RENAL STONE RISK DURING SPACEFLIGHT: ASSESSMENT AND COUNTERMEASURE VALIDATION

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Risk

- **Mission risk and Impacts:**
  - ❖ **Potential risk condition exists during the pre-, in- and postflight phases**
  - ❖ **Risk to crewmember for both acute and chronic health effects**
  - ❖ **Potential for significant impact to mission operational objectives**
    - **Early termination of mission**
    - **Significant impact to affected crewmember's performance**
    - **Significant impact to other crewmembers for medical care and treatment of affected crewmember**

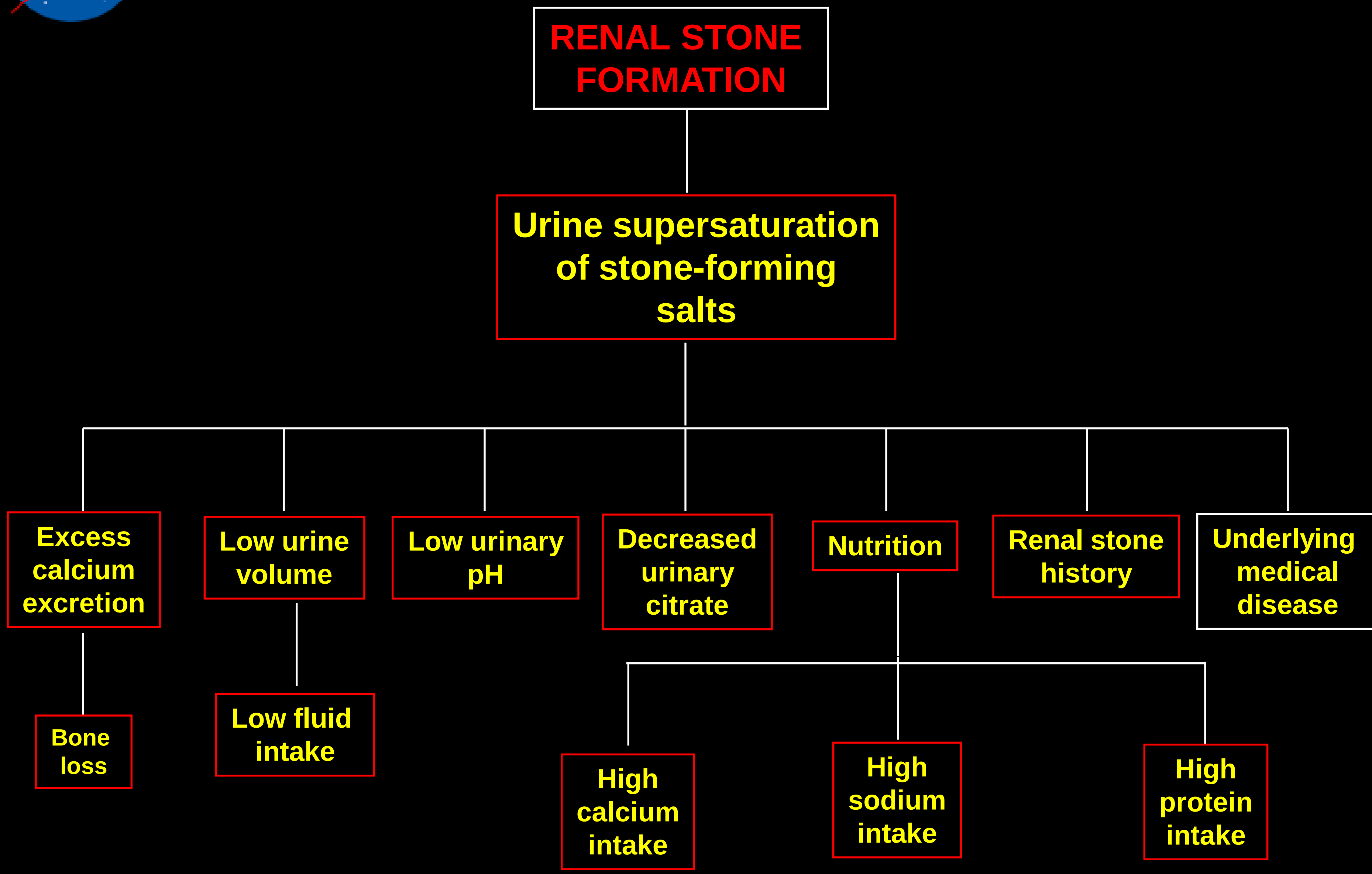
EVIDENCE

➢ **As of 2008, 15 symptomatic urinary calculi have been experienced by 13 U.S. astronauts (Pietryzk, et al, 2006; Jones et al, 2008)**

➢ **Multiple stone events among cosmonauts reported by Russian medical investigators**

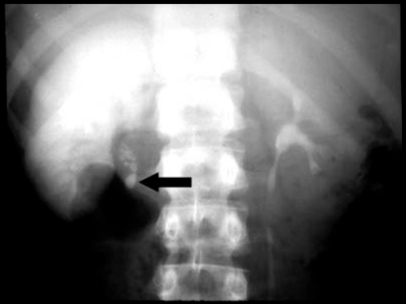
➢ **One in-flight episode nearly causing a mission termination but was resolved by spontaneous stone passage**

NEPHROLITHIASIS – A MULTIFACTORIAL DISEASE



SYMPTOMS/SIGNS

- Severe / agonizing pain in the flank (back just below the ribs spreading around to the front of the abdomen) often extending into the groin area.
- Usually nausea and often vomiting
- Fever chills and sepsis, if infection is present
- Gross or microscopic blood in the urine
- Progression if not treated, hydronephrosis, renal shutdown



Urolithiasis and Stone Passage

Stone Size	Chance of Spontaneous Passage	Time to Pass Stone	Require surgical intervention
<2 mm	>85%	4.5-8 days	5%
<5 mm	78-80	7 – 14.5 days	17%
5-7 mm	20-50% (35% avg)	5.5-22 days	50%
>7 mm	< 10% (8% avg)	53 days - never	>80%

Stones 3 mm in size can cause transient or complete obstruction
Recurrence approx 5-10%/year up to 75% at 20 years

STUDY OBJECTIVES

- Quantitate the pre-, in- and postflight risk of renal stone formation associated with space flight.
- Determine the efficacy of potassium citrate as a countermeasure in reducing the in-flight and postflight for renal stone formation.
- Evaluate dietary impact on the urinary biochemistry.

