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Fragility of Brushite Stones in Shock Wave Lithotripsy: Absence of Correlation with Computerized Tomography Visible Structure

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Abstract

Purpose—Brushite stones were imaged in vitro and then broken with shock wave (SW) lithotripsy (SWL) to assess whether stone fragility correlates with internal stone structure visible by helical computed tomography (helical CT).

Materials and Methods—52 brushite stones were scanned by micro CT, weighed, hydrated, and placed within a radiological phantom. The stones were scanned using a Philips Brilliance iCT 256 system, and the images evaluated for visibility of internal structural features. The stones were then treated by SWL in vitro, and the number of SWs needed to break each stone to completion was recorded.

Results—The number of SWs to break each stone, normalized to stone weight, did not differ by Hounsfield unit value ($P=0.84$), or CT-visible structure that could be identified consistently by all observers ($P=0.053$). Fragility of stones was highly correlated with stone density and with brushite content (both $P<0.001$), with stones of nearly pure brushite requiring the most SWs to break. When all observations of CT-visible structure were used in analysis by logistic fit, CT-visible structure predicted increased stone fragility with an overall area under the receiver operating characteristic (ROC) curve of 0.64.

Conclusions—SWL fragility of brushite stones did not correlate with internal structure discernable using helical CT. However, fragility did correlate with stone density and increasing brushite mineral content, which is consistent with clinical experience with brushite stone patients. Thus, current technology in diagnostic CT does not provide a means to predict when brushite stones will break well using SW lithotripsy.

Keywords

computed tomography; kidney stones; urinary stones

Introduction

Brushite stone disease is characterized by the rapid formation of large stone burdens, with a rate of recurrence that is greater than most types of stone.¹ Brushite stones are also among the hardest to break,² which, combined with the large size of the stones, results in poor outcomes with shock wave (SW) lithotripsy (SWL).³ Distressingly, this form of stone

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disease is accompanied by renal functional defects (such as renal tubular acidosis⁴), by pathological changes in both renal cortex and medulla⁵, and is a stone disease that is increasing in prevalence. Daudon et al. showed a steadily progressive increase in brushite-containing stones, from 0.9% in the early 1980's to 4.3% of all stones between 2005–2009.⁶ Among the US veteran population, Mandel et al. showed a similar increase, with brushite in stones rising from 1.7% in the 1980's to 4.1% in later years.⁷

Although brushite stones are relatively difficult to break using SWL, there is a wide variability in the numbers of SWs required to break these stones.² Similar variability is seen with other stone types, and it has been shown both for cystine stones⁸ and for stones composed of calcium oxalate monohydrate (COM)⁹ that CT-visible structure within a stone marks it as being more susceptible to SWs than stones of the same composition that do not show internal structure on helical CT. The aim of the present study was to determine if the same criterion of a correlation between fragility and CT-visible structure also applies to brushite stones, which would open the possibility of using CT parameters to predict which brushite stones would be amenable to treatment with SWL.

Methods

Brushite stones were obtained as de-identified discards from a stone analysis laboratory, and the analysis list was used to find specimens marked as 90% brushite. As such, the source material was either an intact fragment from a stone that had previously undergone destructive analysis or a companion stone collected at the same time from the patient. Stones were photographed, weighed, and scanned by micro CT using a SkyScan 1172 System (SkyScan, Kontich, Belgium) using settings of 50–60 kV, 170–200 μ A, and reconstructed voxel sizes of 14–22 μ m (depending on stone size). Volumes were measured from the micro CT image stacks as previously described.¹⁰ Of 64 stones scanned, 12 were discarded because of small size (<5 mm average diameter calculated from volume) or because they were not brushite (such as one with low x-ray attenuation, which turned out to be nearly pure struvite).

Stones were hydrated for 4 days in degassed water and placed in plastic centrifuge tubes, spaced apart using water-soaked laboratory wipes. The centrifuge tubes were then packed in two, 10 cm diameter plastic beakers, each filled with gelatin containing iodine to mimic the x-ray attenuation of kidney tissue¹¹, and the 2 beakers were placed in a box and surrounded by bags of saline to form a body phantom. Helical CT scanning was done on a Philips Brilliance iCT 256 detector row scanner. Scans were reconstructed with thicknesses ranging from 0.67–4.2 mm. Unless otherwise specified, observations quoted in the Results were done using the scan at 120 kV, 220 mA, slice thickness 0.67 mm. Values for average CT density (in Hounsfield units) were measured using an oval region-of-interest that was completely enclosed within the outline of the stone.¹²

