USE OF POTASSIUM CITRATE TO REDUCE THE RISK OF RENAL STONE FORMATION DURING SPACEFLIGHT

P.A. WHITSON,[1] R.A. PIETRZYK,[2] C.F. SAMS,[1] J.A. JONES,[1] M. NELMAN-GONZALEZ[2] and E.K. HUDSON[3].
[1]NASA-JOHNSON SPACE CENTER, HOUSTON, TX., [2]Wyle, Houston, TX., [3]JES Tech, Houston, TX.

Introduction: NASA's Vision for Space Exploration centers on exploration class missions including the goals of returning to the moon and landing on Mars. One of NASA's objectives is to focus research on astronaut health and the development of countermeasures that will protect crewmembers during long duration voyages. Exposure to microgravity affects human physiology and results in changes in the urinary chemical composition favoring urinary supersaturation and an increased risk of stone formation. Nephrolithiasis is a multifactorial disease and development of a renal stone is significantly influenced by both dietary and environmental factors. Previous results from long duration Mir and short duration Shuttle missions have shown decreased urine volume, pH, and citrate levels and increased calcium. Citrate, an important inhibitor of calcium-containing stones, binds with urinary calcium reducing the amount of calcium available to form stones. Citrate inhibits renal stone recurrence by preventing crystal growth, aggregation, and nucleation and is one of the most common therapeutic agents used to prevent stone formation. Methods: Thirty long duration crewmembers (29 male, 1 female) participated in this study. 24-hour urines were collected and dietary monitoring was performed pre-, in-, and postflight. Crewmembers in the treatment group received two potassium citrate (KCIT) pills, 10 mEq/pill, ingested daily beginning 3 days before launch, all in-flight days and through 14 days postflight. Urinary biochemical and dietary analyses were completed. Results: KCIT treated subjects exhibited decreased urinary calcium excretion and maintained the levels of calcium oxalate supersaturation risk at their preflight levels. The increased urinary pH levels in these subjects reduced the risk of uric acid stones. Discussion: The current study investigated the use of potassium citrate as a countermeasure to minimize the risk of stone formation during ISS missions. Results suggest that supplementation with potassium citrate decreases the risk of stone formation during and immediately after spaceflight.

RENAL STONE RISK DURING SPACEFLIGHT: ASSESSMENT AND COUNTERMEASURE VALIDATION

PRINCIPAL INVESTIGATOR: Peggy A. Whitson, Ph.D., CB/NASA/JSC

CO-INVESTIGATORS:

Robert A. Pietrzyk, M.S., SK/Wyle
Jeffery A. Jones, M.D., SD/NASA/JSC
Clarence F. Sams, Ph.D, SK/NASA/JSC

SCIENCE TEAM:

Ed K. Hudson, Ph.D., SK/JES Tech
Mayra Nelman-Gonzalez, SK/Wyle

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

Urolithiasis and Stone Passage

(J. Urol. 162:688, 1999; Eur Urol 24:172 1993, J Urol 152:1095, 1994; J Urol 152:1095, 1994)

10-15% in US dx'd w urolithiasis; 20-25% in Middle East.
Stones 3 mm in size can cause transient or complete obstruction.
Recurrence approx 5-10%/year up to 75% at 20 years
Spontaneous passage rates of 12%, 22%, and 45% for proximal, middle, and distal ureteral calculi, respectively

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%

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.
- Evaluate the potential benefit of citrate to inhibit bone loss.
- “Primum non nocere” (First Do No Harm)