SUBJECTS

Placebo Group: n = 18

NASA-Mir missions   12 male subjects, mission duration 129 - 208 days

ISS missions   6 male subjects, mission duration 93 - 175 days

KCIT Group: n = 12

ISS missions   11 male/1 female subjects, mission duration 93 - 175 days

METHODS

- 24-hour urines collected pre-, in-, and post-flight
- Food, fluid, exercise, and medications monitored before and during the urine collection period
- Two potassium citrate (KCIT) pills, 10 mEq/pill, ingested daily (with the last meal of the day) from L-3 days to R+14 days
  - Double-blind study design except for last 3 ISS subjects
- Biochemical analysis of urine samples for urinary factors associated with stone formation
- Dietary analysis completed to assess environmental influences on the urinary biochemistry

INVESTIGATION RESULTS

Potassium Citrate

The majority of oral citrate is metabolized in the liver to bicarbonate, each citrate ion producing three bicarbonate ions.

$\uparrow$ HCO_3

$\uparrow$ pH

$\uparrow$ U-Citrate

$\downarrow$ U-Calcium

$\downarrow$ Urinary Supersaturation

$\downarrow$ Renal Stone

KCIT dosage of 20 mEq/d selected based on;

- results from Shuttle and NASA-Mir missions
- minimize any potential for in-flight GI upset (wax matrix/ slow release prep)
- minimize the potential to exaggerate the risk for CaP stones (higher pH 7.25-7.5)
- minimize impact to crew time

Effects on renal physiology

65-90% of filtered citrate is reabsorbed

10-35% of citrate is excreted into the urine

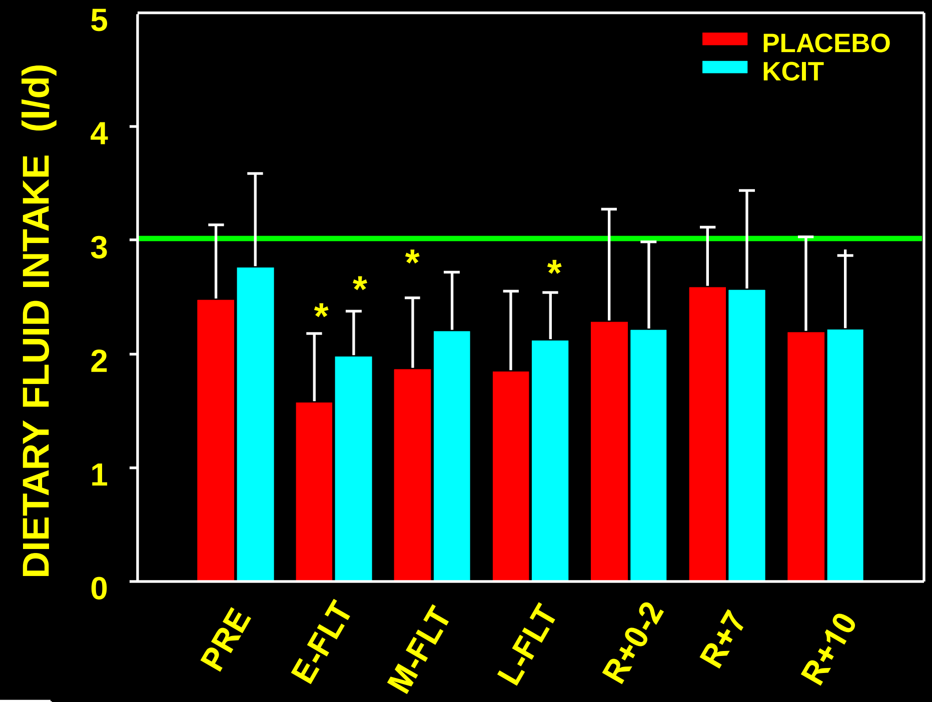
Effects of dosage used (20 mEq/d)

