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Adequacy of a Single 24-Hour Urine Collection for Metabolic Evaluation of Recurrent Nephrolithiasis

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Purpose: There is much debate about whether 1 or 2, 24-hour urinalyses are adequate for metabolic evaluation of stone formers. We determined whether repeat 24-hour urine collection provides information similar to that of the initial 24-hour urine collection and whether repeat collection is necessary.

Materials and Methods: We analyzed 2, 24-hour urine collections in 777 patients obtained from 2001 to 2005. Samples were collected 3 days or less apart before pharmacological intervention and analyzed elsewhere for routine stone risk profiles of urine calcium, oxalate, citrate, uric acid, sodium, potassium, magnesium, phosphorus, ammonium, chloride, urea nitrogen and creatinine.

Results: No parameters showed a statistically significant difference between 24-hour urine samples 1 and 2 when mean values were compared (pairwise t test each $p > 0.05$, range 0.06 to 0.87). Using Pearson's correlation all parameters showed positive correlation coefficients ($r = 0.68$ to 0.89, each $p < 0.0001$). The mean of individual patient differences in samples 1 and 2 were compared to 0 and 6 of 12 showed no difference ($p > 0.05$) while for the remaining 6 p value was < 0.05. The percent difference was 0.5% to 4.19% for all urinary parameters.

Conclusions: One 24-hour urine sample is sufficient for metabolic evaluation of recurrent stone disease. There is no significant difference in 12 urinary parameters between 24-hour urine samples collected within 3 days of each other. This information is useful to providers and may decrease patient inconvenience and the overall cost of metabolic stone evaluation.

Key Words: kidney, nephrolithiasis, urinalysis, hypercalciuria, metabolism

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* Financial interest and/or other relationship with Abbot Laboratories and Takeda Pharmaceuticals.

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For another article on a related topic see page 743.

ROUTINE laboratory 24-hour urine collections are part of metabolic evaluation in patients with urolithiasis.[1–5] Several groups reported that a single 24-hour urinalysis may be sufficient to assess the risk of nephrolithiasis.[6,7] However, others suggested that 2, 24-hour urinalyses may yield a greater number of specific diagnoses[8,9] and, thus, 2 are needed for metabolic evaluation.[10,11] The issue of whether 1 or 2, 24-hour urinalyses are sufficient has important implications for patient care and experience since eliminating the repeat 24-hour collection could lead to significant cost savings and decreased time spent by patient and physician. It would also increase confidence in the results of a single 24-hour urine sample.

We evaluated the variability of repeat 24-hour urinalyses in a large cohort of patients who presented for metabolic evaluation of urolithiasis. We hypothesized that there is a minimal variation between 24-hour urine samples collected within 3 days of each other and a single 24-hour urinalysis is sufficient.

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Table 1. *First and repeat 24-hour urine samples in 777 patients*

24-Hr Urinary Parameter	Mean Sample 1	Mean Sample 2	p Value (pairwise t test)	95% CI
Calcium (mg)	209.9	205.2	0.44	201.4–218.3
Oxalate (mg)	42.1	40.4	0.06	40.8–40.3
Citrate (mg)	562.6	559.8	0.87	537.8–587.4
Uric acid (gm)	0.7	0.7	0.32	0.68–0.72
Sodium (mmol)	173.2	167.5	0.14	167.7–178.7
Potassium (mmol)	67.3	66.7	0.69	65.3–69.4
Magnesium (mg)	107.3	105	0.3	104.2–110.5
Phosphorus (gm)	0.97	0.96	0.49	0.95–1.00
Ammonium (mmol)	39.7	39.3	0.65	38.4–40.9
Chloride (mmol)	167.8	162.7	0.18	162.5–173.1
Urine urea nitrogen (gm)	11.5	11.2	0.19	11.2–11.8
Creatinine (mg)	1,551	1,542	0.74	1,513–1,588

