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ORIGINAL PAPER

CT visible internal stone structure, but not Hounsfield unit value, of calcium oxalate monohydrate (COM) calculi predicts lithotripsy fragility in vitro

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Abstract Calcium oxalate monohydrate (COM) stones are often resistant to breakage using shock wave (SW) lithotripsy. It would be useful to identify by computed tomography (CT) those COM stones that are susceptible to SW's. For this study, 47 COM stones (4–10 mm in diameter) were scanned with micro CT to verify composition and also for assessment of heterogeneity (presence of pronounced lobulation, voids, or apatite inclusions) by blinded observers. Stones were then placed in water and scanned using 64-channel helical CT. As with micro CT, heterogeneity was assessed by blinded observers, using high-bone viewing windows. Then stones were broken in a lithotripter (Dornier Doli-50) over 2 mm mesh, and SW's counted. Results showed that classification of stones using micro CT was highly repeatable among observers ($\kappa = 0.81$), and also predictive of stone fragility. Stones graded as homogeneous required 1,874 ± 821 SW/g for comminution, while stones with visible structure required half as many SW/g, 912 ± 678. Similarly, when stones were graded by appearance on helical CT, classification was repeatable ($\kappa = 0.40$), and homogeneous stones required more SW's for comminution than did heterogeneous stones (1,702 ± 993 SW/g, compared to 907 ± 773). Stone fragility normalized to stone size did not correlate with Hounsfield units ($P = 0.85$). In conclusion, COM stones of homogeneous structure require almost twice as many SW's to comminute than stones of similar mineral composition that exhibit internal structural features that are visible by CT. This suggests that stone fragility in patients could be predicted using pre-treatment CT imaging. The findings also show that Hounsfield unit values of COM stones did not correlate with stone fragility. Thus, it is stone morphology, rather than X-ray attenuation, which correlates with fragility to SW's in this common stone type.

Keywords Kidney calculi · Tomography, X-ray computed · Micro CT

Introduction

Urinary calculi made of calcium oxalate monohydrate (COM) are among the most common stones affecting the populations of industrialized countries [1, 2], and can be especially resistant to shock wave (SW) lithotripsy [3, 4]. However, study of stone breakage in vitro has shown that COM stones vary dramatically in their fragility to SW's, with some stones being very resistant, and others quite fragile [5, 6], and this variability is consistent with clinical experience [4]. Lithotripter SW's can produce adverse effects [7], so it is important to consider ways to reduce dosage of SW's when possible. If the level of susceptibility of a given COM stone to SW lithotripsy could be established at diagnosis, SW dosage could be tailored to that case.

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Helical computed tomography (CT) has been proposed as a means to predict the success or failure of lithotripsy [6, 8], and a number of studies have attempted to utilize CT numbers (in Hounsfield units, which are related to X-ray attenuation values) as a predictor of stone fragility [9–14]. However, given the resolution of clinical CT and the effects of volume averaging, the simple measure of Hounsfield units in stones is most likely to correlate with stone size [15, 16], and stone size correlates with the number of SW's required for comminution [5]. Thus, the use of Hounsfield units alone for predicting stone fragility in lithotripsy becomes little more than an expensive way to measure stone size. What is needed is a way to distinguish COM stones that will break easily with SW's from stones of the same size that will be SW-resistant.

By normalizing Hounsfield unit values to stone diameter, it has been shown that the volume-averaging error can be corrected to some extent, so as to yield attenuation values that are specific for stone type. In this way, uric acid can be distinguished from calcium oxalate [17]. However, such an approach has not been shown to be of value for predicting which COM stones will be resistant to SW's.

A more useful strategy may be to exploit the ability of helical CT to visualize structure within stones [6, 18, 19]. In the present study, COM stones were scanned in vitro by micro CT and helical CT, with independent observers grading stones according to heterogeneity of structure, and these observations were correlated with stone fragility. The results show that visible internal structure within COM calculi is an accurate predictor of increased fragility to lithotripter SW's.

