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Differentiating Calcium Oxalate and Hydroxyapatite Stones In Vivo Using Dual-Energy CT and Urine Supersaturation and pH Values

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Abstract

Rationale and Objectives—Knowledge of urinary stone composition can guide therapeutic intervention for patients with calcium oxalate (CaOx) or hydroxyapatite (HA) stones. In this study, we determined the accuracy of noninvasive differentiation of these two stone types using dual-energy CT (DECT) and urine supersaturation (SS) and pH values.

Materials and Methods—Patients who underwent clinically indicated DECT scanning for stone disease and subsequent surgical intervention were enrolled. Stone composition was determined using infrared spectroscopy. DECT images were processed using custom-developed software that evaluated the ratio of CT numbers between low- and high-energy images. Clinical information, including patient age, gender, and urine pH and supersaturation profile, was obtained from electronic medical records. Simple and multiple logistic regressions were used to determine if the ratio of CT numbers could discriminate CaOx from HA stones alone or in conjunction with urine supersaturation and pH.

Results—Urinary stones (CaOx $n = 43$, HA $n = 18$) from 61 patients were included in this study. In a univariate model, DECT data, urine SS-HA, and urine pH had an area under the receiver operating characteristic curve of 0.78 (95% confidence interval [CI] 0.66–0.91, $P = .016$), 0.76 (95% CI 0.61–0.91, $P = .003$), and 0.60 (95% CI 0.44–0.75, $P = .20$), respectively, for predicting stone composition. The combination of CT data and the urinary SS-HA had an area under the receiver operating characteristic curve of 0.79 (95% CI 0.66–0.92, $P = .007$) for correctly differentiating these two stone types.

Conclusions—DECT differentiated between CaOx and HA stones similarly to SS-HA, whereas pH was a poor discriminator. The combination of DECT and urine SS or pH data did not improve this performance.

Keywords

Dual-energy CT; urinary stones; composition characterization; urine pH; urine supersaturation

Urinary tract stones (urolithiasis) are one of the most common causes of acute and chronic pain causing significant morbidity. The lifetime incidence in developed countries is about 10% to 15%, with a relapse rate of 50% in 10 years and 75% in 20 years (1). One of the key factors for optimizing the management of patients with urolithiasis is the chemical composition of the stone (2). Medical treatment, preoperative evaluation, and the strategy for recurrence prevention are all influenced by stone type. For example, because uric acid stones can dissolve in urine of higher pH, alkalization of the urine is often effective. Extracorporeal shock wave lithotripsy is commonly used for stone removal (3), but certain firm stones, such as brushite and some calcium oxalate (CaOx) stones, resist fragmentation. Overall, unnecessary procedures can potentially be avoided if the chemical composition is readily known in the initial stage of patient evaluation (4).

About 80% of stones are composed of CaOx and/or hydroxyapatite (HA) (5,6). These two stone types form under different physiochemical conditions, making the differentiation between the two stone types desirable for both research and treatment purposes (2,7). Twenty-four-hour urine collection used to measure key components in the urine is the most common method to assess kidney stone risk factors. For example, CaOx stones can form under a wide range of physiologic urinary pH conditions, while HA stones tend to form in alkaline urine (8). Urinary supersaturation (SS) calculated from the composition of a twenty-four-hour urine collection also correlates with the crystalline component of the stones passed (9,10). Therefore, physicians rely largely on urine pH (8,11) and urine SS profile (9) to predict stone composition when a previous stone analysis is not available.

Dual-energy CT (DECT) with advanced postprocessing techniques is an emerging imaging technology that can be used to evaluate patients with urinary stones. It provides physicians with the size and location of the stones, associated features such as anatomic abnormalities in the collecting system (12), and information regarding the stone chemical composition. DECT is nearly 100% accurate at characterizing uric acid (UA) stones both in vitro (13,14) and in vivo (15). Recent progress has been made to further differentiate between non-UA stone types, such as CaOx and HA stones (16–18), with initially encouraging results. Indeed, DECT has great potential for use as a first-line exam in clinical practice for evaluating urinary stone composition.

