Long-Term Treatment with Potassium Citrate and Renal Stones in Medullary Sponge Kidney

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Background and objectives: Medullary sponge kidney (MSK) is a renal malformation typically associated with nephrocalcinosis and recurrent calcium stones. Incomplete distal renal tubular acidosis, hypocitraturia, and hypercalcitiuria are common. For stone prevention, patients with MSK generally receive the standard “stone clinic” recommendations and often receive potassium citrate (KC). However, the effect on stone recurrence of citrate treatment in these patients has never been studied.

Design, setting, participants, & measurements: The issue was retrospectively analyzed on an outpatient basis in 97 patients with a radiologic diagnosis of MSK: 65 had at least one stone risk factor (SRF; hypercalciuria, hypocitraturia, hyperuricosuria, hyperoxaluria) and received KC [29 ± 8 (SD) mEq/d]; 10 patients with SRF and 22 without received only general stone clinic suggestions. Follow-up was 78 ± 13, 72 ± 15, and 83 ± 14 months, respectively. The 24-hour urinary excretion of calcium, oxalate, uric acid, citrate, and morning urine pH were investigated at baseline and at the end of follow-up.

Results: Parallel to a significant rise in urinary citrate and decreased urinary calcium (all P < 0.001), KC led to a dramatic reduction in the stone event rate (from 0.58 to 0.10 stones/yr per patient). The existence of a group of patients with MSK, those without SRF, with a very low stone rate and no SRF was recognized.

Conclusions: Treatment with KC is effective in preventing renal stones in the typical patient with MSK. It seems that two clinical phenotypes among patients showing typical MSK features during radiologic study exist.


Medullary sponge kidney (MSK) is a renal malformation typically associated with nephrocalcinosis and recurrent renal calcium stones. Incomplete and overt distal renal tubular acidosis (dRTA) is reportedly very frequent in patients with MSK (33 to 40% of cases) (1–4), although some have found only a 2.9% prevalence of the overt form (5). Hypercalcitiuria has also been reported frequently (30 to 50%) (6). Incomplete dRTA (idRTA), hypocitraturia, and hypercalcitiuria most likely concur with the distinctive precalcyte cystic anomalies of the Bellini ducts in triggering stone formation.

As in other clinical conditions characterized by hypercalcitiuria and/or renal tubular acidosis, patients with MSK also have reduced bone density, as we have recently shown (7).

The most common presenting clinical sign of MSK is recurrent calcium oxalate and/or phosphate nephrolithiasis. Because there is no specific treatment for renal stones in patients with MSK, they generally receive the standard measures given to any other recurrent calcium stone former, i.e., the general “stone clinic” recommendations concerning diet and water intake. Furthermore, because of the frequent observation of hypocalciuria and idRTA (1,4), they are advised to take alkali citrate, although the effect on stone recurrence of citrate treatment of patients with MSK has never been studied. In a retrospective observational analysis on a group of incident MSK cases observed at our institution and recently described (7), we analyzed renal stone disease after the introduction of oral potassium citrate (KC) therapy. Furthermore, we studied other clinical features of the disease (family history, clinical presentation, etc.). Results of the analysis are reported here, which goes hand in hand with the previously cited paper (7).

Materials and Methods

In the period 1998–2007, 12% of calcium stone formers (SFs) followed up at the Verona University Hospital’s Nephrology Division were found to have MSK. The condition was diagnosed during the work-up for recurrent calcium nephrolithiasis on the strength of classic MSK pictures at intravenous urography or uro-CT scan (8) and exclusion of other causes of nephrocalcinosis. Patients with both kidneys showing typical nephrocalcinosis and/or cystic features at papillary level in at least two papillae in each kidney were diagnosed with MSK.

Only subjects with at least 1 year of follow-up in the clinic are considered in this study; this includes 97 patients with MSK. Clinical records concerning family and personal history, particularly with reference to kidney and stone disease, urologic interventions for stones,
acute urinary tract infection with fever suggesting pyelonephritis (UTI), and symptoms in the period preceding referral and in the follow-up were analyzed.

