populations

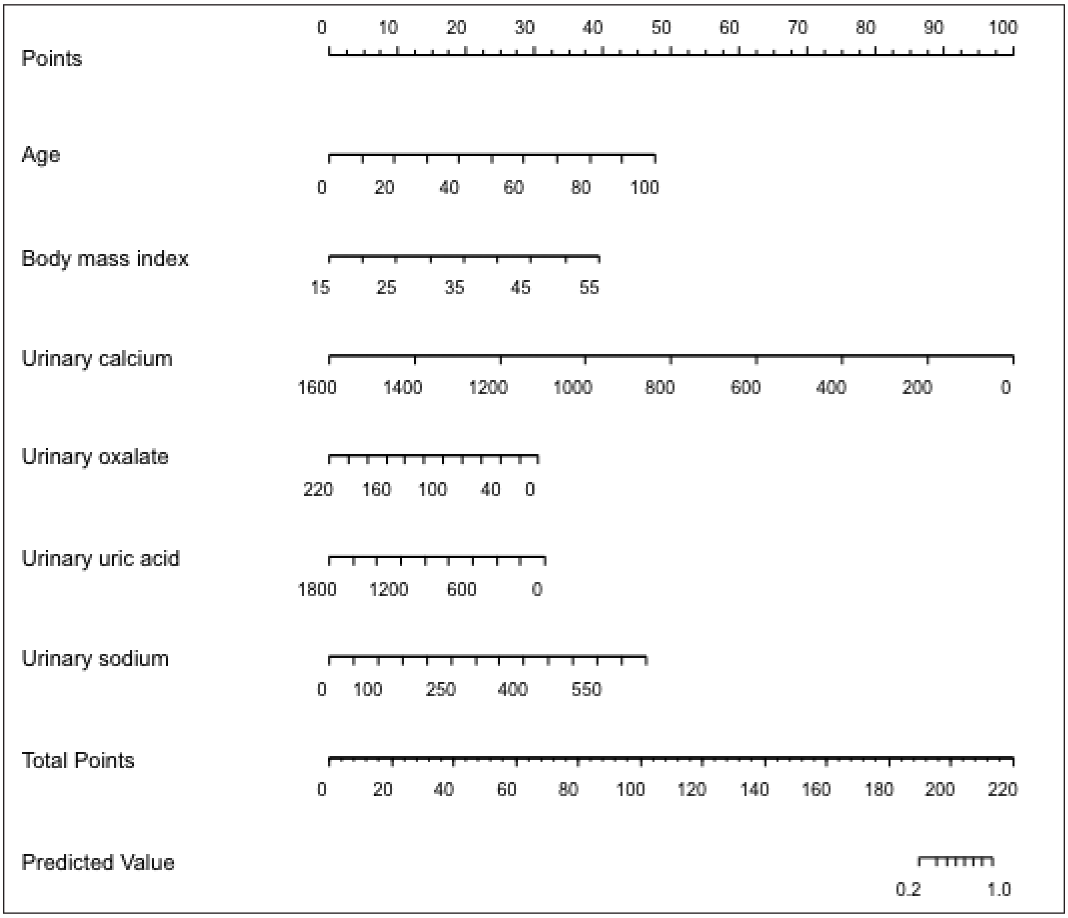

Fig. 1. Nomogram to predict uric acid kidney stones.

(57.3 vs. 50.0, $p = 0.02$; 54.8 vs. 45.7, $p = 0.017$, respectively) and BMI (34.9 vs. 28.8 kg/m^2, $p = 0.003$; 33.4 vs. 28.2 kg/m^2, respectively) than calcium stone formers. Twenty-four-hour urine collections revealed significant lower urinary calcium among uric acid stone formers in both populations (179.4.1 vs. 228.7 mg/day, $p = 0.019$; 124.2 vs. 192.2 mg/day, $p = 0.023$, respectively). Calcium stone formers had a higher urinary volume (1928 vs. 1603 mL, $p = 0.004$; 1757 vs. 1514 mL, $p = 0.549$, respectively) than uric acid stone formers. There were no significant differences in the others urinary parameters. Urinary pH was significantly lower in the uric acid stone formers (5.7 vs. 6.1, $p = 0.003$ in the Cleveland group and 5.3 vs. 6.3, $p = 0.025$ in the Sao Paulo group) when compared to calcium stone formers (Table 1).

Uric acid stone formers also had a significantly higher total points score when compared to calcium stone formers (188.4 vs. 176.6, $p < 0.001$ in the Cleveland group, and 202.5 vs. 182.0, $p < 0.001$ in the Sao Paulo group).

