Evidence against a contribution of conventional urine risk factors to de novo ESRD renal stones

Nicole Stankus, Elaine Worcester, Mary Hammes and Fredric L. Coe

Section of Nephrology, Department of Medicine, University of Chicago, 5841 South Maryland Avenue MC 5100, Chicago, IL 60637, USA

Abstract

Background. The authors measured urine and blood stone risk factors in African-American (AA) haemodialysis (HD) patients with new onset of stones during dialysis.

Methods. Patients with nephrolithiasis (NL) newly manifested during dialysis were matched by age, sex and urine output and dialysis duration to AA HD patients without history or symptoms of stones. Two 24 h urine and serum samples were collected and analysed for conventional stone risk factors.

Results. Three percent of the patients formed new stones while on HD; none had formed stones prior to end-stage renal disease. Newly onset NL patients had higher urine citrate and lower serum potassium levels than HD patients without stones.

Conclusion. Usual stone risk factors did not correlate with new stones during dialysis.

Keywords: African-Americans; haemodialysis; kidney calculi; kidney failure

Introduction

Symptomatic renal calculi occur in 5–13% of all patients with end-stage renal disease (ESRD) [1] and cause morbidity and healthcare expense. Radiological evidence of calcifications in kidneys of patients with ESRD is extremely common – from 51% [2] to as high as 71% in patients with secondarily acquired renal cysts [3]. Some patients become stone formers (SF) while on renal replacement therapies, without having prior history of kidney stones, and they are the object of the present work that aims to identify urine or blood abnormalities that might cause new onset of stones. The usual mineral phase is calcium oxalate (CaOx) [4]; however, many stones are primarily composed of a mixture of proteins, known as matrix calculi, which may be partially mineralized [5]. Patients whose stones antedate ESRD may harbour stone risks apart from those arising from ESRD treatment; we exclude them here. Our specific question here is whether commonly used urine and blood stone risk factors differentiate ESRD patients with and without de novo stones during years of haemodialysis (HD) treatment.

Materials and methods

Dialysis population

The ESRD patients in the three geographically separate HD facilities of the University of Chicago arise from our emergency room and clinic populations, and are 95% AA. The units provide care for patients in the surrounding communities, and are not targets of specific referral per se. Our dialysis units contained a total of 303 AA patients. Of these, 300 (160 females) were eligible to participate (three were demented).

Interview protocol

All prevalent AA chronic patients aged 18 and older at the University of Chicago outpatient HD units, except for those with advanced dementia, were eligible to participate. A face-to-face screening questionnaire was administered by the medical director of each facility to determine presence or absence of history and symptoms consistent with stones. This was done once in each unit over several months during 2002. Specifically, patients were asked: ‘Have you ever had a kidney stone? Has a doctor ever told you that you had a kidney stone?’ Affirmative answer to either of these questions was taken to indicate a history of kidney stones. Twenty-five patients had stones prior to ESRD and are not considered here; none of these patients formed stones while on renal replacement therapy.
Subjects

Nine patients (six females) with symptomatic stones while on but not prior to starting HD were classified as ESRD stone formers (ESRD SF). Two ESRD patients with no prior history of kidney stones or symptoms suggestive for kidney stones by the administered questionnaire were matched as controls (C) to each ESRD SF by age, sex and dialysis duration. All of the ESRD SF produced urine; therefore we selected our controls from the group of ESRD patients who reported still producing urine.

Urine studies

ESRD SF and C each collected two 24 h urine samples following detailed written instructions. Patients who dialyse on a Monday, Wednesday, Friday schedule collected their urine on Sundays; patients who dialyse on a Tuesday, Thursday, Saturday schedule collected their urine on Mondays. Urine samples were delivered to the dialysis unit by the patient on Monday and Tuesday, respectively. Blood samples for biochemical analysis were collected at the start of the first HD session of the same week. Urine was analysed for volume, sodium, potassium, pH, citrate, uric acid, oxalate, calcium, magnesium, phosphorus, creatinine, ammonia, sulphate and chloride using methods previously described [6,7]. Urine supersaturation (SS) with respect to CaOx was calculated using EQUIL2 [8].

