Uric acid versus non-uric acid renal stones: in vivo differentiation with spectral CT

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Authors: F. Lombardo\textsuperscript{1}, M. Bonatti\textsuperscript{2}, G. A. Zamboni\textsuperscript{1}, F. Ferro\textsuperscript{2}, R. Pozzi-Mucelli\textsuperscript{1}, G. Bonatti\textsuperscript{2}; \textsuperscript{1}Verona/IT, \textsuperscript{2}Bolzano/IT
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Aims and objectives

Urolithiasis is a common disease, affecting about 12% of men and 6% of women during their lives, with a prevalence that is progressively increasing in the last decades and with high recurrence rates [1; 2]. Urinary stones chemical composition is quite variable: approximately 80% of stones are composed by calcium oxalates (CaOx) or phosphates (CaP), 10% by struvite, 9% by uric acid and less than 1% by cysteine [3]. Moreover, mixed calculi may be often observed.

Unenhanced CT represents nowadays the imaging modality of choice in the clinical suspicion of symptomatic urolithiasis because of its ability of providing, by means of a single, rapid and reproducible examination, information about stone location and size, presence and degree of urinary obstruction, presence of complications and eventual differential diagnoses [4; 5].

Stone composition is a fundamental parameter that should be known in order to tailor the best therapeutic approach for each patient: in particular, uric acid stones should be recognized as they can be successfully managed with urine alkalinization that facilitates their dissolution [6]. Both single-energy CT (SECT) and DECT generate images using a polyenergetic x-ray beam, generated typically at 100-140 kV in the case of SECT or at 80-100 kV (low-energy x-ray beam) and 120-140 kV (high-energy x-ray beam) in case of DECT. By applying a mathematical model to the source data obtained by scanning at two different energies, it is possible to calculate image-domain virtual monoenergetic images, which resemble the ones that would be generated using a true monoenergetic x-ray source.

X-ray absorption is mainly due to photoelectric effect, which strongly increases as photon energy decreases; furthermore, it depends on the atomic number $Z \sim Z^3$ of the encountered elements. Therefore, attenuation profiles exhibit a marked increase at low energies whenever they encounter elements with a relatively high atomic number (e.g. iodine $Z=53$, calcium $Z=20$, magnesium $Z=12$ or sulfur $Z=16$) [7; 8]. Calcium (Ca) is contained in calcium oxalates (CaOx) and calcium phosphates (CaP) stones, magnesium (Mg) in struvite stones and sulfur (S) in cysteine stones [9; 10]. On the other hand, pure uric acid stones do not contain significant amounts of these elements, being nitrogen (N) their main constituent, in addition to carbon (C), oxygen (O) and hydrogen (H). Consequently, these differences in chemical composition allow us to distinguish between uric acid and non-uric acid renal stones on the basis of their different x-ray absorption at different energies. Therefore, the aim of our study was to differentiate in vivo uric acid from non-uric acid renal stones on the basis of their spectral attenuation values.
Methods and materials

Patient population

We considered for inclusion in our study 194 consecutive patients that underwent CT in the clinical suspicion of urolithiasis during the period October 2012 - March 2015. Inclusion criteria were: presence of renal stones at CT (91/194 patients) and stones extraction or expulsion within 1 month from the CT examination, with subsequent analysis by means of wet chemistry (37/91). Exclusion criteria were: incomplete CT examination or poor image quality because of motion artifacts or high patient BMI (0/37 patients). Furthermore, all the stones with shortest axis $\leq 2$ mm were excluded from the analysis, due to the possibility of partial volume artifacts in their evaluation (4/37 patients). After applying these criteria, our study population included 33 patients, 21 males and 12 females, with a mean age of 55 years (range 20-74).

Stone analysis

15/33 patients spontaneously expelled the stone and 18/33 underwent stone extraction by means of percutaneous nephrolithotripsy or ureterorenoscopy. A total of 42 stones were obtained in 33 patients and their chemical composition was assessed by means of chemical analysis with a commercially available kit (Urinary Calculi Analysis Kit, DiaSys, Diagnostic System GmbH, Holzheim, Germany). Finally, each stone was classified, according to its prevalent composition ($\geq 70\%$), as uric acid or non-uric acid stone. In case of patients presenting more stones at CT, stone composition was considered the same for all the stones.

