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The Kidney in Space

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- 9 impossible wishes

  “To urinate on the moon…”

Pieter Brueghel the Younger (1564-1638): Netherlandish Proverbs

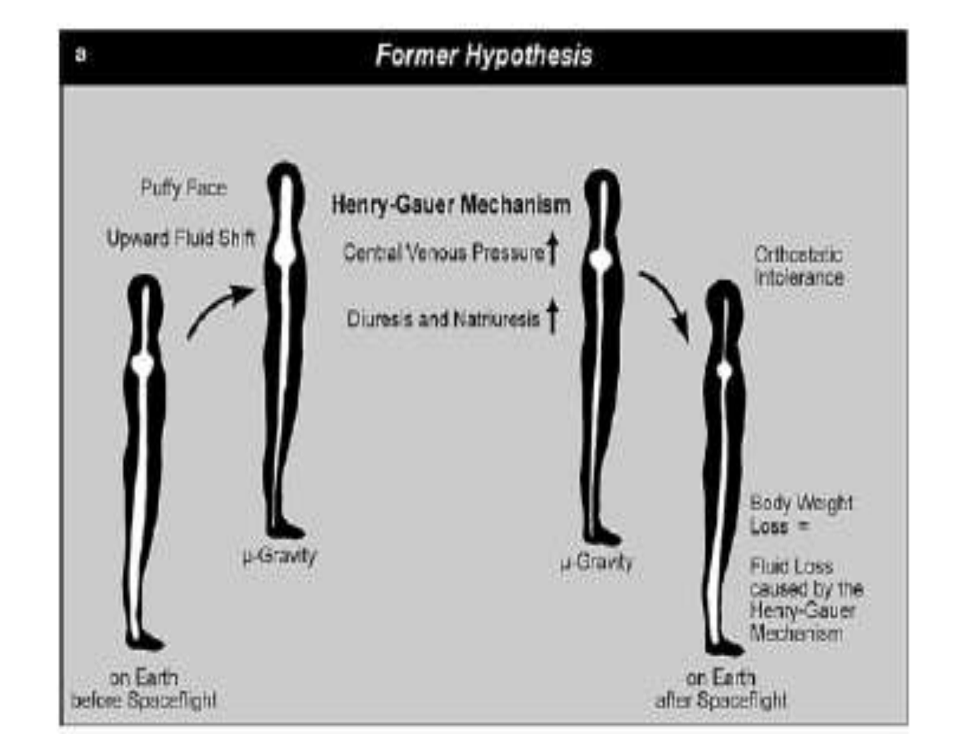
Kidney function in Space

- Fluid balance in space differs than that on Earth
- It also differs from that in the so-called microgravity simulation models on Earth (head-out water immersion and head-down tilting)
- Renal responses to microgravity are complex and far from being completely understood

- Water and sodium homeostasis - GFR
- Urinary Albumin Excretion
- Acute Urinary Retention
- Renal Stone Formation

Henry-Gauer reflex theory

- Central hypervolemia as caused in space by a cephalad fluid shift of 2L the heart stretches and diuresis and natriuresis ensues
- This was supported by the weight loss observed in early astronauts and the Puffy Face and bird legs



Drummer C et al, Nephron 2002

Water balance

- Reduction in water intake (Space Motion Sickness, reduced thirst)
- Reduction in evaporative water loss

(reduced convective air flow, persistent sweat film than sweat dripping, reduced energy requirements and reduced need for thermoregulatory convective heat transfer)

Leach CS et al, J Appl Physiol 1978
Drummer C et al, Am J kidney Dis 2001

Body fluid redistribution in Space

- A 17% reduction of plasma volume
- No indication of an early absolute fluid loss (in contrast to ground simulation models)
- Weight loss due to low caloric diet
- However, blood volume is decreased within the first few days after launch
- Albumin and water spill over to the interstitial fluid (also due to reduced muscle activity/mechanical stress)
- Total Body Water was stable

Leach S et al, J Appl Physiol 1996
Drummer C et al, Am J Kidney Dis 2001

Renal response to i.v. isotonic saline

2% BW i.v. saline load

Comparison among:

- supine position on earth (moderate G-stress)
- seated position on earth (stable G-stress) and
- space flight day 5 (no SMS)

Attenuated diuretic and natriuretic response

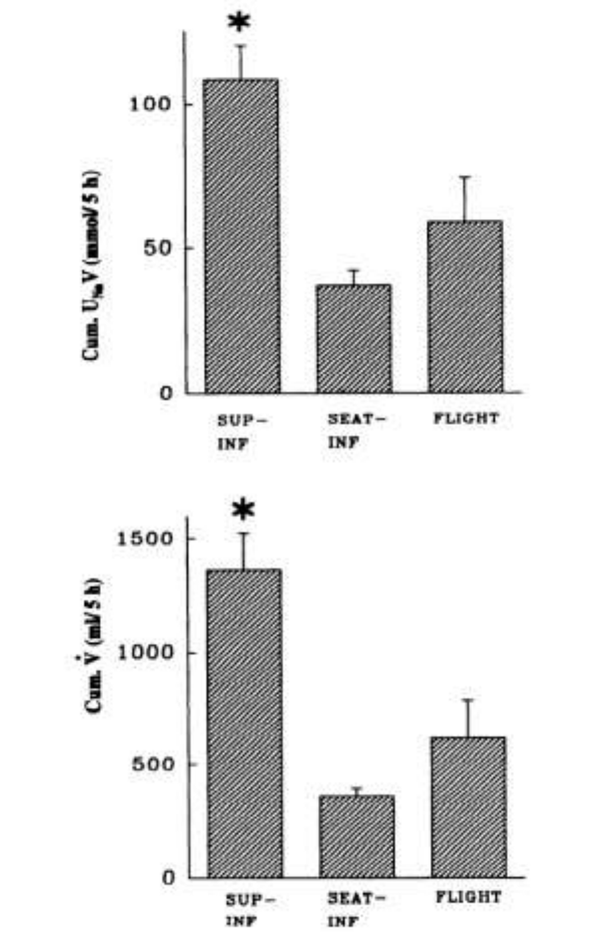


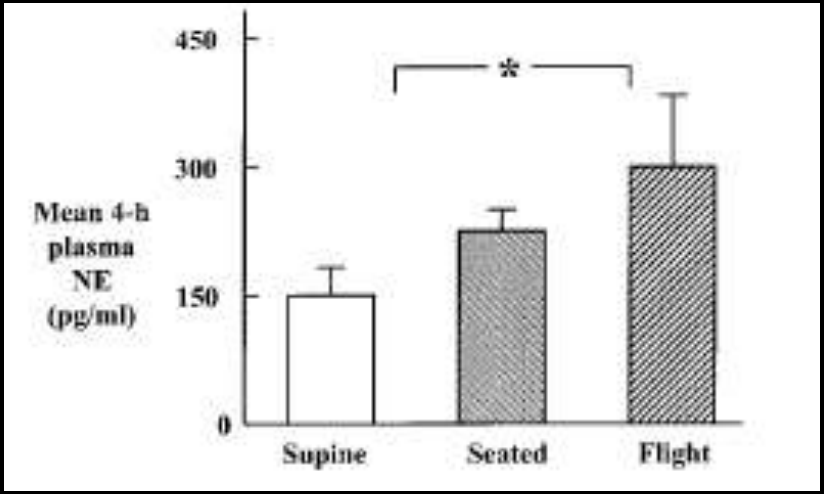
FIG. 2. Cumulative excretion of sodium (Cum $U_{Na}V$) and urine (Cum $\dot{V}$) over 5-h observation period from before to 3 h after infusion (Inf) in ground-based supine (Sup-Inf) and seated (Seat-Inf) positions and during Flight. * Significantly different compared with during Seat-Inf and Flight ($P < 0.05$).

