Adaptation of the Skeletal System during Long-duration Spaceflight

Running Title: Skeletal Adaptation in Space

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Abbreviations: BMD:Bone mineral density; DXA: Dual-energy x-ray absorptiometry; FEA: Finite Element Analysis; ISS: International Space Station; MRI:Magnetic resonance imaging; PTH:Parathyroid Hormone; QCT: Quantitative Computed Tomography; UV:Ultraviolet; WHO:World Health Organization

Abstract

This review will highlight evidence from crew members flown on space missions >90 days to suggest that the adaptations of the skeletal system to mechanical unloading may predispose crew members to an accelerated onset of osteoporosis after return to Earth. By definition, osteoporosis is a skeletal disorder – characterized by low bone mineral density and structural deterioration – that reduces the ability of bones to resist fracture under the loading of normal daily activities. “Involutional” or age-related osteoporosis is readily recognized as a syndrome afflicting the elderly population because of the insipid and asymptomatic nature of bone loss that does not typically manifest as fractures until after age

~60. It is not the thesis of this review to suggest that spaceflight-induced bone loss is similar to bone loss induced by metabolic bone disease; rather this review draws parallels between the rapid and earlier loss in females that occurs with menopause and the rapid bone loss in middle-aged crew members that occurs with spaceflight unloading and how the cumulative effects of spaceflight and ageing could be detrimental, particularly if skeletal effects are totally or partially irreversible.

In brief, this report will provide detailed evidence that long-duration crew members, exposed to the weightlessness of space for the typical long-duration (4-6 months) mission on Mir or the International Space Station --

1. Display bone resorption that is aggressive, that targets normally weight-bearing skeletal sites, that is uncoupled to bone formation and that results in areal BMD *deficits* that can range between 6-20% of preflight BMD;
2. Display compartment-specific declines in volumetric BMD in the proximal femur (a skeletal site of clinical interest) that significantly reduces its compressive and bending strength and which may account for the loss in hip bone strength (i.e., force to failure);
3. Recover BMD over a post-flight time period that exceeds spaceflight exposure but for which the restoration of whole bone strength remains an open issue and may involve structural alteration; and
4. Display risk factors for bone loss -- such as the negative calcium balance and down-regulated calcium-regulating hormones in response to bone atrophy -- that can be compounded by the constraints of conducting mission operations (inability to provide essential nutrients and vitamins).

The full characterization of the skeletal response to mechanical unloading in space is not complete. In particular, countermeasures used to date have been inadequate and it is not yet known

whether more appropriate countermeasures can prevent the changes in bone that have been found in previous flights, Knowledge gaps related to the effects of prolonged (≥ 6months) space exposure and to partial gravity environments are substantial, and longitudinal measurements on crew members after spaceflight are required to assess the full impact on skeletal recovery.

Introduction

Early in the space program, it was recognized that immobilization in those first space crafts for manned missions, coupled with the gravitational unloading, could have detrimental effects on calcium metabolism. The impetus behind the next 40+ years of bone research in space may have come in the 1940's when the premier endocrinologist, Fuller Albright, called attention to the disturbed calcium metabolism evident in a young patient experiencing prolonged bed rest [1]. This was subsequently proven by Whedon and colleagues in studies demonstrating that musculoskeletal atrophy was due to the mechanical unloading of prolonged bed rest and not disease *per se* [2]. Consequently, seminal investigations and evaluations of the skeletal system were initiated with the Gemini flights, as best as could be achieved given the constraints of operating a spaceflight mission and the available technology in the early 1960's. As technology has advanced, so has the characterization of skeletal adaptation to weightlessness. As outlined in Figure 1 the database for the skeletal effects of spaceflight was expanded along with the technologies and analyses available during a spacecraft era.

To this day, the characterization of skeletal adaptation to space (termed "space normal" by the NASA Human Research Program at Johnson Space Center) is paramount as NASA prepares to embark on exploration class missions with a return to the moon and human exploration of other planetary surfaces. Understanding the physiological effects of spaceflight is critical as NASA identifies the health risks associated with these longer-duration flights and develops appropriate countermeasures to eliminate or mitigate these effects. While the current understanding of "space normal" for bone has

been limited by the number of crewmembers and flight opportunities, the current database on the skeletal adaptation to space provides sufficient evidence to document that prolonged exposure to the space environment without appropriate countermeasures, compromises the skeleton and may increase the risk for atraumatic fractures at an earlier age.

In order to understand how the adaptive response to space predisposes crew members to early onset osteoporosis it is important to appreciate how space exposure impacts the multiple facets of skeletal remodeling and how those changes in crew members (predominantly driven by biomechanics) relate to terrestrial changes in the ageing human (predominantly driven by metabolic pathologies).

Background

Osteoporosis is a skeletal disease characterized by several features of a deteriorated skeleton that collectively compromise whole bone strength and increase the propensity for fracture in afflicted individuals. This syndrome can be a consequence of the *ageing* process [3, 4] which begins during late puberty following the closure of epiphyseal growth plates. However, the sex-specific effects of growth also influence age-related bone loss since estrogen suppression of radial and longitudinal bone growth in females, with the onset of puberty, results in smaller bones and less peak bone mass compared to their male counterparts. Later, with the onset of menopause, estrogen-deficient females experience an earlier, more rapid, phase of involutional bone loss which increases the incidence and prevalence of fractures in ageing women [3-5]. Likewise, it is widely acknowledged that osteoporosis can be induced by secondary factors, such as chronic use of glucocorticoid medication, alcoholism or decreased physical activity where the suppressive effects on bone formation unbalance the remodeling process to favor net bone loss. Thus, osteoporosis has multiple pathophysiologies that can have additive effects.

After more than 40 years of human spaceflight, the mechanical unloading of space is a well-recognized risk factor for bone loss [6]. Whether it is a factor for secondary osteoporosis in crew

members is dependent upon the length of time the skeleton is unloaded in space and whether it can be restored to its previous pre-launch state upon return to normal mechanical loading of Earth. If the skeletal decrements during space travel are irreversible, even if osteoporosis is not diagnosed at landing, the result may be an earlier diagnosis in the crew member's life compared to the expected temporal onset with age-related bone loss. Understanding the skeletal response to the mechanical unloading of spaceflight starts with understanding how the adult skeleton undergoes bone turnover through the highly mediated process of bone remodeling in a standard gravitational field.

On Earth, the adult human skeleton renews and repairs itself with approximately one tenth of the skeleton renewed on an annual basis. In response to putative osteocytic cell signaling, skeletal remodeling is initiated in discrete packets of skeletal tissue referred to as "bone remodeling units" where the removal and replacement of bone tissue is the result of a well-orchestrated action of bone resorbing (osteoclasts) and bone forming cells (osteoblasts). This cellular regulation ensures: i) the temporal formation of bone after the resorption of bone (i.e., "bone coupling"); and ii) the spatial formation of a bone volume to replace the resorbed volume in the resorption pit or lacunae ("bone balance"). Any perturbation to this cellular process, e.g., induced by endocrine or nutritional deficiencies or by changes in mechanical stresses, can disrupt this balance in the bone remodeling unit resulting in a deficit of bone, a gain of bone or a change in material properties of bone. With 1-2 million bone remodeling units in the adult skeleton [7], a negative balance of bone in each unit can reduce skeletal mass over time and compromise the skeleton's integrity under normal mechanical loading.