Patients with uric acid kidney stones from Sao Paulo had a significantly higher score than those patients from Cleveland (202.5 vs. 188.4, $p = 0.002$), although there were no significant differences regarding age (54.8 vs. 57.3, $p = 0.59$), BMI (33.4 vs. 34.9 kg/m^2, $p = 0.92$), or urinary parameters (184.8 vs. 166.6 mmoL/day, $p = 0.69$ for sodium; 124.2 vs. 179.4 mg/day, $p = 0.23$ for calcium; 46.0 vs. 46.2 mg/day, $p = 0.73$ for oxalate; 487.5 vs. 509.1 mg/day, $p = 0.80$ for uric acid; 285.4 vs. 599.8 mg/day, $p = 0.11$ for citrate; 5.3 vs. 5.7, $p = 0.125$ for pH).

Patients with calcium stones from Sao Paulo also had a significantly higher score than those patients from Cleveland (182.0 vs. 174.6, $p < 0.001$). They had a significantly lower age (45.7 vs. 50.0, $p = 0.007$) and a similar BMI (28.2 vs. 28.8 kg/m^2, $p = 0.59$). Regarding urinary parameters, they had a significant lower urinary calcium (192.2 vs. 228.7 mg/day, $p = 0.01$) and a significantly lower urinary citrate (404.2 vs. 583.4 mg/day; $p < 0.001$). No significant difference was seen in urinary sodium (178.2 vs. 162.6 mmol/day, $p = 0.17$), urinary oxalate (46.5 vs. 45.7 mg/day, $p = 0.33$), uric acid (542.4 vs. 578.7 mg/day, $p = 0.09$) or pH (6.3 vs. 6.1, $p = 0.50$). There was no difference in the urinary volume comparing uric acid stone formers or calcium stone formers between both populations (1603.1 vs. 1514.0 mL, $p = 0.35$; 1928.9 vs. 1757.7 mL, $p = 0.36$, respectively).

ROC curves for Cleveland population showed an area under the curve (AUC) of 0.80 (Fig. 2). The cutoff value that provided the highest sensitivity and specificity was 179 points (89% and 64%, respectively). ROC curve for the Sao Paulo population showed an AUC of 0.92 (Fig. 2). The cutoff value that provided the highest sensitivity and specificity was 192 points (100% and 82%, respectively). Using 180 points as cutoff in both populations provided a sensitivity and specificity of 87.5% and 68% for Cleveland, and 100% and 42% for Sao Paulo, respectively. Higher cutoffs were associated with a lower sensitivity and a higher specificity to predict uric acid kidney stones.

Discussion

Based on this nomogram, uric acid stone formers had significantly higher total points than calcium stone formers. ROC curves showed good accuracy for both populations (AUC 0.92 for Sao Paulo, and AUC 0.80 for Cleveland),

Table 1. Demographic data and 24-hour urine profiles of patients from Cleveland and Sao Paulo

	Cleveland			Sao Paulo			Combined		
	Uric acid	Calcium	*p* value	Uric acid	Calcium	*p* value	Uric acid	Calcium	*p* value
n	28	327		8	82		36	409	
Age (years)	57.3 ± 11.1	50.0 ± 13.8	0.002	54.8 ± 8.1	45.7 ± 12.9	0.017	56.7 ± 10.5	49.1 ± 13.8	<0.001
BMI (kg/m^2)	34.9 ± 9.6	28.8 ± 6.8	0.003	33.4 ± 4.6	28.2 ± 6.0	0.018	34.5 ± 8.7	28.6 ± 6.6	<0.001
Urinary volume (mL)	1603.1 ± 496.5	1928.9 ± 881.1	0.004	1514.0 ± 804.9	1757.7 ± 716.4	0.549	1589.6 ± 538.6	1912.1 ± 867.0	0.003
Urinary sodium (mmoL/day)	166.6 ± 66.6	162.6 ± 77.8	0.767	184.8 ± 78.5	178.2 ± 86.3	0.832	170.6 ± 68.7	165.3 ± 79.3	0.648
Urinary calcium (mg/day)	179.4 ± 98.9	228.7 ± 126.1	0.019	124.2 ± 62.6	192.2 ± 132.8	0.023	167.2 ± 94.2	221.5 ± 128.0	0.002
Urinary oxalate (mg/day)	46.2 ± 20.1	45.7 ± 23.6	0.928	46.0 ± 2.0	46.5 ± 4.0	0.809	46.1 ± 19.1	45.7 ± 23.4	0.916
Urinary uric acid (mg/day)	509.1 ± 192.2	578.7 ± 215.6	0.078	487.5 ± 136.5	542.4 ± 232.6	0.343	504.3 ±179.7	572.2 ± 218.9	0.040
Urinary citrate (mg/day)	599.8 ± 439.9	583.4 ± 305.1	0.848	285.4 ± 256.9	404.2 ± 240.2	0.367	552.2 ± 429.7	558.5 ± 305.6	0.931
pH	5.7 ± 0.6	6.1 ± 0.7	0.003	5.3 ± 0.7	6.3 ± 0.7	0.025	5.6 ± 0.6	6.1 ± 0.7	<0.001
Total points	188.4 ± 10.7	174.6 ± 13.0	<0.001	202.5 ± 8.9	182.0 ± 13.8	<0.001	191.7 ± 11.8	176.1 ± 13.5	<0.001

