What Happens to bone health during and after spaceflight?

Jean D. Sibonga, PhD[1], Harlan J. Evans, Ph.D.[2], Elisabeth R. Spector[2], Mary J. Maddocks[2], Scott A. Smith[2], Linda C. Shackelford, M.D.[3] and Adrian D. LeBlanc, Ph.D.[1]

[1]Universities Space Research Association, [2]Wyle Laboratories, [3]NASA Johnson Space Center, Houston, TX.

Corresponding Author:
Jean D. Sibonga, Ph.D.
USRA, Division of Space Life Sciences
3600 Bay Area Blvd.
Houston, TX 77058
Phone: 281-483-4556
FAX: 281-244-5734

Summary:

Weightless conditions of space flight accelerate bone loss. There are no reports to date that address whether the bone that is lost during spaceflight could ever be recovered. Space-induced bone loss in astronauts is evaluated at the Johnson Space Center (JSC) by measurement of bone mineral density (BMD) by Dual-energy x-ray absorptiometry (DXA) scans. Astronauts are routinely scanned preflight and at various time points postflight (≥Return+2 days). Two sets of BMD data were used to model spaceflight-induced loss and skeletal recovery in crewmembers following long-duration spaceflight missions (4-6 months). Group I was from astronauts (n=7) who were systematically scanned at multiple time points during the postflight period as part of a research protocol to investigate skeletal recovery. Group II came from a total of 49 sets of preflight and postflight data obtained by different protocols. These data were from 39 different crewmembers some of whom served on multiple flights.

Changes in BMD (between pre- and postflight BMD) were plotted as a function of time (days-after-landing); plotted data were fitted to an exponential equation which enabled estimations of i) BMD change at day 0 after landing and ii) the number of days by which 50% of the lost bone is recovered (“half-life”). These fits were performed for BMD of the lumbar spine, trochanter, pelvis, femoral neck and calcaneus.

There was consistency between the models for BMD recovery. Based upon the exponential model of BMD restoration, recovery following long-duration missions appears to be substantially complete in crewmembers within 36 months following return to Earth.

Introduction

The acceleration of bone loss in crewmembers on spaceflight missions is a well-recognized effect of weightlessness on the skeletal system and is formally identified as a high critical risk factor in the NASA Bioastronautics Roadmap.[1] Identifying how weightlessness affects bone cell biology and skeletal physiology is critical to the development and evaluation of countermeasures to be used for long-duration space missions.

Due to the difficulty of obtaining bone-related measurements during flight, characterization of spaceflight-induced osteopenia has been limited largely to pre- and postflight measurements. Site-specific deficits in bone mineral density (BMD),[2, 3] increased excretion of collagen degradation products,[4, 5] disrupted bone turnover,[6, 7] and negative calcium balances[4] all suggest a net loss of bone mineral as an adaptive response of the skeleton to the unloading during spaceflight.

Assays of bone biomarkers suggest that bone formation is uncoupled from bone resorption as the adult skeleton adapts to the weightless environment of space. The JSC Biochemistry Nutrition Lab detected increased levels of the cross-linked amino-terminal collagen telopeptide (NTX) in urine specimens collected from crewmembers in flight. The levels of this collagen degradation product were reduced back to preflight levels at the time of landing and remained at this level throughout various time-points in the postflight period.[4] Similarly, serum markers for bone formation, i.e., osteocalcin and bone-specific alkaline-phosphatase, were assayed in specimens obtained before, during and after flight. Assays indicate that there was no impact of spaceflight on either of these markers but a significant increase in both of these markers was detected after one month following return to earth.[4] These data suggest that there was delayed stimulation of bone formation after return to earth’s gravity. Interestingly, these results corroborate the increase in bone formation markers observed in subjects in a bed rest study – the gold standard for ground-based space analogs -- during the re-ambulation phase of the experiment.[8] Currently, measurements of bone biomarkers are conducted in long-duration crewmembers and are scheduled to coincide with measurements of BMD.

While there are studies that characterize bone health during spaceflight through calcium kinetics and bone biomarkers, there are no reports that address the impact of spaceflight on bone health after spaceflight, i.e., is there skeletal recovery upon return to earth?

Measurement of bone mineral mass and density has been a long-standing technique to evaluate spaceflight effects on the skeleton. Because of the rapid bone loss reported in spaceflight, densitometry has been capable of detecting site-specific deficits in bone mineral in a crewmember that flew on a mission as short as 2 months.[3] Furthermore, as a technique to evaluate changes in mineral metabolism, pre- and postflight densitometry scans are more easily accommodated by crewmembers when compared to the invasiveness of bone biopsy or the constraints of urine and blood specimen collections.