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

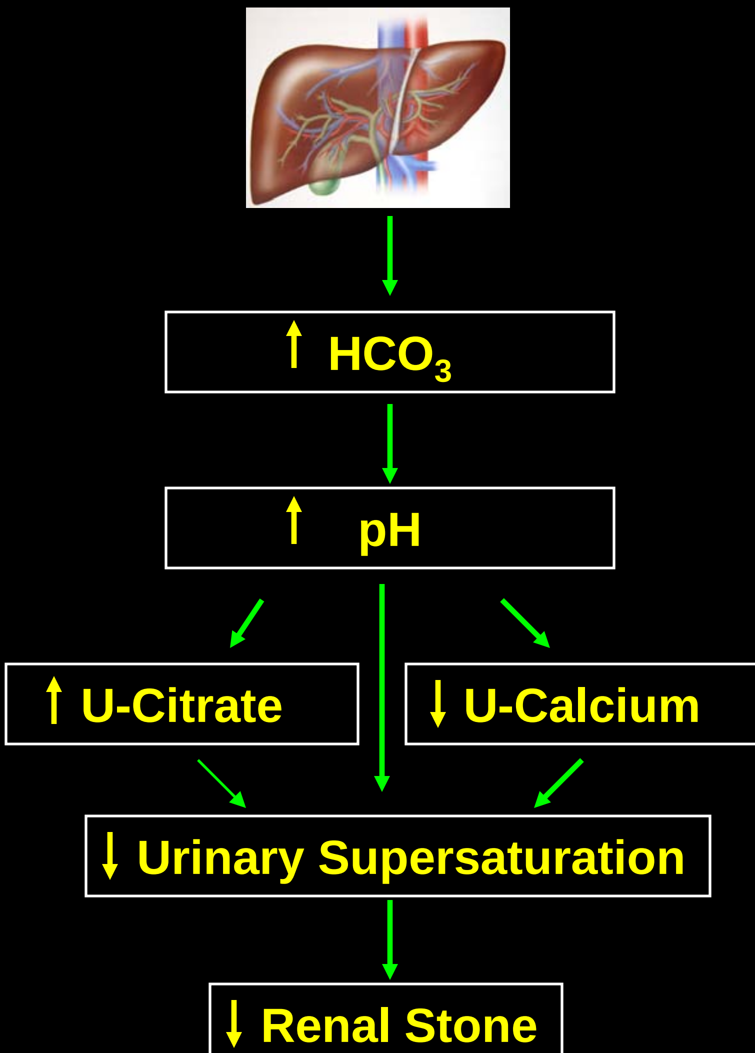
ISS missions	11 male/1 female subjects, mission duration 93 - 175 days