BMI: body mass index.

confirming the nomogram as a reasonable tool when trying to distinguish between uric acid and calcium stones.

Diagnosing a uric acid stone composition identifies those best suited for a trial of dissolution therapy and potentially prevents unnecessary surgical intervention. Dissolution therapy through urine alkalization with potassium citrate or sodium bicarbonate has been reported as an effective and well-tolerated approach.[2] Percutaneous chemolysis has also demonstrated good outcomes with low complication and high stone-free rates.[8-10]

Single and dual-energy CT scan imaging have demonstrated promising results in differentiating uric acid from calcium stones.[7,11,12] Wisenbaugh and colleagues studied 32 renal stones in vitro. When they attempted to differentiate uric acid and non-uric acid stones, they accurately distinguished 40% and 93% of non-uric acid stones using single-energy and dual-energy CT scans, respectively.[7] Stolzmann and colleagues reported a sensitivity and specificity as high as 90% for the in vivo detection of uric acid stones.[11] However, the lack of standard protocols for imaging acquisition and its interpretation, and the concern with radiation exposure when performing dual-energy CT scan has limited its clinical utility. Micro-CT is another imaging exam that has been demonstrated as a useful tool to distinguish different kinds of stones, revealing the mineral composition and its morphological arrangement;[13,14] however it still not available in many centres and its applicability remains under investigation. Moreira and colleagues proposed a model to predict urinary stone composition based on 24-hour urine analysis; however, this model was only able to correctly predict 51% of uric acid stones.[15] Thus, a nomogram putting together only demographic data (age and BMI) and 24-hour urinary parameters from patients with kidney stones was built, achieving a concordance index of 0.855.[6] Our study demonstrated that this nomogram might be applied to different populations, maintaining its high accuracy (AUC 0.92 in Sao Paulo, and AUC 0.80 in Cleveland). Although low urinary pH is usually related to uric acid stones, this variable did not improve the concordance index of the nomogram when it was developed. The advantage of the nomogram is its ability to predict uric acid stones without the need for a CT to determine stone density and without the need of a urine pH that can vary based on modality of measurement and time of urine collection.

In both populations, uric acid stone formers were significantly older and had a higher BMI, which is in accordance with reports that linked uric acid kidneys stones to obesity, high blood pressure, and metabolic syndrome.[3-5] These patients also had significantly higher total points when compared to calcium stone formers due to differences in demographic data and urinary parameters, in particular the lower urinary calcium. Prior studies have already demon-