Dual-energy CT scanner, protocol and image analysis

All examinations were performed on a second-generation dual-source CT scanner (Somatom Definition Flash; Siemens Healthcare, Forchheim, Germany); our protocol included a preliminary 120 kV single-energy low-dose scan of the abdomen from the upper renal poles to the pelvic floor, followed by an additional 100/Sn140 kV dual-energy scan limited to the volume where urinary stones were eventually detected (Table 1). All the examinations were performed with the patient lying supine on the table, with the arms bent over his head whenever possible. CT images were evaluated on a workstation (Leonardo, Version VE52A; Siemens, Erlangen, Germany) by one radiologist with 4 years of experience in genito-urinary radiology. Urinary stones number, location (urinary calices, pelvis, ureter or bladder) and the presence of ureteral catheters were evaluated on 3 mm thick multiplanar reconstruction images obtained from the 120 kV datasets.
Stones maximum diameter, minimum diameter (mm) and volume (mm$^3$) were calculated on the 100/Sn140 kV dataset by means of automated software (Syngo.Via CT Dual Energy - Kidney Stones Application, Version VA30A, Siemens, Erlangen, Germany). On the basis of the 100/Sn140 kV dataset, image-domain virtual monoenergetic images were generated on a workstation (Leonardo CT Dual Energy - Monoenergetic Application, Siemens, Erlangen, Germany). Stone attenuation values were measured drawing a circular ROI on each stone at each selected keV level, from 40 to 190 keV with increments of 10 keV, on 1 mm thick multiplanar reconstructions using a bone window (L=700, W=3200). ROIs were drawn as large as possible in order to include the largest stone area but no adjacent structures (Figures 1, 2). Ratios between values obtained at the extremes of the energy range (40 and 190 keV) were also calculated. Mean attenuation values were plotted in function of the different energies and a qualitative analysis of the spectral attenuation curves was performed.

**Statistical analysis**

Unpaired t-test and ROC analysis were performed using GraphPad Prism version 6.00 for Mac OS X, GraphPad Software, La Jolla California USA, [www.graphpad.com](http://www.graphpad.com).

**Table 1 - CT scanning parameters for single- and dual-energy acquisitions**

<table>
<thead>
<tr>
<th></th>
<th>Single-energy preliminary scan</th>
<th>Dual-energy additional scans</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scanning kV</strong></td>
<td>120</td>
<td>100/Sn140</td>
</tr>
<tr>
<td><strong>mAs ref</strong></td>
<td>50</td>
<td>162</td>
</tr>
<tr>
<td><strong>Collimation</strong></td>
<td>128x0.6</td>
<td>32x0.6</td>
</tr>
<tr>
<td><strong>Rotation time</strong></td>
<td>0.5 s</td>
<td>0.5 s</td>
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<tr>
<td><strong>Pitch</strong></td>
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<td>0.7</td>
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<tr>
<td><strong>Care-DOSE 4D</strong></td>
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<td>On</td>
</tr>
<tr>
<td><strong>Reconstruction thickness</strong></td>
<td>1.0 mm</td>
<td>1.0 mm</td>
</tr>
<tr>
<td><strong>Reconstruction algorithm</strong></td>
<td>SAFIRE® 3 (I31f)</td>
<td>FBP (D30f)</td>
</tr>
</tbody>
</table>
Fig. 1: Spectral evaluation of a uric acid stone on 1 mm thick axial multiplanar reconstruction images. After ROI's placement (a), spectral attenuation curve (b, white curve) shows a sudden decrease of the stone's attenuation values below 70 keV due to its lack of relatively high atomic number elements.

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Fig. 2: Spectral evaluation of a calcium oxalate stone on 1 mm axial thick multiplanar reconstruction images. After ROI' placement (a), the spectral attenuation curve (b) shows a sharp increase of stone attenuation values below 70 keV because of its containing relatively high atomic number elements.
Results

62 stones were considered in 33 patients (range 1 - 4 stones per patient, mean 1.88): 30 stones were located in the urinary calices, 12 in the renal pelvis, 19 in the ureters and 1 in the urinary bladder. At chemical analysis, 15/62 (21%) stones were classified as prevalently composed by uric acid, 39/62 (61%) by calcium oxalates or phosphates and 8/62 (18%) by cysteine, resulting in 15/62 uric acid stones and 47/62 non-uric acid stones. Mean stone maximum and minimum diameters were respectively 6.5 mm (range 2.3 - 19.2 mm) and 3.8 mm (range 2.1 - 12.4 mm). Mean volume was 198 mm$^3$ (range 5.6 - 1910 mm$^3$).

