Data Mining Activities for Bone Discipline – Current Status

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Charge to HRP Discipline Leads

- Support 2006 Programmatic Reviews of Evidence-to-Date for Human Research Program
- Identify GAPS in the evidence that would substantiate a skeletal health risk during and after spaceflight missions.
- Engage in Data Mining Activities to address GAPs: access reviews of medical data and flight analog data, propose additional measures and specific analyses.

Data Mining Activities and Identified GAPs

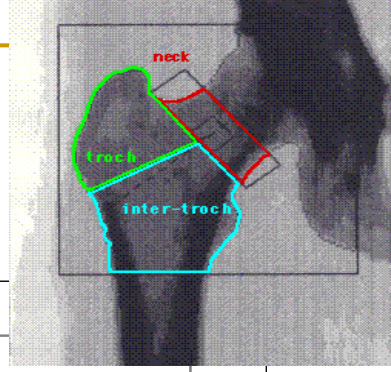
Recent reviews of flight & flight analog data have *partially* addressed GAPS

- **B1:** Is bone strength completely recovered with recovery of BMD**?**
- **B4:** Incidence of IVD injury following spaceflight?
- **B5**: Current renal stone formation knowledge
- Ground-based evidence: Review of bed rest studies conducted at Ames Human Research Facility

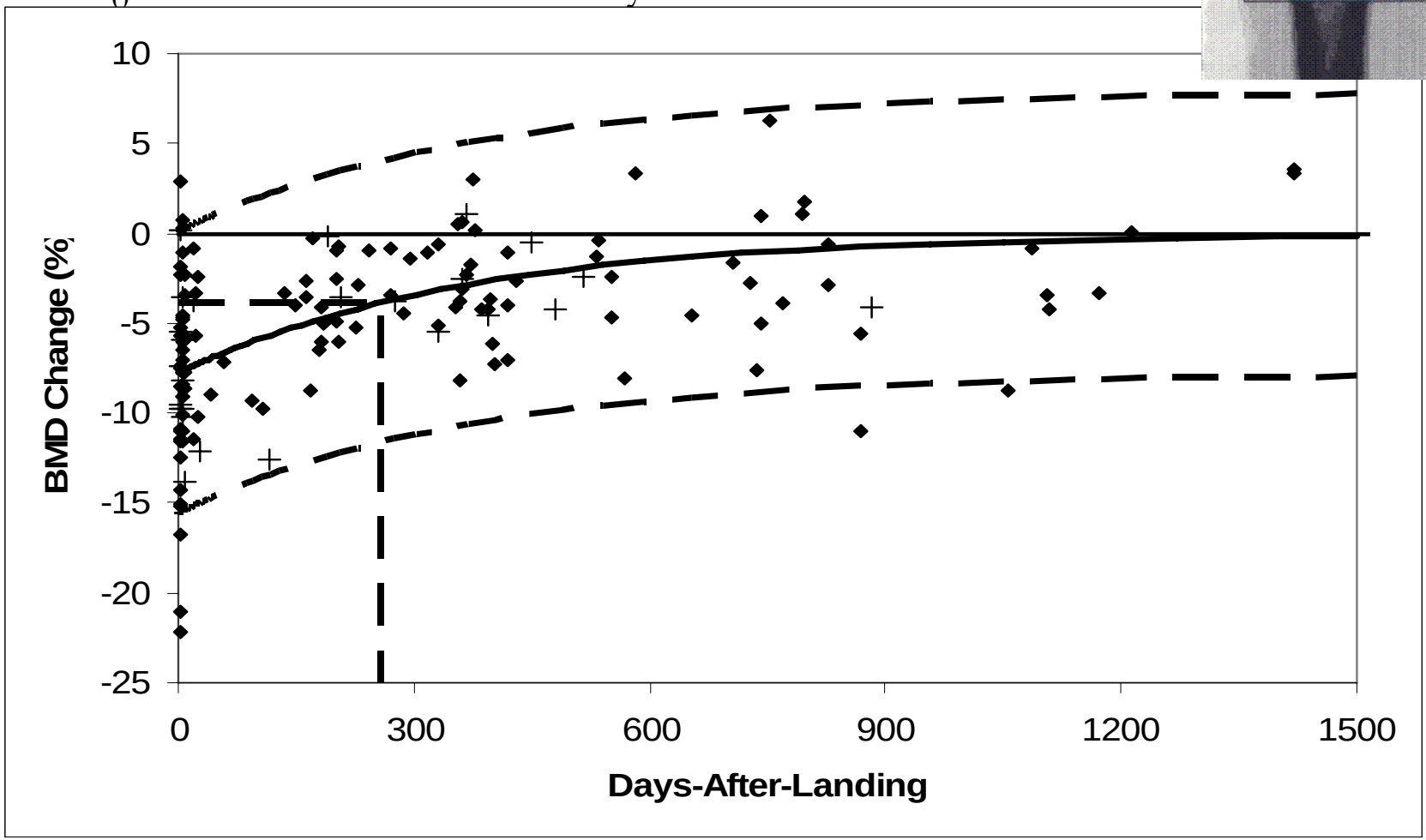
Recovery of spaceflight-induced bone loss: BMD after long duration missions as fitted with an exponential function. Sibonga JD, Evans HJ, Sung HG, Spector ER, Lang TL, Oganov VS, Bakulin AV, Shackelford LC, LeBlanc AD. Bone 41(6):973-978, 2007.