When remodeling is accelerated, as with menopausal bone loss, the "birth rate" of bone remodeling units is high. This acceleration can be quantified by histomorphometry with the index of Activation Frequency which has been shown to increase in the ageing female (Figure 2) [8]. Histomorphometric analyses have further revealed how increased numbers of bone remodeling units can

perforate horizontal trabecular struts of cancellous bone microarchitecture and induce greater porosity in cortical bone. The loss of trabecular elements and of connectivity between trabeculae reduces the mechanical strength of the trabecular scaffold. The accelerated loss of bone with menopause targets the cancellous bone compartment (i.e., trabecular or spongy bone) where resorption preferentially occurs along the bone surfaces adjacent to bone marrow. This mechanism of bone loss leads to: i) thinning of the cortical bone shell and the trabecular plates; ii) perforation of trabecular struts and iii) loss of trabecular elements and connectivity [5, 9, 10]. With menopause, there is a 20-30% reduction in *cancellous* bone compared to the 5-10% losses cortical bone associated with the first decade after menopause and accounting for a higher incidence of fractures in women (compared to men of same age range) at those skeletal sites predominantly composed of cancellous bone (wrist fractures and vertebral crush fractures) [3]. Increased remodeling, moreover, can also be inferred by increased levels of biomarkers for bone formation and bone resorption [11, 12].

More recently, the application of the more sensitive quantitative computed tomography [QCT] to a population study substantiated that there are earlier and persistent losses in cancellous bone in both men and women (~33% and 50% of total lifetime loss, respectively) [13, 14]. Likewise, substantial losses in cortical bone in women were initiated around mid-life with menopause onset while cortical bone loss in men did not accelerate until much later. Together with the observation that women have smaller bones from the outset, the deficiency of estrogen with menopause is a major contributing factor to osteoporosis (and its associated fragility fractures) in women compared to men at the same age.

The knowledge base underlying the spaceflight-induced bone loss is limited in comparison to what is known about the pathophysiology of primary osteoporosis or for the cellular mechanisms of secondary osteoporosis in the terrestrial populations. Spaceflight missions do not typically provide controllable experimental conditions for the systematic collection of data; experiments are restricted by

power, mass, and volume requirements; flight opportunities are few and far between; and subjects for testing or for longitudinal measures are too few to obtain definitive answers. Even so, the limited data from spaceflight can be evaluated in the context of the extensive knowledge base for terrestrial osteoporosis.

Hence this review of spaceflight analyses will span the perturbations in calcium homeostasis and in bone remodeling that were detected with short durations of spaceflight (<90 days as defined herein, but typically <2-3 weeks based on mission durations) to the measurable decrements in bone mineral densities and in bone structure in "long-duration" crew members after spaceflight exposures of typically ~4-6 months. Also described is the computer modeling -- based upon data from 3-dimensional bone images -- that has enabled estimations of hip bone strength immediately following long duration missions. A summary of knowledge gaps will highlight work that remains to be done, with spaceflight and/or with ground-based analogs, to substantiate the risk for an earlier onset of osteoporosis in crew members after prolonged space missions.

HUMAN SPACEFLIGHT DATA

Evidence for perturbed bone remodeling

There is evidence from bone turnover markers to suggest that the remodeling process is uncoupled in space leading to an unbalanced remodeling of bone and a deficit in bone mass. Indirect measures of turnover at the level of the entire skeleton indicate increased bone resorption, while bone formation appears to be unchanged or decreased. Early in the space program, biochemical assays of specimens collected in flight detected a greater excretion of collagen degradation products relative to circulating proteins/peptides that are synthesized and released by osteoblasts during bone formation. Increased bone resorption was evident with the elevated excretion of hydroxyproline relative to pre-flight level detected in all 3 Skylab missions [15]; this finding was corroborated almost two decades

later when archived urine specimens were analyzed by state-of-the-art assays for cross-linked collagen fragments (e.g., N-telopeptide, NTX) [16]. Likewise, Smith et al. [17] documented how spaceflight increased NTX excretion, with minimal influence on circulating levels of the osteocalcin, as determined in flight specimens of Mir crews. This pattern supported the earlier evidence of suppressed circulation of procollagen type I C-terminal peptide, bone-specific alkaline phosphatase, and osteocalcin (i.e., formation markers), concurrent with increased excretion of bone resorption markers in the Mir crew members [18]. Furthermore, measurement of C telepeptide (CTX) in both urine and serum in the two Mir cosmonauts indicated a greater concentration in serum as early as 8 days into the flight. An increase in undercarboyxlated bone gla protein (i.e, osteocalcin) was evident suggesting an impairment of vitamin K metabolism, the origins of which remain to be further investigated [19]. Collectively, these systemic indices of bone turnover suggest that mechanical unloading uncouples bone remodeling and, due to the "aggressive" action of osteoclasts, the resorbed volume of bone exceeds the volume of bone formed by osteoblasts.

Presence of additional risk factors for bone loss

Bone loss in space reflects alterations in many processes. There are several risk factors present in crew members during and immediately after spaceflight, some of which may contribute to or may be a consequence of the bone loss induced by spaceflight. Mineral metabolic studies that were conducted during the 28, 56, and 84-day Skylab missions enabled Whedon and colleagues to characterize the negative calcium (and mineral) balance with spaceflight [20-22]. Despite the large variability in the results, collectively the data suggested that skeletal deconditioning increased with longer mission durations [23]. There was a rapid and sustained elevation in urine calcium, a gradual increase in fecal calcium, and a negative calcium balance averaging – 7.5g/month. These changes were accompanied by increased excretion of hydroxyproline and hydroxylysine (early biomarkers of bone resorption), gradual

decreases in intestinal calcium absorption, minor increases in plasma calcium and phosphorus, and a delayed (>4 weeks) reduction in serum parathyroid hormone (PTH). The data suggested that the negative calcium balance was likely due to bone atrophy (increased excretion) and to calcium mal-absorption (decreased intake).

Measurements of calcium-regulating hormones in Mir crews showed trends for reduced parathyroid hormone [PTH] and 1, 25 dihydroxylated vitamin D concurrent with signs of increased bone resorption during spaceflight [17, 24]; the lack of statistical significance was likely a consequence of small subject numbers. These flight data further documented how increased atrophy of bone mildly increases serum calcium and phosphorus, leading to the reductions in calcium-regulating hormones, to the poor conservation of calcium, and contributing to the negative calcium balance observed with spaceflight [17, 25].

Changes in bone mass, bone mineral density and bone structure

Evaluations of bone density following prolonged space exposure were initially implemented with the 3-manned crew of the Skylab missions and thus first demonstrated the regional specificity of bone loss in space. Measurements by single photon absorptiometry failed to show any impact of spaceflight to measurements in the upper body (wrist), but detected significant losses in the lower extremity (calcaneus, in 3 of 9 astronauts) [26]. BMD changes in crews of different missions became more negative with increasing duration of Skylab flights (28, 56, and 84 days) [Figure 3] [15]. Similarly, Oganov [27] analyzed spine BMD with early application of computed tomography (CT). Evidence from four Russian cosmonauts, after 5-7 month space missions, similarly displayed large variability with losses in vertebral BMD in three cosmonauts (0.3% to 10.8%) and a gain of 2.3% in one cosmonaut [27].

It was with the advent of DXA technology that the measurements of areal BMD showed changes that suggested accelerated bone turnover at skeletal sites that were normally weight-bearing on Earth. LeBlanc et al [28] conducted DXA BMD measurements of crew members (n=16-18) before and after serving on the Mir spacecraft (~4 month duration) to report a BMD change over an entire mission. However, because of the wide range of mission durations (~4 to 14 months) during this data-collection period, BMD losses were normalized to total months-in-space to report an averaged monthly loss of 1-1.5% loss (Table 1). Further assessment revealed large variability in BMD losses amongst crew members, both intraskeletally and interskeletally, and that the BMD losses were greater in the lower limbs and at weight-bearing sites of the central skeletal. These sites included the hip and spine, sites which have a high incidence of osteoporosis fractures in the elderly population on Earth. Based upon these flight data, and the precision evaluation for the densitometry machines, DXA measurement of BMD is only applied to crew members serving on spaceflight missions >30 days.