It is part of the medical requirements for health assessment of the Astronaut Corps that BMD be measured to monitor skeletal integrity. As per the Astronaut Medical Evaluation Requirements Document (AMERD), the Bone and Mineral Lab at NASA JSC routinely performs measurements of BMD in crewmembers by Dual-energy X-ray Absorptiometry (DXA). DXA scans are performed to ensure that crewmembers i) meet the medical standards for flight certification and ii) are restored to preflight skeletal status. In addition to being able to delineate site-specific losses of the adult skeleton to spaceflight, these DXA scans enable an analysis of skeletal recovery in crewmembers, especially in those who return after long-duration spaceflights, i.e., 4-6 months.

Additionally, the accumulation of densitometry data provides an important research database to the space program. The cross-sectional measurements could be analyzed to evaluate the efficacy of in-flight countermeasures or the impact of flight duration (or of previous flights) on skeletal recovery. Assessment of risk factors, as well as the contribution of genomics, could elucidate crew-specific variations in bone loss. Moreover, bone densitometry has had widespread use in the clinical arena which provides an extensive reference database from which to draw comparisons of “spaceflight osteoporosis” to postmenopausal or age-related osteoporosis. BMD is also the primary index by which the efficacy of in-flight countermeasures, such as exercise [10, 11] or pharmacologics [11, 12] are evaluated in ground-based models for spaceflight

The JSC Bone and Mineral Lab analyzed postflight BMD data to model the skeletal recovery of astronauts who returned from long-duration spaceflight. JSC also had access to densitometry data (pre- and postflight scans) of Russian cosmonauts who similarly served on long-duration missions. BMD data were analyzed i) to determine whether the crewmembers were able to recover their skeletal deficits upon return to life on earth and ii) to understand the rate of skeletal recovery following prolonged space occupation(between 4-6 months).

<u>Data Source.</u> The data described herein are a subset of medical data archived by the Office for the Longitudinal Study of Astronaut Health at NASA JSC. Authorization to publish these data was obtained from the office overseeing this study in addition to IRB approval from the JSC Committee for Protection of Human Subjects.

DXA scans of crewmembers were conducted on either the Hologic 1000w, 2000 or QDR 4500 models.. Scans of astronauts were performed preflight, within 45-30 days before launch**,** and postflight at various intervals during the first 3 years after landing. Postflight scans were scheduled for 5 times during this period unless the crewmember is within 2% of preflight BMD, in which case only one other BMD measurement for confirmation is required. A series of six scans were performed for each scan date. Scans included whole body, lumbar spine, hip and the calcaneus. BMD data for the pelvis were obtained from the whole body scan, while scans of hip yielded data for trochanter and femoral neck of the proximal femur.

BMD data came from a combination of 45 crewmembers who served on the ISS and the Mir spacecraft. These BMD data were separated into two datasets. Dataset I was obtained from seven NASA astronauts (Group I) who flew on the Russian spacecraft Mir between 1995 and 1998. As part of a research study of skeletal recovery, these Mir Astronauts were scanned at specific time points following landing (5 days, 6 months, 12 months, 24 months and 36 months after return) -- a protocol that was later adopted by the AMERD to monitor the return of BMD to preflight status. Dataset II was obtained from a total of 39 different crewmembers (Group II) who served on 49 separate missions because of multiple flights by some crewmembers. Crewmembers consisted of 12 astronauts who flew on the International Space Station (ISS) (2000- 2004), as well as 22 cosmonauts who flew on Mir (1990-1998) and 5 cosmonauts who flew ISS (1990-2004). Datasets for the cosmonauts were not as extensive as those for the astronauts; a typical cosmonaut dataset consisted of one preflight scan and one immediate postflight scan. Because the data were obtained under different protocols, analysis of Dataset I was performed separately from the analysis of Dataset II .

<u>Mathematical Model for Skeletal Recovery</u> The difference in preflight and postflight BMD was used as an index of bone changes as a consequence of spaceflight. In cases of multiple preflight BMDs, deficits were calculated from the scan closest to the date of launch. Multiple missions by a single crewmember were treated as independent observations of spaceflight-induced bone loss and recovery.