Therefore, in the current study, we compared the predictive value of DECT and urinary SS for discriminating stone type and postulated that the combination of DECT data with SS and/or pH information would be better than any of the tests alone.

MATERIALS AND METHODS

This retrospective study was approved by our institutional review board and conflict of interest committee. All patient data were treated in a Health Insurance Portability and Accountability Act–compliant manner.

Patient Inclusion

Between June 2009 and January 2012, patients referred for surgical urolithiasis procedures with a preoperative clinically indicated DECT were identified through chart review. Extracted stones were evaluated by infrared spectroscopy for chemical composition in the Mayo Clinic Metal Laboratory (19). Only stones with 80% purity of either CaOx or HA by infrared spectroscopy were included in this study. Patients with multiple stones were excluded to ensure that the removed stone was consistent with the one identified by DECT.

Clinical CT Data Acquisition and Image Processing

Patient image data from DECT scans were retrieved from our institutional database. These patients had been scanned with use of a second-generation dual-source CT scanner (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) using our clinical kidney stone protocol: 100 kV and 140 kV with tin filter, 240 and 185 quality reference mAs, respectively, and 64×0.6 mm collimation, 0.5 s rotation time, spiral mode with pitch = 0.6, and automatic exposure control. The volume CT dose index ($CTDI_{vol}$) was approximately 18 mGy for a standard size adult (70 kg). Images were reconstructed using a medium smooth body kernel (D30) with a field of view of 300 mm and image thickness of 1.0 mm at an 0.8-mm interval.

Dual-energy images were analyzed using custom-built Matlab-based software as reported in previous publications (17). In brief, a square region of interest was defined manually by the observer to indicate the location of the stone. The software then automatically segmented the stone from surrounding tissues using a predefined CT number threshold (150 Hounsfield units in the high-energy image) and extracted a three-dimensional volume of interest containing the stone. The CT ratio (CTR) was calculated as the CT number at 100 kV divided by the CT number at 140 kV for each voxel. The average CTR value of all voxels within the segmented stone was used for characterizing stone composition.

Kidney stone size was measured automatically as the largest dimension across the stone in any plane. For visualization purposes, stones were colored according to stone type (Fig 1).

Clinical Lab Urine Evaluations

The following information was obtained from patient chart review: patient age, gender, twenty-four-hour urine pH, and urinary SS for CaOx (SS-CaOx) and HA (SS-HA) calculated using EQUIL2 (20) (Fig 1).

Statistical Analysis

Standard descriptive statistics were used to summarize the clinical parameters by stone variety. To provide an initial test for differences in these parameters between stone types, two-sample *t*-tests were used. A logistic regression framework was used in SAS version 9.3 (SAS Institute, Cary, NC) to estimate the area under the receiver operating characteristic curve (AUC). Incremental increases in diagnostic performance (AUC) were examined for several combinations of variables. Sample statistics and model performance indices are based on the observed sample composition of 70% CaOx versus 30% HA. That is, summary indices have not been weighted for a population distribution of stone types across these two categories since the relative observed frequencies of stone types in this study were found to be closely related to a prior study on the prevalence of stone types (21). The dependent variable for the logistic regression models was stone type (CaOx versus HA). Candidate predictors included dual-energy CTR and urine pH and urine SS indices for both CaOx and HA (SS-CaOx and SS-HA, respectively).

RESULTS

A total of 242 patients were identified who received a clinically indicated DECT scan using our kidney stone imaging protocol that was followed by stone removal and stone composition analysis with infrared spectroscopy. After applying an additional criterion for stone purity (>80% of CaOx or HA by infrared spectroscopy), 93 stones from 72 patients remained for evaluation in this study. Of these, we excluded 11 patients with multiple stones or missing lab values, leaving 61 stones from 61 patients for analysis, including 27 men and 34 women. Mean age was 55.9 ± 15.3 years (range 21–82 years). There were 43 CaOx and

18 HA stones of a mean size of 6.8 ± 5.3 mm (range 0.8–22.7 mm) and 6.9 ± 6.1 mm (range 2–22.7 mm) ($P > .05$), respectively. The mean $\pm$ SD CTDI_{vol} was 14.5 ± 4.9 mGy and 12.4 ± 3.2 mGy in CaOx and HA cohorts ($P > .05$), respectively. The majority of CaOx and HA patients had undergone an evaluation in the stone clinic (60% and 79%, respectively) and were receiving medical treatment (54% and 74%, respectively).