Norsk P et al, J Appl Physiol 1995

Renal response to i.v. isotonic saline
Sympathetic activity

- Increased sympathetic activity (Nor) resembling the upright position on Earth. Unexpectedly elevated

- Extracellular volume more reduced than anticipated by Henry-Gauer theory



Norsk P et al, J Appl Physiol 1995

Renal response to oral water load

- 600 ml oral water load
- Water load
  - decreases serum osmolality,
  - suppresses ADH leading to diuresis
- In space this response was blunted
- Urine osmolality was less reduced

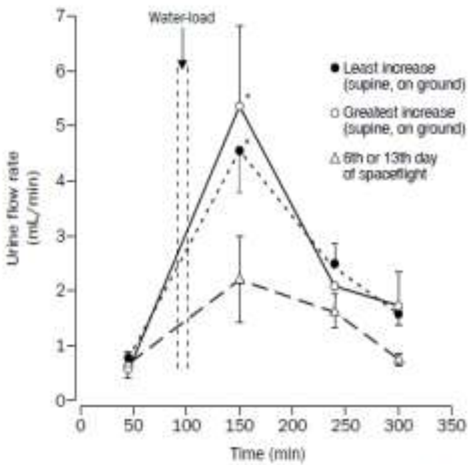


Figure 1: **Urine flow rate after an oral water load of 600 mL in space**
*Significant change (ANOVA, p<0·05) from value before water load.

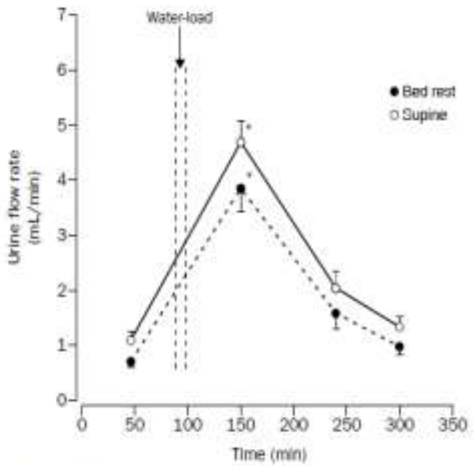
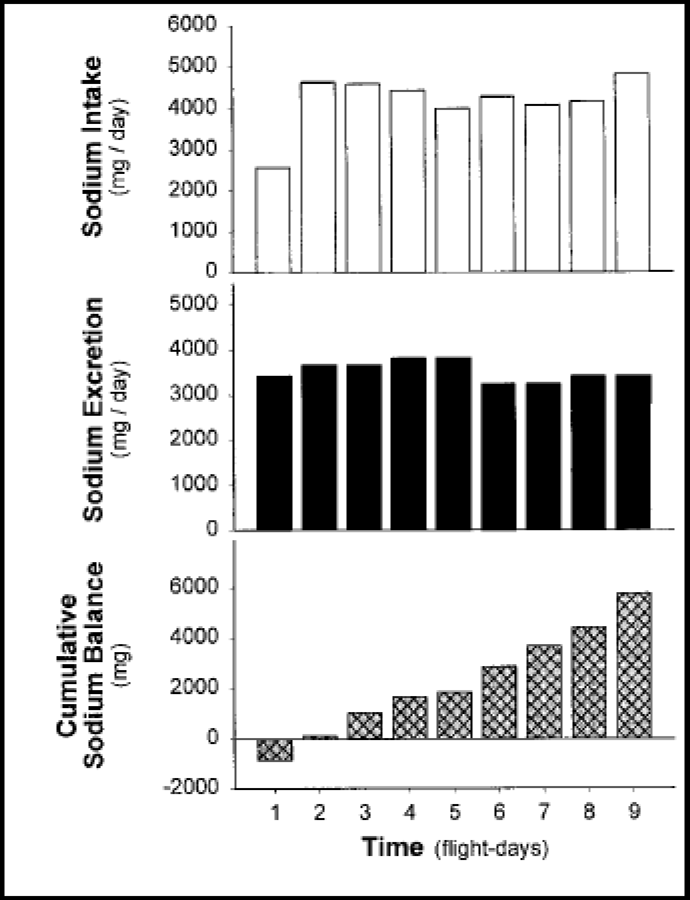


Figure 2: **Urine flow rate following an oral water load of 600 mL during simulation of weightlessness by head-down bed rest**

Norsk P et al, Lancet 2000

Sodium handling

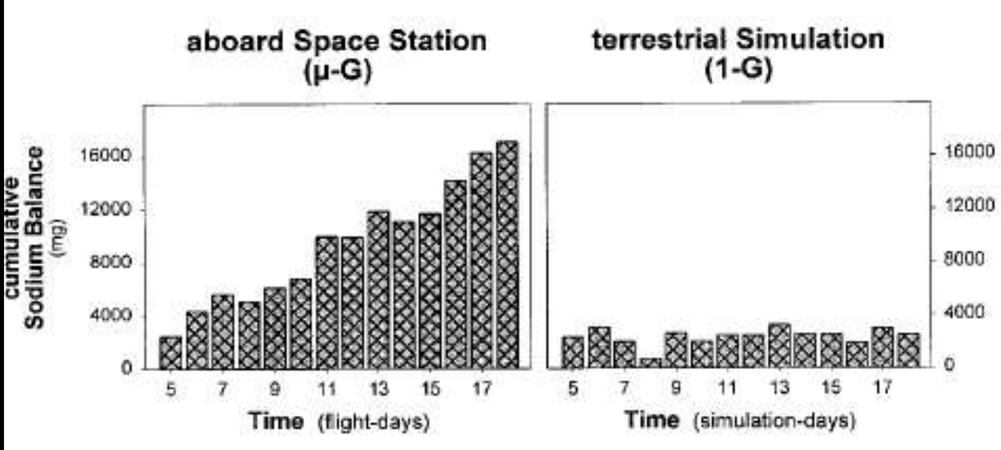
- Insensible losses are Na free
- Fecal losses <2%TBNa
- No severe sweating observed
- Stable sodium intake
- Net daily Na retention of 40-70 mmol



