Recovery of Spaceflight-induced Bone Loss:

Bone Mineral Density after Long-duration Missions as Fitted with an Exponential Function

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Running Head: Recovery of spaceflight-induced bone loss.

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ABSTRACT

The loss of bone mineral in NASA astronauts during spaceflight has been investigated throughout the more than 40 years of space travel. Consequently, it is a medical requirement at NASA Johnson Space Center (JSC) that changes in bone mass be monitored in crew members by measuring bone mineral density (BMD) with dual-energy x-ray absorptiometry (DXA) before and after flight on astronauts who serve on long-duration missions (4-6 months). We evaluated this repository of medical data to track whether there is recovery of bone mineral that was lost during spaceflight.

Our analysis was supplemented by BMD data from cosmonauts (by convention, a space traveler formally employed by the Russia Aviation and Space Agency or by the previous Soviet Union) who had also flown on long-duration missions. Data from a total of 45 individual crew members – a small number of whom flew on more than one mission – were used in this analysis. Changes in BMD (between 56 different sets of pre- and postflight measurements) were plotted as a function of time (days after landing). Plotted BMD changes were fitted to an exponential mathematical function that estimated: i) BMD change on landing day (day 0) and ii) the number of days after landing when 50% of the lost bone would be recovered ("50% recovery time") in the lumbar spine, trochanter, pelvis, femoral neck and calcaneus. In sum, averaged losses of bone mineral after long-duration spaceflight ranged between 2-9% across all sites with our recovery model predicting a 50% restoration of bone loss for all sites to be within 9 months.

Keywords: cosmonauts, astronauts, bone densitometry, mathematical function, mechanical unloading

INTRODUCTION

Accelerated bone loss in crew members in space is a well-recognized effect of weightlessness on the skeletal system and a critical risk factor for the early onset of osteoporosis after return to Earth [1]. Studies using calcium kinetics, site-specific bone densitometry and bone turnover markers document a net loss of bone mineral in the gravitationally-unloaded skeleton of crew members who had flown either on Skylab (28, 56 and 84 days) or on long-duration missions (>4 months) aboard the Russian Mir spacecraft and the International Space Station (ISS) [2-12].

Although calcium kinetics and bone biomarkers have been used to characterize bone health during spaceflight, no reports have addressed the impact of spaceflight on long-term bone health after spaceflight, i.e., the recovery of skeletal integrity, its nature and its time course. Since the Skylab missions of the 1970's, measurements of bone mineral and bone mineral density had been used to evaluate the effects of spaceflight on the skeleton [4, 5, 8, 9]. More recently, QCT scans of long-duration crew members was used to evaluate changes in mineral density and in hip structure after spaceflight [10]. The report described herein expands upon QCT-measured changes in crew members (performed immediately and at 1 year after return from ISS mission) by evaluating the restoration of BMD in long-duration crew members who were scanned by Dual-energy X-ray Absorptiometry (DXA) for almost as much as 5 years postflight.

Therefore, we developed a method to analyze this repository of BMD data to describe the skeletal recovery of astronauts after their return to Earth. Moreover, through cooperative agreements with the Russian Space Agency, we obtained access to DXA data (pre- and postflight BMD) of Russian cosmonauts who similarly served on long-duration missions to increase the value of this analysis. Not only did we analyze the BMD data to determine if the crew members were able to recover their skeletal deficits upon return to Earth, but we attempted to understand the rate of skeletal recovery after prolonged space habitation (typically between 4-6 months). This report is the first to characterize the recovery of spaceflight-induced bone loss over multiple years on Earth in a crew member population of this size.

METHODS

Data Source. The NASA medical requirements for the health assessment of the Astronaut Corps include the measurement of BMD to monitor skeletal integrity. Hence, the astronaut data described herein are a subset of medical data archived by the Office for the Longitudinal Study of Astronaut Health at NASA-JSC. This office operates under the JSC Committee for the Protection of Human Subjects and has authorized the publication of these medical data.