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

Potassium Citrate

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



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

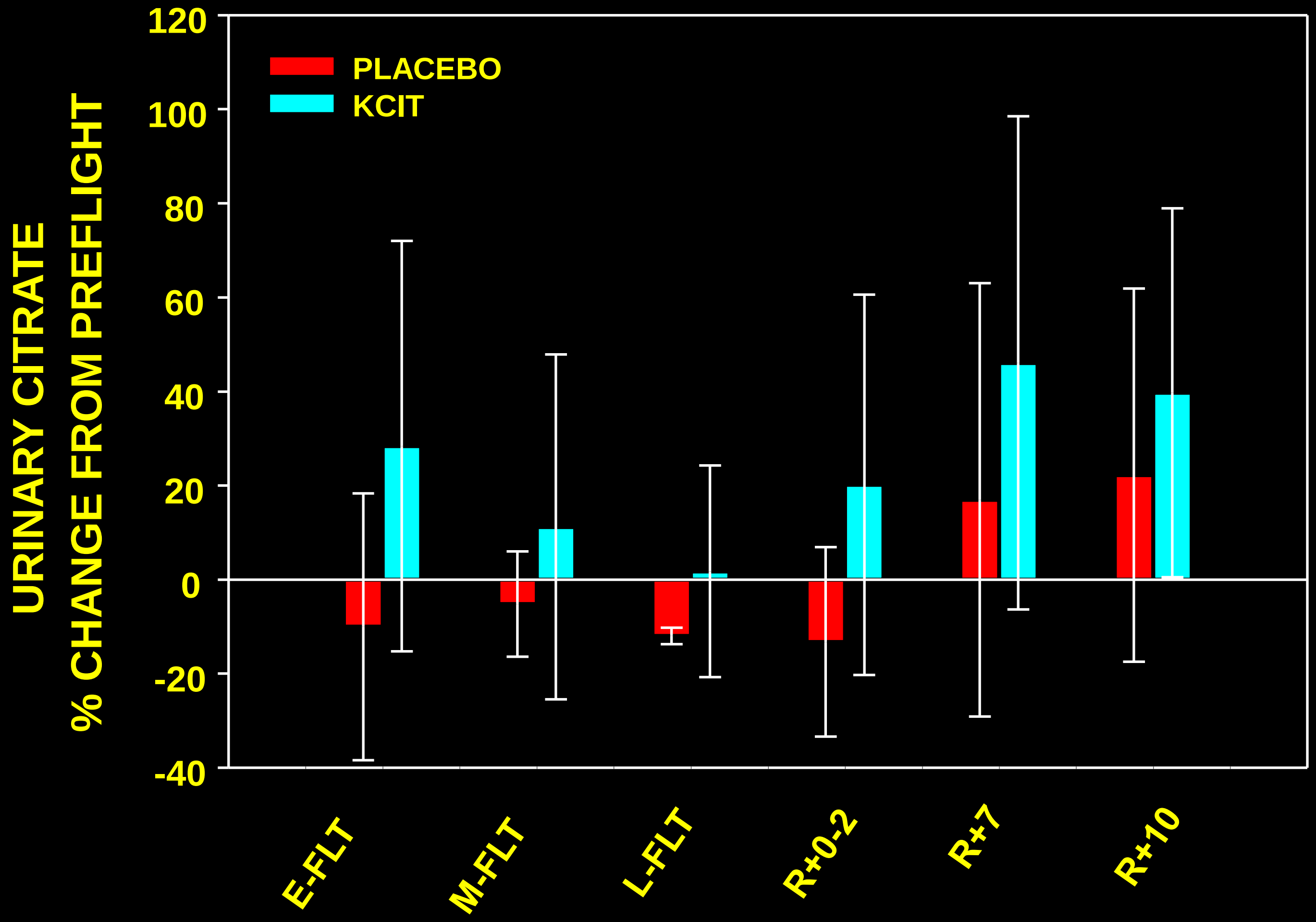
Effects on renal physiology

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

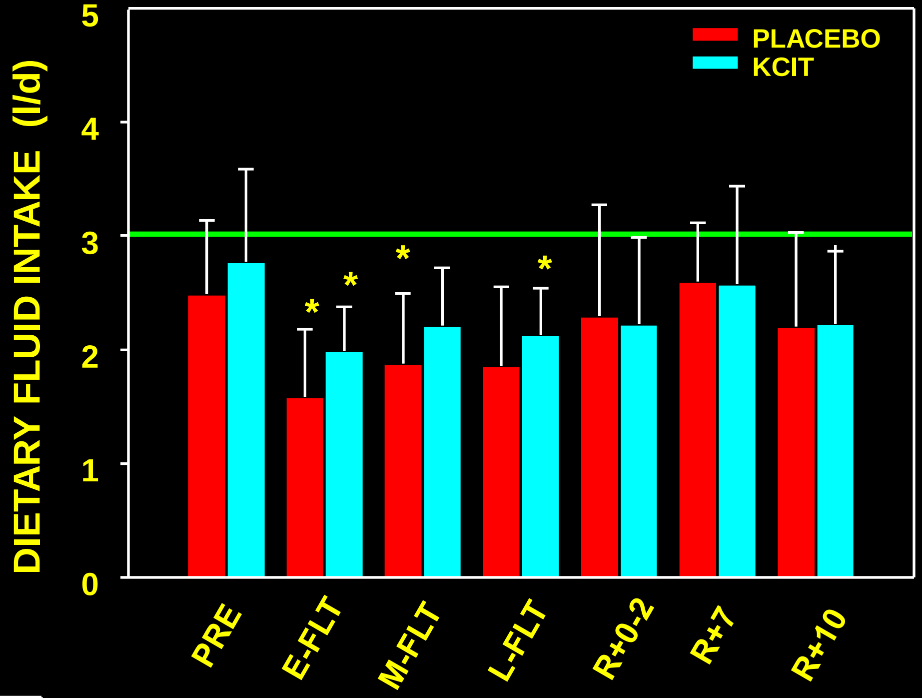
Urinary Citrate Levels
In Long Duration Crewmembers



E-FLT = Flight day <35
M-FLT = Flight day 36-120
L-FLT = Flight day >120
R+ = Postflight days