Methods

COM stones (4–10 mm in diameter) were obtained as discards from a stone analysis laboratory (Beck Analytical Services, Indianapolis, IN, USA); each had been labeled as ≥94% COM by analysis either of a cohort stone or a portion of the stone used for this study. Each stone was scanned with a Scanco mCT20 micro CT system (voxel size from 18 to 34 μm) to verify composition [20] (found to be 98 ± 4% pure COM, mean ± SD, for 47 stones) and also for assessment of heterogeneity (presence of pronounced lobulation, voids, or apatite inclusions) by four blinded observers (Methods described below). Stones were weighed dry, and a mean diameter of each stone was calculated from the stone volume found by micro CT, assuming a spherical shape for the stone. Stones were then packed in degassed water in plastic tubes, separated by absorbent paper, and further degassed under vacuum to help prevent the inclusion of bubbles. After three days of hydration the stones were scanned using helical CT (Phillips Brilliance 64, 80 kV, 297 mA, 0.67 mm slice width, with reconstruction at 0.33 mm intervals), with bags of saline surrounding the plastic tubes to reduce beam hardening artifact. As with micro CT, heterogeneity was assessed by two blinded observers, using viewing windows freely selected by each observer; however, five stones were chosen by the first observer to demonstrate to the second observer the definitions of 'homogeneous' and 'structured,' and these stones were not included in the analysis for helical CT. Regions of interest were drawn using the center slice of each stone, within a region thresholded at 75% of the maximum value [21], and maximum, minimum, and average Hounsfield unit values were recorded. Examples of a homogeneous stone and stones consistently graded as containing structure are shown in Fig. 1.

Stones were broken in randomized order in a lithotripter (Dornier Doli-50, power level 4, 2 Hz) over 2 mm mesh, and SW's counted. In previous studies in which we had broken stones over a 2 mm mesh, we noticed that many natural stones tended to have a single, last fragment that persisted for many SW's before finally falling through the mesh, and sometimes persisting until the maximum number of SW's was delivered. Because these last fragments were quite small, it seemed that the additional SW's required to break a last, tiny fragment would lead to an overestimation of the resistance of the stone to SW's. In the present study, we tracked this phenomenon, and recorded the SW number at which the stone was reduced to a single, last fragment, producing for each stone a *number of SW's to last fragment*, and a *number of SW's to completion* (when the last fragment broke or fell through the mesh). A high-definition video camera was used to magnify the image of the stone-basket interface to help visualize the last fragment and precisely the moment when it fell through the mesh. In one stone, the last fragment persisted through 2,000 SW's, which was the predetermined endpoint for the experiment, and that fragment was collected for further study. The fragment was scanned using a Skyscan 1072 micro CT system (Skyscan, Antwerp, Belgium; 100 kV with no filter) and reconstructed at 13.7 μm voxel size. It was then analyzed by transmission infrared spectroscopy in KBr pellets using a Nicolet Avatar 330 FT-IR spectrometer (Thermo Scientific, Waltham, MA, USA).

Statistics

Observer agreement was assessed using the kappa statistic, calculated as Cohen's κ for two observers using the software JMP IN 5.1 (SAS, Cary, NC, USA), or as Fleiss' κ for more than two observers [22]. For the κ statistic, the strength of agreement beyond chance is ranked as fair for $0.2 < \kappa \leq 0.4$, moderate for $0.4 < \kappa \leq 0.6$, substantial for