DXA scans of crew members were conducted on a Hologic DXA densitometer: models QDR 1000W, 2000 or 4500 (Hologic, Inc., Waltham, MA). All postflight scans, and analysis software, for a given subject were performed on the identical instrument as his/her preflight scans. As documented in the medical requirement, DXA scans of astronauts were performed as close as possible to specified time points before and after long-duration flights. Preflight scans are to be performed within 45 to 30 days before launch while postflight scans are to be conducted 5 times after return to Earth: 5 days, 6 months, 12 months, 24 months and 36 months after landing. As will be discussed in detail subsequently, DXA scans of cosmonauts are not scheduled identically to the NASA medical requirement.

At each scan date, and on a routine monthly basis, a Hologic phantom standard was scanned to verify proper calibration of the densitometer. Regional scans of the lumbar spine, hip and the calcaneus were performed as well as a whole body scan. Scans BMD data for the pelvis were obtained from the whole body scan (12, 13), while scans of the hip yielded data for the trochanter and the femoral neck of the proximal femur. During the 15 year period from which the data were obtained, scans of astronauts were performed by a total of four technicians: a primary and a back-up technician per spacecraft era (e.g., Mir or ISS). The primary technician performed ~90% of the total scans. To ensure consistency in positioning, scanning and analysis, all technicians were trained with standardized operating procedures. For cosmonaut scans, 78% of the scans were performed by the co-author (Dr. Bakulin).

The BMD data in this report came from 45 different crew members who served either on the Mir spacecraft or ISS. Data were obtained from 42 male crew members and 3 female crew members (average age 43.2±5.2 years). There was a total of 56 pre- and postflight datasets with seven long-duration crew members participating in two missions, and two crew members serving on three missions. BMD data from these 56 flights were initially analyzed as two separate datasets, because the data were obtained under two different protocols. Dataset I was obtained from seven NASA Mir 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 after landing (5 days, 6 months, 12 months, 24 months and 36 months after return). This research protocol of scheduled postflight DXA was later adopted by NASA to monitor the return of BMD to preflight status in all ISS astronauts. Dataset II was from BMD measurements conducted on a total of 39 different crew members (Group II), which is composed of all cosmonauts, serving on Mir and ISS, and the astronauts serving on ISS only. Table 1 outlines the number of astronauts and cosmonauts that served on specific space crafts.

There were longitudinal measures conducted in some of the crew members in each of the two datasets. Therefore, we used a Monte Carlo simulation (R and Matlab) to confirm consistency in the abilities of the two sets of data to predict recovery. Once consistency of both models for bone loss and recovery was confirmed, the two datasets were subsequently combined for the analysis presented in this report.

Additionally, scans for cosmonaut BMDs were not as numerous as those performed on astronauts. Typically, a cosmonaut dataset consisted of one preflight session and a single session after flight. There were occasions where a preflight session for a cosmonaut preparing for a subsequent flight also served as a postflight time point to assess recovery from the previous flight. The impact of multiple flights on BMD recovery, however, was precluded by limited access to cosmonaut flight histories.

Mathematical Function for Skeletal Recovery. The change in bone mineral density that is a direct result of spaceflight was calculated as the difference between preflight BMD measurement closest to launch date and the first postflight BMD (i.e., closest to landing date). These delta BMDs were expressed as a percentage of the preflight BMD. For the measurements in this report, the first postflight scans were performed generally within 26 days after landing (6 ±

5 days, mean ±SD, 2-26 days range). There was one exception of a crew member whose first postflight scan was not performed until 116 days after landing. Changes in BMD that were derived from multiple serial postflight scans were treated as independent measurements of bone loss (negative change) or of bone gain (positive change). That is, a change from a single preflight BMD was calculated for each postflight scan of the same crew member and all changes were incorporated into the mathematical function.

Percent BMD changes were plotted as a function of time, i.e., against the number of days after landing when the postflight BMD was measured. Because the review of the plotted data suggested an exponential relationship between the increase in BMD and elapsed time after landing, the data were to a 2-parameter exponential mathematical equation to describe an asymptotic increase:

$$L_t = L_0 * \exp[\ln(0.5) * t/HL]$$

Where L_t is the change in BMD detected at time “t” after landing; L_0 is the change in BMD that is a direct consequence of spaceflight (i.e., at the time of landing), and HL (half-life) denotes the time at which 50% of the bone lost during spaceflight has been restored.

