Variation in Urine Electrolytes, pH and Specific Gravity Throughout the Day and the Effect of Increased Fluid Intake on Intra-Day Urine Composition

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A. STUDY BACKGROUND AND PURPOSE

Nephrolithiasis has an estimated global prevalence of 10-15%, with North America encompassing a larger prevalence compared to Europe and Asia, with the exclusion of Saudi Arabia.[1, 2] Kidney stones have a higher incidence in working adults compared to children and the elderly, and 50% of those who have had kidney stones are likely to develop another episode in the next 5 years, which places a heavy economic burden as those with kidney stones are likely to miss work for pain or medical intervention.[2, 3]

As part of the metabolic work-up for those who have an episode of a kidney stone, the American Urological Association guidelines advocate for a 24-hour urine sample on a random diet, which should be evaluated for volume, pH, calcium, oxalate, uric acid, citrate, sodium, potassium and creatinine.[4] Further, the AUA recommends collecting a 24 hour urine sample within 6 months of any dietary or medical interventions that are taken for nephrolithiasis, as well as a 24 hour urine sample, at a minimum, annually, after therapy is started to assess for adherence and success.[4] However, 24 hour urine collections are problematic because they are cumbersome to execute, especially in working patients, they are time consuming, compliance is poor, and they are wasteful as up to 1/3 are rejected because of collection errors.[5-7]

An alternative to the 24-hour urine is to utilize the first morning void. Many studies looking at first voids and random spot urines compared to 24-hour collection with respect to electrolyte composition and pH have demonstrated that while there is a correlation, there is a large amount of variability, leading to 24 hour urine collections as maintaining their role as the gold standard.[5, 6, 8] Despite this, random spot voids and first morning voids are still used in practice because they are far more convenient and have the potential to be less expensive, however it is not known whether they are easily reproducible over a period of office visits and medically informative.

Spot-urines are assessed for pH and specific gravity, as well as their electrolyte compositions by indexing the electrolyte compositions compared to the creatinine excretion as the creatinine excretion is stable over 24-hours and is independent of the void volume.[5, 7, 9, 10] First morning void samples compared to random day voids are thought to be the best estimates to assess because they are more likely to represent the most concentrated specimens due to the relative dehydration overnight while an individual is asleep.[10]

However, first voids are difficult to attain in patients as clinic appointments vary in time throughout the day, and freshly voided samples of urine should be analyzed within 4 hours of void if they are refrigerated, and within 2 hours of void if left at room temperature.[10, 11] pH for example, can change for more alkaline urine if it is handled aggressively or as a result of the evaporation of carbon dioxide, and urine with urease containing bacteria can have its pH changed as a result of urea break down into ammonia and carbon dioxide[12, 13] Thus, in the clinical setting, voided samples are usually taken at the time of the appointment to assess for pH and electrolyte composition.

Unfortunately, little is known about the variation in excretion of electrolytes such as calcium throughout the course of the day. While many studies have looked at the composition of urine from a single sample compared to 24 hour sample, the hour to hour variations of excretion has not fully been elucidated.[6, 8] This is especially important because factors like temporal changes and orthostatics have already been shown to play a role in altering urinary protein excretion.[10, 14] Further, urinary chemical composition is altered by pre vs post prandial state, water intake, and specific diet changes.[2, 8, 15] Thus, one aim of this study will be to evaluate the intra-day changes (from the morning through the
workday) of urinary composition within a person. This will help to validate the use of spot-urines during clinic appointments in the outpatient urology setting.

Further, AUA guidelines for stone formers is to have a target urine volume output of 2.5L as the primary treatment option in those who are not fluid restricted secondary to renal or heart disease.[4] Multiple studies have demonstrated that increasing fluid intake leads to a reduction in kidney stones, as well as the general observation that non-stone formers have a larger mean urine volume compared to stone-formers.[2, 15] In the clinical setting, the clinician can assess hydration beyond measuring urine volumes is looking at specific gravity as a metric of assessing relative hydration.[12] However the hour to hour changes related to someone who increases their fluid intake have not been evaluated. Thus, we posit to assess how doubling oral fluid intake impacts chemical composition, pH and specific gravity over the course of a day. Similarly, increasing citrate consumption is also recommended but little is known about the hour to hour changes in the urine as a result.

Hypothesis:

1) 1st morning spot urine is more concentrated than others during the day, and the excretion of calcium and other electrolytes will significantly vary during the day.

2) Increasing fluid intake reduces urinary concentration but does not change calcium excretion.