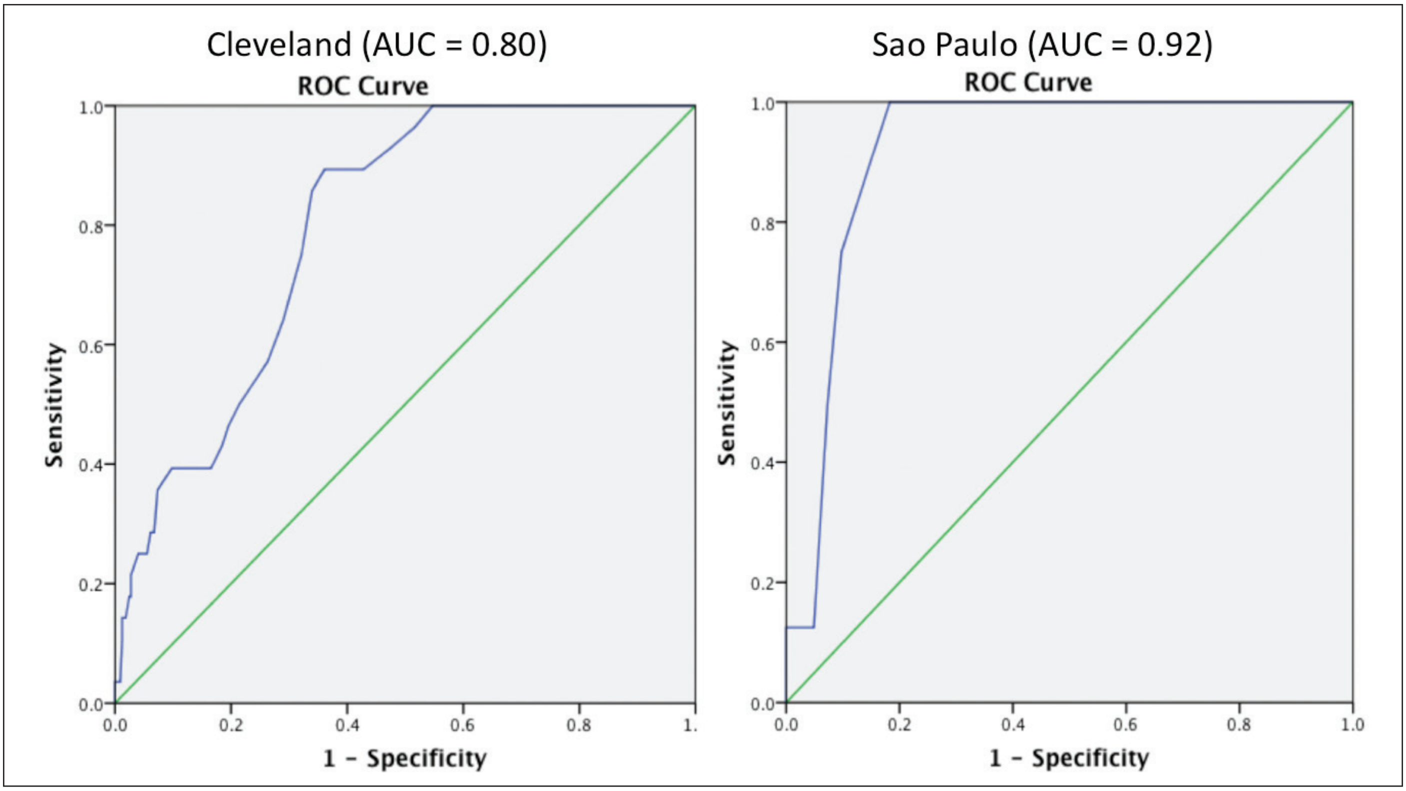

Fig. 2. Receiver operating characteristic (ROC) curves for the Cleveland and Sao Paulo populations. AUC: area under the curve.

strated some particularities in the 24-hour urine collections of uric acid stone formers and in patients with traits of the metabolic syndrome.[16-18] Comparing the populations, uric acid stone formers from Sao Paulo had significantly higher total points that those patients from Cleveland. Although there were no significant differences in the demographic data and 24-hour urine profiles between groups, the higher urinary sodium and the lower urinary calcium and uric acid, when analyzed together, may explain this finding. Calcium stone formers from Sao Paulo also had significantly higher total points that those patients from Cleveland. This difference can be explained by significant lower urinary calcium and lower urinary uric acid, plus higher, but not significantly different, urinary sodium. We speculate that the differences between the urinary parameter values (calcium, uric acid, and sodium) from each population are due to oral intake disparities, possibly related to cultural or socioeconomic status. A lower intake of calcium (milk and milk derivatives) and uric acid (animal protein), and higher dietary sodium may suggest a different nutritional scenario in Sao Paulo compared to Cleveland.

Regarding the cutoff value to be applied to the nomogram, 180 points provided high sensitivity (87%-100%) with reasonable specificity (42%-68%). ROC curves showed different ideal cutoff values for each population, probably reflecting the differences in the oral intake and thus urinary parameters. However, for both populations a higher cutoff was associated with a higher specificity to predict uric acid kidney stones. Therefore, if desiring a lower number of false positives (placing patients on alkalinization therapy who may not succeed), adopting a higher value as the cutoff is recommended.

This study has some limitations that are inherent to its retrospective nature. First, both populations are from high volume hospitals that are referral centres for kidney stone management and may not represent the overall population. Second, patients were limited to those with uric acid or calcium stone compositions, though this does represent most kidneys stone formers. Lastly, dietary, climatic, and behavioural issues were not evaluated.

Conclusions

Predicting uric acid kidneys stones based on a nomogram, which includes only demographic data and 24-hour urine parameters, is feasible. The nomogram has a high accuracy, and a cutoff of 180 points provides good sensitivity. Higher specificity is achieved using higher cutoff values. Population characteristics may have some impact on optimal nomogram cutoff value.