This mathematical function estimates the loss of BMD induced by spaceflight (L_0) from a fit of all data points and describes the temporal recovery of BMD to preflight BMD status. This recovery model – analogous to the decay of a radioisotope – uses the “half-life” term (HL) as a metric to express the temporal response of the skeleton. This half-life term – from here on referred to as “50% Recovery Time” – was calculated for the five skeletal sites of interest (lumbar spine, pelvis, femoral neck, trochanter and calcaneus). Spaceflight-induced bone losses and 50% Recovery Times were compared between skeletal sites by evaluating overlaps in error distributions.

RESULTS

Investigations of the influence of age, flight duration, and gender were attempted (student t –test or Pearson correlation) but the limited range and variability of data points failed to show any significant effect. There was no statistically significant correlation of average % change in BMD (per month) with age at time of launch (range of Pearson Coefficient R between -0.147 and

0.206) when evaluated for the sites of clinical interest (pelvis, trochanter, femoral neck and lumbar spine). For those who flew on "standard" length missions of 4-6 months, the average flight duration was 173±24 days (range126-208 days). However, with the inclusion of the two crew members that flew on atypical prolonged missions of 311 and 438 days, the average flight duration was 181±47 days. There were only 9 crew members who flew on multiple flights; 7 of those crew members flew on only two flights while 2 crew members flew thrice. For these repeat flyers, the average time period between the launches of repeat missions was 1381±549 days (mean±SD). In Figures 1-5 the data points representing the second and third flights for the 9 repeat flyers are denoted as "+" in contrast to BMD changes measured in crew members after a single long-duration mission.

Figures 1-5 present the plots of the BMD change, per skeletal site, as a function of time after landing (days). Ninety-five percent confidence limits (dashed lines) and the determination of 50% Recovery Times are also depicted. Table 2 summarizes the initial loss and 50% recovery time by skeletal region obtained from the plots. In brief, the losses of bone density due to spaceflight appear to be greater in the hip (femoral neck and trochanter) and pelvis than the losses determined in the lumbar spine and calcaneus. The confidence intervals for recovery times for skeletal sites, however, overlapped each other indicating that the rates of recovery were not significantly different between sites. Based upon the mathematical fit of postflight scans, our recovery model estimates that recovery of half of the bone lost in the trochanter (a clinically relevant site that consistently displays what appears to be the greatest deficit) occurs by 9 months.

DISCUSSION

We applied an exponential mathematical function to a database of BMD measurements to describe the temporal, asymptotic recovery of BMD in crew members after return to Earth. The database contained BMD data from forty-five different crew members serving over a total of 56 long-duration flights. There is limited documentation of BMD recovery in spaceflight crew reported in the literature (5, 10). With imaging of eleven Mir cosmonauts by peripheral QCT, Vico et al detects a persistence of tibial BMD loss at 6 months after return suggesting that the time period for recovery, if it occurs, would exceed the duration of spaceflight exposure. Lang et al (10) document the incomplete recovery of femoral neck BMD one year after flight in a QCT evaluation of the hip in 16 ISS crewmembers. To supplement these reports of postflight BMD measurements, this report is the first to use DXA BMD data monitored over an extended postflight period, in a crew member population of this size, to describe the recovery pattern of bone mineral density that was lost during spaceflight.

From this mathematical fit of BMD changes during the postflight period, we assert that most crew members who have flown on long-duration missions (4-6 months) would return to preflight BMD within 3 years – suggesting that the period for recovery is greater than the duration of the mission. Our estimate of a longer recovery period is not only supported by previously mentioned reports on recovery (5, 10) but is consistent with animal models of disuse, as exemplified by Ufthoff and Jaworksi's report on beagles (14).The estimation from our data is based upon BMD changes in the trochanter, which is the skeletal site that consistently displays the greatest loss in BMD in spaceflight [12] and flight-analog studies [13] and appears (Table 2) to take the longest time to recover (albeit, not statistically significant). With our mathematical fit indicating a ~9 month 50% Recovery Time in the trochanter, we estimate a substantial restoration (i.e., 15/16ths recovery at 4x the half-life) to occur within 36 months of return.

