Skeletal Recovery Following Long-duration Spaceflight Missions as Determined by Preflight and Postflight DXA Scans of 45 Crew Members

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CONFLICT OF INTEREST

The authors state that they have no conflict of interest.

MICROABSTRACT

The recovery of bone mineral density (BMD) that was lost during 4- to 6-month spaceflight missions was evaluated in a retrospective study of 45 crew members. Changes between pre- and postflight BMD monitored during the postflight period were fitted to a 2-parameter exponential equation. Our mathematical model suggests that BMD recovery occurs within 36 months of return.

ABSTRACT

Introduction: The loss of bone mineral in astronauts during spaceflight has been investigated throughout the more than 40 years of bone research in space. Consequently, it is a medical requirement at NASA that changes in bone mass be monitored in crew members by measurements of bone mineral density (BMD) with dual-energy x-ray absorptiometry (DXA). This report is the first to evaluate medical data to address the recovery of bone mineral that is lost during spaceflight.

Methods: DXA scans are performed before and after flight in astronauts who serve on long-duration missions (4-6 months) to ensure that medical standards for flight certification are met, to evaluate the effects of spaceflight and to monitor the restoration to preflight BMD status after return to Earth. Through cooperative agreements with the Russian Space Agency, the Bone and Mineral Lab at NASA Johnson Space Center (Houston, TX), also had access to BMD data from cosmonauts who had flown on long-duration missions yielding data from a total of 45 individual crew members. Changes in BMD (between 56 different sets of pre- and postflight measurements) were plotted as a function of time (days after landing); plotted data were fitted to an exponential mathematical model that determined i) BMD change at day 0 after landing and ii) the number of days after which 50% of the lost bone was recovered ("Recovery Half-Life"). These fits were performed for BMD of the lumbar spine, trochanter, pelvis, femoral neck and calcaneus.

Results: In sum, averaged losses of bone mineral after spaceflight ranged between 2-9% for sites in the axial and appendicular skeleton. The fitted postflight BMD values predicted a 50% recovery of bone loss for all sites within 9 months.

Conclusion: As determined by the exponential model of BMD restoration, recovery of crew members after long-duration missions seems to be substantially complete within 36 months after return to Earth.

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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 on three missions on Skylab (28, 56 and 84 days) and on long-duration missions (>4 months) aboard the Russian Mir space craft and the International Space Station (ISS) (2-11).

Although calcium kinetics and bone biomarkers have been used to characterize bone health <u>during</u> spaceflight, no reports have addressed the impact of spaceflight on bone health <u>after</u> spaceflight, i.e., the recovery of skeletal integrity, its nature and its time course has not been reported. Since the Skylab missions of the 1970's, measurement of bone mineral and bone mineral density had been used to evaluate spaceflight effects on the skeleton (4, 5, 8, 9). More recently, DXA scans, which provide faster and precise measures of skeletal changes, have been routinely performed at the Bone and Mineral Lab at NASA Johnson Space Center in crew members to support medical operations for long-duration missions.

Therefore, we analyzed these pre- and postflight BMD data to model the skeletal recovery of astronauts who returned from long-duration spaceflight. In addition, we obtained access to DXA data (pre- and postflight BMD) of Russian cosmonauts who similarly served on long-duration missions on the Mir and ISS Spacecrafts. BMD data were analyzed i) to determine if the crew members were able to recover their skeletal deficits upon return to Earth and ii) to understand the rate of skeletal recovery after prolonged space habitation (typically between 4-6 months). This report is the first to characterize skeletal recovery of space-flight induced bone loss with DXA measurements of BMD.

METHODS

<u>Data Source.</u> It is a NASA medical requirement for the health assessment of the Astronaut Corps to 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 instrument: model QDR 1000W, 2000 or 4500 model (Hologic, Inc., Waltham, MA). All postflight scans were performed on the same instrument as the preflight scan. As documented in the medical requirement, DXA scans of astronauts were performed at specific time intervals before and after long-duration flights. Preflight scans are performed within 45 to 30 days before launch while postflight scans are conducted 5 times after return to Earth. In this report, postflight BMD scans were first performed between 2-26 days after landing and then at approximately 6 months, 12 months, 24 months and 36 months after landing. As will be discussed in detail subsequently, DXA scans of cosmonauts were not scheduled identically to the NASA medical requirement.