During the 2 days following helical CT scanning, the still-hydrated stones were broken in a Dornier Doli-50 lithotripter (power level 4, 2Hz), in a 2-mm mesh basket as previously described.⁹ Number of SWs to last fragment and number of SWs to complete comminution were counted.⁹

Fragments falling from the basket during lithotripsy were collected in a sieve placed at the bottom of the test tank, and these were kept for each stone. Fragments were dried and then examined using a stereomicroscope, looking for variation in fragment color and morphology. Fragments of different color/morphology (Figure 1) were counted in a visual field, and specimens were taken for analysis using Fourier-transform infrared spectroscopy (FT-IR). FT-IR was done using the KBr pellet method¹³ and a Bruker Alpha-T Spectrometer

(Bruker Optics, Billerica, MA). Estimates of mineral content from FT-IR results were combined with fragment counts to calculate percentage brushite content for each stone.

Statistics

Data were analyzed using t-tests, analysis of variance, Tukey-Kramer HSD test, and linear regression as appropriate. Software used was JMP 7 (SAS, Cary, NC). Kappa statistic was calculated after the method of Fleiss.¹⁴

Results

The brushite stones required substantial numbers of SWs (736 ± 344 SWs to last fragment/g; equivalent to 2679 SWs for a 1.5 cm spherical brushite stone) for breakage, and analysis of variance was calculated both for SWs to last fragment⁹ and for SWs to complete comminution, taking into account the independent variables of stone weight, stone volume, stone density, brushite content, and Hounsfield unit values from the helical CT results (Table 1). Stone weights ranged from 0.15 to 1.95 g, and averaged 0.60 ± 0.44 g. Stone volumes, measured from the micro CT scans, averaged 0.29 ± 0.21 mL; treating each stone as a sphere, these volumes reflected average diameters ranging from 5.2 to 12.0 mm. Stone density averaged 2.06 ± 0.10 g/mL, ranging from 1.78 to 2.24 g/mL. Brushite content averaged $85 \pm 20\%$, with 4 of the 52 stones showing brushite content less than 50%.

Weight and volume accounted for the greatest variance in numbers of SWs to breakage (Table 1); that is, breakage was related mainly to stone size. There was little difference in the results (Table 1) for SWs to last fragment compared to SWs to completion; thus, in this study there did not appear to be a significant 'last fragment' effect such as has been observed to inconsistently skew data toward higher numbers of SWs.⁹ On average, a stone required an additional $11 \pm 10\%$ more SWs to get the last fragment through the holding mesh. Nevertheless, SWs to last fragment⁹ was used for all of the following results, as the total error for analyses using this measure was lower than for SWs to complete comminution. Still, the results were substantially the same in every case using either measure of stone fragility, SWs to last fragment or SWs to complete passage through the mesh. In addition, we normalized SWs to stone weight to control for stone size.

Using weight-normalized values for SW fragility, SWs were positively correlated both with brushite content ($P=0.0006$) and stone density ($P=0.0007$), but not with average Hounsfield unit value of stone scans ($P=0.84$). Binning the data into pure brushite stones ($>95\%$ brushite) and less pure stones separated the stones into groups that differed significantly in SW fragility (Figure 2). However, these same groups did not differ in stone density (2.09 ± 0.07 g/mL for pure brushite stones, versus 2.05 ± 0.11 for stones less pure, $P=0.09$) or in Hounsfield unit values (1944 ± 221 for pure brushite stones versus 2031 ± 222 for stones less pure, $P=0.19$).

The lack of correlation of stone fragility with Hounsfield unit values is probably explained by the fact that impure brushite stones may include apatite, which would raise the CT number, or contain other materials that would lower the value (Figure 3). Indeed, among stones with $>90\%$ brushite was the stone with the highest Hounsfield unit value (2336) and the lowest value (1407). Thus, Hounsfield unit value is not a marker for purity in brushite stones, and likewise is not predictive for SW fragility.