Competing interests: The authors declare no competing financial or personal interests.

This paper has been peer-reviewed.

References

1. Sakhaee K. Epidemiology and clinical pathophysiology of uric acid kidney stones. *J Nephrol* 2014;27:241-5. http://dx.doi.org/10.1007/s40620-013-0034-z
2. Trinchieri A, Esposito N, Castelnuovo C. Dissolution of radiolucent renal stones by oral alkalinization with potassium citrate/potassium bicarbonate. *Arch Ital Urol Androl* 2009;81:188-91.
3. Mosli HA, Mosli HH, Kamal WK. Kidney stone composition in overweight and obese patients: A preliminary report. *Res Rep Urol* 2013;5:11-5. http://dx.doi.org/10.2147/RRU.S39581
4. Strohmaier WL, Wrobel BM, Schubert G. Overweight, insulin resistance and blood pressure (parameters of the metabolic syndrome) in uric acid urolithiasis. *Urol Res* 2012;40:171-5. http://dx.doi.org/10.1007/s00240-011-0403-9
5. Cho ST, Jung SI, Myung SC, et al. Correlation of metabolic syndrome with urinary stone composition. *Int J Urol* 2013;20:208-13. http://dx.doi.org/10.1111/j.1442-2042.2012.03131.x
6. Torricelli FC, De S, Liu X, et al. Can 24-hour urine stone risk profiles predict urinary stone composition? *J Endouroul* 2014;28:735-8. http://dx.doi.org/10.1089/end.2013.0769
7. Wisenbaugh ES, Paden RG, Silva AC, et al. Dual-energy vs conventional computed tomography in determining stone composition. *Urology* 2014;83:1243-7. http://dx.doi.org/10.1016/j.urology.2013.12.023
8. Lee YH, Chang LS, Chen MT, et al. Experience with percutaneous nephrostomy, extracorporeal shock wave lithotripsy and chemolysis in the treatment of obstructive uric acid stones. *Eur Urol* 1991;19:209-12.
9. Kachrilas S, Papatsoris A, Bach C, et al. The current role of percutaneous chemolysis in the management of urolithiasis: Review and results. *Urolithiasis* 2013;41:323-6. http://dx.doi.org/10.1007/s00240-013-0575-6
10. Lee YH, Chang LS, Chen MT, et al. Local chemolysis of obstructive uric acid stone with 0.1 M THAM and 0.02% chlorhexidine. *Urol Int* 1993;51:147-51. http://dx.doi.org/10.1159/000282533
11. Stolzmann P, Kozomara M, Chuck N, et al. In vivo identification of uric acid stones with dual-energy CT: Diagnostic performance evaluation in patients. *Abdom Imaging* 2010;35:629-35. http://dx.doi.org/10.1007/s00261-009-9569-9
12. Kulkarni NM, Eisner BH, Pinho DF, et al. Determination of renal stone composition in phantom and patients using single-source dual-energy computed tomography. *J Comput Assist Tomogr* 2013;37:37-45. http://dx.doi.org/10.1097/RCT.0b013e3182720f66
13. Williams JC, McAteer JA, Evan AP, et al. Micro-computed tomography for analysis of urinary calculi. *Urol Res* 2010;38:477-84. http://dx.doi.org/10.1007/s00240-010-0326-x
14. Krambeck AE, Lingeman JE, McAteer JA, et al. Analysis of mixed stones is prone to error: A study with US laboratories using micro CT for verification of sample content. *Urol Res* 2010;38:469-75. http://dx.doi.org/10.1007/s00240-010-0317-y
15. Moreira DM, Friedlander JI, Hartman C, et al. Using 24-hour urinalysis to predict stone type. *J Urol* 2013;190:2106-11. http://dx.doi.org/10.1016/j.juro.2013.05.115
16. Ito H, Kotake T, Nomura K, et al. Clinical and biochemical features of uric acid nephrolithiasis. *Eur Urol* 1995;27:324-8.
17. Eisner BH, Eisenberg ML, Stoller ML. Relationship between body mass index and quantitative 24-hour urine chemistries in patients with nephrolithiasis. *Urology* 2010;75:1289-93. http://dx.doi.org/10.1016/j.urology.2009.09.024
18. Al-Hayek S, Schwen ZR, Jackman SV, et al. The impact of obesity on urine composition and nephrolithiasis management. *J Endourol* 2013;27:379-83. http://dx.doi.org/10.1089/end.2012.0275

Correspondence: Dr. Fabio Cesar Miranda Torricelli, Department of Urology, University of Sao Paulo Medical School, Sao Paulo, Brazil; fabio_torri@yahoo.com.br