It is important, however, to note that skeletal recovery is highly variable among crew members. As displayed in figures of postflight BMD changes, some crew members recover within the first year after return while others do not recover until much later. Factors that contribute to this variability in recovery are likely to include nutrition [15, 16], skeletal muscle reconditioning [17], and genetics [18, 19]; some of these factors may delay the ability and motivation of crew members to become ambulatory and thus mechanically load their skeletons. It is interesting to note that two of the three outliers for BMD loss in the proximal femur (greater than a 15% deficit in femoral neck and trochanter) were older than the average age of, or in space longer than the average duration for, long-duration crew members; the missions corresponding to these outliers also represented their first long-duration flight. There was a regional BMD measurement of the femoral neck that appeared to reflect deficits in excess of 15%; this hip scan was performed on a repeat flyer at R+116 days. However, this data point was beyond the confidence limits of our mathematical fit (Figure 1) and the review of subsequent postflight BMD data for this crew member suggested further that the BMD deficit at 116 days was spurious.

A recent presentation by Keyak et al (20) correlates changes in DXA areal BMD after flight with reductions in hip strength in 11 ISS crew members, as determined by Finite Element Analysis of QCT hip scans. By extrapolation from Keyak's data, we can suggest that the losses of >15% in the trochanter and femoral neck, as seen in our database, could lead to an average reduction in strength of 21.9% with fall loads and 27.1% with axial loads (with stance). These observed reductions, in a crew member population with an average age of 43 years, are similar to or exceed the age-related strength reductions determined with a cross-sectional comparison to elderly, post-menopausal white females (strength losses of 24.4% with falls and 6.9% with stance) (20). Thus, the reductions in DXA areal BMD translate to a much greater reduction in the ability of the hip to withstand applied loads and suggest that crew members are at an increased risk for hip fracture during the first 3 years after return, and possibly much longer.

Risk factors that contribute to bone loss in crew members should also be considered to evaluate their influence on recovery. Collectively, future studies will not only need to evaluate how bone *metabolism* responds to changes in mechanical loading (at the molecular, cellular and tissue level) but how changes in skeletal mass and structure correlate with changes in muscle forces, with expression of skeletally-relevant genes and with nutrient uptake in this crew member population.

All models have limitations. However, we chose to develop a useful recovery model to study the skeleton's re-adaptation to gravitational forces - after a prolonged exposure to weightlessness - by using all available data from every DXA scans performed after spaceflight during a 15-year period. Only some of the data in this report was from a research investigation (Dataset I) which was/is always conducted on crew member volunteers. Hence, we also included medical data from the NASA Astronaut Corps in this analysis. Medical evaluations, however, were restricted to specific times periods before launch and after landing, and there was insufficient time to allow for replicate measures. For a human study, we measured a low number of crew members since there are at most two long-duration missions flown per year with only 2-3 crew members per mission. And while DXA scans were a medical requirement for NASA astronauts, NASA had minimal oversight to BMD measurements of cosmonaut volunteers. Scans for cosmonaut BMDs, as previously mentioned, were not as numerous as those performed on astronauts. Finally, there are strict regulations on reporting identifiable medical data. It could be possible to identify a crew member by his/her data simply by associating BMD with flight duration, gender, age, ethnicity or nationality. In light of these constraints, this mathematical fit of postflight data makes optimal use of all available measurements of BMD in individuals exposed to spaceflight.

Initially, there was some concern regarding the fact that the BMD database contained two distinct datasets of BMD. These datasets represented different numbers of crew members (n=7 vs. 39) and were generated under different protocols. The research data from Group I were more systematically obtained with longitudinal measurements during a postflight period of a small number of individuals (n=7); the data from Group II, conversely, benefited from a large number of individuals (n=39) but were limited in the number of postflight scans performed per crew member. Both datasets, moreover, contained serial measurements of some crew members. In spite of these differences in datasets, we were able to establish consistency between the two recovery models of fitted data by a Monte Carlo simulation; this enabled us to fit <u>all</u> available changes in BMD into our mathematical function thereby optimizing its utility to predict of skeletal recovery.