The averaged 1-1.5% monthly loss in BMD in crew members is truly accelerated compared to the 2-3% loss per year observed in postmenopausal females during what is characterized as the rapid bone loss phase the first decade after menopause onset [3]. Additionally, Figure 4 a,b provides a comparison of longitudinal changes in total hip BMD as a function of age for both men and women as reported by Warming [29]; overlaid on the bar graph are data derived from crew members who served on missions on the International Space Station [ISS] and the Russian Mir spacecraft.

These population changes were measured over 2 years and compared to averaged BMD changes in long-duration crew members over the typical 6 month mission. For hip BMD, crew members in the age range 35-55 display a ~6 fold greater decrement after a 6-month spaceflight mission compared to the losses incurred over 24 months in men of comparable age. Comparisons of age-related losses in BMD were also conducted for the clinically relevant sites of forearm and spine where male crew members

displayed large BMD variability in the lumbar spine and forearm (Figure 4 c, d), The losses quantified in the long duration female crew members may be comparable to losses measured in the 50-59 population age group (Figure 4 e, f) but currently the number of subjects is small (n=3).

Reductions in bone volumetric density, size and structure

There is evidence that indicates a differential loss of mineral mass in bone compartments. A preferential BMD loss in cancellous vs. cortical bone compartments (on basis of percentage) has been detected in both Russian and US crew serving in long duration (>30 day to 6-month missions) as determined by peripheral QCT and QCT technology [30, 31]. In particular, QCT scans performed in the spine and the total hip (femoral neck and proximal femur) of crew members serving on six-month missions on ISS, quantified trabecular bone losses of 2.2-2.7% [31] of the hip and 0.7% of the lumbar spine as averaged to month of duration (n=14 crew members) (Table 2). For the total hip and femoral neck, the percentage BMD loss was greater in the more-metabolically-active trabecular compartment, although the BMD loss, on a total mass basis, was greater in the highly dense, cortical bone due to loss from the endocortical surface [31]. There was no difference in compartment-specific changes in the integral vs. trabecular bone compartments of the spine. These structural changes at the femoral neck imply a reduction in both estimated axial compressive strength and bending strength [31]. The reductions in *integral* volumetric BMDs [31], which measured combined volumetric BMDs of cortical and cancellous bone, highlighted the failure of an in-flight exercise program on the ISS to mitigate the BMD losses detected by DXA in the crew members of the earlier Mir spacecraft era [28].

Response on Earth after Spaceflight

There is evidence that the recovery of space-induced bone loss is delayed in the post-flight period. Vico [30] failed to detect any recovery of BMD in the lower limbs of crew members who had served 6 months in space. Measurement of BMD by peripheral QCT had been conducted soon after

flight and repeated 6 months after landing suggesting that if the skeleton recovered lost BMD it would occur on Earth after a period longer than the mission duration [30]. Additionally, Lang et al [32] repeated QCT scans at the proximal femur in ISS crew members one year after landing where an increase in cross-sectional volume at the femoral neck, compared to the measurements soon after landing, was evident but with a persistent depression in volumetric bone mineral density. These data at one year post-flight indicate that radial bone growth was stimulated upon return to Earth's gravitational field but that the increased volume remained under mineralized. Furthermore, recovery of volumetric BMD in trabecular bone compartment was not evident (Lang, unpublished data).

The spaceflight-induced geometrical changes at the femoral neck are similar to the adaptive response of periosteal osteoblasts to the cortical thinning and trabecular bone loss normally observed with age-related bone loss in the elderly [5, 10] suggesting a compensatory physiological response of the skeleton to recover compressive and bending strength. QCT analysis of age and sex differences in bone geometry [13] similarly documented apposition of bone at the periosteal surface in response to thinning of the cortex by age-related increases in bone resorption at the endocortical surface.

Recently, a novel method of analyzing areal BMD has been reported that characterizes postflight skeletal recovery [33]. BMD measurements have been accumulated over a post-flight period lasting as long as five years. Data points from a repository of DXA BMD measurements (both cross-sectional and longitudinal) of 45 different crew members serving on 56 different missions (4-14 months) were fitted to a two-parameter exponential mathematical equation (Figure 5). The derivation of a "half-life" index provided a time point (days after landing) which represented the timing of 50% restoration of BMD with Table 3 summarizes the "half-lives" and the losses at the time of landing for the skeletal sites evaluated for recovery. In spite of the large variability in the BMD measurements, and the uncertainty in half-life values (generally 3-9 months dependent upon skeletal site), the asymptotic increase in BMD over the

post-flight period was clearly apparent and provided the basis for substantial recovery at ~ 4 times the half-life [33].

Furthermore, biochemical analyses of bone markers indicated that with return to Earth's gravity there was a reduced NTX excretion in urine, and there was a subsequent increase in serum levels of osteoblast-specific proteins (bone specific alkaline phosphatase and osteocalcin)[17] (Figure 6). This trend in biomarkers preceded the positive change in BMD, a pattern also observed in the re-ambulatory period following bed rest [34].

Reductions in Whole Bone Strength

A Finite Element Analysis [FEA] had been developed from three dimensional images of QCT hip scans to determine force to failure for loading of the femoral neck in two orientations: the posterior lateral direction (associated with backward falls to the side) and the axial direction (associated with stance) [35]. Keyak et al. applied this FEA to the QCT scans previously performed in crew members who served on the space station to determine compartmental bone effects [31, 36]. The FEA determined significant reductions in the estimated failure load (i.e., hip strength) after the six-month mission relative to the determination made from pre-launch scans (Keyak, unpublished data).

The FEA was applied to QCT scans performed in five crew member subjects 1 year after returning providing complete modeling at 3 time points (preflight, postflight and 1 year after return). There is a greater trend towards recovery of strength in stance loading (4/5 show minimal recovery in fall, 4/5 show strong recovery in stance) (Lang, personal communication). QCT, however, does not have the resolution for trabecular microarchitecture and consequently the FEA [35] may have underestimated the impact on hip bone strength. The same FEA was applied in a cross-sectional comparison of hip strength in young vs. elderly women [N=128 (70 – 80 yr) postmenopausal females

versus n=30 (35-45 yr) pre-menopausal females] (Keyak, personal communication). This comparison suggested that the reduction in hip strength after 6 months of mechanical unloading by spaceflight was comparable to the lifetime reduction in hip strength (for fall loads) in an ageing female. And just as with the BMD losses during spaceflight at specific skeletal sites, the greater deficit in hip strength occurred at the site *within* the bone that adapts to weight-bearing while walking and standing on Earth.

Evidence of decreased bone formation

Mechanical unloading by spaceflight impairs the mineralization of bone. Histomorphometry of tetracycline-labeled iliac crest bone biopsies is the standard method for evaluating mineralization rates and mineralizing surfaces in skeletal tissue. However, no bone biopsies have been obtained from a crew member before or after flight to assess the impact of spaceflight on either the production or the mineralization of matrix. Histomorphometry data, however, have been obtained from bone biopsies of non-human primates that were administered tetracycline prior to being flown in space [37, 28]. Compared to biopsies obtained pre-flight and from controls on the ground, there was a significantly reduced area of bone (with a tendency for thinner trabeculae) and reduced percentage of mineralizing surfaces in biopsies obtained post-flight. Histomorphometric changes were accompanied by a reduction in bone mineral content with flight.