The mean CTR, SS-CaOx, SS-HA, and urine pH values were calculated and tested for their performance to discriminate between CaOx and HA stones (Table 1). As seen in Table 1, a significant difference ($P < .01$) of SS-HA between CaOx and HA stones was observed. However, there was no significant difference ($P = .32$) of SS-CaOx between CaOx and HA stones. Therefore, in the following data analysis, we only focused on stone differentiation using SS-HA. Figure 2 shows the box-plots of CTR, SS-HA, and urine pH for CaOx and HA stones. In simple (i.e., single predictor) logistic regression models, the findings of the *t*-tests were supported by a reasonable discrimination (AUC) between CaOx and HA stones. The AUCs for CTR and SS-HA were 0.78 (95% CI 0.66–0.91, $P = .016$) and 0.76 (95% CI 0.61–0.91, $P < .01$) (Fig 3 and Table 2), respectively. Urine pH alone provided poor discrimination (AUC 0.60, 95% CI 0.44–0.75, $P = .20$).

The multiple logistic regression framework (ie, combination of variables) yielded little increase in discrimination. For example, when both CTR and SS-HA were used as predictors of stone type, the overall AUC was 0.79 (95% CI 0.66–0.92, $P = .007$). There was evidence of some collinearity between the two predictors, though. The incremental effect of CTR was not statistically significant ($P = .06$), but the overall model performance remained acceptably high and essentially identical to models in which each variable was modeled separately. A similar pattern of findings was observed for other combinations of variables (Table 2).

DISCUSSION AND CONCLUSION

This cohort study suggests that the performance of DECT for differentiating CaOx and HA stones was comparable to that of urine SS-HA. A combination of both variables did not improve the performance of either test used in isolation. Therefore, DECT can noninvasively discriminate between HA and CaOx in vivo reasonably well with an AUC value of about 0.78, comparable to the widely used urinary SS measurements.

CaOx and HA, either alone or in combination, are the most common components of urinary stones, accounting for about 80% of all stones (5,6). Since these two compositions are associated with different metabolic milieus and respond differently to certain types of surgical interventions, there is clinical value to efficiently and reliably discriminate between CaOx and HA stones. If a passed or retrieved stone is not available for analysis, most clinicians use metabolic urine profiles to infer stone type (6). However, reliable urinary SS results require patient compliance with accurate collection of a 24-hour urine sample, which is not always easy or feasible to obtain (e.g., in small children or incontinent adults) (22). In addition, under certain circumstances, SS and stone composition results are discrepant (23). These discrepancies may reflect the sometimes complicated and changing physiological environment when stones are forming, and, in principle, stone composition based on structural analysis might better capture this information.

In our study, SS-HA discriminated CaOx and HA stones well, with an AUC of 0.76 ($P < .01$). Urine pH was also on average slightly lower in CaOx (6.0) than HA stone formers (6.2). However, this pH difference was not statistically significant in this smaller cohort ($P = .20$), and there was significant overlap between the two groups (Fig 2C), CaOx can form equally well across the physiological urinary pH spectrum, reflected by the wide range of

pH in our CaOx stone formers (4.7–7.5). Thus, urine pH alone is not particularly helpful for discriminating between these two stone types. CTR alone provided comparable discrimination to SS-HA alone based on the nearly identical point estimates and 95% CIs. This result is comparable to that achieved in a previous patient study (18). However, combining DECT and urinary SS or pH data also did not improve separations compared to DECT or SS-HA alone ($P > .05$).