- Recovery of bone mineral that was lost during spaceflight was tracked by evaluation of the repository of astronaut BMD medical data
- Data were fitted to a mathematical function to describe the asymptotic increase in BMD during postflight period
- Uncertainty in mathematical fit was reduced by supplementing medical data with research measurements and cosmonaut data
- Mathematical fit provided an index of "50% recovery time" which was used to relate the temporal recovery of BMD

Trochanter



$Loss_0$=7.8% 50% Recovery=255d



NOTE: BMD accounts for only 50-70% of bone strength.

Report Conclusions (Sibonga et al)

- Model predicts that long-duration crew members recover BMD lost during spaceflight with substantial restoration occurring within 3 years of return – recovery period > duration to induce bone loss.

- DXA BMD needs to supplemented with other measurements (e.g., structural indices by QCT) for the complete assessment of bone strength restoration.

Renal stone formation among astronauts. Aviat Space Env Med. 78(4):A9-13, 2007. Pietrzyk RA, Jones JA, Sams CF, Whitson PA.

- Retrospective analysis of urinary data from US space shuttle crew members.
- 24-hour urine specimens were collected pre-launch (~L-10) and immediately post-landing.
- Analysis: Urine characteristics of renal stone formation and relative supersaturation of stone-forming constituents
- Pre- and postflight data were stratified (see Data Tables) for Shuttle crew members (n=329-332).
- 14 kidney stone episodes in US astronauts but urine analysis for only 9 subjects; majority of stone material recovered after flight was of mixed calcium oxalate

Mean Values for Urinary Biochemical Parameters in Crewmembers During Short Duration Space Flight

Parameter	Preflight (n=332)	Postflight (n=339)	p
Total Volume (L/d)	2.1 ± 0.06[a]	2.0 ± 0.06	NS
<1 L/d:	13%	13.1%	
<1-2 L/d	38.9%	46.2%	
>2 L d	48.2%	40.7%	
Oxalate (mg/d)	38 ± 0.9	37 ± 0.9	NS
Calcium (mg/d)	183 ± 5	234 ± 6	NS
pH	6.05 ± 0.02	5.79 ± 0.03	<0.05
Citrate (mg/d)	714 ± 16	629 ± 18	NS
Magnesium (mg/d)	116 ± 3	99.0 ± 2.2	NS

[a]Mean ± SEM; Preflight urines collected 10 days before launch and postflight urines collected on landing following missions of <16 days.

Mean Values for Relative Saturation of Stone-Forming Salts in Urine from Crewmembers During Short Duration Space Flight

Parameter	Preflight n=332	Postflight n=329	P
Calcium Oxalate	1.53 ± 0.06[a]	2.26 ± 0.07	<0.05
Brushite	1.25 ± 0.06	1.00 ± 0.06	<0.05
Sodium urate	2.41 ± 0.11	1.42 ± 0.07	<0.05
Struvite	3.05 ± 0.83	3.69 ± 2.21	NS
uric H^+	1.69 ± 0.08	2.27 ± 0.09	<0.05

[a]Mean ± SEM

Prevalence of Biochemical Abnormalities in Urine in Astronauts Before and Following Short Duration Space Flight

Abnormality	Pre-flight	Post-flight
Hypercalciuria (>250 mg/d)	20.8%	38.9%
Hypocitraturia (<320 mg/d)	6.9%	14.6%
Hypomagnesuria (<60 mg/d)	6.0%	15.8%
Urinary supersaturation (>2.0)		
Calcium oxalate	25.6%	46.2%
Uric acid	32.8%	48.6%
Brushite	19.3%	13.1%
Sodium Urate	44.9%	25.8%

Report Conclusions (Pietrzyk et al)

- Prediction of stone formers amongst astronauts still uncertain at this time.
- Greater potential for renal stone formation appears to be associated with increased relative saturation values.
- Spaceflight effects can alter urine biochemistry although risk may be present before flight.
- Increasing occurrence of kidney stone episodes may be related to increasing mission durations.