expected urinary increase of 130-140 mg/d

expected rise in urinary pH of 0.2 – 0.3 units

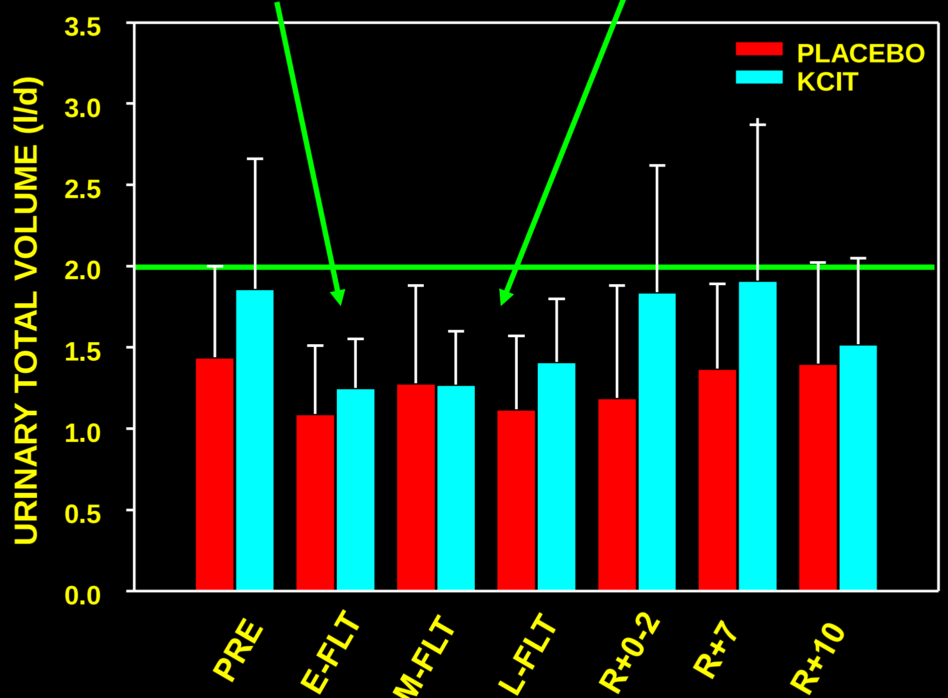
FLUID BALANCE

Similar fluid intake and total urine volumes between groups

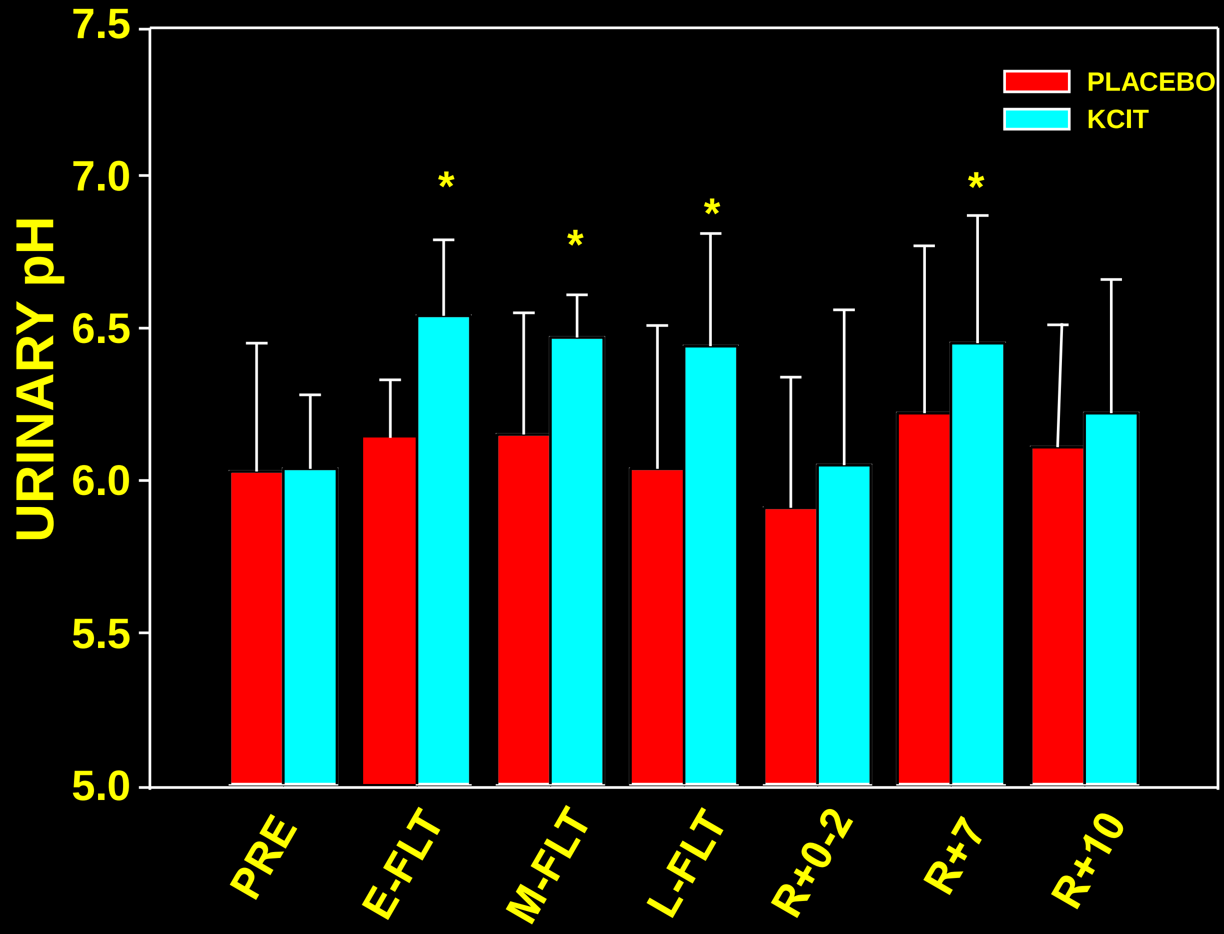


↓ Fluid intake during flight

Low urine volumes (< 2L/d)