GROUND-BASED ANALOGS OF SPACEFLIGHT UNLOADING OF THE SKELETON

Spaceflight analogs, both for human test subjects and animals, provide better controlled experimental conditions and opportunity for more extensive and invasive analytical methods to evaluate the effects of mechanical unloading. The following list highlights how these analogs are critical for corroborating and enhancing the limited spaceflight evidence base which is impacted by the constraints associated with mission operations: a) mechanical unloading by bed rest down-regulates calcium regulating hormones [39, 40]; b) mechanical unloading by prolonged bed rest appears to uncouple bone

formation and bone resorption as reflected by changes in bone turnover markers [41, 42]; c) mechanical unloading appears to uncouple osteoclastic (increases) and osteoblastic (decreases) mediation of bone remodeling as determined in bone biopsies [43-45]; d) mechanical unloading, both by bed rest (120 days at the time point of biopsy) [46] and by spinal cord injury (2 years following injury) [47], results in a loss of connectivity in trabecular microarchitecture; e) mechanical unloading in non-human primates immobilized in a spaceflight analog impairs mineralization, accelerates bone resorption, and reduces bending strength [48-50]. These analyses of humans and non-human primates in ground-based models of mechanical unloading specifically detail the uncoupling of bone remodeling and the activity/number of bone cells. Delineating the impairment in turnover, at the cellular and tissue level, is critical for the selection of pharmaceutical countermeasures for the effects of skeletal adaptation in space.

More recently, the NASA Flight Analogs Project at the Johnson Space Center conducted a review of its recently initiated bed rest protocol to evaluate its validity as a standardized test bed for studies of mechanical unloading and as a critical research platform for the pre-flight evaluation of countermeasures to spaceflight-induced bone loss (and other physiological changes). DXA BMD measures in the first 13 test subjects are consistent with BMD changes documented in earlier bed rest and in spaceflight studies (Figure 7), with statistically significant losses occurring in the hip, pelvis and heel [51].

Countermeasures Used to Date

The primary countermeasure for bone loss employed to date by both the US and Russian space programs has been exercise. The approaches used have been reviewed by a number of authors [52-56] and evidence suggests that none of the programs have been effective [28, 30, 31] in preventing skeletal changes.

A treadmill has always been a central component of the Russian countermeasures [53, 57] either as an exercise device or as a platform for static exercises [54]. Treadmills on the Russian space stations were fixed rigidly to the vehicle and were passive, that is there was no motor and the belt was driven by the exercising crew member. The load applied to the body during treadmill exercise in space depends critically on the "gravity replacement force" that is applied through a harness and there are no published data to indicate the magnitude of forces that were used during Russian countermeasures. A cycle ergometer has also been used in the Russian program [52], as has a compression garment called a "Pingvin suit" [58]. Despite its widespread use, there is no published evidence that the "Pingvin suit" is effective in preventing musculoskeletal changes during spaceflight.

The first use of exercise by the US space program was the bungee exerciser device flown on early Gemini missions, primarily to provide an exercise stimulus that would allow cardiovascular responses to be examined [59]. Exercise countermeasures were not conducted during Apollo missions and were first introduced by NASA during the Skylab program (1973-1979). The modalities included a Mini-Gym exerciser (a rope and pulley device) and a Teflon plate on which in-place stepping to simulate walking and running could be conducted [60]. Calcium balance experiments conducted on SkyLab 4 indicated that significant bone loss was occurring despite the countermeasures [61, 62].

In the era of short-duration US flights on the Space Shuttle, exercise during the missions was not mandatory, partly because of the desire to maximize time available for the performance of experimental payload tasks. However, a stowable passive treadmill known as the "Thornton treadmill" (after its developer William Thornton, a physician-astronaut [63]) was flown on many Shuttle missions. No controlled experiments were conducted to determine if exercise on this device was beneficial to bone.

Long-duration US presence on the International Space Station (ISS) provided the opportunity to study the efficacy of exercise countermeasures since each crew member was required to participate in a

supervised exercise program. There is a widespread misconception that US astronauts exercise for up to 2.5 hours per day during their time on-orbit, but quantitative measurements have shown this not to be the case [6] since set-up and tear-down activities consume almost 60% of assigned time.

The exercise modalities available to US crew members during missions to the ISS up to and including Increment 16 (2008) were an interim resistance exercise device (iRED [64]); a free floating motorized treadmill (TVIS, [65]) that could be used in active or passive mode; and a vibration isolated cycle ergometer (CVIS). Crew members kept careful logs of their exercise bouts on these devices [66], and foot forces measurements during exercise in 4 crew members [6] confirmed that low harness forces resulted in foot forces that were substantially below those found in similar activities on earth. This no doubt contributed to the lack of efficacy of these countermeasures in preventing bone loss [31].

Many questions remain unanswered regarding the optimal prescription of exercise countermeasures to prevent bone loss. The most important of these is whether or not a single "bolus" of exercise of any intensity can replace a full day of intermittent loading such as occurs on earth. An additional critical issue is the interaction of concomitant changes in bone and muscle – since the integrity of the two systems are intimately connected. The fact that exercise countermeasures have been unsuccessful to date does not mean that they might not be successful in the future once personalized, high load exercise of adequate duration is performed. There is one case study of impact loading that appears to have been successful in the calcaneus of a single crew member [67].

Based on publicly available information, it appears that no pharmacotherapeutic interventions have yet been conducted [68]. This is despite the fact that bisphosphonates have been shown to be effective in a bed rest setting [69].

Knowledge Gaps

Because of the many difficulties of conducting research in space, knowledge of changes to the skeleton and of appropriate countermeasures has and will be plagued with limitations. However, as the space program embarks on longer duration missions, the occupational risks of space travel need to be defined if appropriate countermeasures are to be developed. In terms of the risk for early onset osteoporosis, the following is a list of open issues that need to be addressed in order to characterize the skeletal adaptation to the mechanical unloading of spaceflight:

- The factors or mechanisms that contribute to the variability in losses of BMD with spaceflight have yet to be identified. In particular, the role of genetics remains to be elucidated [56].
- The impact on whole bone strength is not fully known. Crew member deficits in areal BMD as measured by DXA do not reflect changes in "bone quality" or forces actually induced on bone during high physical load activity. There is a need for non-invasive assessments of indices known to influence whole bone strength such as whole bone geometry, cortical bone thickness or cancellous bone microarchitecture, as well as a method to determine force loads on bone.
- Extensive longitudinal measures over the lifetime of crew members need to be conducted to monitor the effects of spaceflight and of recovery. Cross-sectional comparisons, such as those conducted with the ageing population, are limited in their ability to define patterns of lifetime bone loss for different sites and would not provide meaningful information for the management of astronaut long-term health.

- The impact of spaceflight on balance, coupling, and rate of remodeling has not been quantified at the level of the bone remodeling unit; neither have the impacts on cell function and number yet been quantified.
- QCT technology does not have the resolution to assess how loss of volumetric BMD in the trabecular compartment affects the microarchitecture. The time course and the impact of spaceflight-induced losses on trabecular microarchitecture (i.e., trabecular thinning or loss of trabecular connectivity) are unknown.
- The timing, extent and variability of volumetric BMD recovery in bone compartments are still not established.
- The impact of multiple long-duration flights on bone loss and recovery, and on cortical bone thinning and subsequent periosteal expansion, is not known.
- Sex-based differences in bone loss during spaceflight have not been fully evaluated.
- The multiple factors that influence the variable rates of BMD recovery between individuals after spaceflight have not been assessed.
- The efficacy of anti-resorptive agents under weightless conditions of spaceflight has not been validated.
- The efficacy of exercise or nutritional countermeasures have not been fully investigated or validated.
- Estimations of whole bone strength for other skeletal sites (arm, wrist, spine) with a large number of crew member subjects need to be performed.