B. STUDY DESIGN

Research team will consent subjects in the Urology Clinic office. Subjects will all get a questionnaire asking about weight, height, history of kidney stones, whether they are on any diuretics, medications that alter urine chemistries, or special diets.[14] BMI will be calculated and stratified to assess whether the day-to-day variations are different for those with larger BMI. Those taking diuretics, have known kidney disease or history of known nephrolithiasis will be excluded. Those that do not comply with the void times on Day 1 and 2 will be excluded. [10]

Subjects will receive 4 sterile cups and receive education on mid-stream urine collection. Day 1 will begin 5p.m. on the day before first morning void is collected. Subjects will collect 20-30 ml urine per collection. The cup will be marked at the 20-30 ml line to indicate how much urine should be collected. First morning voids: Subjects will be instructed to refrigerate their first voids.[10, 17] Time of void and time of presentation of specimen to study representative will be recorded to track how the length of that interval affects composition. The 2nd, 3rd and 4th void samples will be collected in the office during the designated times, and given to study personnel for dipstick analysis. Subsequently, the samples will be frozen, and batch sent to Litholink (Litholink, LabCorp Specialty Testing Group, Corporate Office 2250 W Campbell Park Drive Chicago, IL 60612).
Table 1 – Study schematic

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 pm day before – 5pm</td>
<td>5 pm – 5pm</td>
<td>5 pm – 5pm</td>
<td>5 pm – 5pm</td>
</tr>
<tr>
<td>Fluid intake Record volumes and times of day</td>
<td>Normal intake – record all</td>
<td>Normal intake – record all</td>
<td>Double daily intake - record all</td>
</tr>
<tr>
<td>True Lemon drink mix in one bottle of Poland Spring water, 16.9 oz (500 mL)</td>
<td>-</td>
<td>5 pm – 12 am: Drink one bottle</td>
<td>5 pm – 12 am: Drink one bottle</td>
</tr>
<tr>
<td>Urine void times – record times of all voids, and collect 20 – 30 mL samples at the specified times</td>
<td>First void, 9-10 am, 1-2 pm, 4-5 pm</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Food intake – record times of all meals and snacks</td>
<td>Record all</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
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1) Day 1: Normal Drinking Habits
   a. Day 1 begins at 5pm (the night prior to the 1st urine collection)
   b. All subjects will collect spot urine sample on the first void at home, then at 9-10AM, 1-2 PM and 4-5PM. They will be provided 4 sterile urine cups labeled for the different timed collections.
   c. Subjects will be educated on how to collect a mid-stream specimen. Females will further be instructed to void normally without cleansing as this adds an extra layer of burden on participants and studies have demonstrated that mid-stream non-cleansed sample is not inferior to a cleansed mid-stream specimen.[11, 16-19]
   d. Starting on Day 1 at 5pm until 5pm the following day subjects will be asked to record the times they eat, and to record their approximate fluid intake. Post-prandial urine excretion may be different compared to other voids.[20]
   e. Subjects will be asked not to void outside of the timed collections. If they do void outside of these times, they will be asked to record the extra times that they void.

2) Day 2 and 3: True lemon Intake
   a. Day 2 will begin 5p.m after the last collected void of Day 1.
b. Subjects will be provided 3 True Lemon packets (True Citrus, 11501 Pocomoke Court Suite D, Baltimore, MD 21220). They will be instructed to mix 1 packet in one 16.9oz (500 mL) bottle of Poland Spring water (Nestle Waters North America). They will drink one bottle on Day 2 after 5 p.m., and another bottle after 5pm on Day 3 , All True Lemon packets and Poland Spring bottles will be provided to subjects by the research study team.

c. Subjects will be asked to record the time and the approximate volume of their fluid intake. Subjects will record the 2 True Lemon water bottle intakes, as well as any additional fluid intake they have.

d. On Day 3 all subjects will be asked to double their fluid intake based on the previous days’ diaries.

3) Day 4

a. Day 4 will begin at 5pm (the night prior to urine collection) and the subjects will drink the last bottle of water with True lemon.

b. All subjects will collect spot urine sample on the first void at home, then at 9-10AM, 1-2 PM and 4-5PM.

c. Subjects will be asked to record the times they eat, and to record their approximate fluid intake and times of intake. Subjects will also be asked to double their fluid intake, using Day 1 and Day 2 as a guide of their normal daily intake (including the True Lemon Bottle volume).

d. Subjects will be asked not to void outside of the timed collections. If they do void outside of these times, they will be asked to record the times of the extra voids.

e. Subjects will be educated on how to collect a mid-stream specimen. Females will further be instructed to void normally without cleansing as this adds an extra layer of burden on participants and studies have demonstrated that mid-stream non-cleansed sample is not inferior to a cleansed mid-stream specimen.[11, 16-19]

4) UA dipsticks will be used in office to evaluate for pH and specific gravity – dipsticks are within 0.5 pH effective accurate compared to pH meters.[21] Dipstick analysis should be done as soon as possible after the urine is collected as pH changes the longer it is left out as a result of the natural breakdown of urea.[12] It will be analyzed by study coordinators. Samples will also be sent to lab for evaluation of chemical composition of creatinine, citrate, and calcium. Electrolytes will be indexed against creatinine to evaluate their concentrations without having a 24-hour void volume amount.[5, 9] A pH-meter will also be used to correlate the accuracy of pH values reported by the dipsticks.