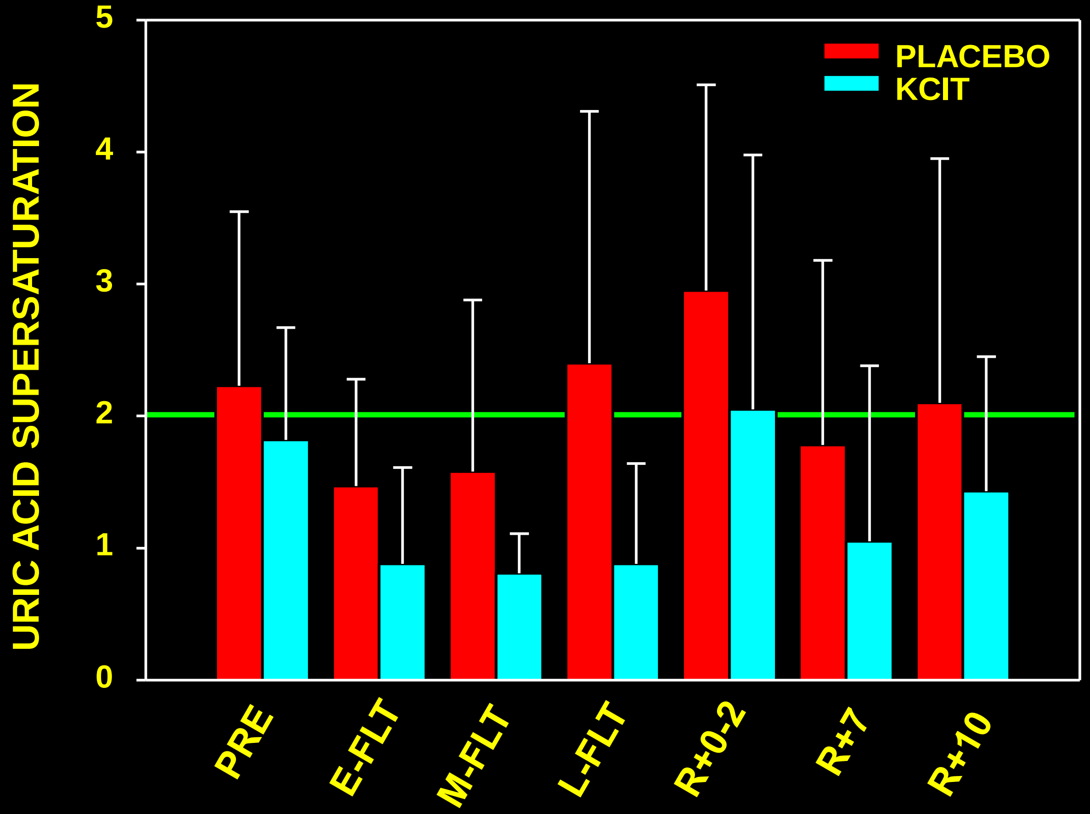


Effect of Potassium Citrate on Urinary pH

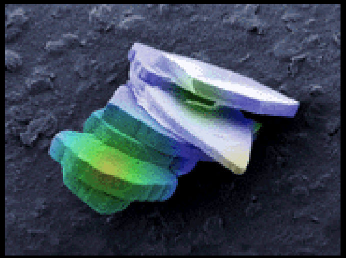


↑ Urinary pH in KCIT crewmembers, but not too high

Effect of Potassium Citrate on Uric Acid Supersaturation

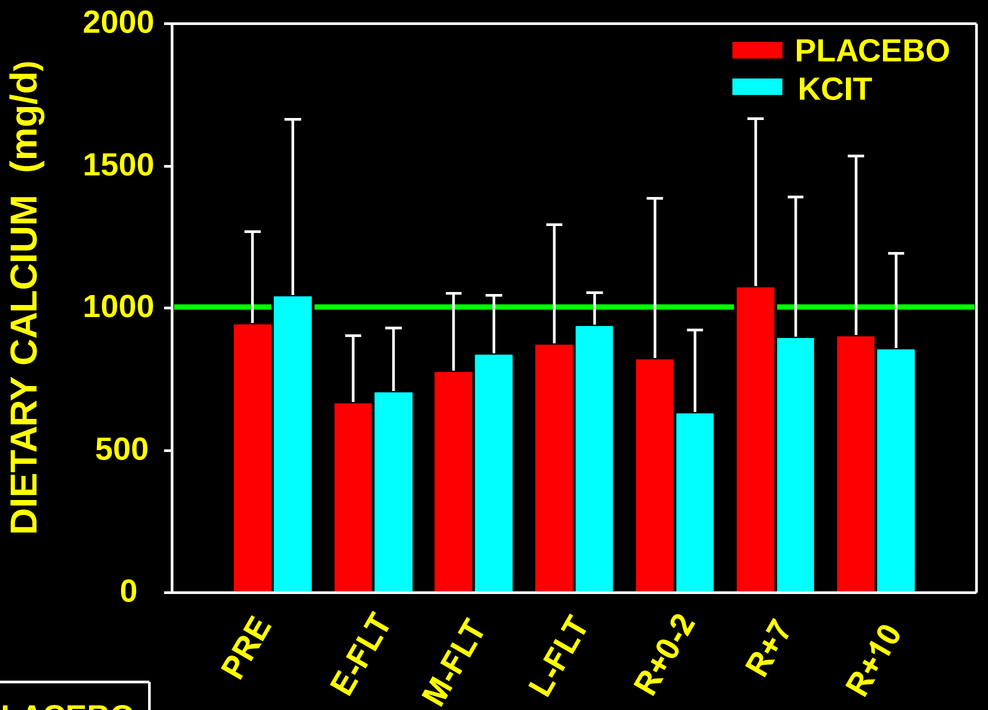


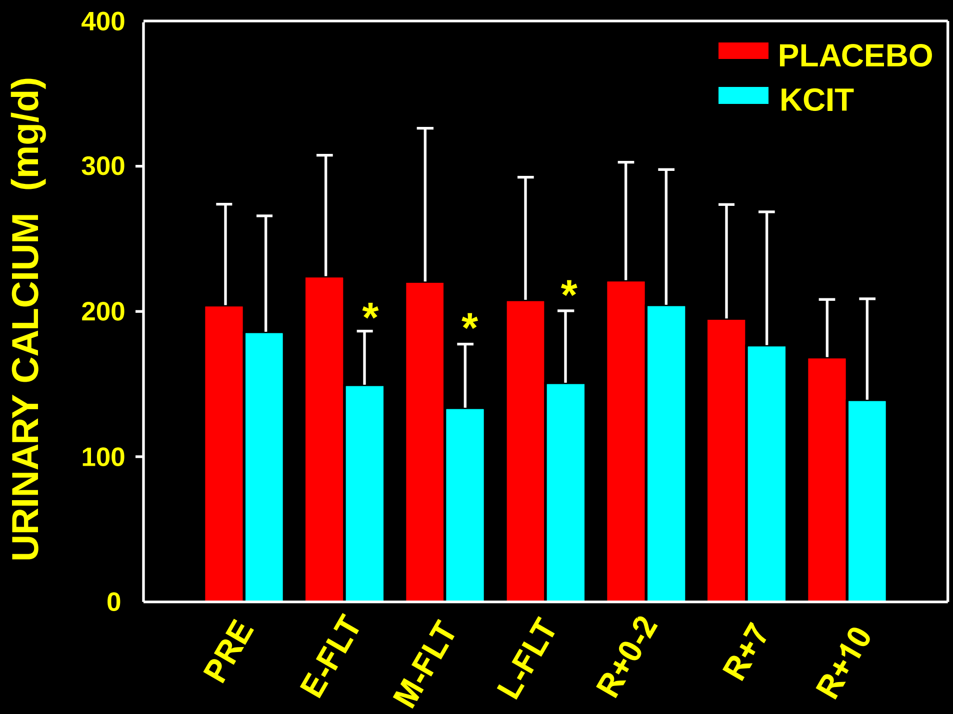
↓ Risk of uric acid stone formation in KCIT crewmembers