MATERIALS AND METHODS

We performed a retrospective, institutional review board approved study of 24-hour urine collection. Patients were referred to a urinary stone practice at a tertiary medical center for urolithiasis management. Sample data were obtained on all 24-hour urine collections from 2001 to 2005. Patients submitted an initial outpatient 24-hour urine collection and stone history questionnaire. A total of 1,035 patients performed 2, 24-hour urinalyses as part of the initial evaluation. Of these collections 777 were obtained within 3 days of sample 1 and included in analysis. The remaining second samples were obtained more than 3 days after sample 1 and, thus, were excluded from study. Samples were collected and analyzed elsewhere for routine stone risk profiles. Standard urinary parameters were evaluated, including sodium, calcium, citrate, creatinine, uric acid, oxalate, potassium, phosphorus, magnesium, sulfate, pH and urine volume. Calcium oxalate, calcium phosphate and uric acid supersaturation ratios were calculated using the iterative computer program EQUIL 2.

Since many patients were referred to our kidney stone center from elsewhere, they may or may not have undergone previous 24-hour urine collections, made general or specific dietary modifications or been prescribed medications to decrease recurrent stone disease. The patient questionnaire contained information on 19 clinical parameters, including family history, personal stone history and stone risk modifying medication. The Student t test was used to compare means. Pearson's correlations were calculated for each variable. Statistical analysis was done with SAS® for Windows®, version 9.2.

Individuals were divided into 2 groups for all urinary parameters except 24-hour creatinine. That was excluded since normal 24-hour creatinine is based on creatinine divided by body mass, which was unavailable. One group consisted of patients with consistent normalcy or abnormality, meaning that the 2 samples were normal or each was abnormal based on normal values at the evaluating laboratory. The other group consisted of individuals with a change in normalcy or abnormality, meaning that sample 1 was normal and sample 2 was abnormal or vice versa.

RESULTS

A total of 777 patients with recurrent stone disease met study inclusion criteria, that is they performed 2, 24-hour urine collections within a 72-hour period. None of the 12 variables studied in the 24-hour urine collection, including urine calcium, oxalate, citrate, uric acid, sodium, potassium, magnesium, phosphorus, ammonium, chloride, urine urea nitrogen and creatinine, showed a statistically significant difference between samples 1 and 2 when means were compared (pairwise t test $p > 0.05$, range 0.06 to 0.87). Table 1 lists means and p values.

Comparing correlations of the 12 variables using Pearson's correlation showed a high degree of correlation between urinalyses 1 and 2 ($r = 0.68$ to 0.89, each $p < 0.0001$). All 12 values of the 24-hour urine collection correlated for urine collection 1 and for collection 2 obtained within 3 days of collection 1. Table 2 lists individual correlation coefficients and p values.

The difference between samples 1 and 2 was also calculated in each individual and the mean was compared to 0 using Student's t test. No significant differences were noted when comparing

Table 2. *Correlation of first and repeat 24-hour urine samples in 777 patients*

24-Hr Urinary Parameter*	r
Calcium	0.81
Oxalate	0.74
Citrate	0.89
Uric acid	0.78
Sodium	0.68
Potassium	0.84
Magnesium	0.74
Phosphorus	0.76
Ammonium (mmol/day)	0.79
Chloride	0.68
Urine urea nitrogen	0.82
Creatinine	0.88

* Each $p < 0.0001$.

24-hour urinary calcium, citrate, potassium, phosphorus, ammonium and creatinine ($p > 0.05$, range 0.08 to 0.63). Significant differences were observed when comparing urinary oxalate, uric acid, sodium, magnesium, chloride and urine urea nitrogen (each $p < 0.05$, range 0.0002 to 0.04). The difference in all parameters was 0.5% to 4.19%. Table 3 lists individual means, p values and percent differences.

Patients were divided into group 1—2 samples with normal or 2 with abnormal values based on normal values at the evaluating laboratory and group 2—a change in normalcy or abnormality between the 2 samples (table 4). Patients with no change between normal and abnormal values represented 71.4% to 90.7% of the cohort depending on the parameter.