Leach CS et al, J Appl Physiol 1996

Sodium handling

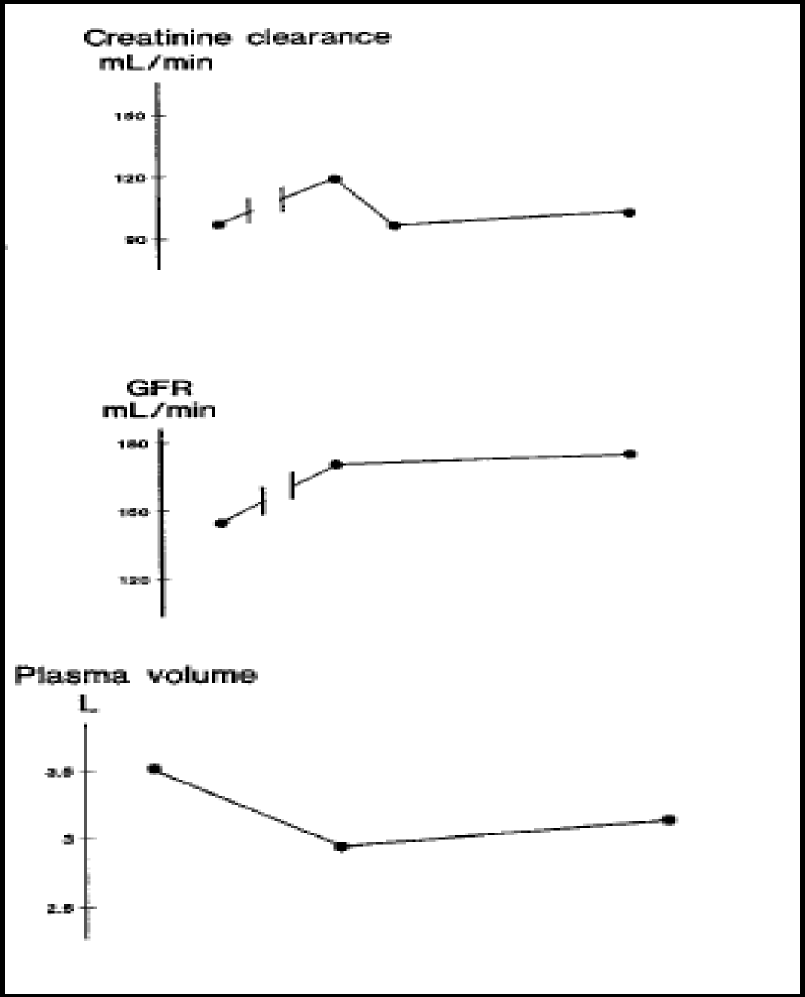
- A metabolic ward experiment in one astronaut in space and in a terrestrial simulation model
- Fixed and identical Na intake
- Significantly lower urinary Na excretion in Space resulting in a positive Na balance



Drummer C et al, Eur J Clin Invest 2000

Glomerular filtration rate (GFR)

- A moderate transient increase in GFR during the first 2 days in space
- Stable renal plasma flow
- Subsequently filtration fraction increases and a new equilibrium is reached



Leach S et al, J Appl Physiol 1996
Kramer HJ et al, Am J Kidney Dis 2001

Renal hemodynamics

- The increased Na reabsorption and the normal GFR indicate that changes in the tubular handling of Na play a primary role
- A low interstitial hydrostatic pressure in the kidney leads to an increase in filtration fraction (tubulo-glomerular feedback) and Na reabsorption
- Low fluid intake and increased ADH leads also to Na reabsorption and maintains normal renal hemodynamics despite the low plasma volume

Kramer HJ et al, Am J Kidney Dis 2001

ADH

- Early in flight ADH is expected to be very high (SMS)
- During chronic adaptation ADH levels were considerably elevated accordingly to the reduced plasma volume
- There are some data suggesting diminished bio-activity of ADH during flight

Drummer C et al, Am J Kidney Dis 2001

Atrial Natriuretic Peptide (ANP)

- ANP is released upon atrial stretching
- In Space ANP exhibits a biphasic profile
  - Increases during the first hours in space (contributing to increased vascular permeability and fluid extravasation)
  - Decreases later (50% of pre-flight levels on day 7)
- Similar results for c-GMP (ANP’s second messenger)

Drummer C et al, Am J Kidney Dis 2001

Plasma Renin Activity (PRA)

- Persistently increased PRA indicating that the retained Na is rapidly transferred to extravascular compartments

Table 1. Plasma Renin Activity in Astronauts During Space Flight and on Ground (Preflight)

	Plasma Renin Activity			
			Preflight	
	Units	µG	Supine	Seated
Spacelab D-2	pg/mL	18.3*	3.2	13.6
MIR	µU/mL	30.2†	8.2	17.9
Eur 1997	µU/mL	78.0‡	46.0	NM

Abbreviation: nm, not measured.
*Flight day = 5.[18]
†Flight day = 26.[10]
‡Flight day = 3 through 11 (4 repeats).[9]

Drummer c et al, Eur J Clin Invest 2000

Albuminuria (I)

- Urine Albumin Excretion (UAE) depends on:
  - glomerular load of albumin,
  - GFR,
  - glomerular hydrostatic pressure,
  - permselectivity of the glomerulus and
  - albumin reabsorption in the proximal tubule
- In space, an escape towards the interstitium could be hypothesized

De Santo NG et al, J Ren Nutr 2005

Albuminuria (II)