The following laboratory tests are routinely performed in recurrent calcium SFs (including subjects with MSK) in our center: serum calcium, phosphate, sodium, potassium, chloride, magnesium, osmolality, intact molecule parathyroid hormone (PTH), bone alkaline phosphatase, creatinine clearance. Two 24-hour urine collections were obtained with a 4- to 6-week interval, following the usual diet; the mean values of the two collections were considered: volume, pH, sodium, chloride, potassium, citrate, calcium, phosphate, magnesium, uric acid, and oxalate. Whenever patient’s stones were available, they were chemically analyzed.

Hypercalciuria is defined as 24-hour urine calcium >300 mg in men and 250 mg in women; hyperuricosuria is defined as >350 mg/24 h; and hyperoxaluria is defined as >40 mg/24 h.

On a fresh morning urine spot sample (in the absence of urinary tract infections), pH was measured by a pH electrode. Blood gas analysis was performed in subjects with a morning urine pH higher than 5.5, hypokalemia (<3.5 mEq/L), and/or hypocitraturia to rule out overt dRTA. Patients showing no overt dRTA were generally not tested for idRTA.

Treatment with KC is generally recommended at our clinic for patients with MSK with at least one stone risk factor (SRF; hypercalciuria, hypocitraturia, hyperuricosuria, hyperoxaluria). A crystal preparation is suggested in two to three administrations per day; the initial dosage is 20 mEq (2 g)/d of citrate; if tolerated, the dosage is increased gradually for patients initially failing to achieve a citraturia level >450 mg/24 h, adding 10 mEq (1 g) citrate at a time until the desired citrate level is reached, provided the urine pH in a 24-hour collection is <7.5. Patients are followed up once a month until the treatment dose has been adjusted and then once every 6 months.

Among those patients with MSK with at least 1 year of follow-up in the clinic, 65 had SRF and received KC for >1 year (group A), 10 with SRF did not accept or were not compliant to the suggested treatment (group B), and 22 did not have any SRFs (group C).

All patients with MSK, irrespective of the existence of SRFs, received general stone clinic recommendations concerning diet and water intake. In particular, we advised patients to follow a balanced diet, rich in fruit and vegetables, with a daily intake of 1 g/kg proteins, 1 g calcium, and <6 g sodium chloride. At follow-up visits, patients were asked about their compliance with the suggestions and encouraged to adhere to them. None were given thiazides or allopurinol.

Events (stones, urinary tract infections, or urologic treatments) were counted in the pretreatment period and during follow-up. A stone episode was defined as the passage, or the surgical extraction or fragmentation, of a stone. Although kidney, ureters, and bladder (KUB) x-ray or renal ultrasound (US) was performed at least yearly during follow-up, we did not have access to them (only physicians’ notes, which were not precise enough to consent the implementation of the definition of stone episode with the appearance of new stones at imaging).

Bone mineral density was measured at baseline and during follow-up in a subgroup of patients with MSK with SRF (reported in ref. 1) and in 15 patients in group C using dual-energy x-ray absorptiometry (QDR 4500 fan beam densitometer with software version 8.21; Hologic, Waltham, MA).

Statistical Analyses
A statistical analysis was performed on the data obtained during the diagnostic work-up and the latest available assessments during the follow-up. Analysis was carried out with no censoring for any kind of event. To obviate the problem of statistical regression to the mean, we excluded from the analysis stone episodes that had occurred in the 6 months before ascertainment. The results are given as mean ± SD except urinary calcium and citrate, which, because of their skewed distribution, are shown as median and interquartile range (Q1, Q3). Paired and unpaired t tests, one-way ANOVA, Wilcoxon and Mann-Whitney tests, and χ² tests were used to compare data as appropriate.

Results
Demographic data and the prevalence of SRFs in the three groups are shown in Table 1. None of the patients had overt dRTA, chronic bowel diseases, or hyperparathyroidism. On average, the number of affected papillae per kidney was 5 ± 3, which was similar in all groups.