The qualitative appearance of these brushite stones in helical CT was assessed independently by four viewers, each blind to the results of the SW lithotripsy. Each viewer was instructed to classify each stone as to whether or not it showed visible internal structure on CT. Viewers were free to alter windows and levels during viewing, and were able to go

through the slices of each stone as many times as they wanted. In general, stones identified as having structure on helical CT were more likely to break with fewer numbers of SWs. A two-way ANOVA comparing CT readings with SWs to last fragment showed no effect for which viewer did the reading of CT-visible structure ($P=0.89$), but did disclose a significant effect of whether or not the stone was seen to have structure ($P=0.004$). However, viewers disagreed on the visibility of stone structure by CT in the majority of the stones (as discussed further below) such that visibility of stone structure was overall a poor predictor of stone fragility. Using the mean for all stones (736 SW/g) as a cut-off value, CT-visible structure indicated easier-to-break stones with a sensitivity of only 0.62, a specificity of 0.51, and an overall area under the receiver operating characteristic (ROC) curve of 0.64.

Identification of a stone as having CT-visible structure did correlate with the stone being <95% pure brushite, with pure stones being identified as having visible structure only 22% of the time, while less-pure stones were seen to have visible structure in 46% of the viewer identifications ($P=0.0007$ by chi-square test). However, that still means that most of the less-pure brushite stones did not show visible internal structure on CT, even though it was, in general, the less-pure stones that were easier to break. Analyzing these data by logistic fit yielded an area under ROC of 0.68.

Analysis of overall viewer agreement using the kappa statistic yielded a value of $\kappa=0.30$, which indicates only a fair degree of agreement between observers.¹⁵ Discrimination was improved only a little by eliminating the least experienced of the four viewers, with $\kappa=0.38$ for agreement among the three more experienced CT viewers.

Using a t-test, as has been done previously^{8,9} to compare stones seen consistently as having CT-visible structure with those that did not, showed no significant difference ($P=0.053$). However, the numbers for this test were low, as 15 stones were classified by all viewers as showing no structure, while only 7 stones were classified by all viewers as having CT-visible structure. That is, in 30 of the 52 brushite stones, viewers disagreed as to the visibility of structure on CT. Overall, this suggests that identification of CT-visible structure in brushite stones is more subtle than with other stone types.

Discussion

Brushite stone disease is especially difficult to manage, as the stones tend to grow at a fast rate, making their removal necessary and frequent, but the stones also tend to be large and physically very hard, making them difficult to remove.¹ These stones also tend to be mixed in mineral composition¹⁶; in the present study, brushite stone purity averaged $85\pm 20\%$, with only 10% of the samples being 100% brushite, even though the samples were selected initially by analysis of being 90% brushite. The four stones with brushite <50% show that, even though the patient sample was initially analyzed as being 90% brushite, another piece or another stone in the patient sample can show a very different composition.

The method of stone analysis used in the present study is unique, and was made possible by the fact that the brushite stones tended to break in the lithotripter into fragments of roughly similar size, as shown in Figure 1A. By examining these fragments with a stereomicroscope, it was relatively easy to identify fragments that looked different from the fragments of pure brushite, which typically are bundles of long crystals.

This analysis showed clearly that brushite stones are harder to break when they are pure in composition (Figure 2). Unfortunately, purity in brushite stones did not correlate with x-ray absorption (HU value), probably because the impurity in brushite stones can either raise or lower the HU value (Figure 3). Even relatively pure brushite stones showed a large variability in CT density, and impure stones had Hounsfield unit values with a similar range

as pure stones. This variability would not, however, completely rule out the use of Hounsfield units in low-resolution CT for identifying fragile stones, as in that mode low attenuation values could correlate with small size in brushite stones, as it does for any stone type.¹⁷

But Hounsfield unit values are not the only way that CT can provide information about stone fragility. In studies of calcium oxalate monohydrate stones⁹ and cystine stones,⁸ both required lower numbers of SWs for breakage when structure was visible in the stones by CT. A similar trend was seen in the present study for brushite stones. However, the overall results of multiple viewers of the CT scans suggest that, with a specificity of only 0.51, viewing structure in brushite stones by CT will likely be of little help in identifying those stones that would be either sensitive or resistant to lithotripter SWs.

It is also not possible, at the present time, to accurately distinguish brushite stones from other types by non-invasive imaging. Even using dual-energy CT—which is the best method presently available for identifying stone composition in a patient before treatment—brushite stones cannot be separated from stones composed of calcium oxalate.¹⁸ However, the vast majority of brushite stone patients form stones recurrently, so many of these patients can be expected to have brushite stones because of their history.¹

One weakness of the present study is that morphological differences among brushite stones was not assessed as a variable. Brushite stones have been described as occurring in two morphologies: one with long crystals radiating out in fan clusters, and the other with crystals packed very tightly.¹⁰ It seems reasonable that the more compact form would be especially resistant to breakage by SWs, but these different morphologies are not distinguishable explicitly by helical CT. However, one might also expect that such morphological differences could show up in the identification by CT of ‘structure’ or ‘no structure’ in the stones, and this identification did not correlate well with stone fragility.

