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ORIGINAL PAPER

Prediction of calcium level in melamine-related urinary calculi with helical CT: diagnostic performance evaluation and clinical significance

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Abstract The aim of the study was to investigate the relationship between CT-attenuation and stone calcium level in melamine-related urinary calculi (MRUC). A total of 25 MRUC with known composition and calcium level were included (11 uric acid stones, 2 calcium oxalate stones and 12 mixture stones of uric acid and calcium oxalate). Of all, 18 renal stones accepted alkalization therapy except for 5 lower urinary tract stones and 2 stones of unknown position. With well-matched composition, 61 adult urinary stones were included as controls. Every stone was scanned by helical CT (80 kV/120 kV, 300 mA, pitch 0.625 mm) and the highest CT-attenuation value measured. CT-attenuation values of MRUC increased gradually from uric acid stones, mixture stones to calcium oxalate stones, but were always lower than the values of controls. Furthermore, a strong positive correlation was found between stone CT-attenuation value and stone calcium level ($n = 25$, $r_{80kV} = 0.883$, $p = 0.000$; $r_{120kV} = 0.855$, $p = 0.000$). Compared with alkalization-therapy-alone group, stone CT-attenuation values and stone calcium level in the comprehensive-therapy group were significantly greater (CT_{80kV} 1,057 ± 639 vs. 172 ± 61 HU, $p = 0.001$; CT_{120kV} 783 ± 476 vs. 162 ± 60 HU, $p = 0.001$; Ca 19.83 ± 7.48% vs. 1.30 ± 1.51%, $p = 0.000$). Fisher's exact test suggested that the stones with higher CT-attenuation values tended to resist alkalization when 400 HU served as the cutoff value ($P_{80kV} = 0.002$, $P_{120kV} = 0.000$). In conclusion, the study was the first to illustrate that the CT-attenuation value could reflect calcium level in MRUC and found that stones with higher CT-attenuation value were not amenable to alkalization because they probably contained greater calcium. For those patients, we believe that comprehensive therapy will be the best choice.

Keywords Calcium · Melamine · Renal stone · Uric acid · Computed tomography

Introduction

Since the outbreak of childhood urinary stones induced by melamine-tainted milk powder in September 2008, this disease has drawn a lot of public attention. As previously reported, urine alkalization was considered as the first treatment choice for melamine-related urinary calculi (MRUC), because it was mainly composed of uric acid. Most of the MRUC were soft, loose and sand-like. Then, it was likely passed out with urine after alkalization therapy [1–4]. However, in our previous study, we found composition changes in MRUC (primarily, occurrence of calcium crystals) and not all stones were sensitive to urine alkalization [5, 6]. Those higher calcium level stones often failed to dissolve by urine alkalization. Also, most of them failed to fracture by extracorporeal shock wave lithotripsy (ESWL) and had to be removed by percutaneous nephrolithotripsy (PNL). Therefore, evaluation of stone calcium

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level in MRUC pretreatment is valuable and will benefit the doctor's decision making.

Compared with adult urinary stones, the composition in MRUC is single and simpler despite calcium crystals increasing gradually with the stone's remaining time in the body. Uric acid stones contain light chemical elements (H 1, C 6, N 7, O 8), but stones containing calcium have heavy elements (Ca 20, S 16, P 15). The X-ray attenuation of chemical compositions depends on their density, atomic number and energy (X-ray spectrum) of the penetrating beam. The energy dependency of the attenuation is linked to the atomic number; with increasing atomic numbers of the penetrated chemical elements, the energy dependency of the attenuation also increases. In addition, X-ray attenuation properties in uric acid stones at high and low kVp are very different compared with those in calcium-containing stones [7, 8]. Therefore, stone's highest CT-attenuation probably reflects stone calcium level in MRUC. So far, no studies have been conducted on this issue.

