The use of non-contrast computed tomography and color Doppler ultrasound in the characterization of urinary stones – preliminary results

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ABSTRACT

Objective: To investigate the role of density value in computed tomography (CT) and twinkling artifact observed in color Doppler analysis for the prediction of the mineral composition of urinary stones.

Material and methods: A total of 42 patients who were operated via percutaneous or endoscopic means and had undergone abdominal non-contrast CT and color Doppler ultrasonography examinations were included in the study. X-ray diffraction method was utilized to analyze a total of 86 stones, and the correlations between calculated density values and twinkling intensities with stone types were investigated for each stone.

Results: Analyses of extracted stones revealed the presence of 40 calcium oxalate monohydrate, 12 calcium oxalate dihydrate, 9 uric acid, 11 calcium phosphate, and 14 cystine stones. The density values were calculated as 1499 ± 269 Hounsfield Units (HU) for calcium oxalate monohydrate, 1505 ± 221 HU for calcium oxalate dihydrate, 348 ± 67 HU for uric acid, 1106 ± 219 HU for calcium phosphate, and 563 ± 115 HU for cystine stones. The artifact intensities were determined as grade 0 in 15, grade 1 in 32, grade 2 in 24, and grade 3 in 15 stones.

Conclusion: In case the density value of the stone is measured below 780 HU and grade 3 artifact intensity is determined, it can be inferred that the mineral composition of the stone tends to be cystine.

Keywords: Color Doppler; computed tomography; Hounsfield unit; urinary stones; twinkling artifact

Introduction

Urinary tract stone disease affects 5-10% of the population in the developed countries. However recently, increase in the prevalence, and incidence of the stone disease has been reported.^[1] Urolithiasis is considered as a serious health problem due to the increased prevalence of stone formation in the urinary system, and its higher recurrence rates.^[1]

Urinary stones have been classified based on their compositions widely as calcium oxalate monohydrate (CaOxMH), calcium oxalate dihydrate (CaOxDH), calcium phosphate (CaP), uric acid (UA), and cystine stones.^[2] Knowledge about the chemical composition of the stone is an important factor in the determination of an accurate treatment approach.^[2,3] Prediction of stone fragility using imaging

modalities may be a guiding tool before application of extracorporeal shock wave lithotripsy (ESWL), and endoscopic laser lithotripsy. Besides, it is also beneficial in the planning of dietary therapy, and other metabolic approaches.^[3] CaOxMH, and some cystine stones are resistant to fragmentation, while CaOxDH, and uric acid stones can be easily broken into pieces.^[2] Up to now, multiple number of *in vivo*, and *in vitro* studies have been performed to predict mineral composition of urinary stones using imaging modalities.^[2-5] Ultimately, these studies –mostly *in vitro* trials– basically have focused on two radiological imaging techniques. These investigations have concentrated on density values of the stones as estimated based on non-contrast helical computed tomographic (CT) examinations or clarification of the relationship between twinkling artifact observed on

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Submitted:
23.06.2015

Accepted:
27.08.2015

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Available online at
www.turkishjournalofurology.com

color Doppler ultrasonograms (CDUS), and chemical composition of the stone.

Previously, in their *in vitro* study, Hassani et al.^[2] evaluated both density value of the stone in Hounsfield Units (HU) using non-contrast helical CT, and also twinkling artifact observed on color Doppler sonograms, and investigated the predictive value of combined use of these two imaging techniques in the determination of the mineral composition of urinary stones. In the current study, we evaluated the role of density value in CT imaging and twinkling artifact observed in color Doppler analysis for the prediction of the mineral composition of urinary stones. To the best of our knowledge, for the first time, in the present study similar approach has been used in a patient group. Besides the presence of any correlation (if any) between stone density, and intensity of the twinkling artifact has been investigated.

Material and methods

The study was approved by the faculty ethics committee with protocol number (2014/1964). Due to the retrospective design of this study written informed consent forms from the patients were not requested. A total of 80 patients (46 male, and 34 female cases) who were having non-contrast abdominal CT evaluations performed between April 2014, and April 2015 which revealed urinary tract calculi were retrospectively included in the study. Patients not having postoperative stone analysis results or those with multiple stones with different chemical compositions were excluded from the study. As a result, the study population consisted of 42 patients (24 male, and 18 female cases) with eligible criteria whose CT, and CDUS results were available in the archives of the Radiology Department. All patients were older than 18 years with a mean age of 47 ± 9 years (range 21–68 yrs). Mineral compositions of all stones were analyzed in an experienced center using X-ray diffraction method.