SUMMARY AND CONCLUSION

The skeletal system of crew members adapts to the gravity unloading by reducing its mineral mass through increased bone resorption and uncoupled bone formation. The averaged monthly loss in

bone mineral density during a typical 6-month mission in low Earth orbit is 1-2% of pre-flight areal BMD (range 6-20% loss per 6 months of spaceflight). The changes in BMD are site-specific and geometrical changes in the proximal femur have been associated with decrements in hip strength. There is evidence for greater loss in the trabecular compared to cortical compartment. The time course for the loss and recovery of bone mass during periods in space and back on Earth, and with various gravity levels, has not been determined nor completely characterized. It is necessary to expand skeletal measures and to characterize the response of the skeleton to the various levels of loading potentially encountered during exploration missions in order to manage any associated skeletal health risks by mitigation or treatment. Countermeasures used to date have not adequately loaded the skeleton to 1G levels.

Substantiating whether spaceflight increases the risk for accelerated osteoporosis ultimately centers on determining if spaceflight-induced skeletal changes are irreversible after return to Earth. If spaceflight-induced bone loss is not restored and decrements in whole bone strength are not recovered in the post-flight period, then crew members will experience the combined effects of space and of ageing on the skeleton and be predisposed to an earlier incidence of osteoporosis and fragility fractures. This risk will be even greater for female crew members since bone loss with spaceflight will be compounded by bone loss with menopause.

What determines if bone loss and whole bone strength are restored? Pre-flight and post-flight measurements of bone should include bone size and geometry, volumetric BMD of bone compartments, bone microarchitecture, and mechanical strength testing by computer modeling and virtual loading, as developed with these expanded measurements. Additionally, longitudinal measures during the post-career lifetime of a crew member should be conducted. Moreover, the time course of bone turnover during spaceflight will improve the ability to evaluate the risk of longer exposures to skeletal integrity

and its impact on recovery back on Earth. These additional indices will enhance the probabilistic risk assessments for crew members returning from long duration spaceflight missions.

REFERENCES

[1] Albright F, Burnett CH, Cope O, Parson W. Acute atrophy of bone (osteoporosis) simulating hyperparathyroidism. J Clin Endoc 1941 Sep;1(9):711-716.

[2] Deitrick JE, Whedon GD, Shorr E Effects of immobilization upon various metabolic and physiologic functions of normal man. Am J Med 1948:3-36.

[3] Riggs BL, Melton LJ, III. Involutional Osteoporosis. New Eng J Med. 1986;314(26):1676-86.

[4] Riggs BL, Khosla S, Melton LJ, 3rd. A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. J Bone Miner Res. 1998 May;13(5):763-73.

[5] Seeman E. Pathogenesis of bone fragility in women and men. Lancet. 2002 May 25;359(9320):1841-50.

[6] Cavanagh, P.R.; Rice, A.J.; Licata, A.A.; Forty Years of Bone Loss in Space. In: Cavanagh, P.R.; Ed. Bone Loss During Spaceflight: Etiology; Countermeasures; and Implications for Bone Health on Earth. Cleveland Clinic Press. 2007: 1-15.

[7] Riggs BL, Parfitt AM. Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodeling. J Bone Miner Res. 2005. 20:177–184.

[8] Recker R, Lappe J, Davies KM, Heaney R. 2004. Bone remodeling increases substantially in the years after menopause and remains increased in older osteoporosis patients. J Bone Miner Res. 19(10):1628-33.

[9] Kleerekoper M, Villanueva AR, Stanciu J, Rao DS, Parfitt AM. The role of three-dimensional trabecular microstructure in the pathogenesis of vertebral compression fractures. Calcif Tissue Int. 1985 Dec;37(6):594-7.

[10] Mosekilde L. Age-related changes in bone mass, structure, and strength--effects of loading. Z Rheumatol. 2000;59 Suppl 1:1-9.

[11] Garnero P, Sornay-Rendu E, Duboeuf F, Delmas PD. Markers of bone turnover predict postmenopausal forearm bone loss over 4 years: the OFELY study. J Bone Miner Res. 1999 Sep;14(9):1614-21.

[12] Bonnick SL, Shulman L. Monitoring osteoporosis therapy: bone mineral density, bone turnover markers, or both? Am J Med. 2006 Apr;119(4 Suppl 1):S25-31.

[13] Riggs BL, Melton LJ, 3rd, Robb RA, Camp JJ, Atkinson EJ, Peterson JM, et al. Population-based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. J Bone Miner Res. 2004 Dec;19(12):1945-54.

[14] Riggs BL, Melton LJ, Robb RA, Camp JJ, Atkinson EJ, McDaniel L, et al. A population-based assessment of rates of bone loss at multiple skeletal sites: evidence for substantial trabecular bone loss in young adult women and men. J Bone Miner Res. 2008 Feb;23(2):205-14.

[15] Rambaut P, Johnston R. Prolonged weightlessness and calcium loss in man. Acta Astronaut. 1979;6:1113-22.

[16] Smith SM, Nillen JL, Leblanc A, Lipton A, Demers LM, Lane HW, et al. Collagen cross-link excretion during space flight and bed rest. J Clin Endocrinol Metab. 1998 Oct;83(10):3584-91.

[17] Smith SM, Wastney ME, O'Brien KO, Morukov BV, Larina IM, Abrams SA, et al. Bone markers, calcium metabolism, and calcium kinetics during extended-duration space flight on the Mir space station. J Bone Miner Res. 2005 Feb;20(2):208-18.

[18] Caillot-Augusseau A, Vico L, Heer M, Voroviev D, Soubervielle JC, Zitterman A, Alexandre C, Lafage-Proust MH. Space flight is associated with rapid decreases of undercarboxylated osteocalcin and increases of markers of bone resorption without changes in their circadian variation: observations in two cosmonauts. Clin Chemistry 2000 Aug;46(8 Pt 10:1136-1143.

[19] Caillot-Augusseau A, Lafage-Proust MH, Soler C, Pernod J, Dubois F, Alexandre C. Bone formation and resorption biological markers in cosmonauts during and after a 180-day space flight (Euromir 95). Clin Chem. 1998 Mar;44(3):578-85.

[20] Whedon G, Lutwak L, Rambaut P, Whittle M, Leach C, Reid J, et al. Effect of weightlessness on mineral metabolism; metabolic studies on Skylab orbital flights. Calcif Tissue Res. 1976;21 Suppl:423-30.

[21] Whedon G, Lutwak L, Rambaut P, Whittle M, Reid J, Smith M, et al. Mineral and nitrogen balance study observations: the second manned Skylab mission. Aviat Space Environ Med. 1976;47:391-6.

[22] Whedon GD, Lutwak L, Rambaut PC, Whittle MW, Smith MC, Reid J, et al. Mineral and nitrogen metabolic studies, experiment M071. In: Johnston RS, Dietlein LF, eds.

Biomedical results from Skylab (NASA SP-377). Washington, DC: National Aeronautics and Space Administration 1977:164-74.

[23] LeBlanc AD, Spector ER, Evans HJ, Sibonga JD. Skeletal responses to space flight and the bed rest analog: a review. J Musculoskelet Neuronal Interact. 2007 Jan-Mar;7(1):33-47.