Another limitation of the recovery model lay in its inability to evaluate the influence of previous flights on skeletal recovery. In Dataset II there were 49 sets of preflight and postfight scans available from the 39 crew members (Group II) because of nine crew members who flew on multiple missions. As previously mentioned, two of those same nine crew members flew on three missions each and one astronaut in Group II had previously flown on a Mir mission (Group I). There was an average elapsed period of 1381±549 days (774 – 2347 days) between repeat flights. Because of the small number of repeat flyers in our database, as well as the limited variation in flight durations, it was not possible to account for the impact of both multiple missions or of mission duration on a crew member's spaceflight-induced bone loss or on BMD recovery.

A regression analysis has been conducted by our Russian co-author who analyzed BMD of L1-L4 from fourteen cosmonauts who have served on multiple missions of 5.5-11 months duration. In a previously conducted analysis by our co-author, Oganov reports the results of multiple regression analysis of variables from an earlier flight to predict BMD changes in a subsequent flight. In brief, there is a significant correlation (R=0.627) of bone loss in the first flight, combined with the bone restoration before the second flight, with BMD change in the second flight; there was only a slight improvement when baseline bone mineral density for the first flight was added as a third independent variable (R=0.632) [21]. Further study is warranted; investigations that address bone phenotypes that may serve as predictive indices for bone loss during and recovery after spaceflight are currently in progress by our Russian colleagues.

Finally, DXA measurement of BMD alone is no longer considered a sufficient surrogate for bone strength [22]. With the results of this study, we do not assert that the restoration of bone mass in crew members implies a restoration of bone strength particularly since DXA measurement of areal BMD fails to take into account bone geometry or material properties which all together or combination could influence fracture resistance.

In summary, a two-parameter exponential function was applied to serial BMD measurements of 45 crew members who served on a total of 56 long-duration spaceflight missions (>4 months). The recovery model, based upon a fit of data points (approximately 62-119) over 5 regional sites, provided a numerical estimate for the length of time to restore 50% of bone lost during spaceflight. The results indicate that deficits in BMD are gradually restored after return to Earth, and the recovery model estimates that restoration of BMD would be expected to occur within 3 years after return for most crew members. This investigation addresses a fundamental issue of how bone mass responds to changes in skeletal loading. These results would have an additional relevance to patient populations that are subjected to prolonged periods of immobilization and to the skeleton's capacity to recover.

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Figure 1. Changes in BMD at the Femoral Neck after Landing. For each postflight BMD scan, the percentage change between postflight and preflight BMD was plotted against the number of days after landing when the scan was performed. The intercept of the fitted line represents the change in BMD as a direct consequence of spaceflight (at the time of landing). Dotted lines represent 95% confidence limits for the BMD data. Data points denoted by circles (vs. diamonds) represent BMD changes measured in a flyers who have served on multiple long-duration missions. For the femoral neck the spaceflight-induced loss is 6.5% where 50% Recovery Time for the loss would occur at 211 days or about 7 months.

Figure 2. Changes in BMD at the Trochanter after Landing. Data points were derived and plotted as described in Figure 1. The intercept of the fitted line shows the spaceflight-induced bone loss of 7.8% where 50% Recovery Time for the loss would occur at 255 days or about 8.5 months.

Figure 3. Changes in BMD at the Pelvis after Landing. Data points were derived and plotted as described in Figure 1. The intercept of the fitted line shows the spaceflight-induced bone loss of 7.7% where 50% Recovery Time for the loss would occur at 97 days or about 3 months.

Figure 4. Changes in BMD at the Lumbar Spine after Landing. Data points were derived and plotted as described in Figure 1. The intercept of the fitted line shows the spaceflight-induced bone loss of 4.9% where 50% Recovery Time for the loss would occur at 151 days or about 5 months.