Uric Acid Stones
Image from Mission Pharmacal

CALCIUM BALANCE

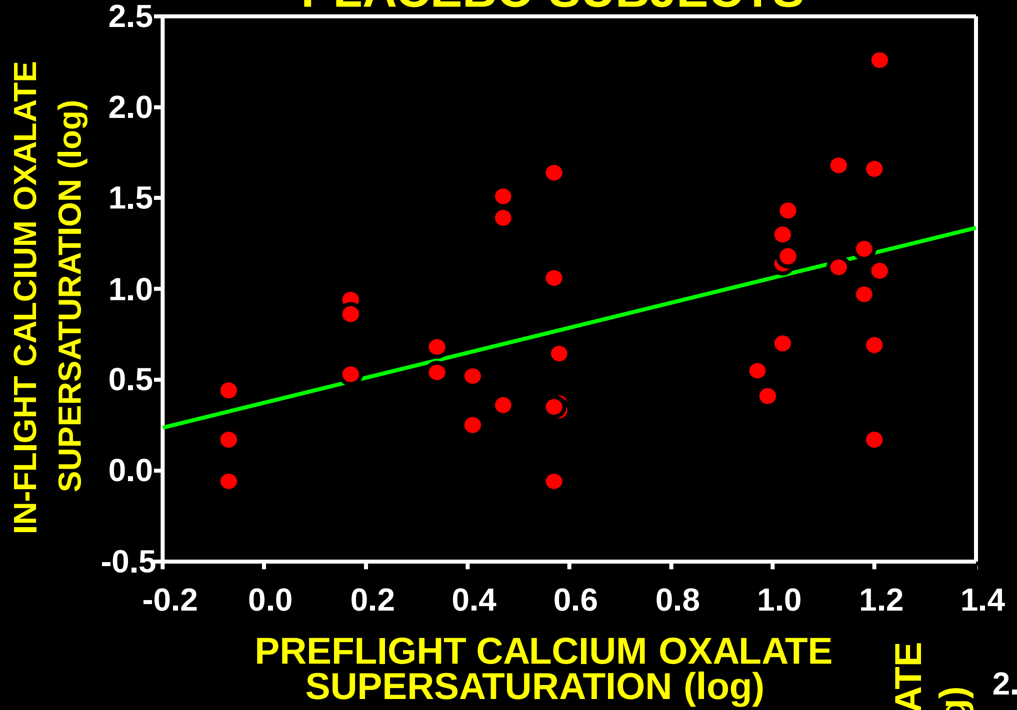




Dietary Ca intake below recommended levels

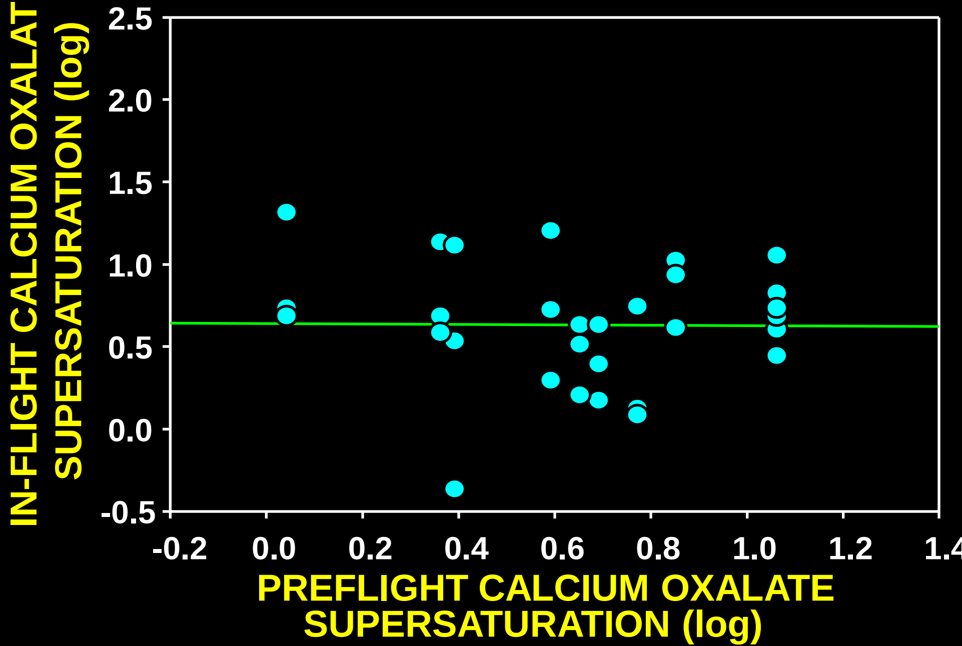
↓ Urinary Ca excretion in KCIT crewmembers