[24] Smith SM, Wastney ME, Morukov BV, Larina IM, Nyquist LE, Abrams SA, et al. Calcium metabolism before, during, and after a 3-mo spaceflight: kinetic and biochemical changes. Am J Physiol. 1999 Jul;277(1 Pt 2):R1-10.

[25] Zittermann A, Heer M, Caillot-Augusso A, Rettberg P, Scheld K, Drummer C, et al. Microgravity inhibits intestinal calcium absorption as shown by a stable strontium test. Eur J Clin Invest. 2000;30:1036-43.

[26] Vogel JM, Whittle MW. Bone mineral changes: the second manned Skylab mission. Aviat Space Environ Med. 1976 Apr;47(4):396-400.

[27] Oganov VS, Cann C, Rakhmanov AS, Ternovoi SK. [Study of the musculoskeletal system of the spine in humans after long-term space flights by the method of computerized tomography]. Kosm Biol Aviakosm Med. 1990 Jul-Aug;24(4):20-1.

[28] LeBlanc A, Schneider V, Shackelford L, West S, Oganov V, Bakulin A, et al. Bone mineral and lean tissue loss after long duration space flight. J Musculoskelet Neuronal Interact. 2000;1:157-60.

[29] Warming L, Hassager C, Christiansen C. Changes in bone mineral density with age in men and women: a longitudinal study. Osteoporos Int. 2002;13(2):105-12.

[30] Vico L, Collet P, Guignandon A, Lafage-Proust M-H, Thomas T, Rehaillia M, et al. Effects of long-term microgravity exposure on cancellous and cortical weight-bearing bones of cosmonauts. Lancet. 2000;355(9215):1607-11.

[31] Lang T, LeBlanc A, Evans H, Lu Y, Genant H, Yu A. Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight. J Bone Miner Res. 2004 June;19(6):1006-12.

[32] Lang TF, Leblanc AD, Evans HJ, Lu Y. Adaptation of the proximal femur to skeletal reloading after long-duration spaceflight. J Bone Miner Res. 2006 Aug;21(8):1224-30.

[33] Sibonga JD, Evans HJ, Sung HG, Spector ER, Lang TF, Oganov VS, et al. Recovery of spaceflight-induced bone loss: bone mineral density after long-duration missions as fitted with an exponential function. Bone. 2007 Dec;41(6):973-8.

[34] LeBlanc AD, Schneider VS, Evans HJ, Engelbretson DA, Krebs JM. Bone mineral loss and recovery after 17 weeks of bed rest. J Bone Miner Res. 1990;5:843-50.

[35] Keyak JH, Kaneko TS, Tehranzadeh J, Skinner HB. Predicting proximal femoral strength using structural engineering models. Clin Orthop Relat Res. 2005 Aug(437):219-28.

[36] Keyak JH, Koyama GK, LeBlanc A, Lu Y, Lang TF. Reduction in proximal femoral strength after long-duration spaceflight. 53rd Annual meeting of the Orthopaedic Research Society; 2007; San Diego, CA; 2007.

[37] Zerath E, Novikov V, Leblanc A, Bakulin A, Oganov V, Grynpas M. Effects of spaceflight on bone mineralization in the rhesus monkey. J Appl Physiol. 1996 Jul;81(1):194-200.

[38] Zerath E, Grynpas M, Holy X, Viso M, Patterson-Buckendahl P, Marie PJ. Spaceflight affects bone formation in rhesus monkeys: a histological and cell culture study. J Appl Physiol. 2002 Sep;93(3):1047-56.

[39] Arnaud SB, Sherrard DJ, Maloney N, Whalen RT, Fung P. Effects of 1-week head-down tilt bed rest on bone formation and the calcium endocrine system. Aviat Space Environ Med. 1992;63:14-20.

[40] LeBlanc A, Schneider V, Spector E, Evans H, Rowe R, Lane H, et al. Calcium absorption, endogenous excretion, and endocrine changes during and after long-term bed rest. Bone. 1995;16(4 Suppl):301S-4S.

[41] Lueken SA, Arnaud SB, Taylor AK, Baylink DJ. Changes in markers of bone formation and resorption in a bed rest model of weightlessness. J Bone Miner Res. 1993;8:1433-1438.

[42] Smith SM, Davis-Street JE, Fesperman JV, Calkins DS, Bawa M, Macias BR, et al. Evaluation of treadmill exercise in a lower body negative pressure chamber as a countermeasure for weightlessness-induced bone loss: a bed rest study with identical twins. J Bone Miner Res. 2003;18:2223-2230.

[43] Minaire P, Meunier P, Edouard C, Bernard J, Courpron P, Bourret J. Quantitative histological data on disuse osteoporosis: comparison with biological data. Calcif Tissue Int. 1974;17:57-73.

[44] Vico L, Chappard D, Alexandre C, Palle S, Minaire P, Riffat G, et al. Effects of a 120 day period of bed-rest on bone mass and bone cell activities in man: attempts at countermeasure. Bone Miner. 1987;2:383-294.

[45] 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.

[46] Thomsen JS, Morukov BV, Vico L, Alexandre C, Saparin PI, Gowin W. Cancellous bone structure of iliac crest biopsies following 370 days of head-down bed rest. Aviat Space Environ Med. 2005 Oct;76(10):915-922.

[47] Modlesky CM, Majumdar S, Narasimhan A, Dudley GA. Trabecular bone microarchitecture is deteriorated in men with spinal cord injury. J Bone Miner Res. 2004 Jan;19(1):48-55.

[48] Young DR, Niklowitz WJ, Brown RJ, Jee WS. Immobilization-associated osteoporosis in primates. Bone. 1986;7(2):109-117.

[49] Young DR, Niklowitz WJ, Steele CR. Tibial changes in experimental disuse osteoporosis in the monkey. Calcif Tissue Int. 1983 May;35(3):304-8.

[50] Mechanic GL, Young DR, Banes AJ, Yamauchi M. Nonmineralized and mineralized bone collagen in bone of immobilized monkeys. Calcif Tissue Int. 1986 Aug;39(2):63-68.

[51] Spector ER, Smith SM, Sibonga JD. Skeletal turnover in response to bed rest duration as determined by BMD and bone biomarkers. Aviat Space Env Med. 2008 Submitted manuscript .

[52] LeBlanc A, Schneider V. Countermeasures against space flight related bone loss. Acta Astronaut. 1992 Jul;27:89-92.

[53] Kozlovskaya IB, Grigoriev AI. Russian system of countermeasures on board of the International Space Station (ISS): the first results. Acta Astronaut. 2004 Aug-Nov;55(3-9):233-7.

[54] Cavanagh PR, Licata AA, Rice AJ. Exercise and pharmacological countermeasures for bone loss during long-duration space flight. Gravit Space Biol Bull. 2005 Jun;18(2):39-58.

[55] Iwamoto J, Takeda T, Sato Y. Interventions to prevent bone loss in astronauts during space flight. Keio J Med. 2005 Jun;54(2):55-9.

[56] Andrew, T. MacGregor, A.J. Genes and Osteoporosis In: Cavanagh, P.R.; Ed. Bone Loss During Spaceflight: Etiology; Countermeasures; and Implications for Bone Health on Earth. Cleveland Clinic Press. 2007: 201-218.

[57] Popov DV, Khusnutdinova DR, Shenkman BS, Vinogradova OL, Kozlovskaya IB. Dynamics of physical performance during long-duration space flight (first results of "Countermeasure" experiment). J Gravit Physiol. 2004 Jul;11(2):P231-2.

[58] Sologubov EG, Iavorskiĭ AB, Kobrin VI, Barer AS, Bosykh VG. Role of vestibular and visual analyzers in changes of postural activity of patients with childhood cerebral palsy in the process of treatment with space technology. Aviakosm Ekolog Med. 1995;29(5):30-4.