DISCUSSION

We determined whether there was inherent variability in 2, 24-hour urine collections done within 72 hours of each other in patients with urolithiasis to determine the usefulness of repeat 24-hour urinalysis for routine metabolic evaluation. All 12 variables showed no statistically significant differences between 24-hour urine collections 1 and 2 done within 3 days of each other (each $p > 0.05$). For urine oxalate analysis approached statistical significance ($p = 0.06$). However, the difference in mean urine oxalate in urinalyses 1 and 2 was less than 1.8 mg per day (less than 5%), which likely is not clinically significant, although the p value approached 0.05.

Also, all 12 variables highly correlated positively when urine collections 1 and 2 were compared (each $p < 0.0001$). Six parameters analyzed showed no difference when comparing the mean of the difference in samples 1 and 2 to 0 (each $p > 0.05$). However, urinary oxalate, uric acid, sodium, magnesium, chloride and urine urea nitrogen showed a mean sample difference of 1.73 mg, 0.01 gm, 5.68 mmol, 2.33 mg, 5.06 mmol and 0.27 gm per day, respectively ($p < 0.05$). Differences in means were less than 5% (range 0.5% to 4.19%) and no means appeared clinically significant. Thus, while these differences were statistically significant, a difference of less than 5% in 24-hour urine excretion likely does not represent a clinically significant difference, nor would it alter patient treatment.

However, urine sodium, calcium and oxalate are most likely to be affected by dietary changes, and their differences of 3.33%, 2.26% and 4.19%, respectively, may be more meaningful since dietary therapy may be directed at these parameters. As many as 9.3% to 28.3% of patients had a change in normalcy or abnormality in urinary parameters (table 4). Given the small magnitudes of the changes, these differences are unlikely to be clinically significant and may in fact reflect assay variability in at least some cases. For example, urinary oxalate has the highest percent of variance and a patient with urinary oxalate 39.9 mg per day (normal 20 to 40) in sample 1 may show 42.5 mg per day (mean 39.9 + 2 SD) in sample 2. A second 24-hour urine sample may change a urinary parameter from normal to abnormal or vice versa but the interpretation of just below or just above the threshold of normal would likely not significantly alter clinical treatment decision making. These results suggest that a second 24-hour urinalysis may be unnecessary since it is unlikely to yield different information than the first sample.

The standard in evaluating recurrent nephrolithiasis involves the collection of 2, 24-hour urine specimens with the patient on a random diet, a third 24-hour urine sample 7 days after dietary changes, and a fast and calcium load test, as originally described in 1980 by Pak et al.[12] Many groups have eliminated the fasting calcium load test from routine

Table 3. *Difference between mean first and repeat 24-hour urine sample values vs 0*

24-Hr Urinary Parameter	Mean Sample 1–2 Difference	p Value (pairwise t test)	% Variance*
Calcium (mg)	4.69	0.08	2.26
Oxalate (mg)	1.73	0.0002	4.19
Citrate (mg)	2.81	0.63	0.50
Uric acid (gm)	0.01	0.03	1.44
Sodium (mmol)	5.68	0.01	3.33
Potassium (mmol)	0.6	0.33	0.89
Magnesium (mg)	2.33	0.04	2.20
Phosphorus (gm)	0.01	0.16	1.04
Ammonium (mmol)	0.42	0.32	1.06
Chloride (mmol)	5.06	0.02	3.06
Urine urea nitrogen (gm)	0.27	0.002	2.38
Creatinine (mg)	8.66	0.34	0.56

* Sample difference/(sample 1 + sample 2)/2.

Table 4. *No change vs change in 24-hour urine sample 1 and 2 normalcy and abnormality*

Urinary Parameter	% Pts No Change	% Pts Change
Calcium	82.1	17.9
Oxalate	71.7	28.3
Citrate	85.5	14.5
Uric acid	83.4	16.6
Sodium	90.7	9.3
Potassium	78.4	21.6
Magnesium	71.4	28.6
Phosphorus	88.7	11.3
Ammonium	81.5	18.5
Chloride	85.7	14.3

evaluation.[13] There is significant controversy about whether this method is appropriate. Pietrow and Preminger discussed standards in evaluating recurrent nephrolithiasis, ultimately recommending 2, 24-hour urinalyses.[14]