Among patients with MSK without SRFs (group C), nine (41%) had renal stones before referral. In four cases, the stone episode was complicated by a urinary tract infection. In only two subjects, the stone had recurred. In eight cases, stones had been or were available for chemical analysis (50% of them being

Table 1. Clinical characteristics of patients with/without stone risk factors at baseline

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 65)</th>
<th>Group B (n = 10)</th>
<th>Group C (n = 22)</th>
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<tbody>
<tr>
<td>Patients, n (% women)</td>
<td>65 (71)</td>
<td>10 (70)</td>
<td>22 (59)</td>
</tr>
<tr>
<td>Age, mean ± SD (years)</td>
<td>26.2 ± 9.0</td>
<td>27.7 ± 5.4</td>
<td>28.0 ± 10.1</td>
</tr>
<tr>
<td>Family history of stones, n (%)</td>
<td>44 (68)</td>
<td>7 (70)</td>
<td>9 (41)</td>
</tr>
<tr>
<td>Hypercalciuria, mg/24 h, median (Q₁, Q₃)</td>
<td>378 (338, 406)</td>
<td>325 (310, 396)</td>
<td>156 (93, 233)</td>
</tr>
<tr>
<td>Citratuira, mg/24 h, median (Q₁, Q₃)</td>
<td>65 (100)</td>
<td>10 (100)</td>
<td>433 (310, 658)</td>
</tr>
<tr>
<td>Hypocitraturia, n (%)</td>
<td>54 (83)</td>
<td>8 (80)</td>
<td></td>
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<tr>
<td>Oxaluria, mg/24 h</td>
<td>41 ± 23</td>
<td>39 ± 26</td>
<td>25 ± 6</td>
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<tr>
<td>Hyperoxaluria, n (%)</td>
<td>3 (5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Uricosuria, mg/24 h</td>
<td>562 ± 181</td>
<td>515 ± 134</td>
<td>447 ± 87</td>
</tr>
<tr>
<td>Hyperuricosuria, n (%)</td>
<td>4 (6)</td>
<td>1 (10)</td>
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</table>

*aThe data of groups A and B have been partly reported previously (7). Statistical significance between group C versus groups A and B together is shown (bP < 0.05; cP < 0.001; and dP < 0.005).
predominantly of calcium phosphate and 50% calcium oxalate). The 13 remaining subjects who did not have any stones were referred because of hematuria (4 subjects), vague loin pain or burning sensation (2 subjects), renal colic (4 subjects), or findings at an abdominal ultrasound performed for other reasons (3 subjects). During follow-up, none of them had any stone episodes. In contrast, patients with MSK with SRFs (groups A and B) were all recurrent SFs (P < 0.001 versus group C). Twenty-eight urinary tract infection episodes complicating renal stones were counted in this group before group C. Patients treated with KC received an average dose of 29 ± 8 mEq (2.9 ± 0.8 g) citrate/d; treatment was generally well tolerated without any major discomfort.

Urine laboratory findings at baseline and at the end of follow-up are shown in Table 2. In group A, compared with the situation before treatment, KC therapy led to a 50% decrease in calcium and a rise in citrate (75%) and potassium. The increase in the latter by a mean of 26 mEq/d confirms good patient compliance with the treatment. During the treatment, diuresis increased (almost 200 ml/d) and sodium excretion decreased by 17%, suggesting patient compliance with the general recommendations. In groups B and C, followed only under the stone clinic regimen, a significant increase in urinary volume (~300 ml/d) and a slight, albeit nonsignificant reduction in urinary sodium (~20 and 15%, respectively) confirmed compliance with the treatment.

At KUB x-ray or renal US monitoring (performed yearly), physicians’ notes did not mention any noteworthy change in the burden of nephrocalcinosis during citrate therapy. With reference to stones, the number of stones passed decreased considerably (80%) after the establishment of KC treatment (P < 0.001), whereas it decreased marginally (not significant) in group B patients who received only the stone clinic regimen (Table 3). No reduction in stone passage was noted in group C, but the stone rate was low with respect to patients with MSK with SRFs (0.01 versus 0.58 stones/yr per patient, respectively).