Johnston SL, Campbell MR, Wear ML, Birzele JA, Hamm PB. Increased incidence of herniated nucleus pulposus among astronauts. Submitted manuscript.

- Herniated nucleus pulposus is known to occur in aviators exposed to high G environments and has occurred in astronauts
- Review of incidence rate in astronauts (LSAH) vs. matched controls indicates higher occurrence in astronaut population
- Higher incidence in high performance jet pilots, at cervical location and within first 12 months of return

LSAH: Longitudinal Study of Astronaut Health

GAP B4

Summary of Rates of Herniated Discs

Ref. Population	# HNP events: # Astronauts	HNP Location	HNP Rate Per 1000 person-yrs	P value vs. LSAH Control Pop
Astronauts Median Age =45.4 yrs	33: 24	 14 cervical 19 lumbar	5.34 :3.89 2.26 3.08	 <0.004
HPJA Astronauts	26: 19	9 cervical 17 lumbar		
non-HPJA Astronauts	7: 5	5 cervical 2 lumbar		
LSAH Control population Median Ave =45.6 yrs	35:34 patients	 3 cervical 32 lumbar	2.23:2.20 0.19 2.02	
US Army Aviators[1], not all HPJA Age range 40-44 yrs	132	 34 cervical 98 lumbar	1.60 0.41 1.19	
General male population[2] 30-60 yrs (Ave=41.5)	466	ND Cervical 423 lumbar	 1.25	

1: Mason KT et al Herniated nucleus pulposus: rates and outcomes among US Army aviators. Aviat Space Environ Med. 1996: 157(9):491-493.

2: Bruske-Hohlfeld I et al. Incidence of lumbar disc surgery. A population-based study in Olmsted County, Minnesota, 1950-79. Spine. 1990. 15(1):31-35.

HNP: Herniated Nucleus Pulposus, LSAH: Longitudinal Study of Astronaut Health. HPJA: High Performance Jet Aircraft, ND: Not Determined

Report Conclusions (Johnston et al)

- Incidence of both cervical and lumbar HNP is increased (2.4x) in astronauts compared to control population (matched by age and BMI)
- Risks factors include: history of high performance jet aircraft exposure (80% of HNP), cervical location (12x) and within 12 months (19.7x) after return
- Pathophysiology appears to be expansion of disc volume in response to axial unloading and damage to annuli fibrosus upon exposure to high and higher G with return to earth.
- Biochemical changes in disc could also be a factor

Bed rest experiments at Ames Research Center. Studies relevant to skeletal health risk, reviewed and summarized by SB Arnaud, M.D.

TITLE/PI (EXPERIMENT #)	UNLOADING DURATION	EXPERIMENTAL DESIGN
Exercise Countermeasures for Bed Rest Deconditioning/ Greenleaf, J. E. (HR 63)	30 d	Comparing high-intensity isotonic and isokinetic exercise as countermeasures to multiphysiological deconditioning.
Life and Microgravity Sciences Spacelab Mission: Human Research Pilot Study/Arnaud, S.B. (HR 146)	17 d	Ground-based pilot study, designed to mimic the Spacelab flight protocols for identifying the functional, metabolic and neurological characteristics of muscle weakness and atrophy during space flight.
Dietary Sodium Effects on Bone and Calcium Metabolism/ Arnaud, S.B. (HR 159)	7 and 30 days	Contrasting 30-day study with restricted dietary salt to a 7-day bed rest study of volunteers fed normal salt diets on calcium excretion.
The effect of bed rest on bone histology and the calcium endocrine system in adult men./Arnaud, S.B. (HR 71)	7 days	Determine the response of human bone to a brief period of unloading as determined in fluorochrome-labeled bone biopsies and by biomarkers of calcium metabolism.

Future DMAs

- "Epidemiologic analyses of risk factors for bone loss and recovery related to long-duration flight." Study proposal in review. Evaluation of flight and medical data for risk factors, aside from weightlessness, that influence bone loss and recovery; compare observed changes in crew members with a well-characterized, age-matched population-based cohort (Rochester Bone Health Study).
- "Data Mining Activity to evaluate the risk for vertebral morphological deformities with spaceflight." Study proposal in definition phase. Characterization with VFA to assess if spaceflight exposure predisposes crew members (earlier incidence and prevalence) to morphological deformities in over life time.

Closing

- Data mining activities and data analyses are an on-going process as the HRP Evidence Base Book is updated with new information and research.
- Such activities are critical as we begin to frame the skeletal health risks during Exploration Missions.