Serum studies

Serum levels of sodium, potassium, uric acid, calcium, magnesium, phosphorus, creatinine, chloride and bicarbonate were measured using previously reported methods [6,9]. Serum calcium was corrected for serum albumin: Ca (corrected) = Ca (measured) + 0.8*(4-albumin), if serum albumin level was below 4.0. Serum intact parathyroid hormone (PTH) was measured using an electrochemiluminiscence immunoassay (RocheTM) and albumin levels were measured using bromcresol green spectrophotometry (RocheTM).

Imaging studies

Non-contrast computed tomography (CT) scans using 5 mm cuts were performed on most ESRD SF with clinical symptoms as a part of standard medical care. Some patients required urological interventions, such as cystoscopies and ureteral stent placements. CT scans were reviewed and the density of the kidney stone was measured in Hounsfield units (HU) using iSite Enterprise, version 3.3.0 (by Stentor, Inc, CA, USA) radiology software programme. Measurement of the density of kidney stones on CT scan has been correlated with stone composition in several studies [10–13].

Statistical analyses

Blood and urine stone risk factors were analysed using standard t-tests, discriminant analysis for continuous outcomes and logistic regression for dichotomous outcomes. Specifically, a model of discriminant function analysis was built step-by-step by reviewing all variables at each step and determining which one will contribute most to the discrimination between groups. That variable was then included in the model. The stepwise procedure was controlled by the respective F to enter value. The F value for a variable indicates its statistical significance in the discrimination between groups, that is, it is a measure of the extent to which a variable makes a unique contribution to the prediction of group membership. Those variables with the largest (standardized) regression coefficients were the ones contributing most to the prediction of group membership (Table 2). A P-value of <0.05 was considered statistically significant. Multivariate linear modelling was performed to analyse correlates of CaOx SS. All statistical analyses were performed using standard software (SYSTAT, Systat Software Inc. Richmond, Ca). The study protocol and the informed consent were approved by the University of Chicago Institutional Review Board.

Results

Clinical characteristics of ESRD SF and C

Mean age (±SD) of the patients at the time of stone episode was 54±19 (females) and 50±5 (males). Time on dialysis of the ESRD SF (grey circles) and C (black circles) is shown in Figure 1, middle panel. Symptoms of nephrolithiasis (NL) started more than 2 years after initiation of HD in six patients and recurrent episodes occurred in three patients. Shortest time from the start of HD to the onset of renal colic was 12 months, longest was 9 years.

In ESRD SF, evidence of existing calculi was found in six patients. One of them had stone fragments and proteinaceous debris documented during cystoscopy. In five other patients, CT scans documented stones in the kidney. The HU density of these stones was between 95 and 400 (median 222 HU). This suggests that these stones are either uric acid calculi or, more likely, calculi composed of a high percentage of protein matrix which has been variably calcified, as has been reported previously in dialysis patients [1,5,14–16]. Hydro-nephrosis, consistent with a recently passed calculus, was demonstrated in the remaining three ESRD SF.

Average dose of intravenous paricalcitol in our patients was 1.9 times higher in the C compared to SF. More C (50%) were treated with calcium acetate (average dose 2.9 tablets per meal) compared to 30% of SF (one tablet per meal). Average dose of calcium carbonate was 1.3 tablets and 1.7 tablets per meal in C and cases (17% and 30% of patients, respectively). In both groups 22% of patients were on sevelamer and 11% were not taking any phosphate binders. Causes of ESRD in SF and C were similar, and distributed as follows: diabetic nephropathy in 44% vs 50%, HTN in 22% vs 17%, systemic lupus erythematosis in 22% vs none, primary glomerular nephritis in none vs 22%, interstitial nephritis in none vs 11% and HIV nephropathy in 11% vs none. Thus, proteinuric renal disease was found about equally in both SF and C.

Measurements that discriminate ESRD SF and C

Blood and urine studies were performed on nine ESRD SF and compared to the 18C subjects. Serum...
potassium was lower and urine citrate higher in ESRD SF vs C (Table 1). These differences reflect a general displacement of population values between the two groups (Figure 1, upper left and right panels). There were no differences between the groups in dialysis duration (Figure 1, middle panel) as expected from our matching protocol. Using linear discriminant analysis with stepping, serum potassium, urine citrate and duration of ESRD treatment were all entered as significant and independent variables (Table 2) with an overall correct classification of 85%; a score derived from the analysis separated the two groups (Figure 1, lower panel). Using logistic regression, urine citrate and serum potassium entered as significant (Table 2), confirming the significance of the univariate comparisons and the linear discriminant analysis.