Spaceflight-induced bone loss is considered recovered when BMDs of an astronaut are within 2% of preflight BMD; only one other BMD measurement is required to confirm stability of this response. At each scan date, regional scans of the lumbar spine, hip and the calcaneus were performed. BMD data for the pelvis were obtained from the whole body scan, while scans of the hip yielded data for the trochanter and the femoral neck of the proximal femur.

The BMD data in this report came from 45 different crew members who served either on the Mir spacecraft or the International Space Station (ISS). Some crew members flew on multiple long-duration flights; thus the total number of pre- and postflight datasets was 56. BMD data from these 56 flights were initially analyzed as two separate datasets because the datasets were obtained under two different protocols. Dataset I was obtained from 7 NASA astronauts 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 protocol was later adopted by NASA to monitor the return of BMD to preflight status in all astronauts. Dataset II was obtained from a total of 39 different crew members who served on 49 separate missions (multiple flights for some crew members). These crew members were 12 astronauts who flew on the ISS (2000-

2004), 22 cosmonauts who flew on Mir (1990-1998) and 5 cosmonauts who flew on the ISS (1990-2004).

Additionally, scans for cosmonaut BMDs were not as extensive as performed for astronauts. Typically, a cosmonaut dataset consisted of one preflight scan and a single scan after flight. There were occasional situations where a preflight scan of a cosmonaut preparing for an additional flight also served as a postflight time point to assess recovery from the previous flight. Due to longitudinal measures in some crew members, averages of BMD from the two datasets could not be statistically compared. Therefore, a Monte Carlo simulation was performed to confirm model consistency between the two sets of data. This simulation analysis indicated that the two datasets generated consistent models for bone loss and recovery, and the two datasets were subsequently combined for the analysis presented in this report.

<u>Mathematical Model for Skeletal Recovery.</u> The change in bone mineral that is a direct result of spaceflight was calculated as the difference between preflight and postflight BMD and expressed as a percentage of the preflight BMD. When multiple preflight BMD values were available, BMD changes (i.e., postflight BMD minus preflight BMD) were calculated from the BMD scan closest to the date of launch. For the measurements in this report, the first postflight scans performed generally occurred within 26 days after landing (6 ± 1, mean $\pm$SEM). 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 <u>each</u> postflight scan of the same crew member. All changes in preflight and postflight BMD that were available were fitted to the mathematical model.

Percentage changes were calculated for all postflight scans performed and plotted as a function of time, i.e., against the number of days after landing when the postflight BMD was measured. Initial review of the plotted data suggested an exponential relationship between the increase in BMD and elapsed time after landing. The data were subsequently fitted 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 model relates 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 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

The average age of all the crew members was 43.2±5.2 y. The average flight duration was 173±24 d (range126-208 d); with the inclusion of the two crew members that flew on prolonged missions of 311 and 438 days, the average flight duration was 181±47 days. Data were obtained from 42 male crew members and 3 female crew members.

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 1a provides the initial loss and 50% recovery time by skeletal region obtained from the plots in Figures 1-5. In brief, the losses of bone due to spaceflight are greater in the hip (femoral neck and trochanter) and pelvis than the losses determined in the lumbar spine and calcaneus. The hip trochanter tended to take the longest time to recover with a 50% recovery time of 255 days, but the recovery times between sites were not significantly different. Likewise, the averaged spaceflight-induced BMD losses (%) (data not shown) -- calculated from the first postflight DXA performed after landing (data points n=43±16, mean ±SD) -- did not appear to differ significantly with BMD loss (%) determined by the fitted model (data points n=99±25, mean ±SD) suggesting that the different determinations of bone loss as a direct consequence of spaceflight were consistent with each other.

DISCUSSION

We applied an exponential mathematical model to a database of BMD measurements to describe the temporal, asymptotic increase in BMD in crew members after return to Earth. Forty-five different crew members provided BMD data after serving over a total of 56 long-duration flights. This is the first report to use DXA BMD data from a crew member population of this size to determine the recovery pattern of bone mineral density that was lost during spaceflight.

From this mathematical fit of BMD changes during the postflight period, we can 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 estimation is based upon BMD changes in the trochanter, which is the skeletal site that consistently displays the greatest loss in BMD in spaceflight (11) and flightanalog studies (12) and appears to take the longest time to recover (NS). With the fit indicating a ~9 month 50% Recovery Time in the trochanter, we predicted the restoration of 15/16ths (i.e., 4x the half-life) to be within 36 months of return.