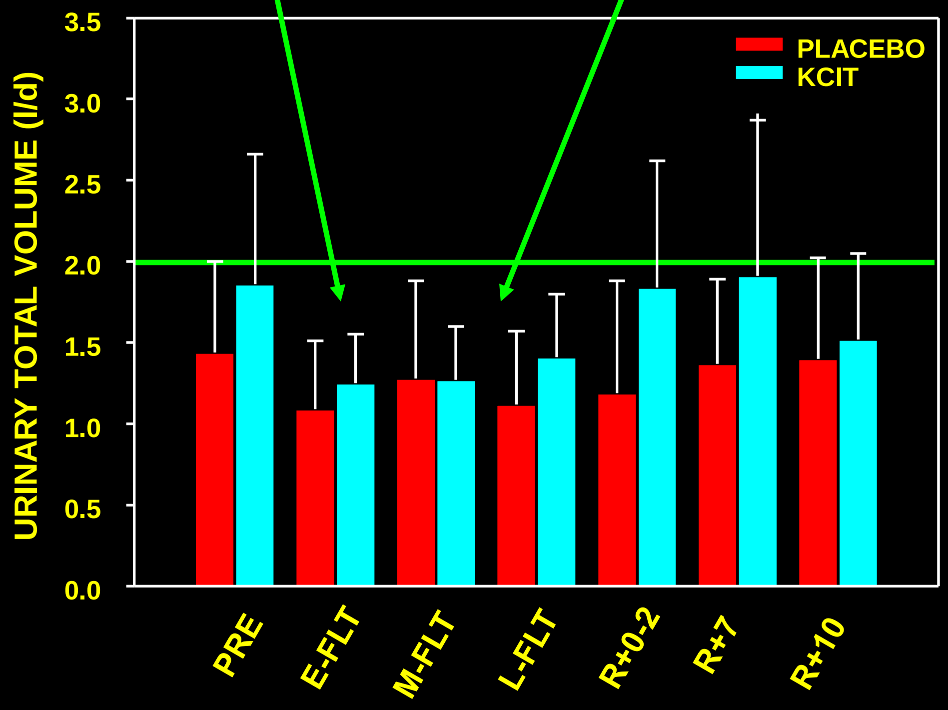
KCIT Pills

FLUID BALANCE



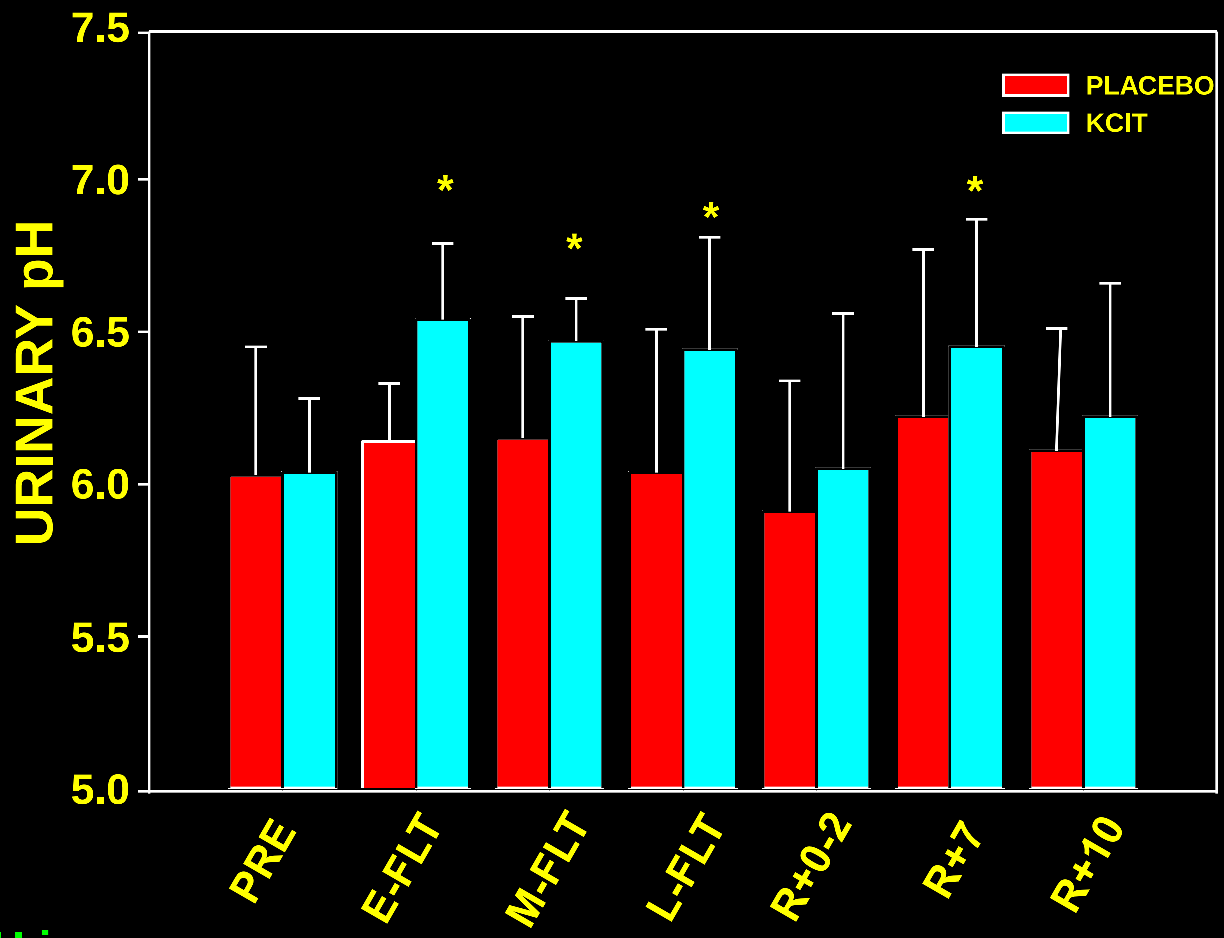
↓ Fluid intake during flight

Low urine volumes (< 2L/d)