Figure 5. Changes in BMD at the Calcaneus after Landing. Data points were derived and plotted as described in Figure 1. The intercept of the fitted line shows the spaceflight-induced bone loss of 2.9% where 50% Recovery Time for the loss would occur at 163 days or about 5 months.

Table 1. Mission Assignments of Long-duration Crew Members. Bone mineral density measurements were conducted in 45 different crew members serving on a total of 56 long-duration flights during the period of 1990-2004. Mission duration is average days $\pm$ SD, with range provided in parentheses. There were 7 flyers (all males) who flew on at least 2 mission and 2 flyers (males) who flew on 3 missions. Four of the repeat flyers studied in this database served on both the Mir and ISS missions. Average time period between launches of multiple flights was 1381$\pm$549 days (mean+SD) ranging between 734 and 2347 days.

Table 2. Summary of Fitted Data per Skeletal Site. The percentage of preflight BMD loss (L_0) at the time of landing and the "50% Recovery Time" are listed per skeletal site. Fifty % Recovery Time represents the number of days after landing at which there is a restoration of half of the bone mineral lost during spaceflight. The L_0 and recovery times were determined from BMD data fitted to a 2-parameter exponential function for recovery of skeletal BMD after landing: $L_t = L_0 *\exp[\ln(0.5)*t/HL]$. Confidence limits (95%) for the fitted values are provided in parentheses. The intercept for the fitted data (L_0) (Figures 1-5) represents BMD loss as a direct consequence of spaceflight.