Although before KC therapy only 5 (2.4%) patients with MSK needed urologic intervention (extracorporeal shock wave lithotripsy [ESWL]), and 28 urinary tract infection episodes were reported, during follow-up, no ESWL was needed and only 9 urinary tract infection episodes occurred. In group B, no ESWL or urinary tract infections were reported either before or during follow-up. In group C, 4 and 1 were the UTI episodes, and patients needed 2 and 0 ESWL, before and during follow-up, respectively. No formal statistical analysis was performed on ESWL or urinary tract infection episodes because of their low numbers.

In group C, total vertebral (L1–L4) T-score was 0.32 ± 0.47 at baseline and −0.22 ± 0.6 at the end of follow-up; total vertebral (L1–L4) Z-score was −0.73 ± 1.61 and 0.53 ± 1.37, respectively; all were in the normal range, without any significant variation. The same parameters were decreased at baseline in groups A and B and improved in group A after citrate treatment (7).

### Discussion
MSK is frequently found in recurrent calcium SFs. About 3 to 5% of renal SFs have MSK, although much larger proportions (up to 20%) have also been reported (6). Differences are probably because of the intensity of study, the interpretation of papillary “blush,” and the selection of the case population (9). It was discovered in 12% of our patients. However, the stone disease in this condition has not been thoroughly described. This retrospective analysis has two main outcomes: first, one fourth of patients with MSK have an indolent clinical presentation and their history is not dominated by stones; second, KC

| Table 2. Urine parameters before and after at least 12 months of treatment |
|-----------------|-----------------|-----------------|
|                 | Group A (n = 65) | Group B (n = 10) | Group C (n = 22) |
|                 | Before          | After           | Before          | After           | Before          | After           |
| Volume (ml/24 h)| 2150 ± 231      | 2319 ± 401b     | 1950 ± 279b     | 2245 ± 251b     | 1650 ± 130b     | 1930 ± 210b     |
| Calcium (mg/24 h)| 378 (338, 406) | 178 (128, 235)  | 325 (310, 396)  | 331 (312, 401)  | 156 (93, 233)   | 178 (110, 242)  |
| Potassium (mEq/24 h)| 63 ± 24       | 89 ± 28d      | 66 ± 28        | 75 ± 21         | 61 ± 27         | 74 ± 20         |
| Sodium (mEq/24 h)| 212 ± 49       | 177 ± 65b      | 207 ± 53       | 165 ± 71        | 190 ± 71        | 165 ± 47        |
| pH              | 6.44 ± 0.33    | 6.91 ± 0.52d   | 6.23 ± 0.39    | 6.31 ± 0.30     | 5.64 ± 0.63     | 5.76 ± 0.35     |
| Citrate (mg/24 h)| 268 (196, 282) | 460 (357, 606)d | 247 (184, 278) | 251 (171, 270)  | 433 (330, 658)  | 480 (345, 590)  |
| Oxalate (mg/24 h)| 41 ± 23        | 35 ± 12        | 39 ± 26        | 38 ± 23         | 25 ± 6          | 29 ± 11         |
| Urate (mg/24 h)| 562 ± 161      | 524 ± 91       | 514 ± 161      | 520 ± 79        | 447 ± 87        | 490 ± 61        |

Group A, MSK with SRF on citrate; Group B, MSK with SRF not on citrate; Group C, MSK without SRF not on citrate. Data presented as mean ± SD except calcium and citrate presented as median (Q1, Q3).

*dThe data of this group have been previously reported in part (7).

Statistical significance compared with the baseline is shown (P < 0.01; *P < 0.05; and dP < 0.001).
Table 3. Rates of stones, infection episodes, and procedures in patients with MSK before and during follow-up in the clinic