Ultrasonographic examination of the patients was performed by the same radiologist (MB) with a 10 years of experience in abdominal ultrasound using the same device (Siemens Sonoline Antares, Siemens Healthcare, Malvern, PA, USA) with a wide band convex ultrasound transducer (4C, bandwidth, 1.5–4.5 MHz). Both static, and cine ultrasonographic image series were evaluated. During CDUS examination single focal zone was always placed somewhat deeper than the level of the targeted stone. The presence of twinkling artifact, and if detected its signal intensity was recorded. Signal intensities of the twinkling artifacts were classified as follows: Grade 0: twinkling artifact not observed (Figure 1); Grade 1: focal, and hardly observed twinkling artifact; strong signal intensity observed on only some part (Grade 2) or all over the stone (Grade 3) (Figure 2).

In our department non-contrast CT images were obtained using routine dose protocol for the evaluation of stone, and 64-multislice CT system (Aquilion 64, Toshiba Medical Systems, Otawara-shi, Japan). Then the helical CT parameters were used as follows: tube current, 300 mA; tube potential, 120 kV; collimation, 64 x 0.5 mm; gantry rotation time, 0.5 s; pitch factor, 1.1. The area from diaphragm down to the pubic symphysis was scanned. In all examinations, 512 x 512 pixel image matrix, 1 mm-thick sections, and 1 mm-reconstruction intervals were used.

Each CT scan was analyzed by a radiologist (MB) experienced in abdominal radiology but blinded to the chemical composition of the stone in a commercial workstation (ExtremePACS, Ankara, Turkey). For each stone mean ($\pm$ SD) density values were recorded in HU. Density measurements were realized in conventional soft tissue window using region of interest (ROI) (Figure 3). We took care to include the entire stone in the ROI without extending the scope of ROI into the surrounding soft tissue. Stones smaller than 5 cm were not included in the study so as to refrain from erroneous density measurements. For each stone similar ROIs were used, and average of three different measurements was calculated. Besides for stones larger than 1.5 cm measurements were taken from different sides of the stone, and average of these measurements was taken as the basis of evaluations. All CT images were retrospectively evaluated, and location, number, and the longest diameters of the stones were

Figure 1. Multiple calculi in the right kidney of a 42-year old female patient. In color Doppler ultrasound imaging twinkling artifacts posterior to the stone location are not observed (Grade 0). Following URS lithotripsy, analysis of the extracted stone was consistent with CaP

URS: ureterorenoscopy; CaP: calcium phosphate

Figure 2. Multiple stones in both kidneys of a 32-year-old female patient. On a color Doppler US image, prominent twinkling artifact behind the stones is seen (Grade 3). Chemical analysis of the stones extracted during PNL operation was consistent with cystine stone.

PNL: percutaneous nephrolithotomy

Figure 3. Density value of a left kidney stone calculated based on its axial image in non-contrast abdominal CT of a 43-year-old male patient. Mean density value of this stone was calculated as 1618 ± 140 HU. Biochemical analysis of the stone extracted via left PNL was consistent with CaOxMH stone.

CT: computed tomography; HU: Hounsfield Unit; PNL: percutaneous nephrolithotomy; CaOxMH: calcium oxalate monohydrate

recorded. Detected stones were categorized based on their locations as renal (right, and left kidney, upper, middle, and lower zones) ureteral, and bladder stones. In addition for one-to-one matching between outcomes of the analysis, and the relevant stone, stones were numbered during the operation, and evaluated separately.

Statistical analysis

All statistical analyses were performed using SPSS 21.0 program. (IBM Statistical Package for the Social Sciences, New York, USA). We evaluated numerous qualitative, and quantitative variables. In statistical analyses variables were expressed in numbers, standard deviation, percentage, and confidence intervals. Normality of distribution was tested using Shapiro-Wilk test. ANOVA test was used to analyze the correlation between stone size, and stone density. Cut-off values for stone density of various types of stones were estimated based on Hounsfield units on non-contrast CT. Cut-off values of stone densities on CT were estimated using ROC analysis. $P < 0.05$ was accepted as the level of significance.