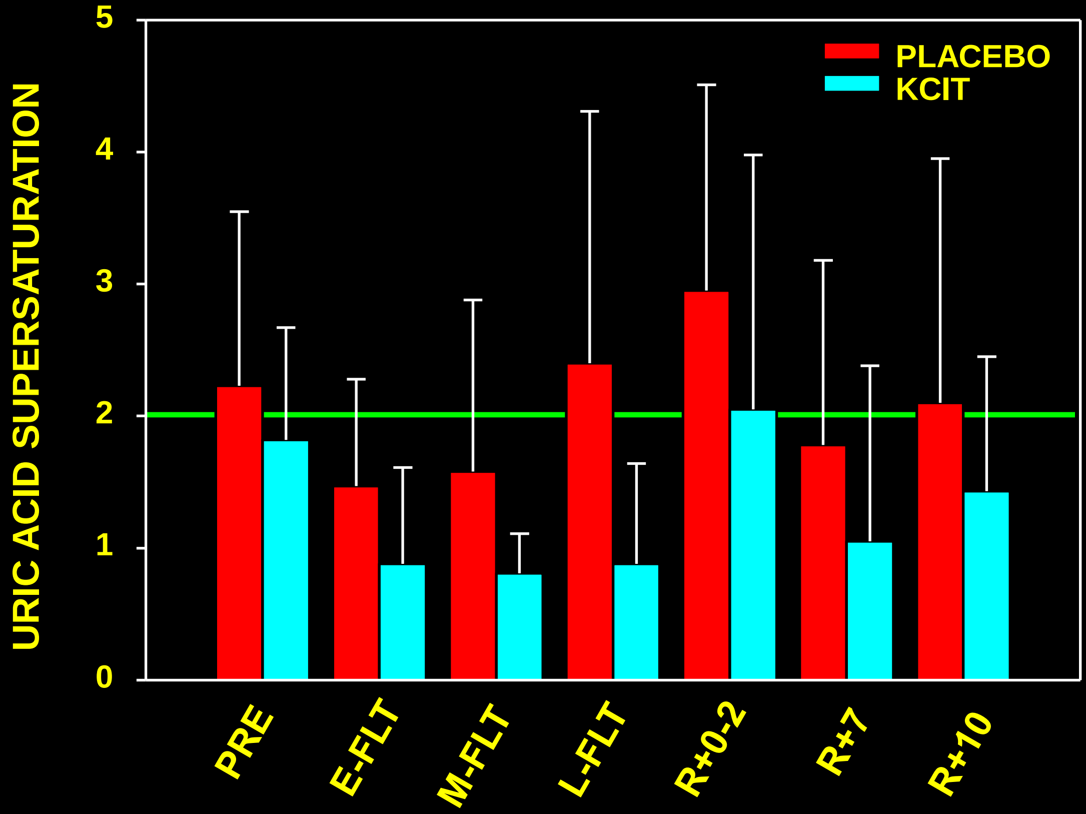
Similar fluid intake and total urine volumes between groups