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group A Versus B</th>
<th>Group A Versus C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>65</td>
<td>10</td>
<td>22</td>
<td></td>
<td></td>
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<tr>
<td>Recurrent stone formers</td>
<td></td>
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<tr>
<td>Duration of known disease before referral/pt (months ± SD)</td>
<td>48 ± 10</td>
<td>51 ± 9</td>
<td>37 ± 37</td>
<td>P = 0.06</td>
<td></td>
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<tr>
<td>Duration of follow-up/pt (months ± SD)</td>
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<tr>
<td>Stone rate (/pt/yr) before KC (no. of episodes ± SD)</td>
<td>0.83 ± 0.20</td>
<td>0.71 ± 0.24</td>
<td>0.02 ± 0.08</td>
<td>P = 0.09</td>
<td></td>
</tr>
<tr>
<td>Stone rate (/pt/yr) after KC (w/o index episode) (no. of episodes ± SD)</td>
<td>0.58 ± 0.18</td>
<td>0.47 ± 0.21</td>
<td>0.01 ± 0.05</td>
<td>P &lt; 0.001</td>
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<tr>
<td>Stone rate (/pt/yr) after KC (no. of episodes ± SD)</td>
<td>0.10 ± 0.08a</td>
<td>0.33 ± 0.13bc</td>
<td>0.01 ± 0.04b</td>
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</table>

Index episode was a renal stone event occurred in the 6 months before referral.

a Versus group A before KC w/o index episode, P < 0.001.
b Versus group B or group C before KC w/o index episode, both not significant, P = 0.09 and 1.00, respectively.
c Versus group A after KC, P < 0.001.

seems to be effective in reducing stone recurrences in patients with MSK.

In the mid-1990s, since MSK has generally been considered a cause of recurrent stones, we decided to treat all patients with MSK who had at least one SRF with KC. We found it appropriate to apply such a policy irrespective of the previous demonstration of recurrent stones, a criterion generally used in idiopathic calcium SFs. However, because there were no trials on the effect on renal stones in patients with MSK of this and other treatments, we decided not to treat those patients with MSK without SRFs except with the stone clinic regimen, which, however, is recommended to all SFs. KC instead of other drugs (for instance thiazides) was given because patients were generally young and quite frequently had also reduced citraturia (64% in the whole population). KC has been shown to prevent stones that are passed mainly spontaneously, a well-known notion (6).

Thus, the only criterion we considered for allocation in the two groups was urine biochemistry, that is the presence or not of SRFs; subjects in the two groups were indistinguishable in terms of the radiologic diagnosis of MSK, gender, and age. In this way, we allocated them into groups that, we have now found, behave quite differently in terms of stone disease and clinical manifestations. Only 41% of patients with MSK without SRFs had a stone episode, and the stone rate is 60 times lower than in those with SRFs. Notably, stones recur infrequently in the former group. Interestingly, family history of stones is also less frequent in the group without SRFs than in those with SRFs (41 versus 68%). In the majority of patients in group C, MSK was diagnosed because of clinical manifestations other than clear stone-related episodes (hematuria, vague loin pain, or burning sensation) or as an incidental finding in different diagnostic work-ups, such as urinary tract infections. Urinary tract infection is considered to be the second most frequent clinical problem after renal stones in patients with MSK (6). With reference to urinary tract infections, the two groups did not differ, because the rate was ~0.1 episode/yr per patient in both groups. We also observed that the group of patients with MSK without SRFs, in contrast to those with SRFs, did not have reduced bone density (7).

Our study extended over a significantly long observation period (on average, 10 years) and showed that a group of patients with MSK exists without SRFs, who have an indolent or even asymptomatic course.

Numbers do not allow us to come to any conclusion in terms of differences concerning urologic treatment of stones in the two groups. Certainly, only 2.4% of patients with MSK (as a whole) needed urologic interventions, which was ESWL in all cases. Thus, the disorder, while being very recurrent (at least in the group with SRFs), is most likely characterized by small stones that are passed mainly spontaneously, a well-known notion (6).

With reference to the prevention of renal stones in patients with MSK, thiazides and KC are suggested (6), although no trial has formally studied their usefulness. Thus, our retrospective, noncontrolled analysis addresses a medical condition virtually lacking evidence.

The change in stone disease in group A is impressive. In the single patient, the rate of stones per year decreased from a stone every 2 years (0.58) to one in 10 years (0.10). The number of urinary tract infections and ESWL also decreased.

Because hypocitraturia, an important risk condition predisposing to calcium stones, is frequently observed in patients with MSK (83% of cases in the MSK with SRF group) and KC increases citraturia as shown here, the decrease in stone recurrences is not surprising. However, a significant decrease in calcium was also observed. This is an unprecedented finding because, in our experience, it does not occur in idiopathic calcium SFs (14).