Results

Renal stones were extracted using percutaneous nephrolithotomy (PNL) in 30 (58 stones), and ureterorenoscopic (URS) lithotripsy in 12 (28 stones) patients. Postoperative laboratory analysis results of a total of extracted 86 stones were as follows: 40 (47%) calcium oxalate monohydrate, 12 calcium oxalate dihydrate (14%), 9 (10%) uric acid, 11 (13%) calcium phosphate, and 14 (16%) cystine stones. Mixed type stones were grouped based on dominant component of cystine. Mean HU ($\pm$ SD) values of the stones were calculated as follows: calcium oxalate monohydrate stones: 1499 ± 269 HU; calcium oxalate dihydrate stones 1505 ± 221 HU; uric acid stones: 348 ± 67 HU; calcium phosphate stones: 1106 ± 220 HU, and cystine stones: 563 ± 115 HU (Table 1, and Figure 4). Cystine stones can be differentiated distinctly from calcium stones based on stone density measurements ($p < 0.001$). In ROC analysis, for cut-off value of cystine stone density was determined as 780 HU. However due to smaller sampling size, statistical power of the study was not adequate to determine a similar cut-off value for grading based on twinkling artifact intensities.

The longest diameters of a total of 86 stones extracted from 42 patients ranged between 6, and 35 mm. The longest diameters of the stones were >20 mm ($n=28$; 33%), between 10-20 mm ($n=41$; 48%), and <10 mm ($n=17$; 19%). The stones were extracted from kidneys (total $n=82$; 95%; right kidney, $n=46$, and left kidney $n=36$), and ureters (total $n=4$; 5%; right ureter, $n=3$, and left ureter, $n=1$). A significant correlation was not detected between stone sizes, and density values ($p=0.306$). Twinkling artifact intensities of grade 0 ($n=15$; 18%), Grade 1

Figure 4. A graph demonstrating distribution of density values of 5 stone types in Hounsfield units (1: CaOxMH, 2: CaOxDH, 3: UA, 4: CaP, 5: Cystine stones)

HU: Hounsfield Unit CaOxMH: calcium oxalate monohydrate; CaOxDH: calcium oxalate dihydrate; UA: uric acid; CaP: calcium phosphate

Table 1. Stone density values measured on CT in Hounsfield units (HU)

	Hounsfield Units - (HU)			Number (%) of stones
	Mean $\pm$ SD	Minimum	Maximum	
CaOxMH	1499 $\pm$ 269	840	1940	40 (47)
CaOxDH	1505 $\pm$ 221	1050	1800	12 (14)
CaP	1106 $\pm$ 220	790	1440	11 (13)
UA	348 $\pm$ 67	270	450	9 (10)
Cystine	563 $\pm$ 115	320	720	14 (16)

SD: standard deviation; CT: computed tomography; CaOxMH: calcium oxalate monohydrate; CaOxDH: calcium oxalate dihydrate; CaP: calcium phosphate; UA: uric acid

Table 2. The correlation between mineral composition of the stones, and their twinkling artifact intensities

	CaOxMH	CaOxDH	UA	CaP	Cystine	Total
Grade 0	8	2	3	2	0	15
Grade 1	17	4	5	6	0	32
Grade 2	13	5	1	3	2	24
Grade 3	2	1	0	0	12	15
Total	40	12	9	11	14	86

(n=32; 36%), Grade 2 (n=2; 28%), and Grade 3 (n=15; 18%) were recorded in respective number of stones. Fourteen renal, and one ureteral stone did not yield twinkling artifacts. Grade 3 artifact intensity was not observed in uric acid, and calcium phosphate stones. Grade 3 (n=12), and Grade 2 (n=3) arti-

fact intensities were recorded in indicated number of cystine stones (Table 2). Still a significant correlation was not detected between CT density values, and twinkling artifact intensities.

Discussion

Knowledge about mineral composition of the stone is important in the determination of optimal treatment.^[6] Urine pH, crystal analysis, measurement of urease-positive bacteria in urine levels plus bacteriological tests, previous history of urolithiasis, and plain X-ray have been used for years for the prediction of stone types.^[6] Recently, CT stone density, and twinkling artifact intensity on color Doppler US have been used.

Previously performed *in vitro* stone analyses revealed different density values for stones with different mineral compositions.^[7-10] In an *in vivo* study, Motley et al.^[11] demonstrated significant overlapping among density values of 4 different stone types, and a highly heterogeneous distribution in the same stone type. Therefore, they asserted that measurement of density in Hounsfield units failed to discriminate between stone types in *in vivo* settings. However Nakada et al.^[12] indicated usefulness of measuring stone densities for the discrimination between calcium oxalate, and uric acid stones. In both of these studies, superiority of density-dimension ratio over density measurements was indicated. Spettel et al.^[13] indicated higher success rates in the prediction of uric acid stones when density measurements were used in combination with urine pH. Although we observed differences between density values in Hounsfield units calculated for each stone type, basically our values were in accordance with those reported in the literature.