It is important 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 of return (i.e., reach a stable postflight BMD within 2% of preflight BMD) while others do not recover until much later. Factors that contribute to this variability in recovery are likely to include nutrition (13, 14), skeletal muscle reconditioning (15), mobility and motor coordination (16), and genetics (17, 18). 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 or in space longer than the averaged age and duration for long-duration crew members. 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 to changes in muscle mass, in gene expression and with nutritional assessments.

All models have limitations. 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 over multiple time points but included only 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 longitudinal measurements of some crew members. In spite of these differences in datasets, a Monte Carlo simulation established consistency between the two models of fitted data and therefore enabled us to fit <u>all</u> available changes in BMD into our mathematical model for recovery, optimizing its prediction of skeletal recovery.

Another limitation of the 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. 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). Because of the small number of repeat flyers, 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. Finally, because DXA measurement of BMD is no longer a sole determinant of bone strength (19), we do not assert that the restoration of mass in crew members implies a restoration of bone strength.

In summary, a two-parameter exponential model was applied to serial BMD measurements of 45 crew members who served on a total of 56 long-duration spaceflight missions (>4 months). The 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 reach 50% restoration of lost bone. The changes in BMD indicate that deficits in BMD are restored after return to Earth and the model estimates that recovery 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 the patient population that is 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. For the femoral neck the spaceflight-induced loss is 6.5% where recovery of 50% of the loss would occur at 211 days or ~ 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 recovery of 50% of the loss would occur at 255 days or ~ 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 show the spaceflight-induced bone loss of 7.7% where recovery of 50% of the loss would occur at 97 days or ~ 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 recovery of 50% of the loss would occur at 151 days or ~ 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 recovery of 50% of the loss would occur at 163 days or ~ 5 months.

Skeletal Site	**Loss (L0) at landing %**	**50% Recovery Time (days)**
Femoral Neck	6.8 *(5.7, 7.9)*	211 *(129, 346)*
Trochanter	7.8 *(6.8, 8.8)*	255 *(173, 377)*
Pelvis	7.7 *(6.5, 8.9)*	97 *(56, 168)*
Lumbar Spine	4.9 *(3.8, 6.0)*	151 *(72, 315)*
Calcaneus	2.9 *(2.0, 3.8)*	163 *(67, 395)*

Table 1. 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 model 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.