Table 1. Laboratory findings related to stone formation

<table>
<thead>
<tr>
<th></th>
<th>Serum studies</th>
<th>Urine studies</th>
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<tbody>
<tr>
<td></td>
<td>ESRD SF</td>
<td>C</td>
</tr>
<tr>
<td>Sodium (mM/l)</td>
<td>138±3</td>
<td>138±3</td>
</tr>
<tr>
<td>Potassium (mM/l)</td>
<td>4.4±0.1</td>
<td>5.3±0.2*</td>
</tr>
<tr>
<td>Uric acid (mg/l)</td>
<td>6.9±0.6</td>
<td>6.2±0.3</td>
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<tr>
<td>Calcium (mg/l)</td>
<td>9.1±0.2</td>
<td>9.3±0.2</td>
</tr>
<tr>
<td>Magnesium (mg/l)</td>
<td>2.2±0.4</td>
<td>2.1±0.4</td>
</tr>
<tr>
<td>Phosphorus (mg/l)</td>
<td>5.0±0.3</td>
<td>4.9±0.3</td>
</tr>
<tr>
<td>Creatinine (mg/l)</td>
<td>9.5±2.7</td>
<td>10.5±3.4</td>
</tr>
<tr>
<td>Chloride (mM/l)</td>
<td>104±3</td>
<td>105±4</td>
</tr>
<tr>
<td>Bicarbonate(mM/l)</td>
<td>21±3</td>
<td>21±3</td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>104±3</td>
<td>105±4</td>
</tr>
<tr>
<td>Volume ml/24 h</td>
<td>535±142</td>
<td>440±68</td>
</tr>
<tr>
<td>Citrate (mg/l)</td>
<td>150±20</td>
<td>90±10*</td>
</tr>
<tr>
<td>SS calcium oxalate</td>
<td>3.24±1.72</td>
<td>3.26±1.91</td>
</tr>
<tr>
<td>SS calcium phosphate</td>
<td>0.32±0.22</td>
<td>0.25±0.18</td>
</tr>
<tr>
<td>SS uric acid</td>
<td>0.07±0.11</td>
<td>0.04±0.08</td>
</tr>
<tr>
<td>Ammonia (mM/l)</td>
<td>2±1</td>
<td>13±25</td>
</tr>
<tr>
<td>Oxalate (mg/l)</td>
<td>40±20</td>
<td>50±20</td>
</tr>
<tr>
<td>pH</td>
<td>7±1</td>
<td>7±1</td>
</tr>
<tr>
<td>Sulphate (mM/l)</td>
<td>23±7</td>
<td>23±10</td>
</tr>
</tbody>
</table>

SS, relative supersaturation. ESRD SF were 3 males, 6 females; C were 6 males and 12 females. Normals are 186 men and women with no known diseases. Normal values are 95% CI; other values are means±SD.

*P<0.05 ESRD SF vs C.
Amounts of protein matrix with a variable amount of mineralization; all the stones had a lower density than the reported for the usual CaOx or phosphate stones seen in ordinary SF (26). Although the density could also be consistent with uric acid stones, these seem much less likely in view of the undersaturation of the patient’s urine with respect to this mineral. Our study addresses the mineralization process for patients such as these. No prior study has reported urine stone risk factors in a group of SF on HD, compared with a group of non-SF ESRD patients.

Determinants of urine SS CaOx

Our data are consistent with the observation that CaOx is the usual mineral phase in ESRD stones, because only SS CaOx is above one (Table 1). Nonetheless, urine calcium and oxalate concentrations did not differ between SF and ESRD C (Table 1), and likewise, SS CaOx did not differ between these two groups. However, while urine calcium concentration (and daily excretion) of both ESRD groups is below that of normals, urine oxalate concentration is high compared to normal values (Table 1); this reflects a surprisingly well-preserved oxalate excretion rate coupled with the usual low urine volumes found in ESRD patients. It is the well-known very low calcium excretion and concentration values in ESRD that prevent extremely high urine SS CaOx.