Overall, the results of the present study confirm that brushite stones are difficult to break by SW lithotripsy and that brushite in stones is often mixed with other mineral.^{1, 3} The frequent appearance of other mineral types along with brushite, combined with the observation of an increasing proportion of stone patients having brushite stones, has led to the hypothesis that some stone patients can undergo transformation in the type of stones they form. That is, some patients with a history of forming other types of stone mineral may progress to forming brushite stones.^{19, 20} It has been suggested that the kidney injury caused by SW lithotripsy could induce this transformation to the formation of brushite stones.²⁰ It is far from certain that there is a real connection between SW injury and induction of brushite stone formation, and there are no data on whether further SW injury might worsen brushite stone disease. Nevertheless, it might be wise to avoid SW treatment of known brushite stone patients, both because the chances of successful treatment are small,³ and to avoid possible exacerbation of their stone disease.

Acknowledgments

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Figure 1.

Analysis of stone fragments broken in vitro by shock wave lithotripsy. **A:** Close-up image of fragments; all of the fragments of this stone together covered the bottom of a 5 cm dish. Fragments were classified by color and morphology for determination of total composition of the stone. **B:** Infrared (FT-IR) spectrum of a fragment such as those marked 'B' in panel A above; these fragments were ivory in color and often showed long crystals packed tightly together. Spectrum is that of pure brushite. **C:** Spectrum from fragment marked 'C' in panel A; these fragments were dark brown, sometimes with short white crystals on their surface. Spectrum shows brushite with substantial amount of calcium oxalate (CaOx, mix of

monohydrate and dihydrate; arrowheads mark CaOx peaks of ~1625, 1316, and 781 cm^{-1} .) Black arrow near bottom of panel A indicates the third type of fragment seen in this stone, which was ivory with a cap of yellow-brown; by FT-IR these fragments were brushite with a trace of CaOx. By counting the numbers of these fragment types in a larger field (not shown), the brushite content of this stone was estimated to be 95%.

Figure 2.

Separating brushite stones by purity showed that the purer stones were significantly harder to break with lithotripter shock waves (SWs) than were the stones with lower brushite content. This relationship was also significant when analyzed by regression of SWs to breakage against brushite content of the stones ($P < 0.001$), with a slope suggesting that each increment of 1% brushite content required an additional 8 SW/g for breakage.

A. Pure, solid brushite; median for all stones was 1690 HU

B. Pure brushite with voids (arrows in micro CT image) has lower HU

C. Less pure brushite with apatite (arrowheads) has higher HU

Figure 3.

Representative examples of brushite stones used in this study. Left column shows photo on millimeter grid paper. Center column shows micro CT slice (scanned using 14 μm voxels for A and C, 18 μm for B). Right column shows helical CT slice with measured CT number (Hounsfield unit value, HU). **A.** Solid brushite stone, showing relatively high CT number. **B.** Pure brushite stone that showed a lower CT number, apparently because of the presence of voids in the stone (arrows). **C.** Stone with minor content of apatite that results in a higher CT number.

Table 1

Numbers of shock waves (SWs) to breakage for 52 brushite stones, with results of multiple variable analysis of variance (_{ANOVA})

	SWs to last fragment	SWs to completion
Mean $\pm$ standard deviation	403 $\pm$ 303	446 $\pm$ 330
Median (range)	329 (44–1719)	367 (44–1864)
Overall _{ANOVA} result	$P<0.0001^*$	$P<0.0001^*$
Stone weight	$P=0.0002^*$	$P=0.0007^*$
Stone volume	$P=0.0007^*$	$P=0.0018^*$
Stone density	$P=0.95$	$P=0.79$
Brushite content	$P=0.58$	$P=0.54$
Hounsfield unit value	$P=0.90$	$P=0.96$

P values for the overall _{ANOVA} result indicate the probability that the results would be found by chance, if indeed the variables of weight, volume, density, brushite content and Hounsfield unit value all have no relationship to the SWs needed for comminution. *P* values for individual variables indicate the same for that variable; for example, for stone weight the *P* value gives the probability that these results would be found if indeed the weight of the stones has no relationship to the SWs required for breakage.

* Less than the nominal alpha of 0.05.