In 2001 Pak et al compared 225 patients to evaluate the need for 1 or 2, 24-hour urine samples in metabolic stone disease evaluation.[7] They noted a correlation between an initial and a repeat sample for urinary calcium, uric acid, pH, total volume, sodium, potassium, creatinine and phosphorus ($r = 0.68$ to 0.93). Urine oxalate, citrate, sulfate and ammonium were compared in 26 patients with no differences ($r = 0.56$ to 0.94). They concluded that only a single 24-hour urine sample was needed since treatment would not have been changed by sample 2. That study was limited by sample size, especially since urinary parameters were compared in only 26 patients.

According to Rivers et al,[11] evaluation of calcium stones and treatment may be done using 2, 24-hour urine collections. However, they examined only patients with calcium oxalate stones and, thus, results may not be generalizable to other nephrolithiasis types. On the other hand, in a study of 119 patients Yagisawa et al compared complete metabolic evaluation to 1 and 2, 24-hour urine collections in recurrent calcium stone formers.[8] A specific metabolic diagnosis was made in 90% of patients with the complete metabolic panel compared to 68% and 75% of those with 1 and 2 urine collections, respectively. That series had a limited number of patients (119) but the diagnostic yield of a single 24-hour urine collection was similar to that of 2, 24-hour urinalyses.

Parks et al collected 2, 24-hour urine samples before beginning treatment in 1,142 patients with nephrolithiasis.[9] Results showed a correlation between the 2 samples in urinary creatinine, sodium, volume, calcium, oxalate, citrate, pH, potassium, magnesium, uric acid, sulfate, phosphorus and ammonium ($r = 0.68$ to 0.89). They concluded that the SD between 24-hour urine collections 1 and 2 was large enough that misdiagnosis could occur in almost 70% of comparisons, possibly resulting in case mismanagement. They did not directly compare the values of urine collections 1 and 2 other than by correlation. Although their correlation coefficients are similar to our results, we conclude that only a single 24-hour urine collection is needed.

We found no significant difference in any urine parameters examined between the 2, 24-hour urinalyses and the 2 samples correlated highly. When comparing mean differences between samples 1 and 2 to 0, 6 values showed no difference while the remainder had differences that were not clinically relevant and would not change case management. Thus, our study adds a large amount of data to the literature on this subject and with our sample size of 777 patients with repeat urinalyses evaluated it provides strong evidence that a single 24-hour urine collection is sufficient for evaluation in stone formers.

Also, our results do not decrease the need for followup studies. A single 24-hour urinalysis should be sufficient for initial patient evaluation but followup studies are needed if the patient begins medical therapy or dietary changes, and in general to monitor any change in urinary parameters.

Our patients came from various previous backgrounds and evaluations, meaning all stone compositions were represented, some patients underwent previous metabolic assessment, some were on a specific stone prevention diet and others were on medication to prevent stone recurrence. While this is a limitation in some sense, it also makes our study more generalizable since patients with recurrent nephrolithiasis for many years have often undergone previous evaluations, dietary changes and medical treatments for stone disease by the time they present to a modern clinic for further evaluation. Furthermore, our study included all stone formers at our clinic and, thus, was not limited to those in whom calcium oxalate stones form, as in some other studies.[8,11] Also, all testing was done elsewhere, making our data more homogeneous than if several laboratories had been used, adding to the integrity of our findings. Importantly we did not address the possible variability in 24-hour urinalyses done by other methods or elsewhere. However, there is no reason to suspect that more substantial variation would be expected at other laboratories. Our sample size of 777 patients provides greater power than previous studies showing the need for only a single 24-hour urine collection for metabolic stone evaluation.

CONCLUSIONS

A single 24-hour urine sample appears sufficient for metabolic evaluation in patients with recurrent stone disease since we found no statistical variation in 24-hour urinalyses for the 12 parameters analyzed. This finding has the potential to decrease cost and save time for patients and physicians by eliminating the second 24-hour urinalysis from evaluation in stone formers.

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