- Russian Data from 2 long term cosmonauts on the MIR showed an increased UAE

Grogoriev AI et al, Clin Invest 1994

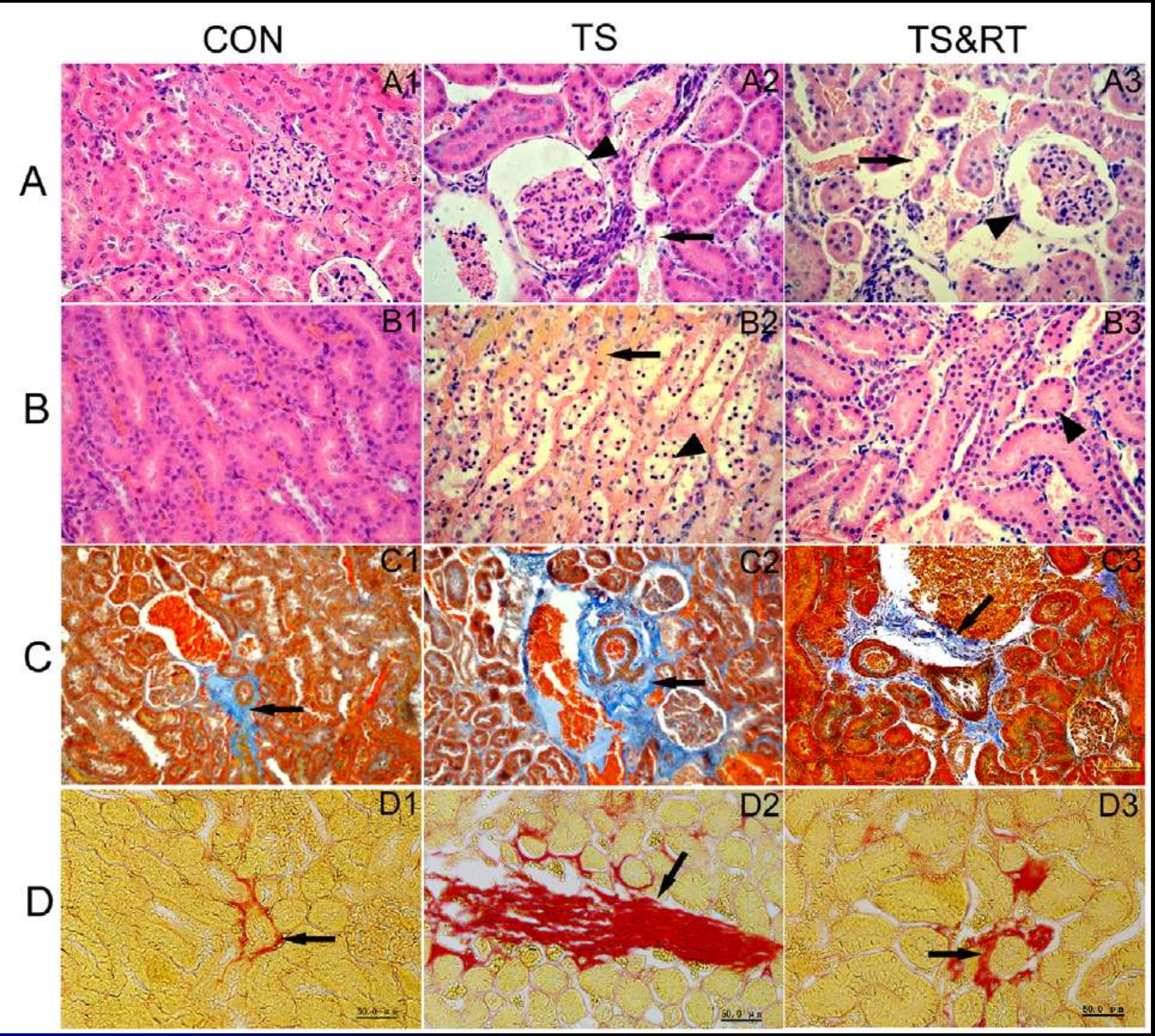
- UAE was 27% less during space flight in astronauts from various missions

De Santo NG et al, J Am Soc Nephrol 2001

- In another study on 4 astronauts UAE was significantly lower in space

Cirillo M et al, Nephron Physiol 2003

Histopathological changes in weightlessness – the effect of resistance training



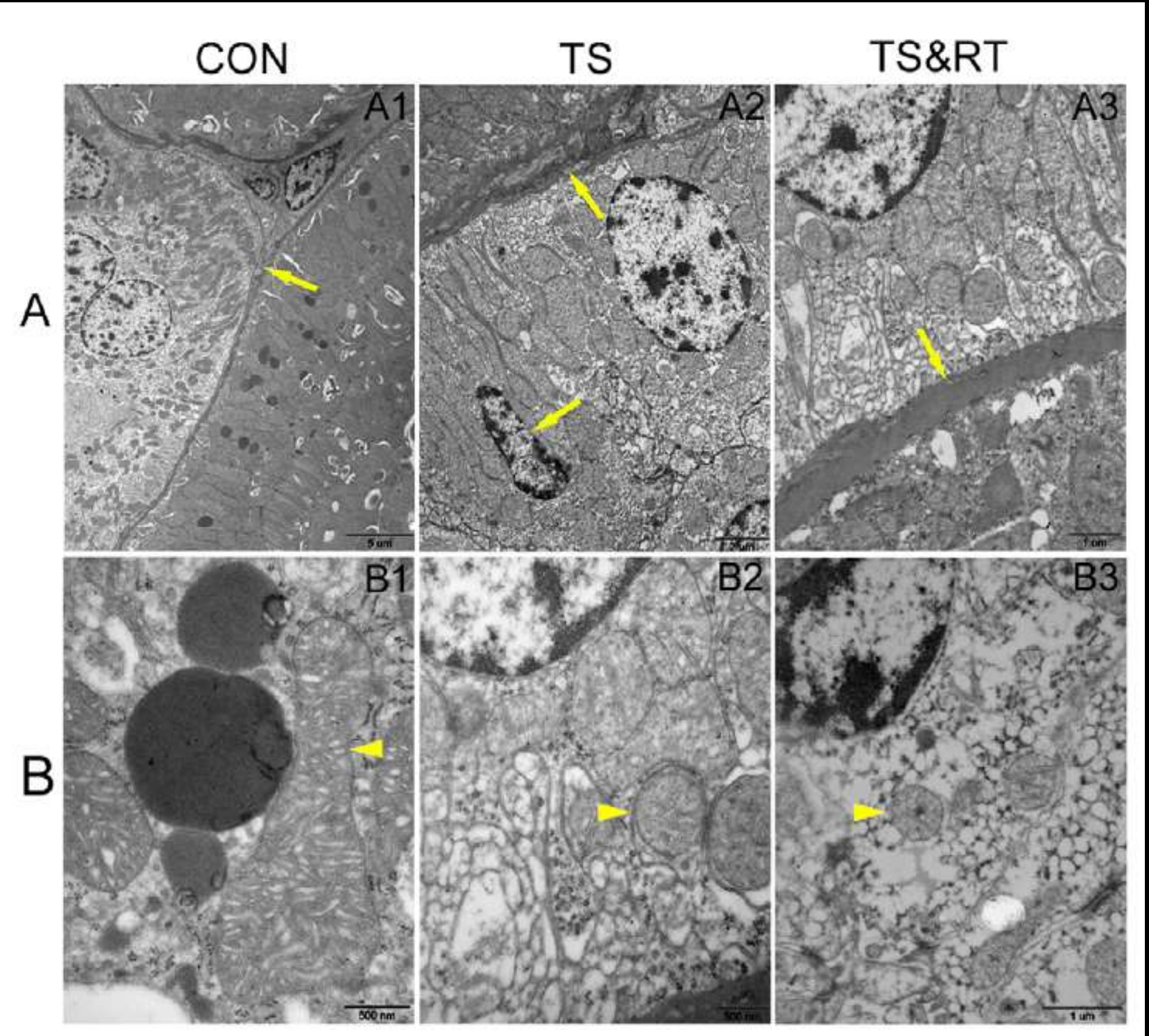
Glomerular atrophy
Interstitial edema
Distension of glom capsular space