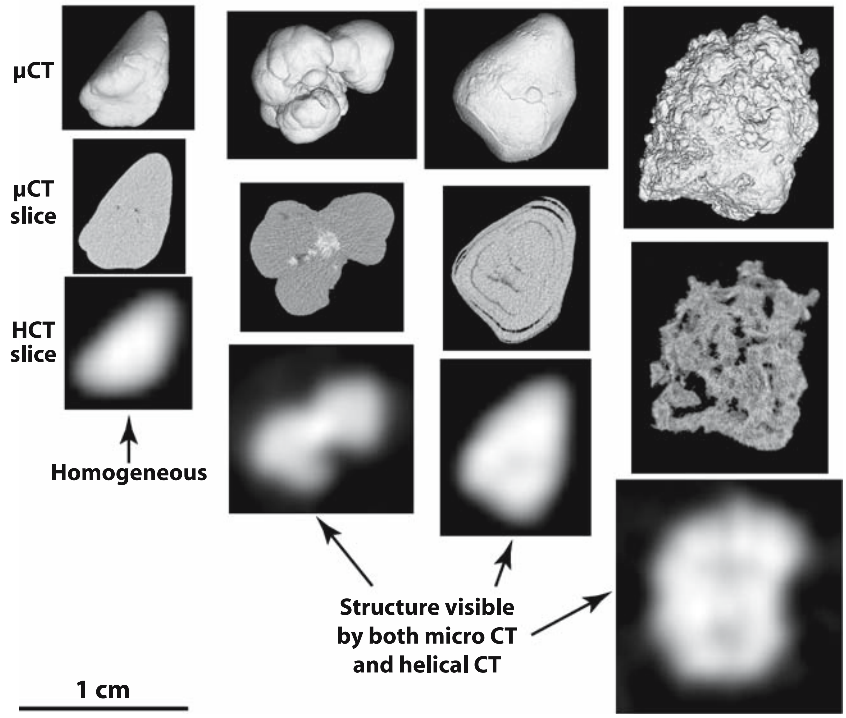

Fig. 1 Examples of COM calculi judged by all observers to be homogeneous (*leftmost column*) or showing internal structure (*other columns*). Each column shows one stone, with the *topmost* image a surface rendering from micro CT, the *middle image* a slice from micro CT, and the *bottom image* a slice from helical CT. Grayscale of images was adjusted for maximum viewing detail, and does not accurately reflect X-ray attenuation values

$0.6 < \kappa \leq 0.8$, and almost perfect for $0.8 < \kappa \leq 1.0$ [23]. For SW number and other data, correlation was assessed using least squares regression, and groups were compared by analysis of variance, using the *t*-test or the Tukey–Kramer HSD test for means comparisons, as appropriate. A probability value of less than 0.05 was considered significant.

Results

Use of SW's to last fragment as appropriate measure of stone fragility

When the stones were broken with SW lithotripsy, over half required a substantial number of SW's after the last fragment was the only piece left on the 2 mm mesh; the median number of additional SW's required for the last fragment was 35.4% of the number administered before that point. However, some stones required over ten times as many SW's for the last fragment to fall as for the fragmentation of the bulk of the stone, such that the mean value for percent of SW's for the last fragment was skewed to 108.4%. When comparing SW's to last fragment with stone size, the number of SW's correlated significantly both with stone weight ($P < 0.0001$) and stone diameter ($P < 0.0004$). In contrast, the total number of SW's for all fragments to fall through the mesh correlated poorly with stone size ($P = 0.05$ for weight, $P = 0.06$ for diameter). Thus, SW's-to-last-fragment was determined to be the more useful measure of stone fragility for this study, and is the number shown for comminution below.

In one stone, the last fragment was still retained on the mesh after 2,000 SW's had been delivered. By micro CT, the fragment was homogeneous in X-ray attenuation, consistent with a composition of COM, and IR spectroscopy showed the fragment to be composed entirely of COM. There was no indication of an unusual composition (such as a content of fibers) that would make this fragment difficult to break. It measured approximately 2 mm across, with a total volume of 4.2 mm^3 (Fig. 2).

Stone structure and stone fragility

About a third of the COM stones (34%) were judged to be homogeneous in composition/structure (see Fig. 1). The rest of the stones were judged by one or more observers to show internal structure, such as regions of apatite or radiolucent voids, or both apatite and voids (Fig. 1, right three columns). Classification of stone structure using micro CT was highly repeatable among observers ($\kappa = 0.81$), and also predictive of stone fragility (Fig. 3a). Stones graded as homogeneous required 1,874 ± 821 SW/g for comminution ($n = 16$), while heterogeneous stones required half as many SW/g, 912 ± 678 ($n = 25$, $P < 0.001$). When observers did not agree as to stone heterogeneity, fragility