Materials and methods

A total of 25 MRUC with known composition (by Fourier transform infrared spectra) and stone calcium level (by flame atomic absorption spectrum) were obtained from our stone analysis laboratory (11 uric acid stones, 2 calcium oxalate stones and 12 mixture stones of uric acid and calcium oxalate). Of the 25 stones, 3 were urethral, 2 were bladder and 18 were renal stones; the position of 2 stones was unknown. The lower urinary tract stones were removed immediately after definitive diagnosis. The renal stones received alkalization therapy. According to the effect of alkalization therapy, they were stratified into two groups: alkalization-therapy-alone group ($n = 9$) and comprehensive-therapy group ($n = 9$). In the former group, all the stones passed out with urine after alkalization therapy. In the latter group, ESWL or/and PNL were adopted in addition to alkalization therapy. Of those nine stones, one was fractured by ESWL and one by lithodialysis via endoscopy, and seven were removed by PNL after failure with ESWL. In addition, a total of 61 adult urinary stones were included as controls (3 uric acid stones, 3 mixture stones and 55 calcium oxalate stones).

The intact stone was hydrated with water and placed in a water-filled 1.5-ml Eppendorf tube. The tubes were fixed in water-filled 96-well microtube racks. All the stones were scanned separately by the same 16-detector single-energy spiral CT (GE, Lightspeed 16) with dual kilovolts setting (80/120 kV, 300 mA, pitch 0.625 mm.) The highest CT-attenuation value of each stone was measured by methods of region of interest (ROI). Each value was measured at least three times and the mean CT-attenuation value recorded.

Statistical analysis

Statistical analysis was performed by SPPSS16.0. Independent t tests were used to analyze CT-attenuation value of uric acid stones, mixture stones and calcium oxalate stones between MRUC and controls, respectively. They were also used to analyze stone CT-attenuation value and stone calcium level between alkalization-therapy-alone group and comprehensive-therapy group. Pearson analysis was used to evaluate the relationship between stone CT-attenuation value at 80 and 120 kV in MRUC, and between stone CT-attenuation value and stone calcium level in MRUC along with regression analysis. Fisher's exact test was used to analyze the relationship between stone CT-attenuation value and treatment modalities.

Results

Stone CT-attenuation value

The 3D image (0.625-mm slices) was easily obtained with water as background. At 80 kV, the stone CT-attenuation value ranged from 80 to 2,001 HU in MRUC and 221 to 2,680 HU in controls. At 120 kV, it ranged from 55 to 1,461 HU in MRUC and 161 to 1,944 HU in controls. From uric acid stones, mixture stones, to calcium oxalate stones, stone CT-attenuation values increased gradually either in MRUC or in controls. Compared with controls, CT-attenuation values of MRUC were always lower (Fig. 1). In addition, stone CT-attenuation values and stone calcium level in the comprehensive-therapy group were significantly higher than those in the alkalization-therapy-alone group (CT_{80kV} 1,057 ± 639 vs. 172 ± 61 HU, $p = 0.001$; CT_{120kV} 783 ± 476 vs. 162 ± 60 HU, $p = 0.001$; Ca 19.83 ± 7.48% vs. 1.30 ± 1.51%, $p = 0.000$, Fig. 2). However, complete data of CT-attenuation values in vivo and in vitro were only available for one stone (from the same CT-scanner). This stone was composed of uric acid and passed out with urine after alkalization therapy alone ($CT_{\text{in vitro-80kV}} = 122$ HU, $CT_{\text{in vitro-120kV}} = 120$ HU, $CT_{\text{in vivo-120kV}} = 86$ HU, stone calcium level 0.80%).

Relationships between stone CT-attenuation value and stone calcium level, and treatment modalities

A strong positive correlation was found between stone CT-attenuation value and stone calcium level in MRUC ($r_{80kV} = 0.883$, $p = 0.000$; $r_{120kV} = 0.855$, $p = 0.000$, Fig. 3). Moreover, a significant correlation was found between CT-attenuation value at 80 and 120 kV ($r = 0.995$, $p = 0.000$). Compared with 120 kV, the predictive ability of CT-attenuation value at 80 kV for stone