However based on literature data, a clear-cut consensus about absolute density values in Hounsfield units has not been established yet. In addition to differences between *in vivo*, and *in vitro* measurements, various devices can yield discrepant results.^[12,14] Besides in the same stone group, very diverse heterogeneous density values can be obtained, and also similar density values can be calculated for different types of stones. This condition reinforces the need for the development of new techniques. In recent years some authors investigated use of dual-energy CT to determine the stone type.^[15-20] These studies have yielded promising results, and this new method has been claimed to be more successful relative to conventional CT. Wisenbaugh et al.^[19] advocated use of this method for the discrimination between uric acid and other stone types. Foreseeing the presence of uric acid stones beforehand which are amenable to medical chemolysis will save many patients from undergoing unnecessary invasive procedures.^[18] Acharya et al.^[20] indicated potential discrimination between subtypes of calcium stones using this method. Thus, identification of CaOxMH stones which are resistant to lithotripsy will guide the treatment plans of the urologists. Indeed, conventional CT could not clearly

discriminate between CaOxMH, and very fragile CaOxDH stones. In our series we also discerned considerable overlapping between measurements of both stone groups.

In color Doppler examinations, behind some calculi, rapidly alternating mixture of colors termed as twinkling artifact can be observed. In the identification of urinary stones this artifact provides additional contribution to gray-scale ultrasound, and increases diagnostic success rates.^[21,22] The origin of this finding is not known for sure. Some stones do not induce formation of artifact, while others lead to greater amount of artifact. This phenomenon suggests the possibility of a correlation between the stone type, and the artifact intensity. For the first time Chelfouh et al.^[4] investigated this correlation. In this *in vitro* study performed with small number of stones, calcium oxalate monohydrate stones generally did not induce formation of twinkling artifact, while a correlation between calcium oxalate dihydrate stones, and twinkling artifact was found. Relatively smooth surface of monohydrate stones which reflects sound waves at a lower rate has been held responsible for the absence of twinkling artifact.

In their *in vitro* studies Hassani et al.^[2] reported that this artifact is helpful in the discrimination between calcium mono-, and dihydrate stones. However its significance in the discrimination between other stones could not be demonstrated. In our own series, generally a significant correlation between stone type, and twinkling artifact intensity could not be established. Calcium oxalate, and monohydrate stones produced twinkling artifact of comparable intensity. For the same stone type, artifact with intensities changing from Grade 0, and 2 were detected. On the other hand, when compared with other stone types cystine stones induced formation of artifact with greater intensity. In our study all cystine stones demonstrated artifact of significantly higher intensity (grade 2-3) when compared with other stone types. However in our literature review, we couldn't encounter reports of such a greater artifact intensity in cystine stones in previously performed *in vitro* studies.^[2,4] This phenomenon may arise from unexpectedly diverse interference of sound waves in stone patients. Greater number of *in vivo* studies or comparative studies with *in vitro* findings may clarify the etiology of this condition.

Our study had some limitations. Firstly the study had a retrospective design. Due to the lower number of patients, and hence stones, statistical power of our study was weakened. Therefore, further prospective studies should be conducted with greater number of patients. However we think that these preliminary data which is contributed to the literature will be helpful as guiding tools for future investigations.

In conclusion, as determined on non-contrast abdominal CT examinations, calcium stones (CaOxMH, CaOxDH, and CaP

stones) have a higher stone density when compared with non-calcium (cystine, and uric acid stones) stones. Different calcium stones have overlapping density values. Also cystine, and uric acid stones have nearly similar density values. Therefore these stone groups can not be differed from each other based solely on density measurements. Overlapping intensities of the twinkling artifact have been also observed among all stone groups. On the other hand, mineral composition of the stones with a density value below 780 HU which also display grade 3 artifact can be evaluated in favour of cystine stone. However prospective studies evaluating stone densities in a greater number of patients should be conducted to reinforce the validity of the data obtained.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Istanbul University, Istanbul Faculty of Medicine.

Informed Consent: Due to the retrospective nature of the study, written informed consent could not obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.B., T.T., F.A., A.S.; Design - M.B., T.T., F.A.; Supervision - M.T.Ö., C.B., Ö.Ş., A.S.; Resources - T.T., F.A., M.T.Ö., C.B.; Materials - T.T., F.A., M.T.Ö., C.B.; Data Collection and/or Processing - M.T.Ö., C.B., T.O.; Analysis and/or Interpretation - Ö.Ş., T.O., A.S.; Literature Search - M.B., T.T., F.A.; Writing Manuscript - M.B., T.T., F.A.; Critical Review - Ö.Ş., T.O., A.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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