Tubular epithelial cells Degeneration
casts

Fibrosis

Ding Y et al, Plosone 2011

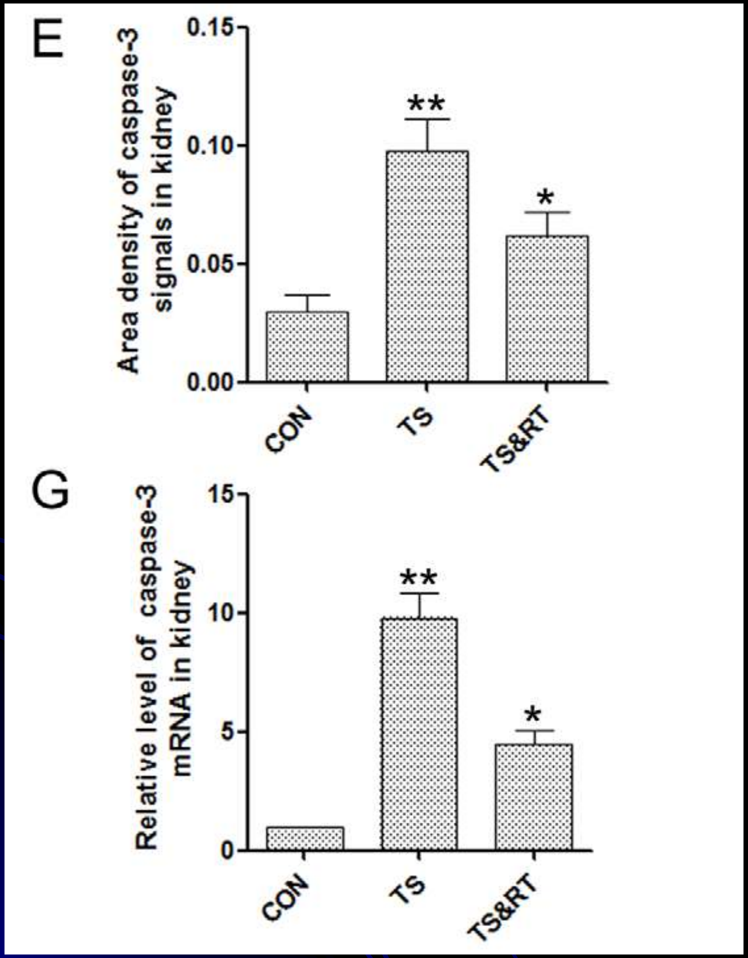
Histopathological changes in weightlessness – the effect of resistance training



Incrassate BM of renal tubules
Swollen mitochondria

Ding Y et al, Plosone 2011

Increased apoptosis of kidney cells in weightlessness



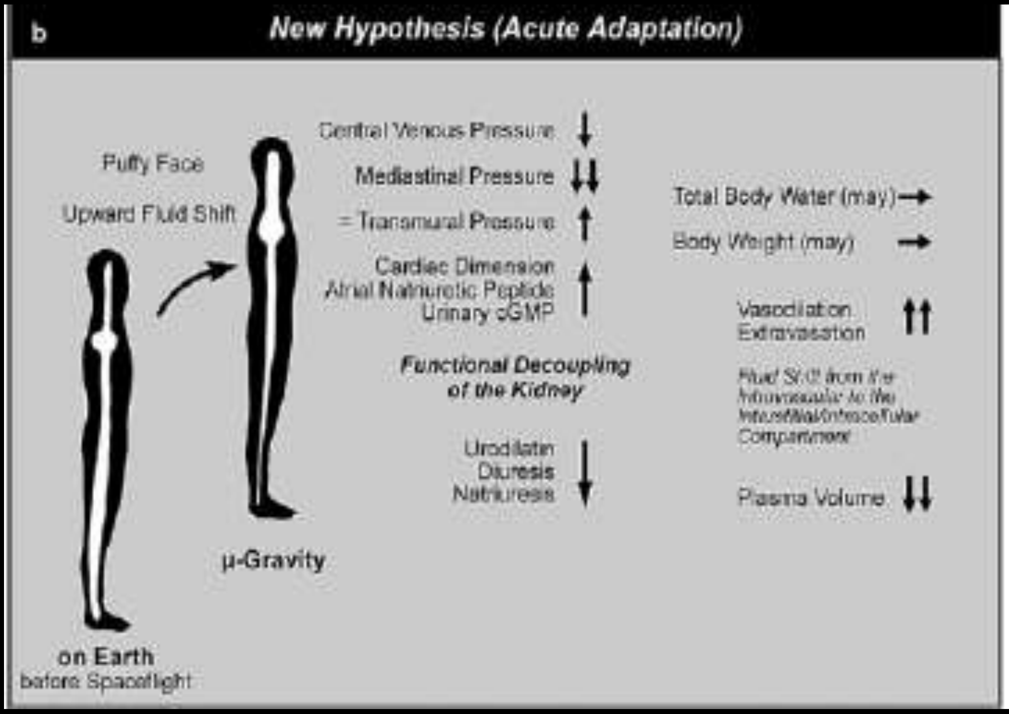
Ding Y et al, Plosone 2011

Kidney function in space

The current hypothesis

Acute adaptation

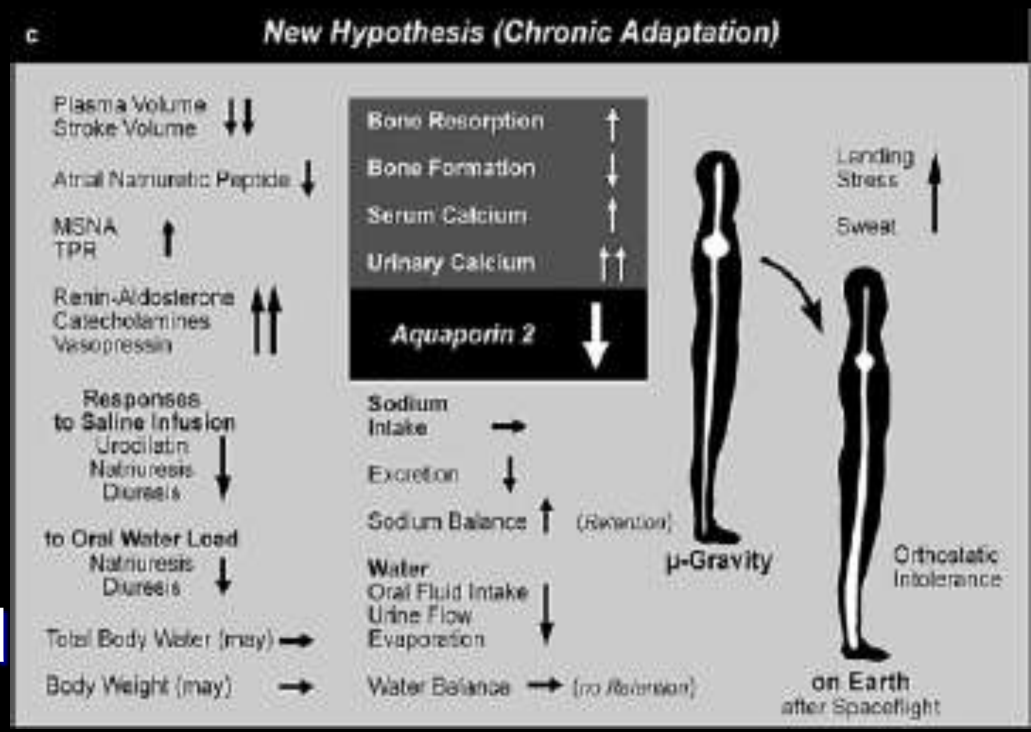
- Increase in central BV
- Reduced CVP and mediastinal pressure
- Release of ANP
- Kidney decoupling
- Diuresis, natriuresis are suppressed
- Stable TBW
- Extravasation of fluid to the interstitium
- Decreased plasma volume