The drop in calciuria induced by treatment with KC may
derive from a higher luminal pH activating the epithelial calcium channel, TRPV5, in the distal nephron (15), although the increase in 24-hour urine pH from 6.44 to 6.91 caused by KC can be responsible for no more than a 15% reduction in calciuria. Moreover, the modest reduction in sodiuria seen in our patients (mean, 35 mEq/24 h) cannot justify the much larger drop in calciuria (200 mg/24 h), because it is generally assumed that the proximal reabsorption of 100 mEq of sodium in hypercalciuric patients drives the reabsorption of 50 mg of calcium (16). The two mechanisms together could consequently explain only 40% of the decrease in calciuria observed in our study, unless in MSK, the above tubular functions are altered, determining a different relationship with the calcium handling.

Thus, to explain such a dramatic reduction in calciuria, we recently advanced the theory that the long-term treatment with KC corrects incomplete dRTA, which we believe is quite frequent in patients with MSK with SRFs (7). Therefore, if indeed an acidification defect exists in these patients with MSK, its correction by KC should lead to a reduced calcium mobilization from bone buffering of acids, thus decreasing calciuria, which is what we observed. The reduction in hypercalciuria and the increase in hypocitraturia, both well-known renal SRFs (17,18), would prevent new lithogenesis.

We propose that, in patients with MSK, the defective acidification is the initial abnormality, which is followed by a sequence made up of defective bone mineralization, hypercalciuria, and stone formation. However, we cannot exclude that the very active renal stone disease in these patients is the primary defect, which by damaging the distal nephron, induces a defective acidification (and hypocitraturia with hypercalciuria), which by itself should fuel the stone disease. In such a setting, the primary event—stone formation—should occur because of urinary stasis in the papillary duct ectasias or some other unknown abnormality. Nevertheless, in view of the variations observed during citrate treatment, a kind of an experiment to test the hypothesis, it seems more reasonable to consider a defective renal acidification as the primary defect. In any case, whether the subtle acidosis observed in MSK is primary, our data suggest that, when established, it has a strong and very prevalent impact on bone mineralization (7) and on lithogenesis.

This study has a number of limitations, mainly because of the retrospective design. In particular, clinical records of KUB x-ray or renal US monitoring were not precise enough to allow the implementation of the definition of stone episode with the appearance of new stones at imaging. On the other hand, KUB x-ray and renal US are not sufficiently sensitive to detect small renal stones. Further limitations were the incomplete dataset concerning dual-energy x-ray absorptiometry and stone composition and the lack of a precise diagnosis of incomplete dRTA and hypercalciuria classification. However, we did the same diagnostic and therapeutic protocol in all our patients with MSK.

Results on renal stones could not be entirely caused by KC treatment; they were also caused by the stone clinic regimen. Because of the low number and nonrandom allocation of subjects in group B, we cannot precisely dissect the contribution of the stone clinic regimen. Therefore, we cannot rule out that the decrease in dietary sodium, the increase in water intake, and the increased content of vegetables and fruits in the diet contributed to the reduction in stone formation.

In conclusion, this study suggests the existence of at least two distinct clinical phenotypes among patients showing typical MSK features at radiologic investigation: (1) an indolent form, rarely characterized by stones and urinary tract infection, frequently diagnosed because of atypical signs and symptoms, possibly totally asymptomatic in some cases; the form is not associated with evident tubular dysfunction or with any bone disease; and (2) the much more prevalent typical form in which the patient manifests with many small stones that only occasionally need urologic intervention; this patient has urinary SRFs, mainly hypercalciuria and hypocitraturia, and bone disease. We proposed that the latter are patients with a defective tubular acidification (7), which could be relevant for the bone and stone disease observed in these patients. Finally, treatment with KC in combination with the stone clinic regimen seems to be effective in preventing renal stones and their complications in typical patients with MSK.

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**Disclosures**

None.

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Access to UpToDate on-line is available for additional clinical information at http://www.cjasn.org/