Recent studies have suggested that the path to stone formation may differ between stone types (24). Many CaOx stones appear to grow from interstitial Randall plaques (25). Other CaOx stones may form from ductal plugs (26). HA stones may form from both plaque and from duct of Bellini plugs (27). It has been observed that stone composition may shift over time in individual patients from CaOx to HA (28,29). The mechanisms are unclear, but use of certain medications, such as citrate to alkalinize the urine or treatments such as shock wave lithotripsy, which can damage the kidneys, might be avoided in patients who are known to harbor HA stones (29). If CT technology can be improved to differentiate plaques and plugs in vivo, that information in combination with stone composition could revolutionize patient phenotyping for clinical investigation and ultimately allow individualized treatment strategies. Although much work remains, the ability to differentiate these two stone types with reasonable AUC values could still influence stone treatment strategies, even today. The integration of all relevant information, including patient history, diet habit, and stone volume, may further improve the performance of DECT in stone type discrimination in future studies.

Our study has several limitations. We have a comparatively smaller sample size (61 stones [and patients]). Also, only stones with high purity (80%) were included in this study. Most patients were being seen in a referral stone clinic, and many were given dietary advice and/or medical interventions that may have influenced the urinary measurements. Analysis based on a stone population that has not yet been evaluated may show different results.

In conclusion, our study showed that newer multidetector DECT techniques not only can inform physicians regarding stone presence, size, location, and overall burden but also can help predict the composition between calcium stone types. Because many stone patients undergo CT to confirm stone presence, the use of noncontrast DECT instead of traditional noncontrast CT, which requires no greater radiation dose than the latter (30), may offer the clinician important information regarding stone type at the beginning of the patient evaluation period in a safe and efficient way and thus may allow for more efficient patient management decisions.

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Figure 1.

Two sample images show characterization of stone compositions. **(a)** A 61-year-old female patient with urine pH 6.8 and supersaturation calcium oxalate of 1.12 and supersaturation hydroxyapatite of 3.2 and **(b)** a 67-year-old female patient with urine pH 6.1, supersaturation calcium oxalate of 0.52, and supersaturation hydroxyapatite of 3.22. Stone compositions were hard to predict using these lab values, while dual-energy computed tomography determined them correctly to be **(a)** a calcium oxalate stone and **(b)** an hydroxyapatite stone.

Figure 2. Box-plots of (a) dual-energy CT number ratio (CTR), (b) supersaturation hydroxyapatite, D.G., and (c) urine pH for calcium oxalate and hydroxyapatite stones.

Figure 3.

Receiver operating characteristic (ROC) curves of (a) dual-energy CT ratio (CTR) ($P = .016$) and (b) supersaturation hydroxyapatite ($P < .01$) and (c) urine pH ($P = .20$) for calcium oxalate and hydroxyapatite stone discrimination.

TABLE 1
Dual-energy CTR, SS-HA, SS-CaOx, and Urine pH of CaOx and HA Stone Patients

	CaOx		HA		P Value
	Mean ± SD	Range	Mean ± SD	Range	
CTR	1.40 ± 0.13	1.17 to 1.68	1.49 ± 0.11	1.35 to 1.71	.016
SS-HA, D.G.	3.29 ± 1.95	−1.94 to 6.72	5.43 ± 2.67	−0.74 to 9.36	<.01
SS-CaOx, D.G.	1.85 ± 0.57	0.29 to 2.86	1.68 ± 0.64	0.45 to 2.54	.32
Urine pH	6.0 ± 0.7	4.7 to 7.5	6.2 ± 0.6	5.2 to 7.6	.20

CaOx, calcium oxalate; CTR, computed tomography number ratio; D.G., delta gibbs; HA, hydroxyapatite; SD, standard deviation; SS, supersaturation.

TABLE 2

Summary of Statistical Analysis Result Using One or Combination of Variables as Predictor(s) of Stone Type

Variable(s)	Area Under ROC Curve (C-statistic)	95% Confidence Interval	P Value
CTR	0.78	0.66–0.91	.016
SS-HA	0.76	0.61–0.91	.003
SS-CaOx	0.57	0.42–0.73	.32
Urine pH	0.60	0.44–0.75	.20
CTR + SS-HA	0.79	0.66–0.92	.007*
CTR + urine pH	0.77	0.65–0.88	.02*
CTR + SS-HA + urine pH	0.80	0.67–0.92	.07*

CaOx, calcium oxalate; CTR, computed tomography number ratio; HA, hydroxyapatite; SS, supersaturation.

* P values are for the incremental increase in discrimination of the CTR relative to the other variables listed.