Drummer C et al, Nephron 2002

Chronic adaptation

- Reduced plasma volume
- Suppression of ANP
- Increased renin, norepinephrin, ADH
- Suppressed AQP-2
- Sodium retention and redistribution
- No water retention
- Descending to Earth: orthostatic intolerance



Drummer C et al, Nephron 2002

Clinical implications
"Life in Space for real Life on Earth"

- Renal responses to microgravity may be similar to those in patients with heart failure (Na retention, oedema, low BV, increased sympathetic activity)
- Question: How can astronauts during prolonged space flight exhibit the same physiological patterns as heart failure patients without being sick?

Norsk P et al, Am J Kidney Dis 2001

Acute urinary retention

- 2 astronauts, 3 cases
- Pharmacologic (scopolamine for SMS, promethazine)
- Psychogenic (diapers, strenuous work schedule)
- Loss of gravitational force (?)
- *Change in SMS medication, appropriate medical supplies (catheters, antibiotics)*

Stepaniak PC et al, Aviat Space Environ Med 2007

Renal stone formation

- Urinary stone formation process: Nucleation, growth, aggregation and concretion in which the solubility of crystalloids exceeds saturation
- Nephrolithiasis has a lifetime incidence of up to 13% in N. America and 20% worldwide
- 75% of stones are calcium containing stones (CaOx and calcium phosphate)
- These stones are often related with hypercalciuria

Ranello A et al, J Nephrol 2000
Zerwekh JE, Nutrition 2002

Renal stone formation in space

- 14 episodes in 12 US astronauts
  (9 episodes post-flight)
- Multiple episodes in Russian cosmonauts (One in-flight episode endangered a flight but was relieved by spontaneous stone passage)

Pietrzyk RA et al, Aviat Space Environ Med 2007

Risk factors for kidney stones in space

- Hypercalciuria (Osteoclastic activity is dramatically increased - 1.5% loss of bone mass/month)
- Hyperphosphaturia
- Low urine volume (decreased plasma volume -10-15% and episodes of dehydration)
- Hypocitraturia (low alkali and high protein diet)
- Low urine pH
- Low urine uric acid but with decreased solubility
- High urine sodium *after landing*
- Low urinary Mg

Zerwekh JE, Nutrition 2002

Jones JA et al, Aviat Space Environ Med 2008

Nanobacteria: a potential cause of kidney stone formation

- Extremely small sized agents that behave as microbes with very slow multiplication rate
- Ca precipitation and P concentration
- Nucleus for crystal formation or allowing growth of crystals under lower supersaturation conditions

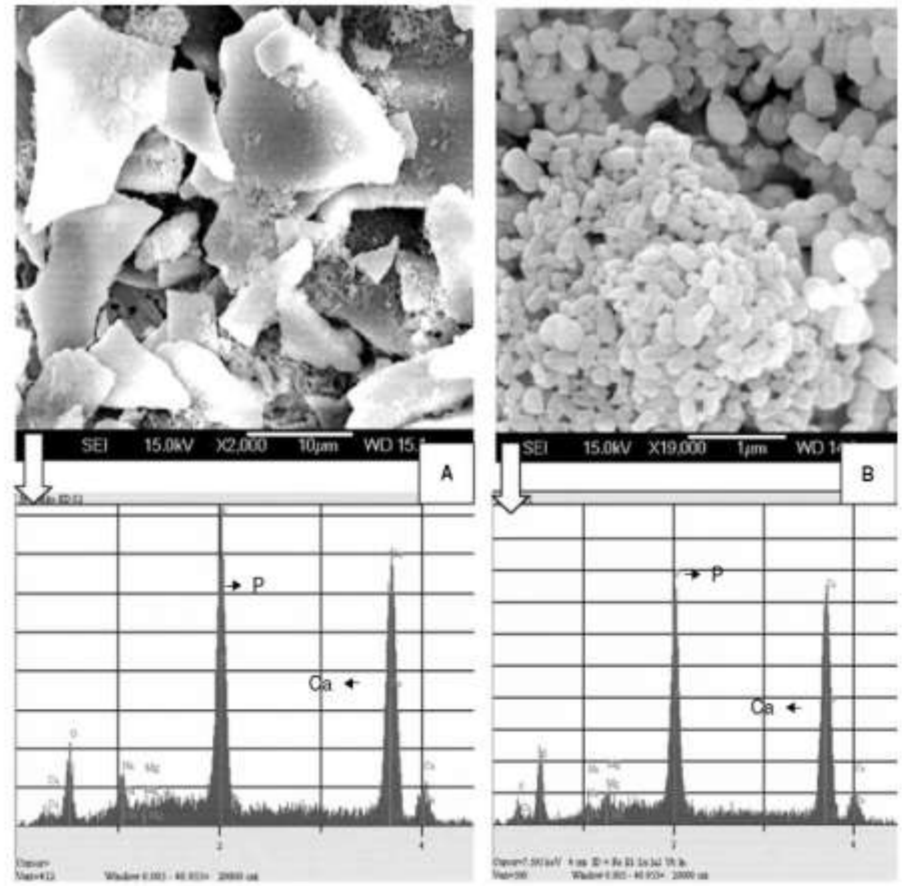


Fig. 5. Ca and P peaks detected by using EDX analyze of commercial hydroxyl apatite (*A*) and nanobacteria culture (*B*). At the top, SEM images of the samples are seen.

Cifcioglou N et al, Kidney Int 2005

Nanobacteria in microgravity

- 5 times faster multiplication in microgravity conditions
- Close confinement of crew members uniform bacterial flora

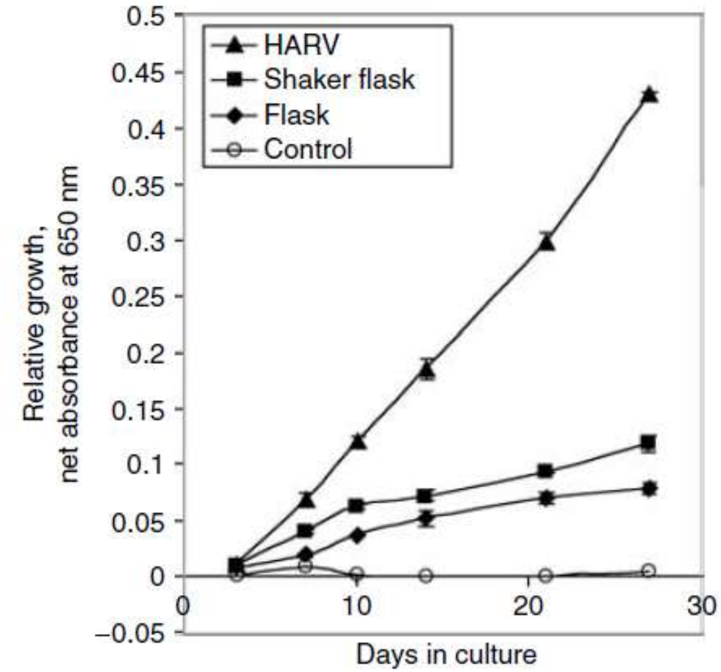


Fig. 2. Growth curve of nanobacteria in three different types of vessels during 27 days culture period. HARV, microgravity simulation system; shaker flasks, cultured on shakers in the incubator; flasks, stationary culture; control, culture medium with no nanobacteria addition.