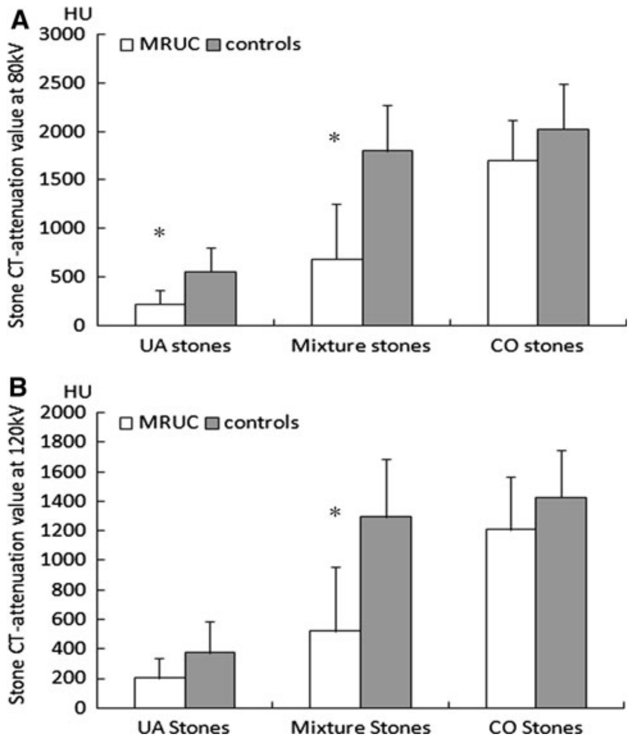

Fig. 1 Stone CT-attenuation value. **a** 80 kV. **b** 120 kV. Compared with controls, CT-attenuation values in three different MRUC composition groups were lower (at 80 kV, $P_{UA} = 0.035$, $P_{mixure} = 0.341$, $P_{CO} = 0.008$; at 120 kV, $P_{UA} = 0.109$, $P_{mixure} = 0.015$, $P_{CO} = 0.349$). *UA* uric acid, *CO* calcium oxalate. $^{*}p < 0.05$, $^{**}p < 0.001$

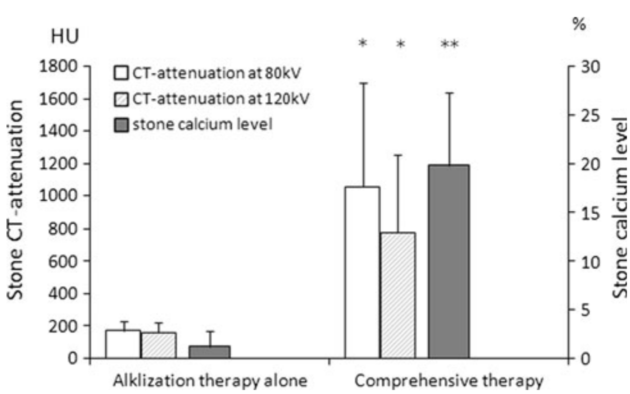

Fig. 2 Compared to alkalization-therapy-alone group, stone CT-attenuation value and stone calcium level in comprehensive-therapy group was significantly higher (CT_{80kV} 1,057 ± 638 vs. 172 ± 61 HU, $p = 0.003$; CT_{120kV} 783 ± 476 vs. 172 ± 61 HU, $p = 0.004$; Ca 19.83 ± 7.48% vs. 1.30 ± 1.51%, $p = 0.000$). $^{*}p < 0.05$, $^{**}p < 0.001$

calcium level was better (adjusted $R^2_{80kV} = 0.770$, adjusted $R^2_{120kV} = 0.719$). In addition, Fisher's exact test suggested that higher CT-attenuation stones tended to need comprehensive therapy when 400 HU served as the cutoff value ($P_{80kV} = 0.002$, $P_{120kV} = 0.000$, Table 1).