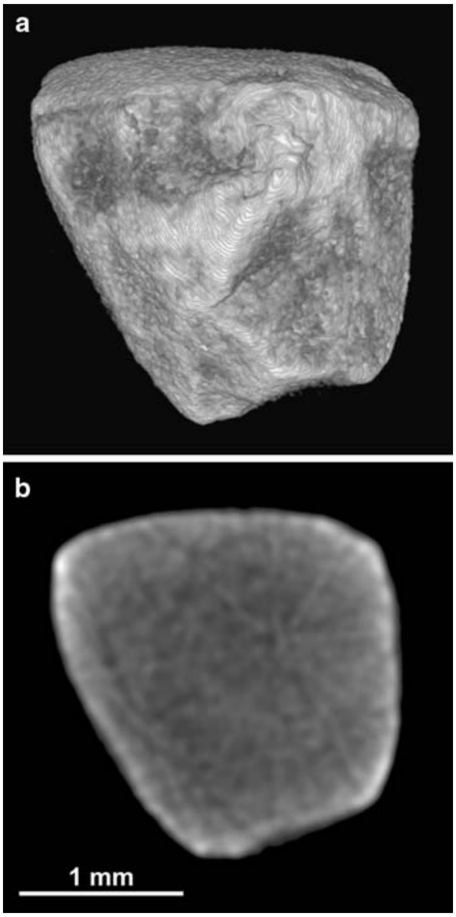

Fig. 2 Fragment of COM stone that did not fall through 2 mm mesh even after 2,000 SW's. Shown is surface rendering of micro CT images (**a**) and slice through middle of stone (**b**). The radial shadows through the middle of the slice image are reconstruction artifact, and the brightness at the edge of the stone is due to beam hardening artifact. Careful examination of the serial slices showed no evidence of content other than COM in this fragment

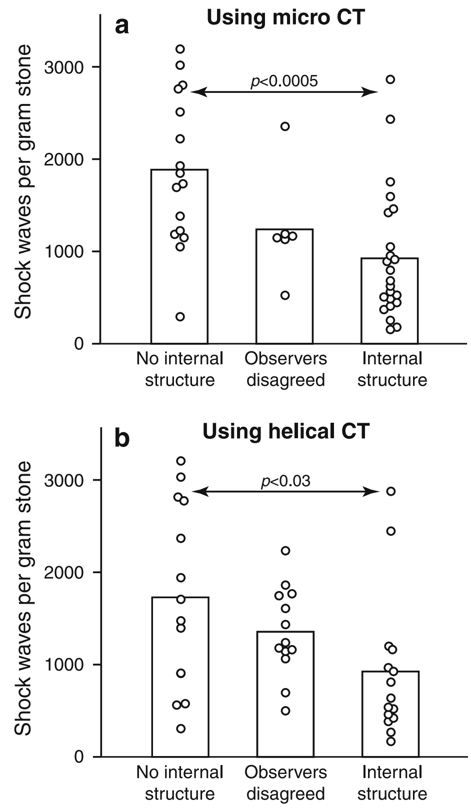

Fig. 3 Number of SW's-to-last-fragment, normalized to stone weight, for stones judged to be homogeneous in composition/structure (no internal structure) and when stones were seen to have internal structure. **a** Micro CT images of stones were used for judging composition/structure. **b** Helical CT images were used. Each *circle* represents a single stone; columns show mean SW count to last fragment for each group. Significance of differences between 'No internal structure' and 'Internal structure' was tested using Tukey–Kramer HSD test, with data from all three groups included

was intermediate between these groups (1,249 ± 598, $n = 6$). Stones were also graded as to presence of internal cracks (probably due to previous handling) and as to whether they appeared to be intact or a fragment of a larger stone; neither the presence of cracks (in five stones of 47 total, $P = 0.20$), nor the appearance of being intact (10 stones of 47 total, $P = 0.37$) had a significant effect on stone fragility.