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Figure 1. Femoral Neck

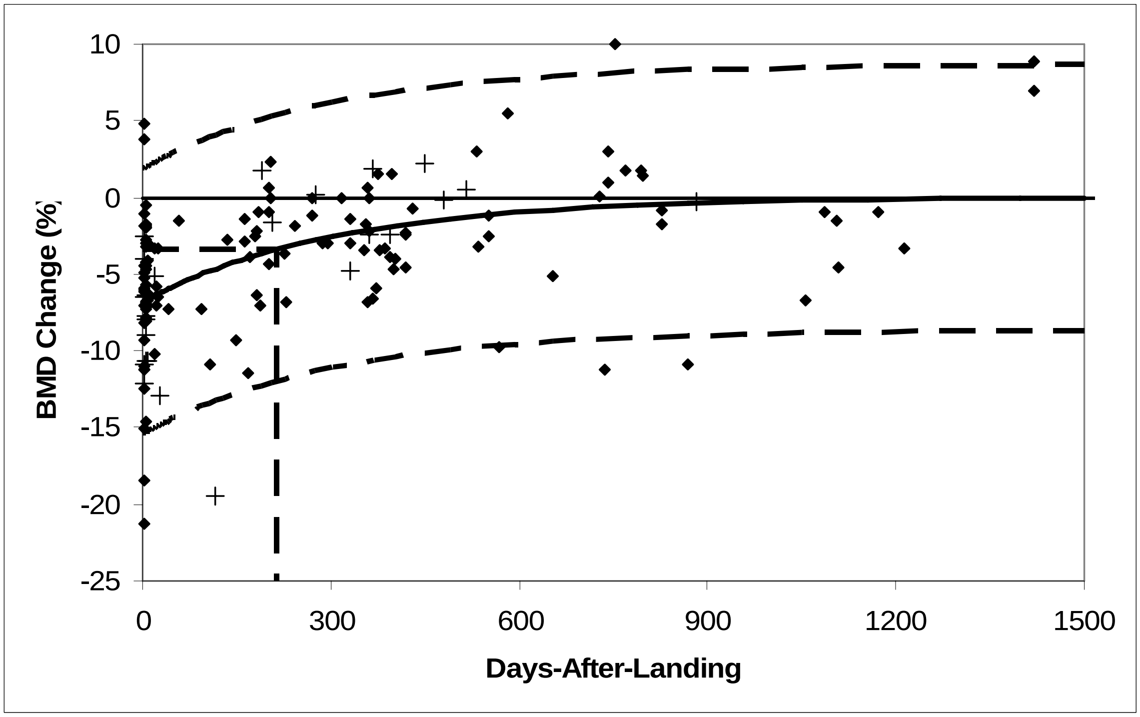

Figure 2. Trochanter

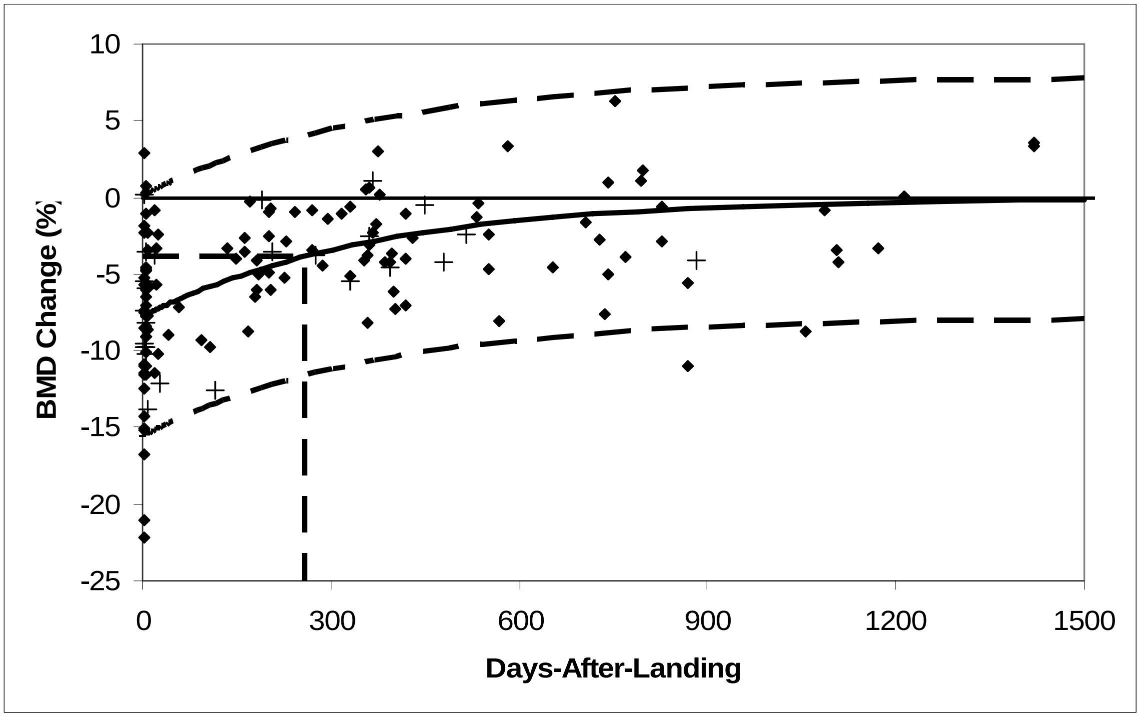