Figure 1. Femoral Neck

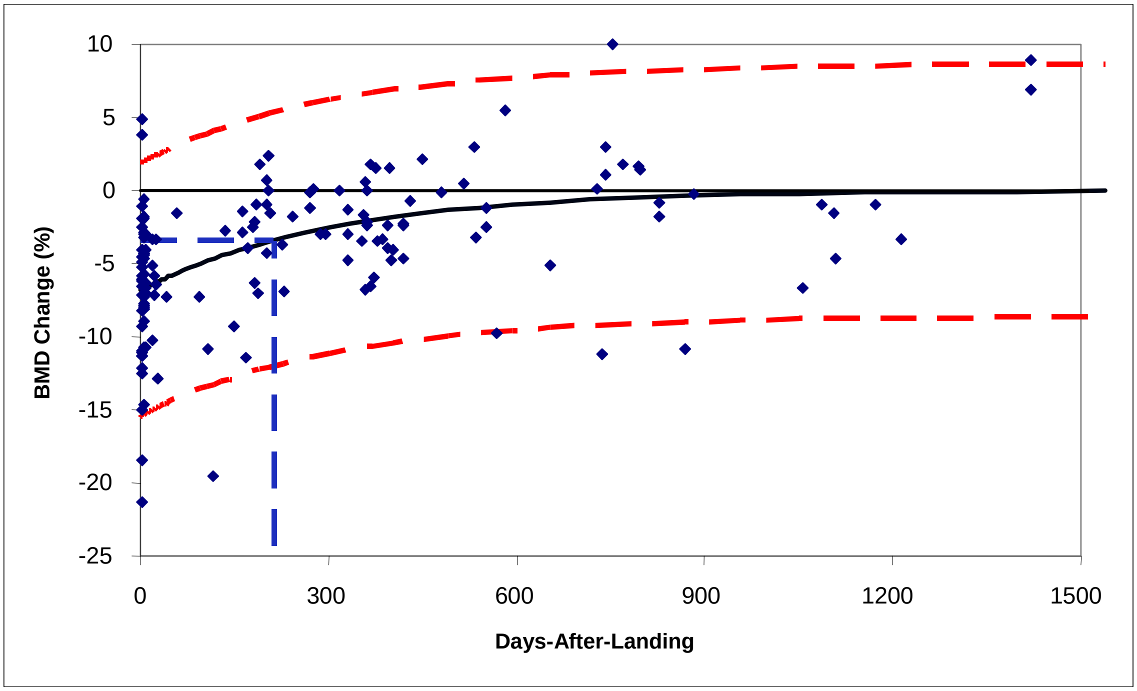

Figure 2. Trochanter

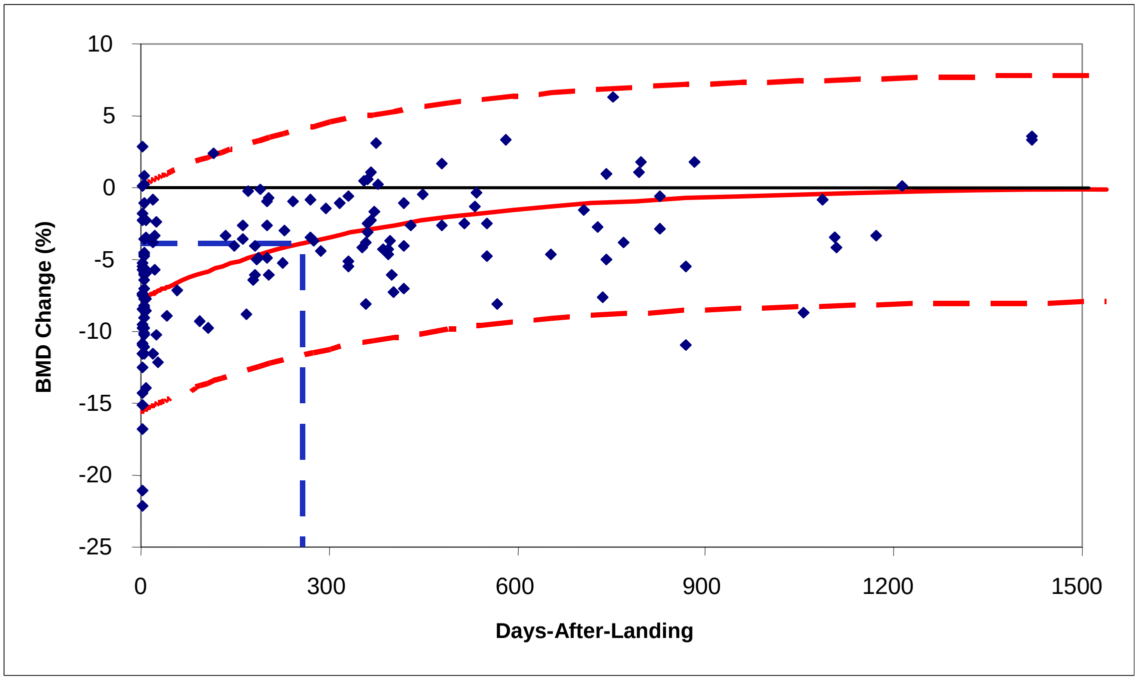

