Data Mining Activity: Flight Data for Renal Stone Risk

Final Research Report
to
Non-Exercise Physiological Countermeasures Project

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A. Abstract

Kidney stone formation and passage has the potential to greatly impact mission success and crewmember health for long-duration missions. The formation of renal stones poses an in-flight health risk of high severity, not only because of the impact of renal colic on human performance, but also because of complications that could possibly require crew evacuation such as hematuria, infection, and hydronephrosis. Evaluating all of the risk factors that contribute to renal stone formation, and how the conditions and contraints of a spaceflight mission may influence these risk factors, help us to understand the risk and probability of kidney stone formation during a mission. To address this aim, this Data Mining Activity [DMA] reviews data obtained from crewmembers who have flown in space, both published and more recently acquired, as a compilation to be published in the NASA Human Research Program, Human Health and Countermeasures Element, Evidence Book.

B. Study Aims/Objectives/Hypotheses

The following GAPS in knowledge were assigned to NxPCM to fund a) the DMA of the DIPT Lead for Bone and b) the on-going flight experiments validating Potassium Citrate [KCIT] as a pharmacological countermeasure for reducing risk factors for renal stone formation in Flight.

B05: what is the current state of knowledge regarding renal stone formation?
B06: what are the contributing factors for renal stone formation other than loss of bone mineral density?
B08: Do pharmaceuticals work effectively in spaceflight to prevent renal stones?
B09: what is the frequency of postflight stone formation, the incidences and types of stones formed, and the time course of formation? How does stone formation correlate with food intake and hydration status?
B16: Can inhibitors of stone formation be sufficiently provided through dietary sources?
N13: Can renal stone risk be decreased using nutritional countermeasures?

C. Background/History

The following text was excerpted from the HRP Evidence Book for the Risk of Renal Stone Formation.

Renal stones are aggregates of crystals that are formed in supersaturated urine (urine is usually supersaturated in terms of its salt components). Hypercalciuria is a characteristic of the skeletal adaptation to space, and contributes to the increased supersaturation of urine such as with calcium phosphate or calcium oxalate stones. The presence of these aggregates in the renal collection or excretion system can potentially result in renal colic, hematuria, infection, and can obstruct urine flow to cause hydronephrosis. Whether a renal stone forms in supersaturated urine can also depend upon other risk factors. Notably, the formation of a renal stone during a spaceflight mission could cause acute illness with loss of that crewmember to the mission.

Nephrolithiasis is the condition marked by the development of renal stones and the primary risk factors for nephrolithiasis in space are the increased excretion of calcium and lower urine output. Other contributing risk factors include dehydration, diet (high sodium, high animal proteins), low urinary citrate, genetics, and environmental derangements (ambient temperatures)
because these factors can increase the supersaturation of salts in urine, the acidity of urine pH, and the reduction in urine volumes – all favorable conditions for crystallization.

Renal stones come in different types, and the formation of a specific stone-type depends upon the presence of particular risk factors. 1) The most common renal stone, and a main component in stones of mixed composition, is calcium oxalate. This type may occur as multiple stones or may recur, can induce pain with both passage and obstruction, and is commonly caused by treatable metabolic disorders of hypercalciuria. 2) Similar to calcium oxalate stones, uric acid stones induce the same adverse effects but differ with their rarer occurrence (only 5% of renal stones). Uric acid stones are also translucent and, unlike the other stones, cannot be distinguished by radiographs. 3) Struvite stones are generated by infections of urease-containing microorganisms that are capable of hydrolyzing the urea in urine to carbon dioxide and ammonia. When urine pH exceeds 7.2, struvite stones may form, and the resulting obstruction can fill the renal collection system and erode into the renal tissue. Treatment is by surgical removal unless stone size is <2 cm where lithotripsy can be applied to fragment the stone. 4) Unlike other renal stones, cystine stones have a single etiology – hereditary cystinuria – where stone formation begins in childhood and can grow large enough to fill the renal collection system. 5) Finally, brushite is the name for a calcium phosphate stone, the formation of which is promoted by high urine pH and supersaturation of urine with the calcium phosphate salt. Just as on Earth, it is more cost effective to prevent stone formation during a spaceflight mission than it is to treat a crewmember (Parks, 1996). Thus, understanding the etiology for the formation of specific stone types and identifying which stones are more likely to be formed during spaceflight missions will direct the application of appropriate countermeasures for nephrolithiasis.