5) All urines will be frozen immediately upon acquisition until batch sent to Litholink for electrolyte and pH analysis.[10, 17] All samples will only be identifiable by the study identification number. The lab will be instructed to discard all samples after the necessary tests are conducted.

6) A sample of citrate-Poland Spring will be sent to Litholink for analysis of Calcium and Citrate for reference.
C. SUBJECT POPULATION

- Healthy adult subjects will be accrued from outpatient urology office employees, residents, medical students, and faculty members who volunteer to participate in the study. A recruitment flyer will be posted in the outpatient Urology office and given to interested persons. A recruitment email will also be sent to office personnel, residents, medical students and faculty.

- The study will recruit 20-30 subjects.

D. DATA ANALYSIS

- Data collected with respect to subject demographics will include that from the questionnaire, including use of medications that affect kidney excretion, body weight and height, age, history of kidney disease or stones, types of diet, and supplements use. These points will be linked with the subject’s urinalysis and urine chemistry results, however the subject’s name will be removed during the statistical analysis. Data will be stratified by these demographics to identify any patterns that could potentially be studied by future studies.

- Those subjects who identify as having renal disease/history of nephrolithiasis, or who take diuretics will be excluded from the study. Those who are required to be on a fluid restriction for their health will not be allowed to participate in the study for safety reasons. Those that do not have voids at the appropriate time intervals will also be excluded.

- Data analysis will be conducted by Dr. Bhatt and Dr. Feustel at Albany Medical Center.

- All questionnaires and diaries will be kept in research office, input into password-protected software, and analyzed at Albany Medical Center.

- Data Points: After discussing data points with Dr. Feustel the study will aim to recruit at least twenty subjects, which will give 87% power to detect a difference in any urine variable that is at least as large as one standard deviation of that variable in the normal fluid intake session (two tailed alpha of 0.05). Since, assuming a normal distribution, one standard will encompass 68% of patients, we consider a one standard deviation difference to be the minimally important clinically significant difference in these measures. Data points will be statistically analyzed by a repeated measures ANOVA test. Further, changes in the below variables after doubling fluid intake will be calculated for statistically significant changes compared to normal fluid intake.
  - pH
  - Specific gravity,
  - Calcium
  - Creatinine
  - Citrate
  - Changes in the above after doubling fluid intake

E. RISKS

- There are minimal risks to this study.

- If subjects are on a fluid restricted diet, the second component of the study could potentially be harmful to their health. For this reason, these subjects will be excluded from the study.

- There is a risk that there is a violation of privacy due to a breach in study data. However, the data will not be able to be linked to a specific individual.

- There is a risk of exposing underlying illness while evaluating urines of otherwise healthy subjects.
F. **BENEFITS**

- The main benefits of this study are to improve the quality of care provided to stone-forming patients in the urologic clinical setting.
- Add to the general medical knowledge about urine composition and its variation.

G. **CONFIDENTIALITY**

- After consent is collected, all subjects will receive and be referred to by a study number ie. 1, 2, etc., which all collected specimens and documentations will utilize. The master key containing the names and corresponding study numbers will be securely stored on an AMC network drive to which only the research staff have access. The master key will be destroyed after all data collection and analysis.
- A portion of the subjects’ past medical history and current medication regimens will be collected, but their name will be replaced by a study ID# to de-identify the data – please see questionnaire.
- Urine specimens will be pre-labeled with the times they are to be collected and a subject study number.
- Data will be de-identified after questionnaire is collected and input into excel document that will house all study data points. After the lab analyzes the urine, more data will be added, but matched using the subjects study number. See “Data Entry” File.
- Data will be analyzed after all subjects are collected by co-investigators at Albany Medical Center.
- Data will be stored in an encrypted file, with the password only available to co-investigator: see “Data Entry” file.

H. **OPTIONS**

Participation is optional. Subjects may choose not to participate in this study. There will be no penalty or other negative effect if they choose not to participate.

I. **REFERENCES**