The deficits from preflight BMD were calculated for <u>each</u> postflight scan that was conducted on a crewmember and expressed as a percentage of preflight bone density. Percentages were plotted as a function of time, i.e., against Days-after-Landing. Initial review of the plotted data suggested an exponential relationship between the increase in BMD and the increased time after landing. Thus, the data were fitted to a 2-parameter exponential mathematical equation: $L_t = L_0 * \exp[\ln(0.5)*t/HL]$ where Lt is the change in BMD detected at time "t" after landing, L_0 is the change in BMD that could be estimated for the time of landing ("R+0") and HL denotes the time at which there is a 50% restoration of the bone lost during spaceflight.

This mathematical fit generated a model that could relate the loss of BMD induced by spaceflight (L_0) and the temporal recovery of BMD to preflight status (HL). This mathematical model -- analogous to the decay of a radioisotope – uses the "half-life" term (HL) as a metric to assess how quickly the skeleton recovers. Half-life -- hereto in referred to as "50% Recovery Time" -- was calculated for the five skeletal sites of interest (i.e., lumbar spine, pelvis, femoral neck, trochanter and calcaneus).

As mentioned previously, there were two datasets representing different numbers of crewmembers (n=7 vs. 39) and obtained under different levels of stringency. The research data of Group I were more systematically obtained but limited by a small number of individuals; the data from Group II conversely benefited from the large number of individuals but were not obtained with as much scientific rigor. In addition, there were 49 sets of preflight and postflight scans in Dataset II available from the 39 crewmembers (Group II). The apparent "inconsistency" stems from nine crewmembers that flew on multiple missions with two of those same crewmembers flying on three missions. Each BMD set from a man-mission was treated as an independent observation even though the crewmember may have flown on a previous long-duration space mission. Finally, one male astronaut in Group II previously flew on a Mir mission (Group I). Because of the variability between datasets, each dataset was fitted separately to the mathematical model and the two models were evaluated for consistency between the respective estimations of bone loss and recovery times per skeletal site.

Analysis The presence of repeated measures of a single crewmember would not allow a direct comparison of model averages. The consistency between the two models for bone loss, however, could be evaluated by a Monte Carlo Simulation. In brief, a random sampling of the respective datasets was performed and fitted to the exponential recovery model. This “simulation” was performed 10,000 times and a distribution of error for the most probable estimation for bone loss was obtained. The error distributions were compared to evaluate consistency between the spaceflight-induced bone losses as simulated by both groups of data (Group I vs. Group II). Likewise, the error distributions for the 50 % Recovery Times were compared to evaluate the consistency between skeletal site-specific recovery times and between the two datasets.

Results

The average age of all the crewmembers was 43.2±5.2 years (Group I: 42.8±0.7; Group II” 45.9±2.3). The average flight duration was 173±24 d (range126-208 d); the average flight duration was 181±47 days with the inclusion of the two crewmembers that flew on prolonged missions of 311 and 438 days. Data were obtained from 42 male crewmembers and 3 female crewmembers (Group I: 6 males:1 female; Group II:37 males:2 females)

The bone loss estimated from the fit of Dataset I was consistent with the loss estimated from the fitted Dataset II with a few exceptions With its smaller number of crewmembers, Dataset I estimated that the least amount of bone loss occurred in both the calcaneus and the lumbar spine In contrast, Dataset II suggested that the calcaneus was a site that lost the least amount of BMD compared to the other sites. . Additionally, Dataset I estimated a significantly greater bone loss in the trochanter than the loss predicted by Dataset II.

Due to the large distributions of error, there was no indication that one dataset provided an advantage over the other in the prediction of skeletal recovery or that one skeletal site had a shorter recovery time over another site.

There were limitations to this evaluation of skeletal recovery. The impact of multiple long-duration missions or of spaceflight duration on crewmember recovery could not be evaluated due to insufficient power in the analysis. These data were also a mixture of cross-sectional and longitudinal measurements which required simulation analysis in order to take full advantage of the limited number of data-points. More importantly, skeletal recovery is a crew-specific phenomenon influenced by nutrition, exercise re-conditioning, neurosensory re-adaptation and a likely genomic component.[13] There were some crewmembers who recovered within the first year of return.

However, if skeletal recovery were modeled by the data from the largest number of crewmembers (i.e., Group II) and the 95% confidence limits were not taken into account, then a fair estimation of skeletal recovery could be "within" 3 years of return to earth. This prediction is based upon the estimated recovery in the trochanter which has the longest 50% Recovery half-life. With 50% recovery at around 9 months for the trochanter, a restoration of 15/16ths, or 94% of lost bone would occur four half-lives later (i.e., 36 months).