Figure 3. Pelvis

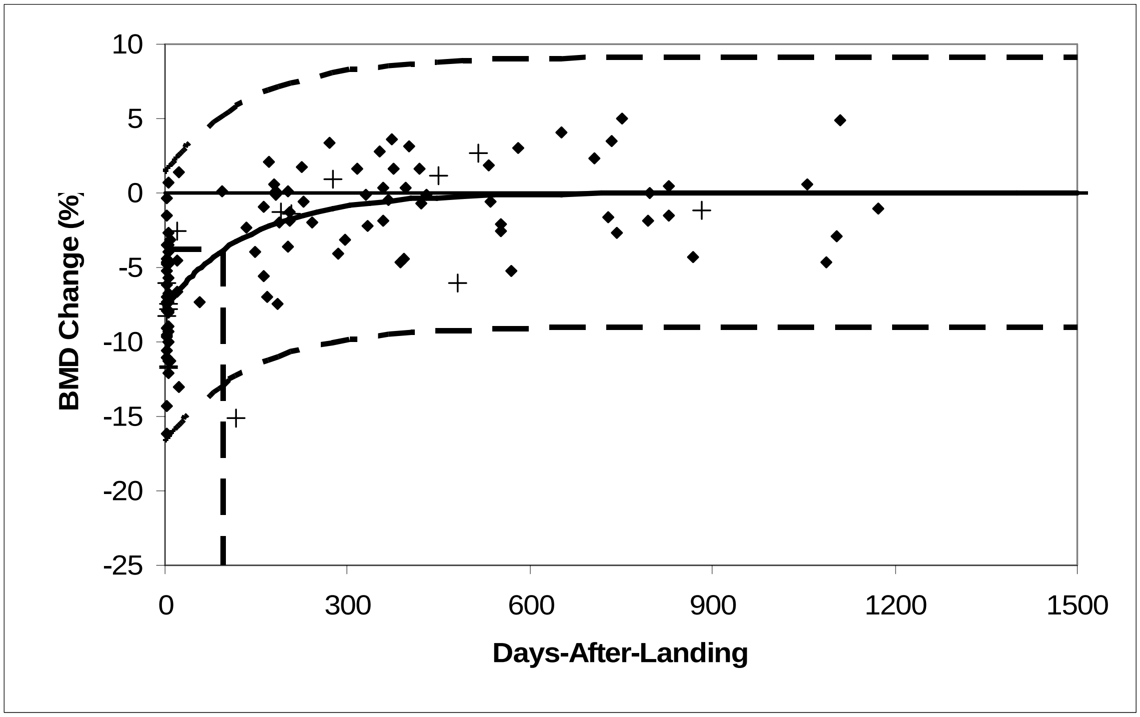

Figure 4. Lumbar Spine

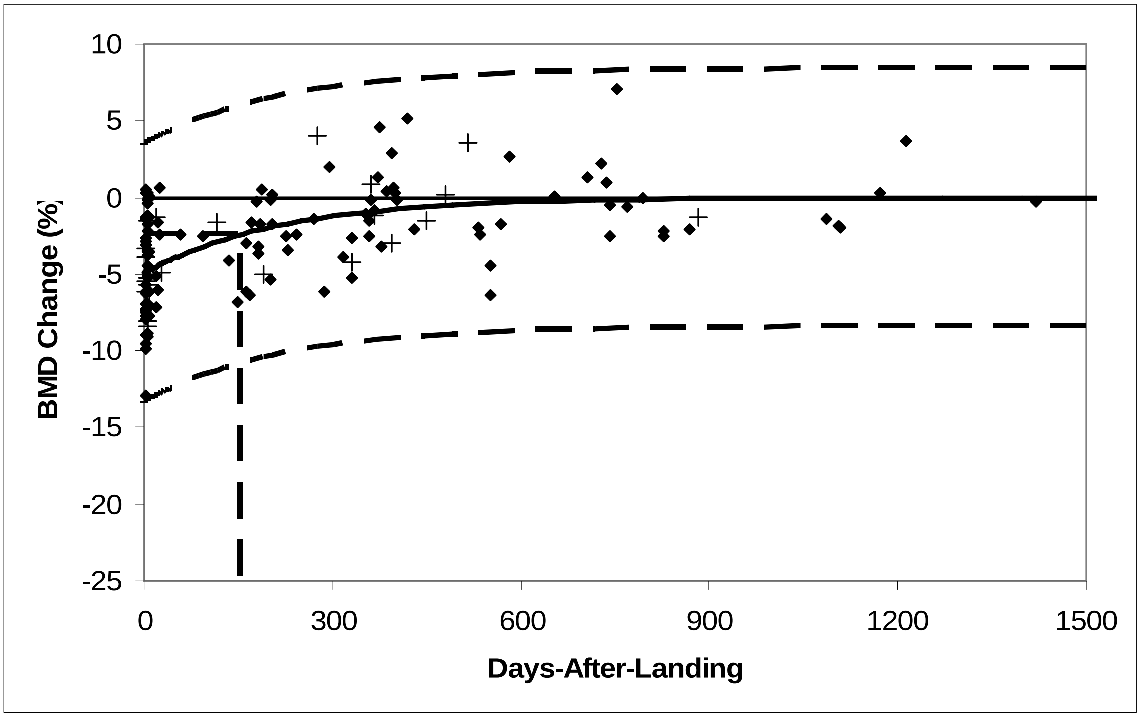

Figure 5. Calcaneus