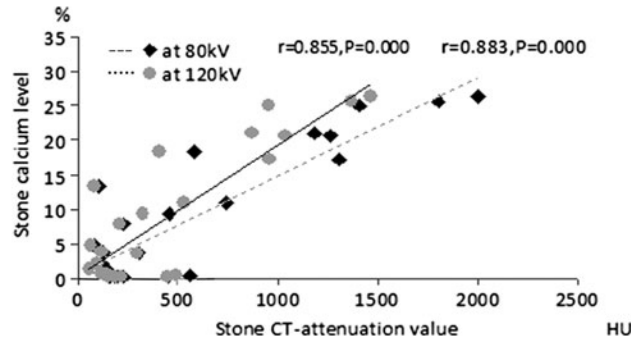

Fig. 3 The positive correlation between stone CT-attenuation value and stone calcium level in MRUC ($r_{80kV} = 0.883$, $p = 0.000$; $r_{120kV} = 0.855$, $p = 0.000$)

Discussion

Most of uric acid stones are radiolucent on abdominal radiographs; then, CT has special importance in the evaluation of uric acid stones though urinary stones are heterogeneous in density [9, 10]. In reports, uric acid stones have values of 200–400 HU at 120 kV in vivo and calcium oxalate stones have higher values [11]. To obtain accurate data on urinary stone's CT-attenuation value, many different measurement methods have been recorded in image analysis, such as calculating the mean of ROIs (randomly or in three vertical pixels) or developing automated image processing software [12, 13]. Brian et al. [13] performed a test to compare urinary stone's CT-attenuation value in three different measurement methods and obtained similar results with significant difference. Of all the different kinds of methods, some indeed can capture significant difference but they are complex, tedious and difficult to apply in routine clinical CT scan. In the present study, therefore, we adopted a relatively large ROI to as closely approximate a clinical protocol as possible. As expected, CT-attenuation value of MRUC increased gradually from uric acid stones, mixtures stones, to calcium oxalate stones, but were always lower than the values of controls (Fig. 1).

In routine abdominal CT scan, regardless of in vitro or in vivo, uric acids stones have 200–400 HU in vivo [11] and rarely exceeded 700 HU (Table 2). On the basis of the syllogistic reasoning: $a < b$ and $b < c$ then $a < c$, we deduced that the stones with CT-attenuation values in vivo >700 HU MRUC probably contained more than 10.28% calcium level. The reasons were as follows: first, the CT-attenuation value of stones in vivo (a) should be lower than those in vitro (b) due to absorption of skeleton, muscle and tissues though the detailed difference in the CT-attenuation value between in vitro and in vivo for the same voltage is unknown. Second, our results suggested that CT-attenuation value in vitro of uric acid stones, mixtures stones and calcium oxalate stones in MRUC

Table 1 The relationships between stone CT-attenuation value and treatment modalities

	At 80 kV		At 120 kV	
Treatment modalities	<400 HU	>400 HU	<400 HU	>400 HU
Alkalization therapy alone	9/10 (90%)	0/8 (0%)	9/11 (82%)	0/7 (0%)
Comprehensive therapy	1/10 (10%)	8/8 (100%)	2/11 (18%)	7/7 (100%)
Fisher's exact test *p* values	0.000		0.002	

Table 2 CT-attenuation values of uric acid stones in other studies

Studies	Values at 80 kV	Values at 120 kV	Values at 140 kV
1. In vivo [8]			
UA ($n = 3$)	–	439 ± 70	–
COM ($n = 11$)	–	795 ± 180	–
CON ($n = 7$)	–	844 ± 173	–
2. In vivo [11]			
UA ($n = 17$)	–	344 ± 153	–
CO ($n = 82$)	–	652 ± 490	–
3. In a tissue phantom [13]			
UA[a]	344 ± 57	–	321 ± 68
CO[a]	895 ± 350	–	620 ± 240
4. In a jelly phantom [14]			
UA ($n = 38$)	417 (350–484)	437 (392–482)	–
COM ($n = 63$)	1,307 (1,190–1,424)	797 (703–891)	–
CON ($n = 35$)	1,341 (1,235–1,547)	1,017 (816–1,218)	–
5. Ex vivo [15]			
UA ($n = 3$)	154	–	174
COM ($n = 2$)	1,549	–	908
CON ($n = 4$)	1,726	–	920

Values are mean ± SD in study 1–3, mean (95%CI) in study 4 and mean in study 5

UA uric acid stones, *COM* calcium oxalate monohydrate stones, *CON* calcium oxalate dehydrate stones, *CO* calcium oxalate stones