Countermeasure approaches for preventing renal stones can include dietary approaches to reduce risk factors. For instance, hypercalciuria (> 300 mg [males] or 250 mg [females] per day) is the primary risk factor for calcium stones and the decalcification of bones is strongly associated with skeletal atrophy in space. Pharmacological agents or dietary adjustments can suppress bone atrophy or promote renal calcium reabsorption (such as with thiazide diuretics). Avoiding foods high in oxalate (nuts, pepper, chocolate, rhubarb, spinach, dark green vegetables, fruits) and diets high in fat will reduce hyperoxaluria (>75-150 mg/day). Reducing the ingestion of purine-containing foods (e.g., meats) will suppress hyperuricosuria. Ingesting an oral alkali such as potassium citrate will suppress calcium oxalate crystallization (by raising pH) and provide an inhibitor of crystal aggregation and growth (by binding the calcium ion to form the soluble calcium citrate). Increasing fluid intake to increase urine output can reduce the saturation of the stone-forming salts. Even persons homozygous for cystinuria can dilute out the concentration of cystine by high fluid intake. The full understanding of the risk factors incurred during missions in space and knowledge of the incidence of renal stone types is warranted in order to make judicious selection of prophylactic approaches.

Identification of the type of formed renal stone, however, is difficult because it is not always possible to recover the stone itself. It is easier to assess the presence of risk factors for stone formation because of laboratory evaluations to measure the saturation levels of calcium, oxalate, and uric acid measured in 24-hour urine specimens. Moreover, the urine pH, urine volumes, urine citrate levels (an inhibitor of stone formation) and serum creatinine levels (a marker of optimal renal function) in urine and of calcium in serum will elucidate if the conditions were optimal for stone formation. Such measures have been conducted in crewmembers of Shuttle and long-duration missions to evaluate the risk of stone formation in space.
Evidence for actual renal stone formation in crewmembers include a single documented episode of an in-flight renal stone in a cosmonaut (Lebedev) in addition to a recent survey of renal stones in US astronauts which has revealed a total of 14 episodes of kidney stones (Pietrzyk, 2007). Some of these episodes occurred in the preflight period (n=5) with the balance (n=9) having occurred in the postflight phase. Six of the nine postflight episodes had occurred after 1994, which corresponded with the extended durations of space shuttle missions to 12 days. Discussion of DMA results (below) further characterizes the occurrences of these renal stones in crewmembers that have flown in space.

In general, this DMA review links the results of multiple flight studies (reports in the literature and one recently completed) to the HRP GAPs for HHC.

D. **Significance to NASA Human Research Program (HRP)**

1) *HRP Risk(s) addressed by the study:*
   - Risk for Renal Stone Formation

2) *Project-assigned gap(s) addressed by the study:*
   - NxPCM

E. **Materials & Methods**

NA for DMA

F. **Results**

B05: what is the current state of knowledge regarding renal stone formation?
See HRP HHC Evidence Book Risk of Renal Stone Formation. An abbreviated discussion of clinical knowledge base has been provided earlier in section C:background/history

B06: what are the contributing factors for renal stone formation other than loss of bone mineral density?
See Background section of HRP HHC Evidence Book Risk of Renal Stone Formation for known terrestrial risk factors of renal stone formation in the clinical sector.

Whitson, 1993; Whitson, 2001: Factors for an increased risk of stone formation after spaceflight -- aside from increased bone resorption -- included low citrate (an inhibitor) levels, low pH and low urine volume.

Whitson, 1997: Nutrition is another contributing factor to the risk for renal stone formation. Pietrzyck, 2007: The survey of 12 astronauts who have formed kidney stones in postflight period indicate that two astronauts had multiple episodes at a sex ratio of 10:2 Male to Female suggesting a personal history of renal stones and the male sex as risk factors for renal stone formation (although a sex effect is debated in the literature) (Curhan, 2001)

At this time, there has been no reports in the literature of systematic, retrospective evaluations of personal and family history of nephrolithiasis and of urinary tract infections in crewmembers that would assess if risk factors prior to flight were exacerbated by spaceflight exposure itself.
B08: Do pharmaceuticals work effectively in spaceflight to prevent renal stones?
Zerwekh, 2007: The validation of potassium magnesium citrate, which has been documented in a 5-week flight analog study, has yet to be conducted in a Flight mission.