In a linear multivariate model with SS CaOx as dependent and urine concentrations of calcium, oxalate, citrate, sodium, and phosphate, and stone formation as predictor variables, urine calcium and oxalate concentrations, and stone formation entered (all three P values <0.02). Adjusted means differed (2.82±0.2 vs 3.46±0.1, P = 0.014, C vs SF, respectively) whereas unadjusted values (Table 1) did not differ; this presumably reflects allowance for the higher calcium concentration of the ESRD SF vs C.

Discussion

ESRD stones can contain CaOx

Prior studies have described ESRD stones as predominantly containing calcium oxalate as their mineral phase [4][17,18]; however, these stones often contain a large amount of protein matrix as well. Oxaloprotein stones (containing more than 30% of calcium oxalate) were found in 50% of the cases by Daudon; another 30% were composed largely of protein that was more sparingly mineralized with CaOx [19]. Likewise, Cheng found a spectrum of composition with varying amounts of protein and CaOx in such stones [20]. In the study by Oren et al. [21] the ultra structural composition of five out of seven analysed stones in ESRD patients was that of CaOx. In our study, the density of the stones seen on CT scan is consistent with the presence of larger amounts of protein matrix with a variable amount of mineralization; all the stones had a lower density than that reported for the usual CaOx or phosphate stones seen in ordinary SF (26). Although the density could also be consistent with uric acid stones, these seem much less likely in view of the undersaturation of the patient’s urine with respect to this mineral. Our study addresses the mineralization process for patients such as these. No prior study has reported urine stone risk factors in a group of SF on HD, compared with a group of non-SF ESRD patients.

Increased SS CaOx is not an explanation for ESRD stones in our patients

Conventional urinary stone risk factors do not predict ESRD stone formation. SS values for CaP and UA are below one. For CaOx SS, mean values are not high compared to normal subjects (Table 1). However, mean urine oxalate concentration is above normal; in fact, if urine calcium levels were in the normal range, CaOx SS would be quite high. The high urine oxalate concentration reflects the approximate 10:1 urine to serum creatinine ratio (12 and 10, ESRD SF vs C, P, NS), the fact that oxalate is not reabsorbed by renal tubules and may be secreted, and the usual serum oxalate levels in ESRD that approximate 30–50 μM/l [22]. Although high urine oxalate concentration could well play a role in stone production, it was not higher in the ESRD SF vs C, and therefore cannot explain stones in our patients.

Higher urine calcium may be a factor in ESRD stone formation

In the only other study of urine stone risk factors in ESRD patients (who were on CAPD) [21], ESRD CaOx SF had higher urine ionic-oxalate molarities than normal subjects, but their CaOx activity product correlated with the ionic-calcium not the ionic-oxalate concentration. We did not measure oxalate ion specifically, but our data are compatible with their result in that it was urine calcium that was higher, though not to a statistically significant degree among the ESRD SF vs our ESRD C. Taking the two studies together, it is indeed possible that urine calcium may control whether CaOx mineral phases form in the kidneys. This should be tested in other populations to confirm the matter, as it could have an influence on calcium and vitamin D dosing in ESRD. Nonetheless, our SF did not receive more calcium-containing binders or more vitamin D than the non-SF ESRD C.

Urine citrate and serum potassium define ESRD SF vs C but do not explain stones

Our ESRD SF had higher urine citrate and lower serum potassium levels than C. We cannot easily link these differences to stone formation. A natural hypothesis is that ESRD SF have higher residual values for glomerular filtration. However, 24h creatinine

Table 2. Linear discriminant analysis and logistic regression

<table>
<thead>
<tr>
<th>Discriminant</th>
<th>F to enter</th>
<th>P-value</th>
<th>% correct</th>
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<tbody>
<tr>
<td>Urine citrate</td>
<td>7.2</td>
<td>0.013</td>
<td>78</td>
</tr>
<tr>
<td>Serum K</td>
<td>4.5</td>
<td>0.006</td>
<td>78</td>
</tr>
<tr>
<td>Years of HD</td>
<td>3.7</td>
<td>0.004</td>
<td>85</td>
</tr>
<tr>
<td>Logistic regression</td>
<td></td>
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</tr>
<tr>
<td>Urine citrate</td>
<td>0.028</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum K</td>
<td>0.053</td>
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</tbody>
</table>

Final X2 value for logistic regression P = 0.001.
clearances (l/d) were 5.3 for both groups. Certainly the higher urine citrate was not a cause of stones, in that citrate is actually felt to be an inhibitor of calcium stone formation [23]. We cannot presently explain the association.