When stones were graded by appearance on helical CT, classification was repeatable ($\kappa = 0.40$), and homogeneous stones required more SW's for comminution than did heterogeneous stones (1,702 ± 993 SW/g, compared to 907 ± 773, $P < 0.03$, Fig. 3b). Again, when observers did not agree, the number of SW's to comminution was intermediate in value (1,340 ± 482, $n = 13$). Stone fragility normalized to stone size did not correlate with simple measurement of average Hounsfield units measured by helical CT (Fig. 4). Similarly,

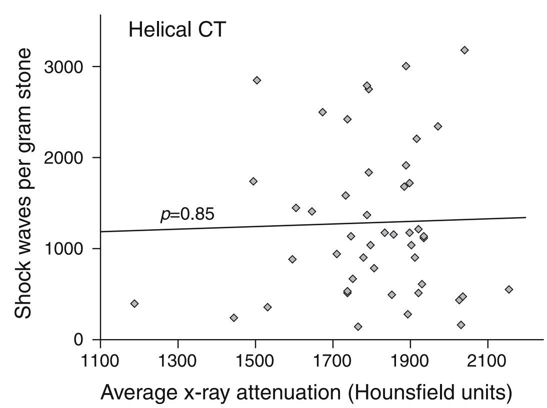

Fig. 4 Number of SW's-to-last-fragment for COM stones plotted against the average Hounsfield unit values for each stone, as measured by helical CT. Stone fragility showed no correlation with Hounsfield unit values

neither minimum nor maximum Hounsfield unit values correlated with stone fragility ($P = 0.59$ and $P = 0.76$, respectively).

Discussion

The concept of viewing urinary stones by X-ray to evaluate their ability to be treated by SW's dates back to the earliest days of lithotripsy [4]. At that time it was already known that some stones could be SW-resistant, and it was thought that X-ray at diagnosis could be used to avoid subjecting the patient to an ineffective procedure. It is now known that lithotripter SW's can cause significant renal injury [7], and that SW trauma may be contributory to subsequent development of other disorders [24, 25]. Thus, the application of unnecessary SW's should be considered a risk to the patient, and it would be of value to determine in advance the dose of SW's required for a given stone.

Dretler and Polykoff [26] sought to distinguish the relative fragility of different calcium oxalate stones by their appearance on plain X-ray. The present study is a refinement of this approach, utilizing the powerful ability of CT to display the internal structure of urinary stones [18, 20]. The results demonstrate that COM stones that show visible structure on CT are more fragile to SW's than COM stones that appear to be homogeneous in their structure (Fig. 3). For some stones, the stone shape may also have been seen by observers to indicate internal structure (see especially the highly lobulated stone in Fig. 1). This correlation between stone appearance by CT and susceptibility to SW's is consistent with results from numerical modeling showing that irregularities in the structure of the stone can act as sites for focusing of SW energy [27], so that the stone may break more easily. Stone shape can also have profound effects on the interaction of SW's with a stone [28, 29].

In the present study, the Hounsfield unit values of COM stones did not correlate with their fragility to SW's (Fig. 4). This result differs from several published studies [9–14]. The likely explanation for this discrepancy is that the fragility data in the present study were normalized to stone size, a procedure that was not done in any of the previous studies. As has been described elsewhere, the resolution of clinical CT is such that the X-ray attenuation values correlate well with stone size [15, 16], and thus the number of SW's to comminution can correlate with Hounsfield unit values as a simple prediction of the larger stones requiring more SW's [5, 16]. The approach in the present study avoids that error, and the result is that Hounsfield units are not a predictor of stone fragility.

A methodological note of importance involves the choice in the present study of using the number of SW's required to reach a single, small fragment as the end-point for assessing stone comminution. These last fragments were all quite small (2 mm or smaller, Fig. 2) and their small size may have contributed to their resistance to SW's, as the mechanism of spallation operates poorly on fragments smaller than the spatial thickness of the SW [30]. Counting the number of SW's to complete breakage is viewed as a clinically relevant measure of stone comminution [31]. The adjustment of this protocol used in the present study may make the assessment of stone fragility more realistic, as it avoids overestimation of SW number due to the SW-resistance of fragments that are so small as to be clinically insignificant.

In summary, COM stones of homogeneous composition required almost twice as many SW's to comminute than COM stones that showed internal stone structure by CT. This suggests that stone fragility in patients could be predicted using pre-treatment CT imaging. The findings also show that Hounsfield unit values of COM stones did not correlate with stone fragility. Thus, it is stone morphology, rather than apparent X-ray attenuation, which correlates with fragility to SW's in this common stone type.

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