Bisphosphonate SMO: No flight data has been collected for the experiment to validate the efficacy of alendronate (sole bisphosphonate offered to US astronauts) to suppress bone resorption and thereby the urinary excretion of calcium, a risk factor for renal stone formation.

Whitson, 2008 Final Report: To date, there has only been one pharmaceutical that specifically targets the mitigation of renal stone formation. Data on the pharmaceutical potassium citrate [KCIT] have been collected over ISS Expeditions 3-6, 8 and 11-14 missions to evaluate the ability of KCIT to reduce the risks factors for renal stone formation and thus prevent the formation of renal stones. There were 12 crewmembers treated with KCIT and 18 crewmembers treated with placebo. Refer to Final report for experimental details, analysis methodology and data graphics. Some of the results are summarized below (see graphs in appendix):

- Greater % increase in urinary citrate levels, from preflight, was observed with KCIT at the R+7 and R+10 time points; urinary citrate levels also increased in placebo group at R+10 days.
- KCIT (n=12) reduced urinary calcium excretion compared to placebo (n=18) during Flight (“early” during first 35 days, “middle” during 36-120 days and “late” after 120 days) but urinary calcium excretion was no different between groups preflight, R+(0-2), R+7 and R+10 days.
- Urinary pH was increased in KCIT group during Flight (early, middle and late) and at R+7 compared to preflight pH and to the placebo group.
- The relative urine supersaturation with salts for calcium oxalate stones was significantly higher in the placebo group compared to KCIT group at the R+(0-2) time point.
- Regression analysis of long-transformed calcium oxalate supersaturation data indicates that the group of crewmembers on placebo, and not the group of crewmembers on KCIT, is at a significantly greater risk for calcium oxalate stones during flight than before flight.

The flight data have been presented at the Human Systems Risk Forum (HSRB), the Medical Operations Branch (MOB) and the Space Medicine Configuration Control board (SMCCB). The transition to space medical operations is currently in process.

B09: What is the frequency of postflight stone formation, the incidences and types of stones formed, and the time course of formation?
Pietrzyk, 2007: A total of 14 occurrences of kidney stones were identified in the postflight period with the onset of symptomatic stone formation occurring within 9-120 months after return. Two astronauts had multiple occurrences of renal stones.
Whitson, 1993: As previously mentioned, identification of stone-types formed are precluded by the difficulty in stone recovery. However, urine biochemistry do indicate greater risk for the formation of calcium oxalate and uric acid stones.

and How does stone formation correlate with food intake and hydration status?
Whitson, 2001a: Increasing fluid intake to increase urine volume may dilute the urinary risk factors to bring these factors under the upper limit of metastability for solubility of the stone-forming salts.

Whitson, 1997: Nutrition is another contributing factor to the risk for renal stone formation.

Whitson 2008 final report: Cannot correlate nutrition and hydration impact on actual stone formation; however, some assessment of food intake and hydration on risk factors for bone formation was conducted. The in-flight data of fluid intake in ISS crewmembers, indicated that crewmembers had not ingested adequate fluids to produce the 2L per day minimum urine output recommended to reduce supersaturation of calcium salts. The additional intake of citrus-based juices rich in orange juice and in potassium, however, may have had a favorable effect on the risk by increasing urine pH, providing the citrate inhibitor of stone formation and by reducing calcium excretion independent of vitamin D regulation (Preminger, 1987). See final report for detailed discussion.

B16: Can inhibitors of stone formation be sufficiently provided through dietary sources? and N13: Can renal stone risk be decreased using nutritional approaches and countermeasures?

Nutritional SMO: The reduction in the dietary intake of sodium, and of animal protein, will be evaluated to as a mitigator of increased bone demineralization during skeletal adaptation in space. The efficacy and the extent of this nutritional modification to reduce the increased urinary excretion of calcium will be contribute to the understanding of nutritional countermeasures to the risk for renal stone formation.