Effect of Potassium Citrate on Urinary pH

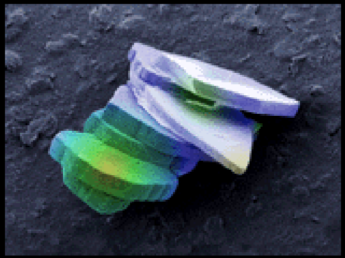


↑ Urinary pH in KCIT crewmembers, but not too high

Effect of Potassium Citrate on Uric Acid Supersaturation

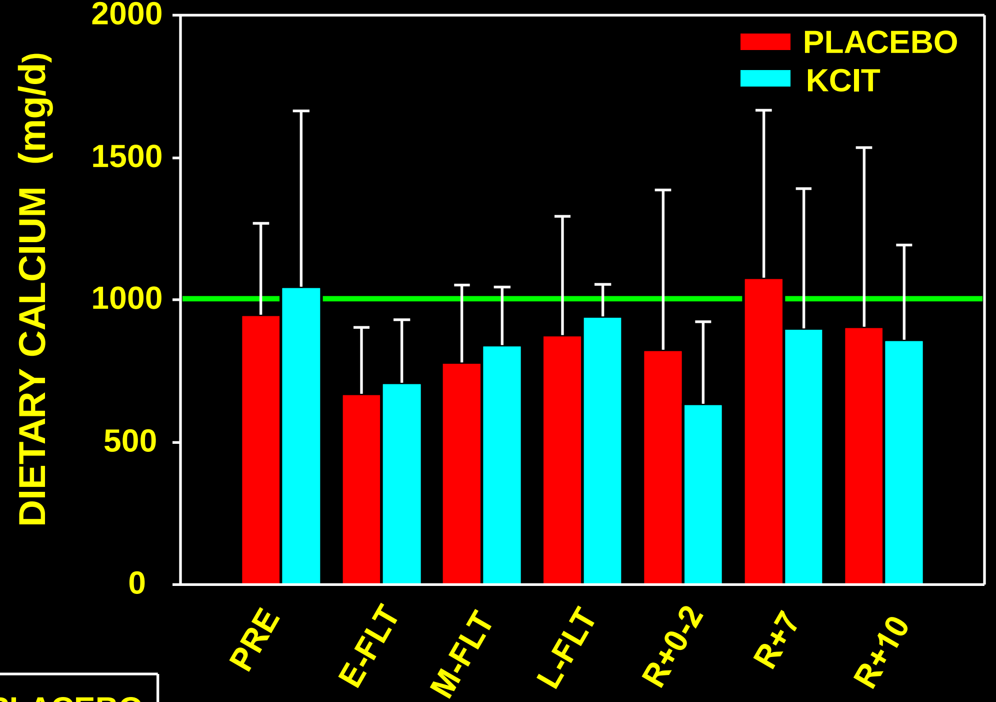


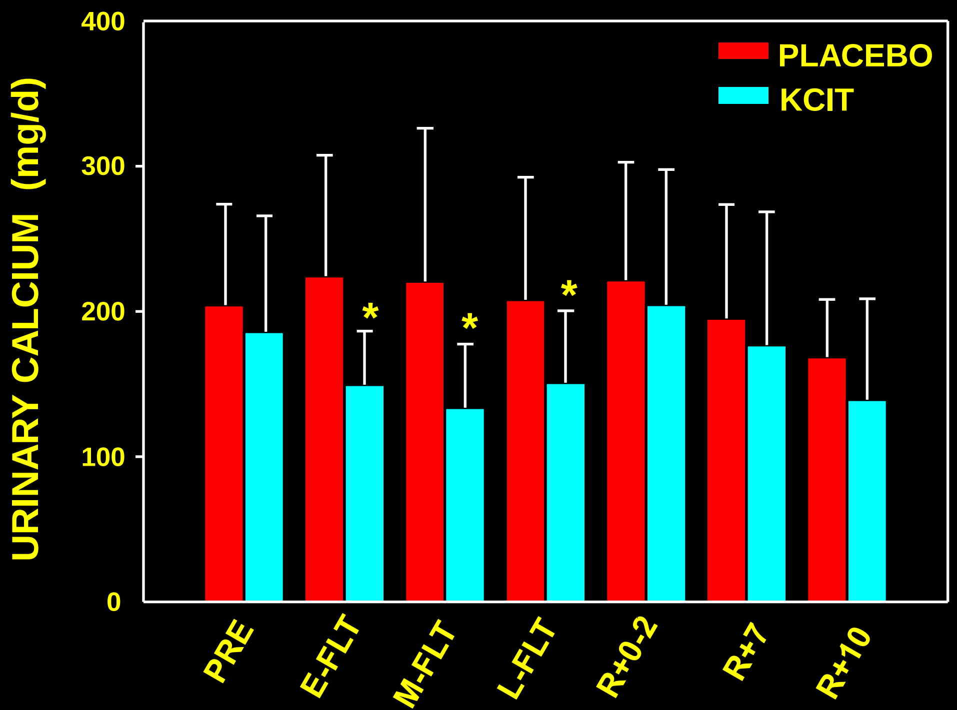
↓ Risk of uric acid stone formation in KCIT crewmembers