[59] Dietlein, L.F.. Experiment M-3, inflight exerciser on Gemini IV. In: Manned Space Flight Experiments Symposium. Gemini missions III and IV. 1965. Washington DC: National Aeronautics and Space Administration.

[60] Thornton, W.E., and Rummel, J.A.. Muscular deconditioning and its prevention in space flight. In:Biomedical Results From Skylab. (Johnson, R.S., and Dietlein, L.F., Eds.) 1977. Houston: National Aeronautics and Space Administration, pp. 191-97.

[61] Michel EL, Johnston RS, Dietlein LF. Biomedical results of the Skylab Program. Life Sci Space Res. 1976;14:3-18.

[62] Rambaut, P.C., Leach, C.S., and Whedon, G.D.. A study of metabolic balance in crew members of Skylab IV. Acta Astronautica 1979; 6:1313-22.

[63] Thornton, W. Work, exercise and space flight. III.Exercise devices and protocols. In: Proceedings of the 1986 Workshop on Exercise Prescription for Long-Duration Space Flight. (Harris, B.A., Jr., and Stewart, D.F., Eds.) 1989 NASA Office of Management.

[64] Schneider SM, Amonette WE, Blazine K, Bentley J, Lee SM, Loehr JA, Moore AD Jr, Rapley M, Mulder ER, Smith SM.Training with the International Space Station interim resistive exercise device.Med Sci Sports Exerc. 2003 Nov;35(11):1935-45.

[65] McCrory JL, Lemmon DR, Sommer HJ, III, Prout B, Smith D, Korth DW, Lucero J, Greenisen M, Moore J, Kozlovskaya I, Pestov I, Stepansov V, Miyakinchenko Y, and Cavanagh PR. Evaluation of a Treadmill with Vibration Isolation and Stabilization (TVIS) for use on the International Space Station. J Appl Biomech, 1999.15(3): 292-302,.

[66] Gopalakrishnan R, Rice AJ, Lee SM, Evans HJ, Maender CC, Cavanagh.PR. Changes in muscle volume, strength, and endurance after long-duration space flight. Submitted to Aviation, Space and Environmental Medicine. 2008

[67] Goodship AE, Cunningham JL, Oganov V, Darling J, Miles AW, Owen GW. Bone loss during long term space flight is prevented by the application of a short term impulsive mechanical stimulus Acta Astronaut. 1998 Aug-Sep;43(3-6):65-75.

[68] Pavy-Le Traon A, Saivin S, Soulez-LaRivière C, Pujos M, Güell A, Houin G. Pharmacology in space: pharmacotherapy. Adv Space Biol Med. 1997;6:93-105.

[69] LeBlanc AD, Driscol TB, Shackelford LC, Evans HJ, Rianon NJ, Smith SM, et al. Alendronate as an effective countermeasure to disuse induced bone loss. J Musculoskelet Neuronal Interact. 2002;2(4):335-343.

Figure legends.

Figure 1. History of Early Measures in Space Program. Ca - calcium; SPA - Single Photon Absorptiometry; OH-Pro – Hydroxyproline; NTX –N-telopeptide; DXA – Dual-energy x-ray absorptiometry; QCT – Quantitative Computed Tomography; DPA – Dual Photon Absorptiometry; CT – Computed Tomography; BMD - Bone Mineral Density.

Figure 2. Increases in Activation Frequency in females as a function of menopausal status and the number of years following menopause onset. Activation frequency (expressed in year^{-1}) is calculated from histomorphometric indices of bone remodeling and serves as a measure of bone turnover. Adapted figure from [8].

Figure 3. Early determination of changes in calcaneal BMD with spaceflight. BMD (Mean $\pm$ SE) measured in 3-man crews serving on Skylab missions of varying durations and compared to measurements conducted in crew of 14-day missions (Apollo 14, 15 and 16). Adapted figure from [15].

Figure 4 a,b. Comparison of total hip BMD after spaceflight and in population. Changes in DXA-measured BMD male (a) and female (b) crew members serving on typical 6-month mission aboard the International Space Station. BMD change in space is compared to 2-year change in population of 239 Danish males (a) and 491 Danish females (b). Adapted figure from [29].

Figure 4 c,d. Comparison of forearm and lumbar spine BMDs after spaceflight and in population. DXA-measured BMD change at the forearm (c) and lumbar spine (d) of male crew members serving on typical 6-month mission aboard the International Space Station compared to 2-year change in population of 239 Danish males. Adapted figure from [29].

Figure 4 e, f. Comparison of forearm and lumbar spine BMDs after spaceflight and in population. Comparison of DXA-measured BMD change at the forearm (c) and lumbar spine (d) of female crew members serving on typical 6-month mission aboard the International Space Station compared to 2-year change in population of 491 Danish females. Adapted figure from [29].

Figure 5. Recovery of BMD after landing as represented by data from the trochanter. Changes between pre- and postflight BMD are plotted as a function of days after landing when the scans were performed. Data points are fitted to a two-parameter equation where the intercept of the fitted trochanter data identifies a spaceflight-induced bone loss of 7.8% of preflight BMD and a 50% recovery time for the loss to occur after about 8.5 months. Adapted figure from [33].

Figure 6 a,b. Bone turnover markers measured in specimens collected pre-flight, during flight and after flight suggest that return to Earth's 1 G environment reverses the increased excretion of bone resorption marker (N-telopeptide) and eventually stimulates expression of bone formation markers (e.g., osteocalcin). Adapted figure from [17].

Figure 7. Changes in BMD after bed rest and spaceflight. P values based on two-tailed Student's t-test assuming equal variances, bed rest (BR) vs. spaceflight (SF); SF subjects are 23 US astronauts from Mir and ISS spaceflights; BR subjects are 13 controls from NASA Johnson Space Center Flight Analog bed rest studies [51].

Tables

Table 1. Change in BMD (averaged change per month) compared to preflight measurement in crew members serving on missions on the Mir spacecraft [28].

* signifies p value <0.01.

Table 2. Changes in volumetric BMD for combined cortical and cancellous bone compartments ("integral") and for trabecular bone compartment of the lumbar spine, total hip and femoral neck. Significant reductions from baseline (* p value <0.05) in volumetric BMD, expressed as loss averaged per month, for all sites with greater percentage deficit for trabecular bone of proxmal femur [31].

Table 3. Summary of fitted postflight BMD data per skeletal site. The percentage of preflight BMD loss 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 time there is a restoration of half of the bone mineral that was lost during spaceflight. The L0 and recovey times were determined from fitted BMD data to 2-parameter exponential equation [33].