PLACEBO SUBJECTS



Risk of Calcium Oxalate Stone Formation

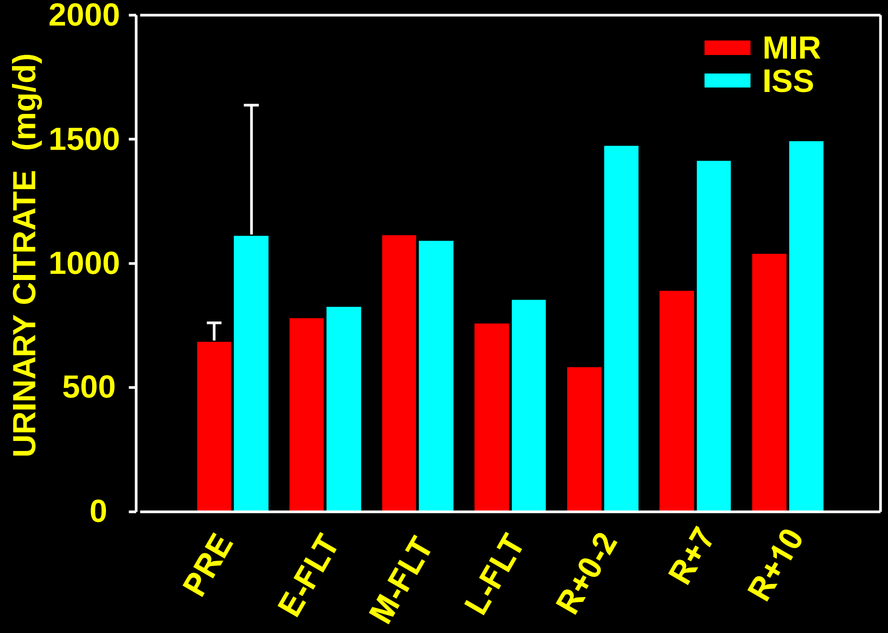
KCIT SUBJECTS



Comparison of in-flight risk to individual's preflight risk

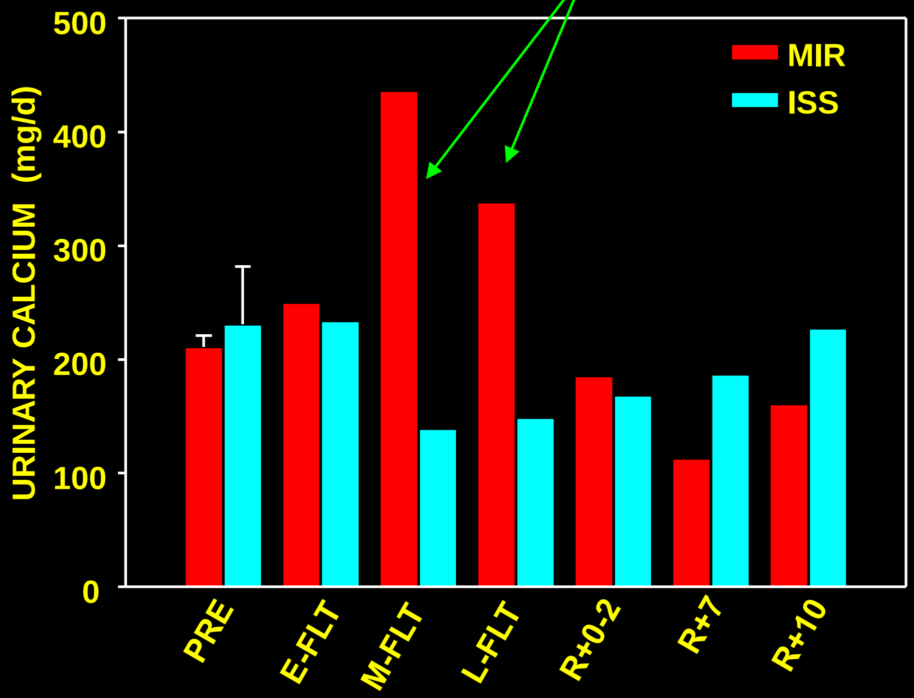
KCIT subjects maintained calcium oxalate risk at preflight levels

CASE STUDY



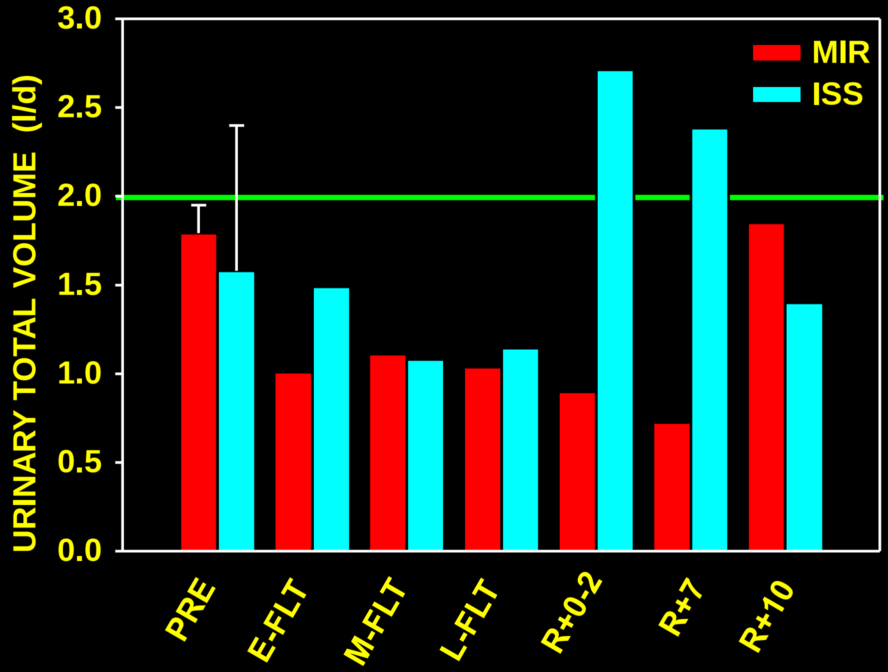
CREWMEMBER PARTICPATED
IN BOTH MIR AND ISS MISSIONS
MIR – No Treatment
ISS - KCIT

MIR IN-FLIGHT
HYPERCALCIURIA



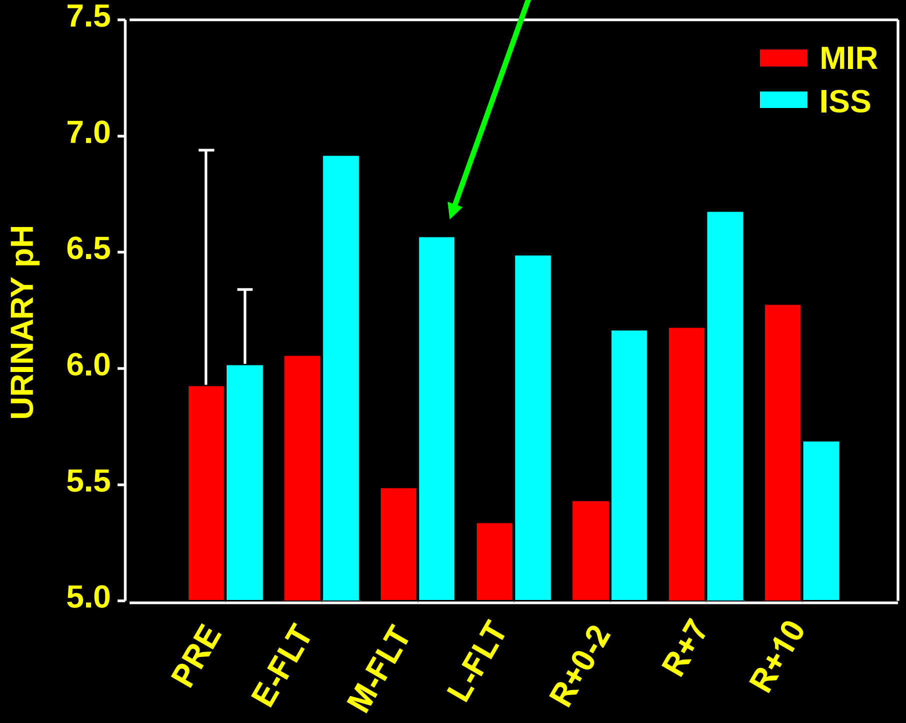
↓ IN-FLIGHT CALCIUM EXCRETION
DURING KCIT INGESTION