Uric Acid Stones
Image from Mission Pharmacal

CALCIUM BALANCE

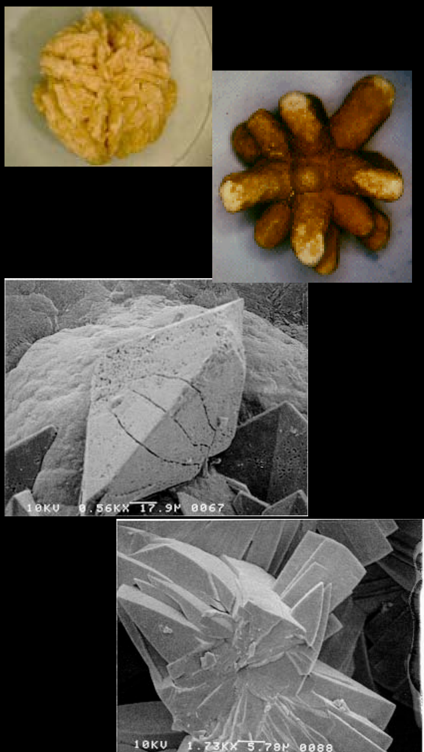


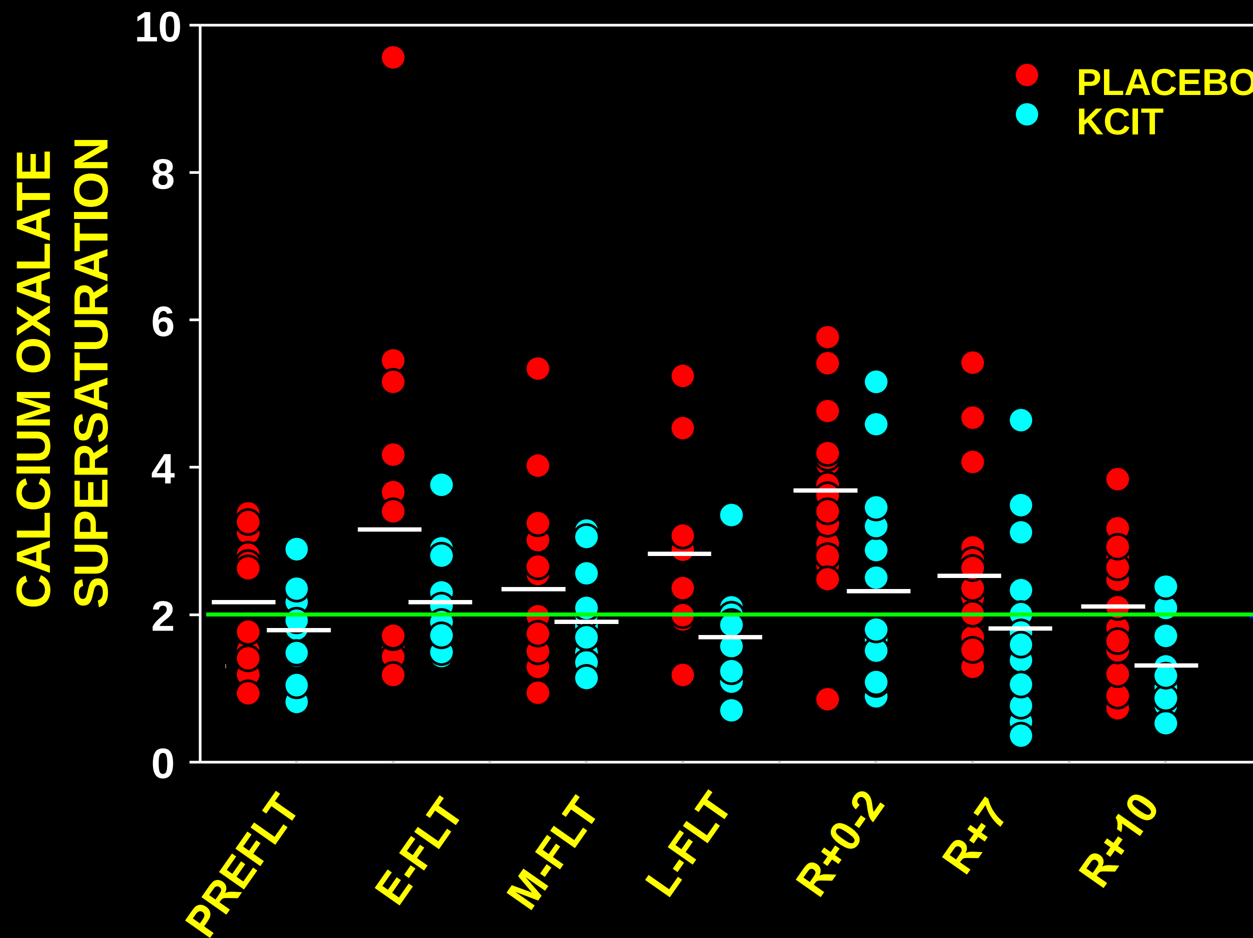


Dietary Ca intake below recommended levels

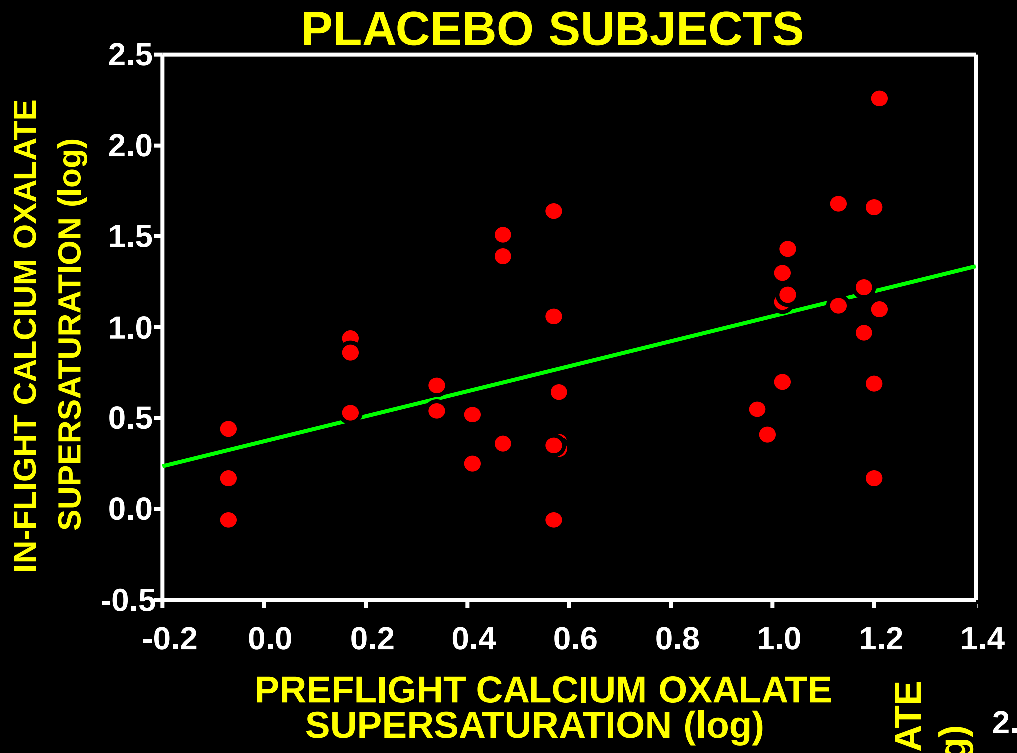
↓ Urinary Ca excretion in KCIT crewmembers

Calcium Oxalate Supersaturation Data From Long Duration Crewmembers