Whitson 2008 final report: Refer to report which further details data which evaluated the influence of ingested protein, calcium, phosphorus, oxalate, sodium, potassium and magnesium on the risk factors for renal stones in ISS crewmembers. Diet was not restricted and food consumption was monitored by an automated bar-code scanning system. Consumption was monitored for the 24h period prior to and during each urine-collection period

G. Conclusions

Because of the reduced level of care, the formation of renal stones could cause acute illness resulting in loss of human performance during the mission and possible evacuation. Therefore it is a critical requirement to have a validated countermeasure to prevent renal stone formation. Data mining activities for the renal stone risk were facilitated because of the spaceflight mission data base, much of which are reported in the literature. The multiple risk factors associated with renal stone formation are highlighted in these reports, but are further compounded by constraints of mission operations and the unique conditions of space and planetary habitability (e.g., dietary restrictions, food stability issues, and water availability). And while the primary risk factor for the formation of calcium renal stones in space is the increased calcium excretion resulting from bone atrophy, the risk is exacerbated by low urinary output and supersaturation of the stone-forming salts. Simply increasing urine volume alone would not address the underlying physiological adaptations to spaceflight. Furthermore, research priorities related to understanding the time course of bone loss (a contributor to urinary calcium), and the influence of mechanical loading (a mitigator of bone atrophy) are relevant to the risk for renal stone formation during prolonged missions.

In conclusion, based upon this DMA it seems likely that the most optimal countermeasure for the renal stone risk would be a combination of countermeasure approaches: bone anti-
resorptives, hydration, diet counseling and prevention of skeletal adaptations by exercise loading. The countermeasure should be customized for each crewmember as dictated by the mission architecture and following a personal risk assessment to identify metabolic, environmental and physicochemical alterations. The effectiveness of pharmaceutical countermeasures may be improved by combined approaches.

References


H. Publications Resulting From This Research
   Manuscript in final draft preparation by Principal Investigator.
Appendix A – Data Tables and Graphs

EFFECT OF KCIT ON RISK FACTORS FOR RENAL STONE FORMATION

Effect on urinary calcium: a mitigation strategy is to reduce calcium excretion in urine.

![Graph showing urinary calcium excretion comparison between KCIT and Placebo groups.](image1)

**Figure 2.** Urinary calcium excretion before, during and after long-duration spaceflight. KCIT, potassium citrate treated group (n=12); Placebo (n=18); *p<0.05 compared to Placebo Group.

Effect on urinary pH.: a mitigation strategy is to raise pH > 6.

![Graph showing urinary pH comparison between KCIT and Placebo groups.](image2)

**Figure 3.** Effect of potassium citrate on urinary pH. The urinary pH was significantly increased during spaceflight in the potassium citrate (KCIT) Group compared to preflight values and to the Placebo Group.
Mitigation strategy is to reduce the relative supersaturation of urine for uric acid stones to < 2.0.

![Graph](image)

Figure 6. Data represent the effects of spaceflight and potassium citrate on the urinary uric acid supersaturation and the potential risk for stone formation. Crewmembers ingesting daily potassium citrate demonstrated significantly lower risk for uric acid stone risk (p = 0.005). Values greater than 2.0 indicate an increased risk for stone formation.

Mitigation strategy is to reduce relative supersaturation of calcium oxalate to < 2.0.

![Graph](image)

Figure 4. Data represent the individual crewmember’s calculated risk of calcium oxalate stone formation. The relative supersaturation of calcium oxalate was significantly higher in the Placebo Group as compared to the KCIT Group (p=0.002). Values greater than 2.0 indicate an increased risk for calcium oxalate stone formation. Horizontal bars indicate the mean at each time point.
A mitigation strategy is to reduce the supersaturation of stone forming salt during flight relative to preflight.

**Figure 5A and 5B.** Regression analysis of log-transformed calcium oxalate supersaturation data. Data represent a comparison of in-flight values to the crewmember’s respective preflight data. The Placebo Group demonstrated significantly increased risk during spaceflight.