The role of matrix may be important, and was not considered here

Some believe that the organic matrix component plays a major role in ESRD stone formation [19]. Protein stones may be difficult to detect by radiographic methods and they may present as recurrent episodes of hydronephrosis [24]. Various protein structures have been detected in HD stone formers, microfibrillary [5,24], amyloidal [14] among them. Japanese investigators [15] compared protein composition of these stones to the protein matrix composition of CaOx stones in non-dialysis patients and found the structural patterns to be different: in chronic HD patients (β2 microglobulin > lysozyme > albumin, serum amyloid P component (SAP), Tamm-Horsfall protein (THP) vs non-dialysis patients (albumin > lysozyme > SAP, THP). However, Watanabe et al. [16] did not detect any significant differences in urinary or serum levels of β2 microglobulin in patients with amyloidic protein calculi versus patients without urinary calculi. Our work does not address the matter of matrix, however, if CaOx mineral is to be deposited in the matrix, the driving forces are the ones we have explored here.

Our work has obvious limitations

Our analysis would have been strengthened if stone analysis was available on our patients. This work may not have been able to fully discern the causes of NL, but it does suggest that standard NL preventive measures would not be effective in an ESRD population.

Although we cannot distinguish pure or nearly pure protein—SF from ones who form CaOx stones with a variable protein content—our results suggest that CaOx containing stones do not form quite the same way in patients with renal failure as they do in patients with normal renal function, thus favouring proteinaceous matrix stone formation theory. It is also supported by the low density (under 400 HU) of CT documented stones. Use of non-contrast helical CT for assessing the chemical composition of urinary tract stones has been tested in both in vitro and in vivo settings [25,26]. CaOx stones are among the most dense, usually measuring about 650 HU or more [10].

Stone formation risk factors were originally determined in non ESRD populations [27]. The level of SS with respect to CaOx in our ESRD patients, both C and SF, is below that of normals. The ability of normal subjects to tolerate a level of SS above the thermodynamic solubility product implies the presence of inhibitors of crystallization [28,29], and these may well be lacking in ESRD. The level of SS at which mineral begins to precipitate in urine, referred to as the upper limit of metastability (ULM), is known to be lower in ordinary SF compared with normal C [30]. The ULM for CaOx was not tested in our patients, but could in fact be lower than in subjects with normal renal function, accounting for stone formation at lower levels of SS. In addition, increased urinary protein, which is often seen in chronic kidney disease, may influence the precipitation threshold, probably by lowering it, as protein debris could serve as a nidus and a matrix. We did not measure urine protein in our SF and C but a similar proportion of patients in both groups had proteinuric renal disease prior to initiation of HD.

The time of occurrence of the first stone is important in that the closer symptoms of NL are to the initiation of HD, the more likely the stone was already preformed. We had three patients who manifested stones between 1 and 2 years after the start of HD. Two of them had recurrent episodes of pain and hydronephrosis without radiological evidence of a stone, which would be consistent with protein stones. They underwent cystoscopies and proteinaceous debris was documented. The third patient had a kidney ultrasound 1 year prior to the renal colic episode, which did not demonstrate NL. He manifested symptoms 1 year after the start of HD. CT scan documented a stone that was very small and of a very low density – only 95 HU, which would also point to a protein matrix stone. Though we cannot totally exclude the pre-existence of stones prior to ESRD, we thought it to be rather less likely.

It would be interesting to compare our findings in African-American patients to other ethnic groups. It is possible that mechanisms which play a protective role in kidney stone formation in the African-American population are somehow disabled in patients on HD. Or, as our data would suggest, traditional mechanisms of stone formation do not apply to HD patients, and currently available preventive strategies therefore would not be effective.

Summary

Our studies of patients with first onset of stones during ESRD are new in that we are the first to make comprehensive stone risk measurements of such patients compared to reasonably well-chosen parallel C. Observed findings, however, are not easy to interpret. Higher urine citrate and lower serum potassium might reflect higher residual renal function that permitted stones to form. This is mere conjecture. Of importance, conventional stone risk measurements do not appear useful, and therefore are not promising in stone management of this particular population.

Conflict of interest statement. None of the authors had involvement that might raise the question of bias in the work reported or in the conclusions, implications or opinions stated.

References


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