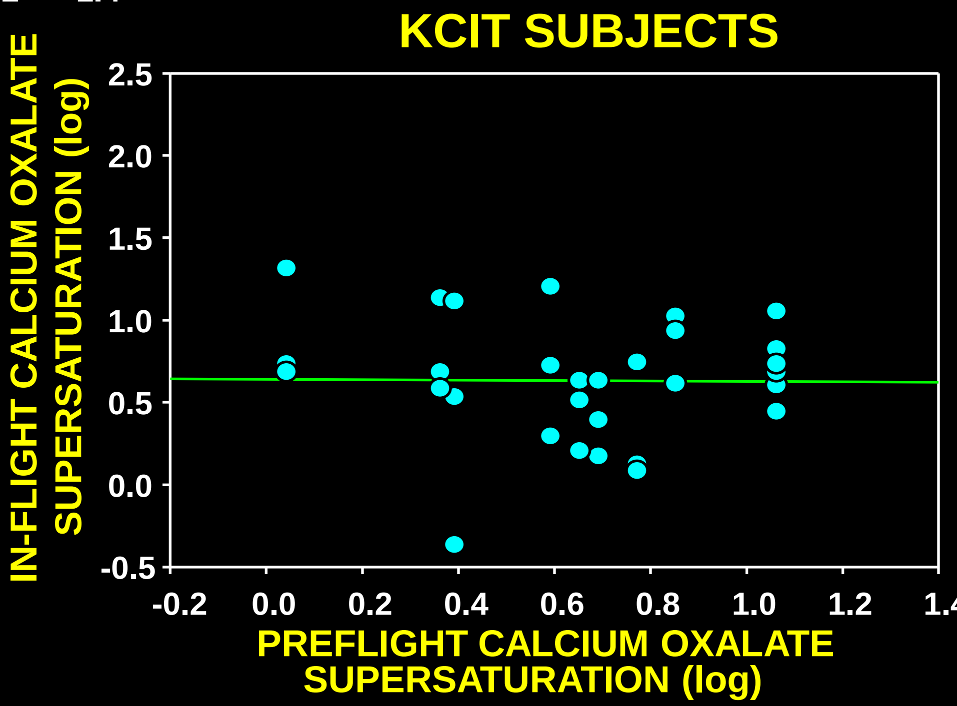




Values > 2.0 indicate increased risk



Risk of Calcium Oxalate Stone Formation



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

KCIT subjects maintained calcium oxalate risk at preflight levels

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.

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