CASE STUDY

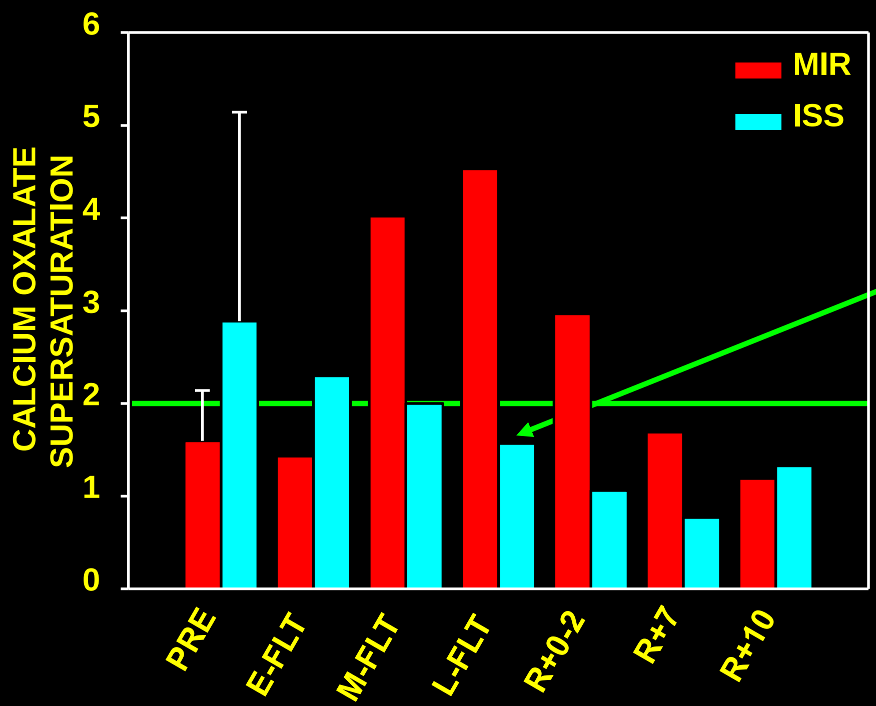


Low urine volume during both missions

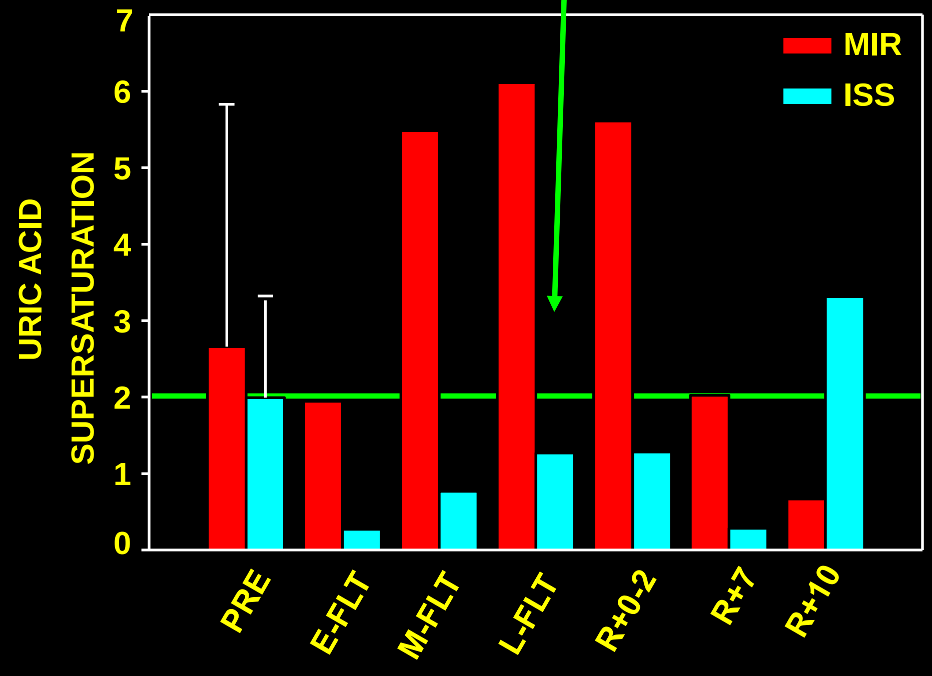
In-flight urinary pH during KCIT ingestion