Cifcioglou N et al, Kidney Int 2005

Urinary composition in astronauts

TABLE III. PREFLIGHT AND POSTFLIGHT URINARY DATA OF U.S. SPACE SHUTTLE CREWMEMBERS

	Preflight		Postflight	
Calcium ($mg \cdot d^{-1}$)	183.0 (5.3)	% Hypercalciuria: 20.8%	233.5 (6.5)	% Hypercalciuria: 38.9%
Oxalate ($mg \cdot d^{-1}$)	37.8 (0.9)	%Hyperoxaluria: 22.3%	37.0 (0.9)	% Hyperoxaluria: 15.2%
Citrate ($mg \cdot d^{-1}$)	713.7 (16.3)	%Hypocitraturia: 6.9%	628.8 (17.9)	% Hypocitraturia: 14.6%
pH	6.05 (0.02)		5.79 (0.03)*	
Total Vol. ($L \cdot d^{-1}$)	2.10 (0.06)	<1 $L \cdot d^{-1}$: 13.0% 1–2 $L \cdot d^{-1}$: 38.9% >2 $L \cdot d^{-1}$: 48.2%	2.00 (0.06)	<1 $L \cdot d^{-1}$: 13.1% 1–2 $L \cdot d^{-1}$: 46.2% >2 $L \cdot d^{-1}$: 40.7%
Magnesium ($mg \cdot d^{-1}$)	115.7 (2.5)	% Hypomagnesuria: 6.0%	99.0 (2.2)	% Hypomagnesuria: 15.8%

Relative Supersaturation	Preflight	% Increased Risk	Postflight	% Increased Risk
Calcium Oxalate	1.53 (0.06)	25.6%	2.23 (0.07)*	46.2%
Brushite	1.25 (0.06)	19.3%	1.00 (0.06)*	13.1%
Sodium Urate	2.41 (0.11)	44.9%	1.42 (0.07)*	25.8%
Struvite	3.05 (0.83)	0.90%	3.69 (2.21)	0.61%
Uric Acid Saturation	1.69 (0.08)	32.8%	2.27 (0.09)*	48.6%

Data represent the mean ± SEM from 24-h urine samples collected approximately 10 d before launch (preflight, n = 332) and immediately after landing (postflight, n = 329). Normal ranges for urinary values and decreased risk for relative saturation values are detailed in Table I. Hypercalciuria was defined as urinary levels greater than 250 $mg \cdot d^{-1}$, hypocitraturia <320 $mg \cdot d^{-1}$, and hypomagnesuria <61 $mg \cdot d^{-1}$.
*$p < 0.05$.

Pietrzyk RA et al, Aviat Space Environ Med 2007

Longitudinal Study of Astronaut Health (LSAH)

TABLE I. URINARY BIOCHEMISTRY DATA FROM STONE-FORMING ASTRONAUTS PRIOR TO SYMPTOMATIC STONE FORMATION.

	Normal Range	Subj. 1 n = 7	Subj. 3 n = 3	Subj. 4 n = 1	Subj. 5 n = 2	Subj. 6 n = 12	Subj. 8 n = 12	Subj. 10 n = 4	Subj. 11 n = 1	Subj. 12 n = 1
Calcium ($mg \cdot d^{-1}$)	80–338	245	56	494	241	144	274	258	327	447
Oxalate ($mg \cdot d^{-1}$)	<45	45.8	15.5	N/A	33.1	30.2	30.0	26.6	31.2	44.8
Uric Acid ($mg \cdot d^{-1}$)	376–1182	781	397	730	609	642	730	861	712	1116
Citrate ($mg \cdot d^{-1}$)	>320	547	716	N/A	639	418	949	732	976	691
pH	4.70–7.80	5.97	7.30	N/A	5.30	5.98	5.93	5.87	5.42	5.91
Total Volume ($L \cdot d^{-1}$)	0.8–1.8	2.08	0.75	1.52	1.83	2.59	2.31	2.85	1.22	1.83
Sodium ($mEq \cdot d^{-1}$)	27–287	192	77	214	134	126	269	141	109	293
Sulfate ($mmol \cdot d^{-1}$)	0–32	20.1	8.3	N/A	18.6	20.6	23.3	25.8	30.9	37.5
Phosphorus ($mg \cdot d^{-1}$)	300–1300	1038	403	1246	847	736	962	1358	1015	2031
Magnesium ($mg \cdot d^{-1}$)	60–158	120	54	162	84	72	111	89	98	168
Creatinine ($mg \cdot d^{-1}$)	1000–2000	2015	832	1642	1846	1903	1806	1847	2550	2050
Potassium ($mEq \cdot d^{-1}$)	26–123	64	23	59	52	51	73	66	55	80
Relative Supersaturation										
Calcium Oxalate	<2.0	2.29	0.63	N/A	2.37	0.93	1.32	0.95	3.38	2.84
Brushite	<2.0	1.41	1.42	N/A	2.21	0.45	0.92	0.83	1.12	3.81
Sodium Urate	<2.0	2.56	4.43	N/A	2.31	0.82	1.58	0.98	2.30	6.15
Struvite	<75	0.63	98.35	N/A	1.23	0.12	0.77	0.24	0.10	0.88
Uric Acid Saturation	<2.0	2.04	0.16	N/A	1.19	1.11	2.01	1.97	5.95	2.90

332 astronauts, 14 episodes in 12 subjects
(Hypercalciuria, low volume, low pH)

Pietrzyk RA et al, Aviat Space Environ Med 2007

Longitudinal Study of Astronaut Health (LSAH)

Post flight:

- all stone forming astronauts had higher urine Ca levels
- Most of them had also high urine P and oxalate and low urine pH
- Urine volumes were less than 2 L in 4 of them despite the before landing protocol of water and sodium loading

Pietrzyk RA et al, Aviat Space Environ Med 2007

Renal stone risk after long duration space flight

- 11 crew members from the MIR space station
- Space flight duration 129-208 days
- 24h urine collections pre-, early in-, late in- and post-flight
- Dietary logs
- Fluid intake ad lib (return protocol)

Whitson PA et al, Nephron 2001

Renal stone risk after long duration space flight

Results I:

- Decrease in urine volume (47% early in-flight and 39% late in-flight)
- Increase in urine Ca in-flight (5/11 hypercalciuric)
- Net alkali absorption correlated with urinary citrate excretion and urine volume

Whitson PA et al, Nephron 2001

Renal stone risk after long duration space flight

Results II:

- During flight an increased risk for CaOx and bruschite stones
- CaOx and UA stones immediately after flight
- Generally supersaturations were higher early in-flight
- Early phase (<30 days) of space flight may generate a greater risk for renal stone formation than the later phases

Whitson PA et al, Nephron 2001

Hypercalciuria and water handling

- ADH translocates AQP-2 water channels to the luminal surface of the collecting duct and in a later stage increase its renal expression, promoting thus water reabsorption
- Hypercalciuria has been shown to promote AQP-2 proteolysis and decreasing water reabsorption
- CaR is expressed in the renal tubules and its activation may contribute to blunted water reabsorption

Drummer C et al, Nephron 2002
De Santo NG et al, J Ren Nutr 2005

Countermeasures against stone formation in space

- High urine output
- Measures against bone resorption
- KMgCit (Mg lowers oxalate, citrate inhibits stone formation, urinary alkalization prevents sodium induced hypercalciuria)

Zerwekh JE, Nutrition 2002

Potassium-Magnesium Citrate

- Bed rest, 5 weeks, 20 normocalciuric subjects, double blind, placebo controlled
- Same diet (Ca, prot, Na, Kcal)
- In n=11 42mEq K, 21 mEq Mg, 63 mEq citrate/day
- Bed rest increased Ca excretion by 50 mg/d
- Treated subjects: decrease in CaOx sat

Zerwekh JE et al, J Urol 2007

Potassium Citrate

- Double blind placebo controlled study
- 30 crew members
- ISS: (n=18) 20 mEq Pot citrate daily
- MIR: (n=12) placebo

- ISS: decreased urinary Ca excretion, maintained CaOx superstauration risk, increased urine pH

Whitson PA et al, J Urol 2009

Countermeasures for bone loss

- High Ca and/or P diet
- UV light
- Vit. D
- Biphosphonates
- Exercise

Smith SM and Heer M, Nutrition 2002

Exercise and Pamidronate

- 25 men 6° head-down tilt bed rest for 90 days
- 3 groups: control, exercise and pamidronate (60 mg i.v. 2 weeks before)
- Pamidronate group: urinary Ca and supersaturation for CaOx and bruschite were lower than control
- Exercise group: urinary oxalate and P were higher than control

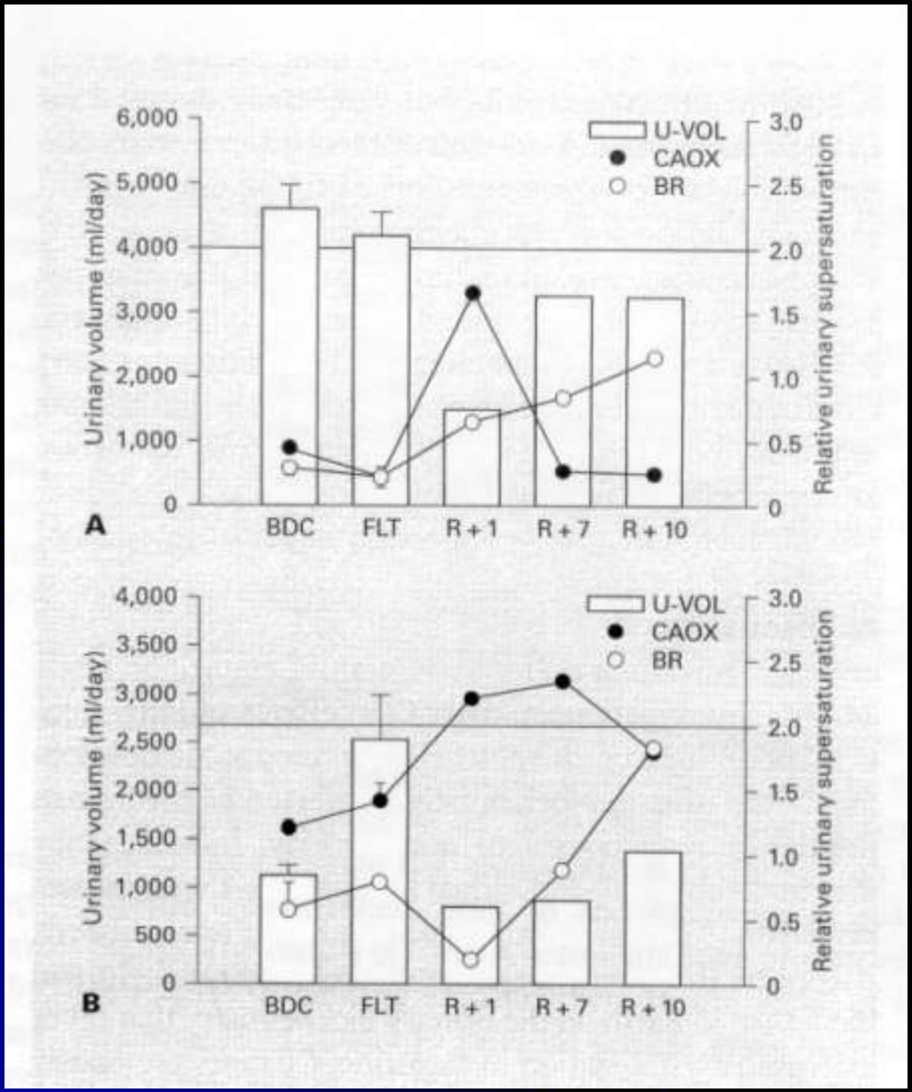
Okada A et al, Int J Urol 2008

Impact of exercise with lower body negative pressure

- 11 sets of identical twins
- 6° head down tilt bed rest for 30 days
- No increase in urinary Ca in the exercise group
- Lower increase for bruschite supersaturation
- However, lower urine volumes and lower urine pH

Monga M et al, J Urol 2006

Effect of urine volume on renal stone risk in space



- Low risk for CaOx and Bruschite stones in two crew members with relatively high urine volumes

Whitson PA et al, Nephron 2001

Increased urine output: An effective countermeasure

- 356 astronauts, 24h urine samples before and after 4-17 days in space
- Urinary supersaturation levels of stone-forming salts (CaOx, bruschite, sodium urate, struvite, uric acid) were inversely related to urinary output before and after space flight
- Urine volume > 2 L/day reduced the risk of renal stone development

Whitson PA et al, Aviat Space Environ Med 2001

Although a prescription of increased fluid intake would be deemed appropriate, crew member compliance is complicated as the result of motion sickness, heavy workloads, and extravehicular activities. In addition, increased urination in the microgravity environment is often regarded as an additional inconvenience.

Zerwekh JE, Nutrition 2002


ΑΧΕΠΑ
ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΘΕΣΣΑΛΟΝΙΚΗΣ ΑΧΕΠΑ