Figure 3. Pelvis

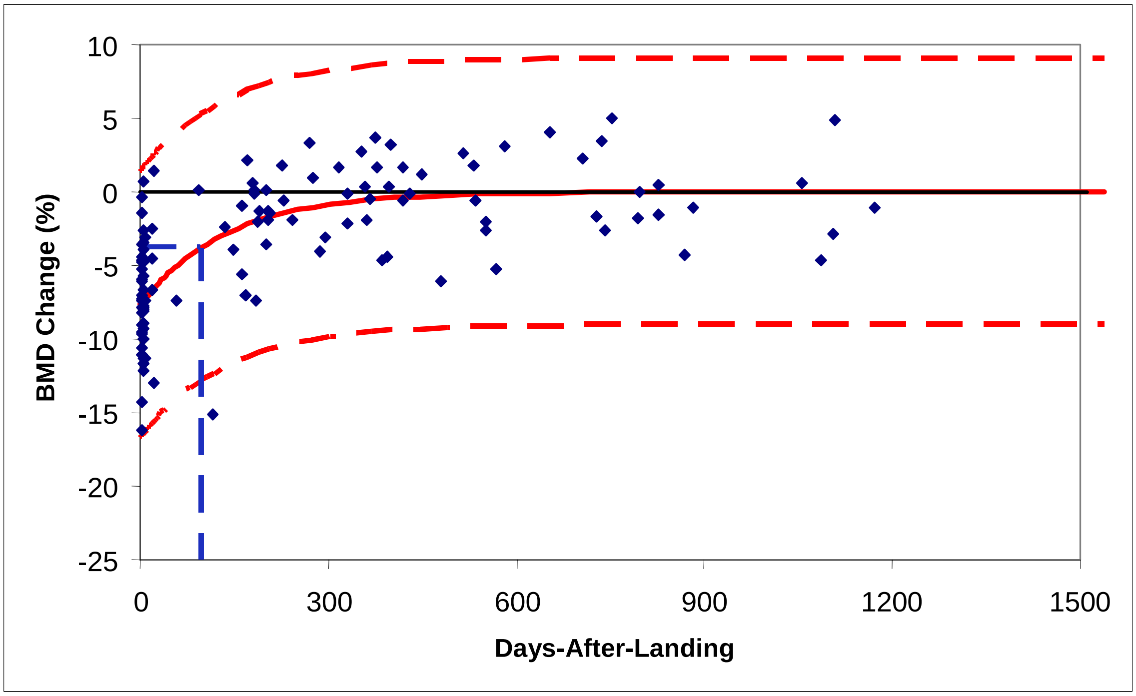

Figure 4. Lumbar Spine

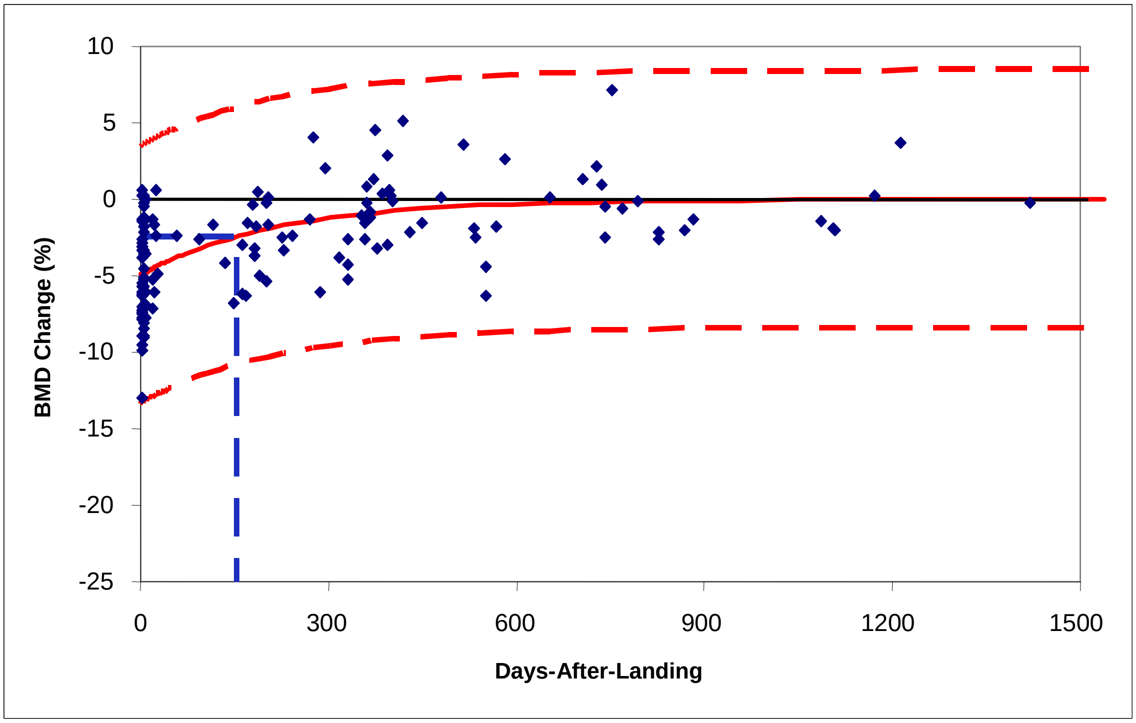

Figure 5. Calcaneus