CASE STUDY



Decreased urinary supersaturation during KCIT ingestion



Supersaturation values >2.0 indicate greater risk for stone formation

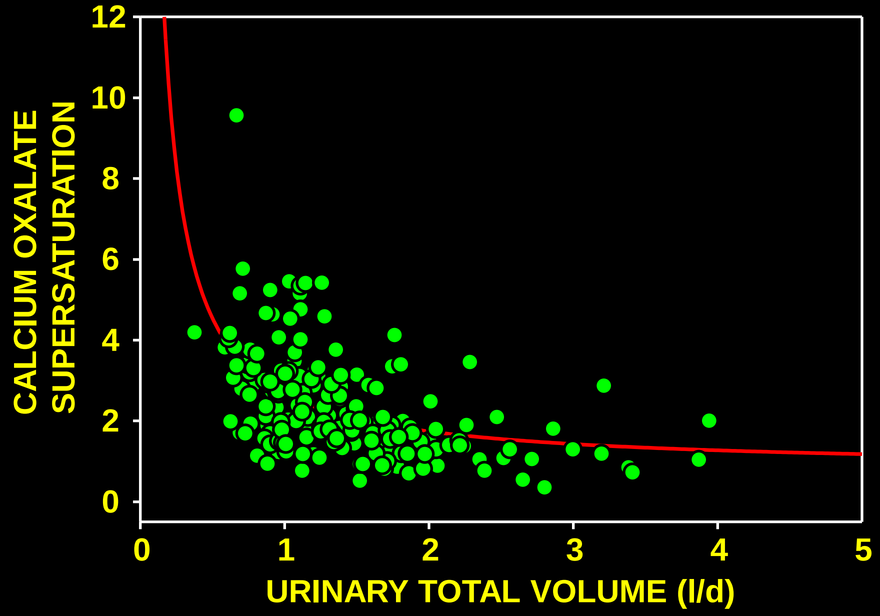
SIGNIFICANT FINDINGS

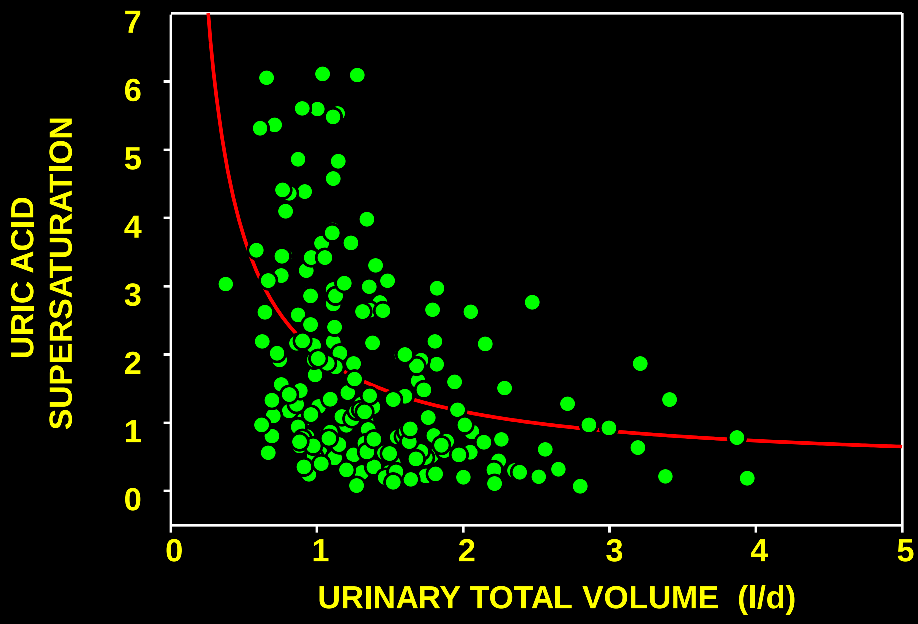
- KCIT treated subjects exhibited decreased urinary calcium excretion.
- KCIT subjects maintained the levels of calcium oxalate supersaturation risk at their preflight levels.
- Increased urinary pH levels in KCIT treated subjects reduced the risk of uric acid stones.
- Individual crewmember response may play a role in renal stone susceptibility and efficacy of countermeasures.

Risk Mitigation Strategies
and
Recommended Actions

Recommendations

➢ **Encourage increased fluid intake to increase urine volume**





Recommendations

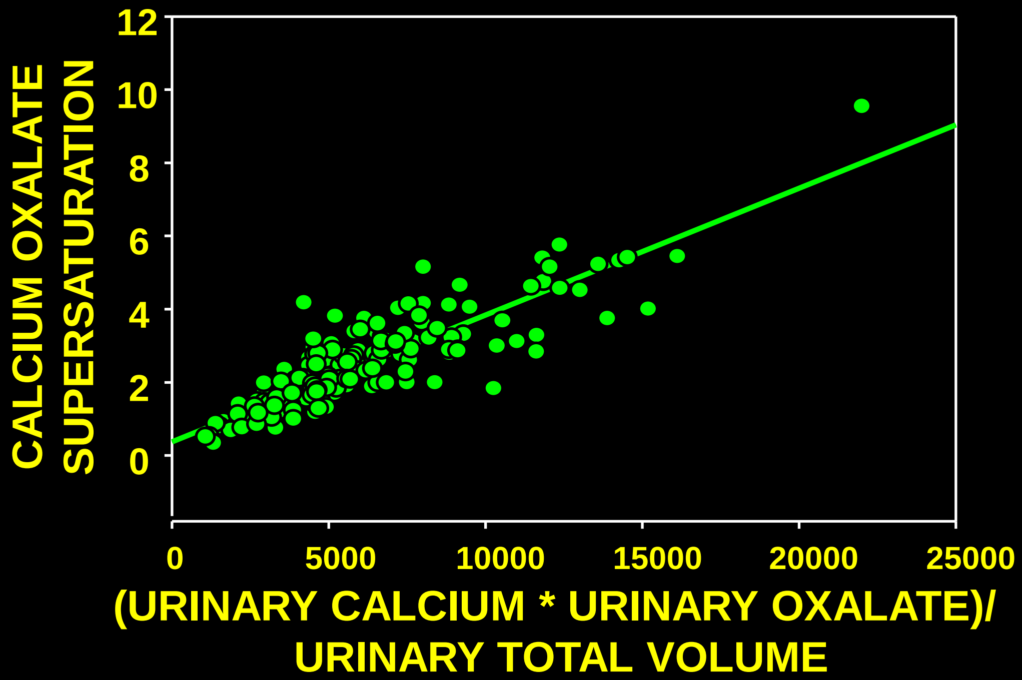
- **Use of Potassium Citrate**
  - urinary inhibitor of calcium-containing stones, binds with calcium reducing the amount of calcium available to form CAOX
  - inhibits crystal growth, aggregation and nucleation
  - alkalinizes urine and decrease urinary calcium excretion
  - supported by Space Medicine
  - in Transition to Medical Practice process for operational use

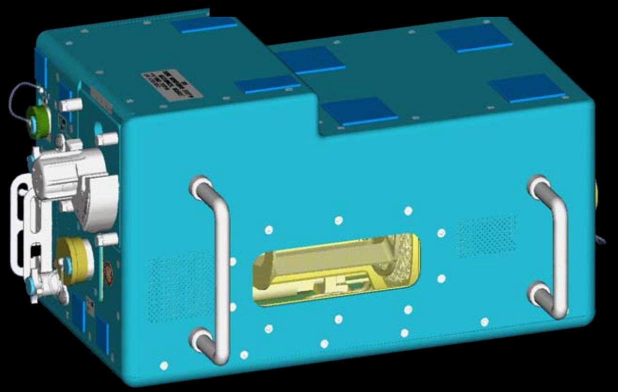
- **Assess dietary influences**
  - decrease protein, sodium and oxalate intake
  - maintain calcium intake to recommended levels

- **Perform urinary risk assessments**
  - identify crewmembers who are at any elevated risk
  - provides an education program to help humans remain healthy during space exploration

FUTURE POTENTIAL

Potential In-Flight Prediction of Stone Risk





Urine Monitoring System (UMS)

Capability to measure urine volume provided with the installation of the UMS on Flight 20A and the addition of the in-line calcium sensor for real-time data collection

Development of an oxalate sensor would be required to optimize real-time risk

PATIENT COMMENTS:
Characterizing the symptoms

“ I'd rather give birth to an elephant than go through this”.

“ Like being hit with a two-by-four” .

“ Like being shot with an arrow”.

“ Pain came on suddenly and did not pass until doctors hopped me up on pain meds. I've had my gall bladder removed and nearly severed my thumb but I never in my life felt pain like this. Would wish it upon no one!!

“ I have had my leg crushed by a car backing over it and that has nothing compared to the pain of a kidney stone” !!!!

ACKNOWLEDGEMEMTS

- All the astronauts and cosmonauts who participated in this study
- Mission Pharmacal, San Antonio, TX. for kindly providing both the potassium citrate and placebo drugs (Space Act Agreement)
- Mineral Metabolism Lab, Center for Mineral Metabolism & GCRC, UT Southwestern Med.Ctr. Dallas, TX
- NASA Johnson Space Center Clinical Laboratory
- NASA Johnson Space Center Nutritional Biochemistry Laboratory
- ISSMP Science and Flight Hardware support teams