Quantitative evaluation - The mean attenuation values at 40 and 190 keV were respectively 417 ± 164 HU (range 124 - 731 HU) and 480 ± 72 HU (range 350 - 610 HU) for uric acid stones and 2201 ± 670 HU (range 618 - 3042 HU) and 587 ± 188 HU (range 177 - 984 HU) for non-uric acid stones. The mean 40/190 keV attenuation ratios were 0.87 ± 0.3 (range 0.30 - 1.34) for uric acid stones and 3.80 ± 0.6 (range 2.18 - 5.27) for non-uric acid stones (Table 2). The 40/190 keV attenuation ratios were significantly lower for uric acid stones than for non-uric acid (unpaired t-test, p<0.0001) (Figure 3). According to ROC analysis, with a cut-off value of 1.760 both sensitivity and specificity were 100%, correctly classifying 15/15 stones as composed by uric acid and 47/47 stones as composed by CaOx, CaP or cysteine; no overlap of values between the two main groups was observed (Figure 4). Moreover, there were no significant differences between the CaOx, CaP or cysteine stones attenuation ratios.

Qualitative evaluation - Qualitative evaluation of spectral attenuation curves showed two different shapes of curve between the two stone types. Indeed, uric acid stones did not show any significant attenuation increase at low energies, leading to a relatively flat curve with a tendency to decrease below 70 keV (Figures 1, 5), whereas non-uric acid stones showed a sharp attenuation increase at low energies, leading to a hyperbole-like curve (Figures 2, 5).

Table 2 - Mean attenuation values and ratios for uric acid and non-uric acid stones

<table>
<thead>
<tr>
<th></th>
<th>Mean attenuation values at 40 keV</th>
<th>Mean attenuation values at 190 keV</th>
<th>Mean 40/190 keV attenuation ratios</th>
</tr>
</thead>
<tbody>
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Fig. 2: Spectral evaluation of a calcium oxalate stone on 1 mm axial thick multiplanar reconstruction images. After ROI's placement (a), the spectral attenuation curve (b) shows a sharp increase of stone attenuation values below 70 keV because of its containing relatively high atomic number elements.
**Fig. 3:** Box-and-whiskers plot shows ranges (whiskers) and 25th to 75th quartiles (boxes) of 40/190 keV attenuation ratios for uric acid and non-uric acid stones. Notice the complete separation with no overlap of values between the two groups.

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Fig. 4: Graph shows combination of attenuation values of individual renal stones. A 40/190 keV attenuation ratio cut-off of 1.760 (black line) completely separates uric acid from non-uric acid stones.

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Fig. 5: Mean attenuation values (HU) and SD for uric acid and non-uric acid stones at different energies. Notice the completely different shape of the curves for the two groups.

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Conclusion

Differentiation between uric acid and non-uric acid stones is probably the most relevant information that urologists want to know in order to tailor the best therapeutic approach for each patient, as uric acid stones may be dissolved by pharmacological treatment, while non-uric acid stones often require an interventional approach [6]. Quantitatively, the availability of a wider energy range (40 - 190 keV) leads to an increased difference in attenuation values between stones that contain high atomic number elements and stones that do not. Despite this, a certain degree of overlap was found in attenuation values between the two categories of stones, starting from 40 keV, probably due to their relatively different content in high atomic number elements (Figure 6), which mainly influence stone attenuation at low energies. On the other hand, the ratio between the attenuation values obtained at the extremes of the energy range led to a complete separation between uric acid and non-uric acid stones with no overlap in values, leading eventually to an increased diagnostic accuracy. Qualitative analysis of the spectral attenuation curves, a graphic representation of the monoenergetic attenuation values as a function of energy, showed two completely different behaviors for stones containing light or heavy elements, which may be an advantage in terms of evaluation rapidity (Figure 5). From a physics point of view, this approach largely shares the principles with the stone specific software application provided by the manufacturer, but manipulates the data differently. Excellent results in this field have already been reported by Primak et al, who showed a 92 - 100% accuracy in differentiating uric acid from non-uric acid stones using a three-material decomposition algorithm [11].

In conclusion, in this study we demonstrated, in vivo, that urinary stones differentiation (UA vs. n-UA) by means of monoenergetic attenuation ratios and spectral attenuation curves is feasible and has a similar accuracy to the one of the stone specific software application provided by Primak, leading to an accurate and personalized treatment planning. Moreover, qualitative evaluation of spectral attenuation curves may be an easy and rapid method to discriminate between these two main categories at a glance.
Fig. 5: Mean attenuation values (HU) and SD for uric acid and non-uric acid stones at different energies. Notice the completely different shape of the curves for the two groups.

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**Fig. 6:** Box-and-whiskers plot shows ranges (whiskers) and 25th to 75th quartiles (boxes) of attenuation values of uric acid and non-uric acid stones at different energies. Notice the progressive overlap of HU values between different stones as energy increases.

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References