'–' represents none

[a] Case numbers not mentioned

(b) were lower than those in controls (c), respectively (Fig. 1). Third, according to the positive correlation between stone CT-attenuation value and stone calcium level in MRUC and the evidence that urinary stone's CT-attenuation values decreased as X-ray energy levels increased [13], we found that the CT-attenuation value equal to 700 HU stone's calcium level was about 10.28% at 80 kV and 13.50% at 120 kV, respectively ($r_{80\mathrm{kV}} = 0.883$, $p = 0.000$; $r_{120\mathrm{kV}} = 0.855$, $p = 0.000$, Fig. 3).

Compared with the alkalization-therapy-alone group, stone CT-attenuation values and stone calcium level in the comprehensive therapy were significant greater, respectively ($\mathrm{CT}_{80\mathrm{kV}}$ 1,057 ± 639 vs. 172 ± 61 HU, $p = 0.001$; $\mathrm{CT}_{120\mathrm{kV}}$ 783 ± 476 vs. 162 ± 60 HU, $p = 0.001$; stone calcium level 19.83 ± 7.48% vs. 1.30 ± 1.51%, $p = 0.000$, Fig. 2). Considering the correlation between stone CT-attenuation value and stone calcium level (Fig. 3), we consider 400 and 700 HU can serve as references for treatment choice in MRUC. That is to say, CT-attenuation value >700 HU stones will be probably resistant to alkalization therapy alone and need comprehensive therapy. In our experience, they often resist urine alkalization and ESWL, and surgical intervention is the best treatment of choice. On the contrary, CT-attenuation value <400 HU stones will be probably dissolved by alkalization therapy alone. In fact, all easily treated MRUC by alkalization alone in the present study were <400 HU (Fig. 2). The presumption was supported, as we obtained one stone with complete data of CT-attenuation values in vivo and in vitro. The stone was composed of uric acid and passed out with urine after alkalization therapy alone ($\mathrm{CT}_{\mathrm{in\ vitro\text{-}80kV}} = 122$ HU, $\mathrm{CT}_{\mathrm{in\ vitro\text{-}120kV}} = 120$ HU, $\mathrm{CT}_{\mathrm{in\ vivo\text{-}120kV}} = 86$ HU, stone calcium level 0.80%). Also, Fisher's exact test suggested that higher CT-attenuation value stones tended to need comprehensive therapy ($P_{80\mathrm{kV}} = 0.002$, $P_{120\mathrm{kV}} = 0.000$, Table 1) when 400 HU served as the cutoff value. Therefore, stones between 400 and 700 HU were suspected of containing higher stone calcium levels.

Our study is limited by its nature of being a retrospective and small sized study. In regression analysis, sample size directly influences confidence interval (CI) of regression coefficient value, and may further influence the predictive CI of the dependant factor. In addition, MRUC enrolled in the present study ranged from 0.4 to 1.7 cm in size. It means not all data of stone calcium level may reflect the highest calcium level in MRUC accurately due to stone heterogeneity. In spite of this, the trend between stone CT-attenuation value and stone calcium level is obvious and significant (Fig. 3).

Routine abdominal CT scans are often performed with 120 or 140 kV. In the present study, the ability of predicting calcium level in MRUC using CT-attenuation values at 80 kV was better than that at 120 kV, similar to previous studies that had reported the diagnostic ability of CT in uric acid stones [14, 15]. In addition, single-energy CT with low-dose protocols also can detect non-urinary tract-related disorders with high sensitivities compared with standard dose-unenhanced CT [16–18]. On the basis of those evidences, we believe that utilizing low kilovolts in clinical CT scan setting will be enough for children to evaluate urinary tract- and non-urinary tract-related disorders.

In conclusion, the study is the first to illustrate the significance of CT-attenuation value for MRUC in diagnostic performance evaluation. The stones with higher CT-attenuation values are not amenable to alkalization, because they probably contain greater calcium. For those patients, we believe that comprehensive therapy will be the best choice.

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