Based upon this estimation, most crewmembers that have flown on long-duration missions (4-6 months) could be re-certified for flight within 3 years – suggesting that recovery is approximately 6x mission durations. Bone biomarkers suggest that the uncoupled bone formation is not stimulated immediately upon return to unit gravity.[4] This delayed recovery is not unexpected when one considers that its takes relatively less time to lose bone (weeks) than it does to produce and mineralize matrix (months).[14] The observed increase in bone formation markers, after the normalization of bone resorption markers, is not only corroborated by bed rest studies[8] but predictive for the BMD response.

Nevertheless, there are issues that remain unresolved. For example, the kinetics of bone loss during spaceflight will not be fully characterized until technologies to assess bone mass in flight are validated and manifested for in-flight implementation. Furthermore, it is recognized that BMD is not the sole determinant of bone strength: BMD, rather, needs to be supplemented by indices that more appropriately reflect “bone quality.” Measurements of microarchitecture in cancellous bone, assessments of bone size and geometry, evaluations of anisotropy and trabeculae distribution are a few of the parameters considered reflective of bone quality. In vivo assessments are emerging that could allow non-invasive measurements of these indices. In the meantime, the recovery of BMD after spaceflight should not be perceived as a restoration of mechanical strength until these additional indices can be evaluated in crewmembers. Only then can bone health after spaceflight be fully evaluated.

References:

1. Bioastronautics Roadmap. A risk reduction strategy for space exploration. NASA SP-2004-6113.
2. Lang T, LeBlanc A, Evans H, Lu Y, Genant H and Yu A. Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight. J Bone Miner Res 2004 ;19(6):1006-1012.
3. Vico L, Collet, P, Guignandon A, Lafage-Proust MH, Thomas T, Rehailia M, Alexandre C. Effects of long-term microgravity exposure on cancellous and corticalweight-bearing bones of cosmonauts. The Lancet 2000;355:1607-1611.
4. Smith SM, Wastney ME, O Brien KO, Morukov BV, Larina IM, Abrams SA, Davis-Street JE, Oganov V, LC Shackelford. Bone markers, calcium metabolism and calcium kinetics during extended-duration space flight on the Mir space station. J Bone Miner Res 2005;20(2): 208-218.
5. Smith SM, Nillen JL, LeBlanc A, Lipton A, Demers LM, Lane HW, Leach CS. Collagen cross-link excretion during space flight and bed rest. J Clin Endocrinol Metab 1998;83:3584-3591.

6. Caillot-Augusseau A, Lafage-Prous MH, Soler C, Pernod J, Bubois F, Alexandre C. Bone formation and resorption biological markers in cosmonauts during and after a 180-day space flight. Clin Chem 1998;44:578-585.
7. Heer M, Kamps N, Biener C, Korr C, Boerger A, Zittermann A, Stehle P, Drummer C. Calcium metabolism in microgravity. Eur J Med Res 1999;4(9):3578-360.
8. LeBlanc AD, Schneider VS, Evans HJ, Engelbretson DA, Krebs JM. Bone mineral density and recovery after 17 weeks of bed rest. J Bone Miner Res 1990;5:843-50
9. Zerwekh JE, Ruml LA, Gottschalk F, Pak CY. The effects of twelve weeks of bed rest on bone histology, biochemical markers of bone turnover, and calcium homeostasis in eleven normal subjects. J Bone Miner Res 1998;13:1594-1601
10. Shackelford LC, LeBlanc AD, Driscoll TB, Evans HJ, Rianon NJ, Smith SM, Spector E, Feeback DL, Lai D. Resistance exercise as a countermeasure to disuse-induced bone loss. J Appl Physiol 2004;97:119-129.
11. Rittweger J, Frost HM, Schiessl H, Ohshima H, Alkner B, Tesch, Felsenberg D. Muscle atrophy and bone loss after 90 days' bed rest and the effects of flywheel resistive exercise and pamidronate: results from the LTBR study. Bone 2005;36(6):1019-1029.
12. LeBlancAD, Driscol TB, Shackelford LC, Evans HJ, Rianon RJ, Smith SM, Feeback DL, Lai D. Alendronate as an effective countermeasure to disuse induced bone loss. J Musculoskelet Neuronal Interact. 2002;2(4):335-43
13. Arden NK, Spector TD Genetic influences on muscle strength, lean body mass, and bone mineral density: a twin study. J Bone Miner Res 1997;12:2076-2081.
14. Parfitt AM The physiological and clinical significance of bone histomorphometric data. In Bone Histomorphometry: Techniques and Interpretation. Editor: Robert R. Recker.