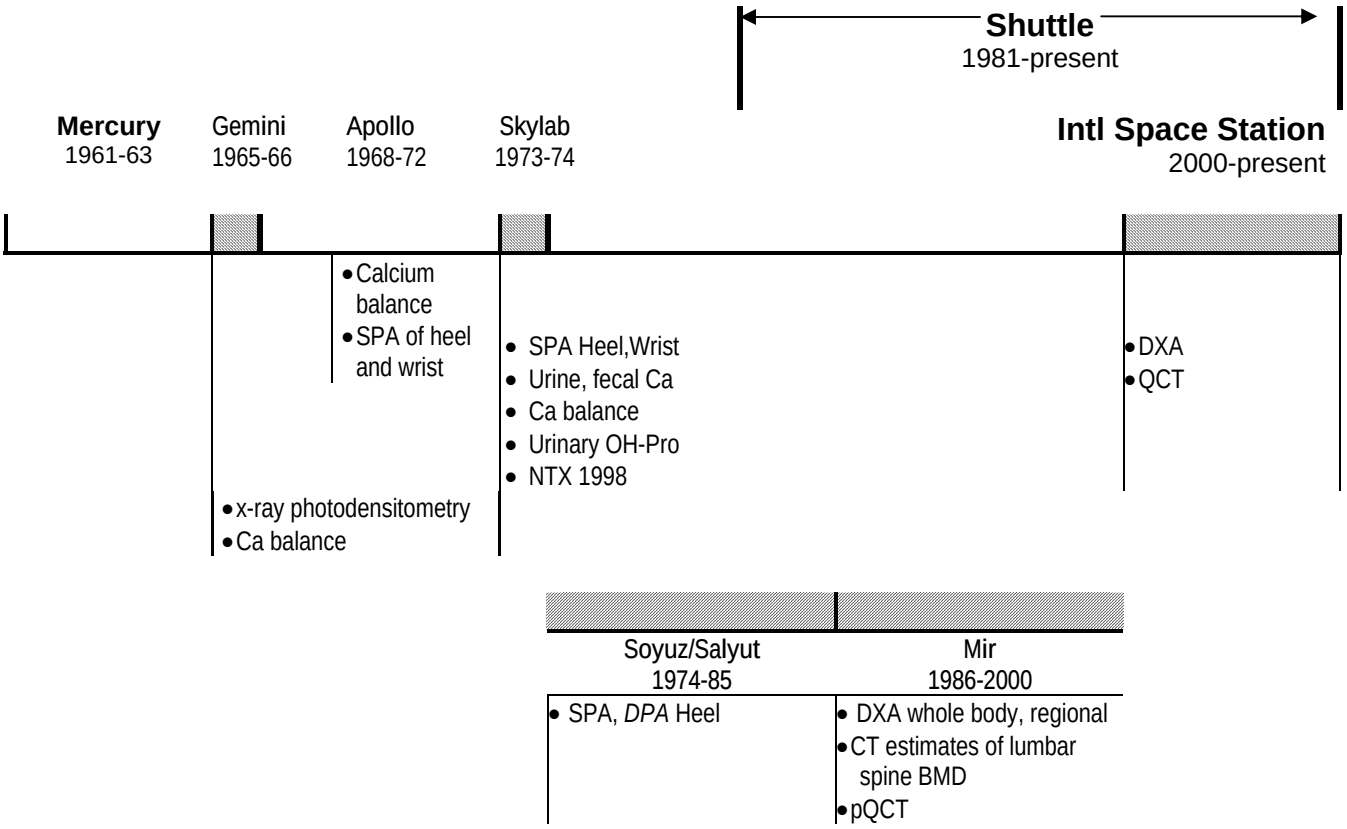

Shuttle
1981-present
Mercury
1961-63
Gemini
1965-66
Apollo
1968-72
Skylab
1973-74
Intl Space Station
2000-present
• Calcium balance
• SPA of heel and wrist
• SPA Heel,Wrist
• Urine, fecal Ca
• Ca balance
• Urinary OH-Pro
• NTX 1998
• DXA
• QCT
• x-ray photodensitometry
• Ca balance
Soyuz/Salyut
1974-85
Mir
1986-2000
• SPA, DPA Heel
• DXA whole body, regional
• CT estimates of lumbar spine BMD
• pQCT

Figure 1.

Figure 2.

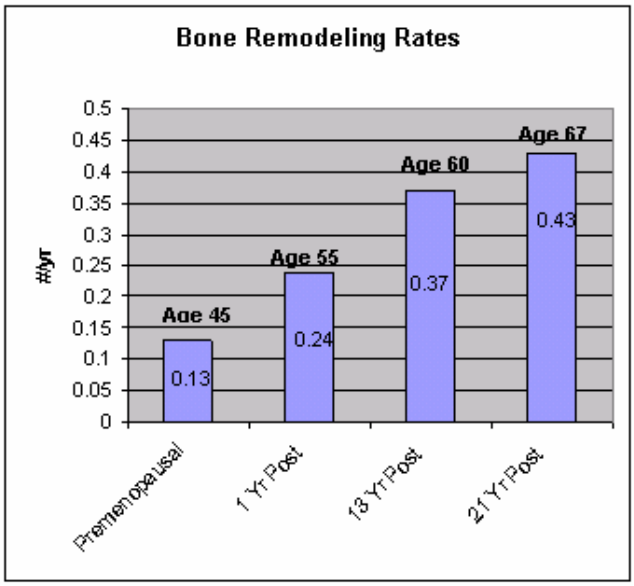

Bone Remodeling Rates
#/yr
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Age 45
Age 55
Age 60
Age 67
0.13
0.24
0.37
0.43
Premenopausal
1 Yr Post
13 Yr Post
21 Yr Post

Figure 3.

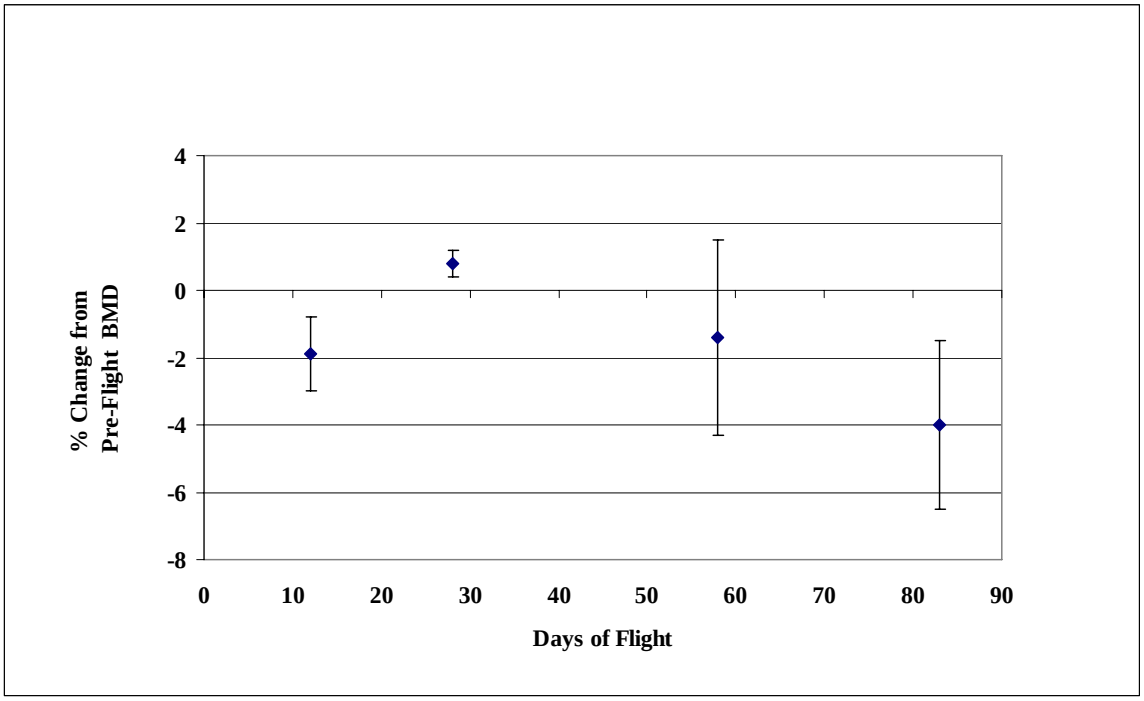

4
2
0
-2
-4
-6
-8
% Change from
Pre-Flight BMD
0
10
20
30
40
50
60
70
80
90
Days of Flight

Figure 4 a,b.

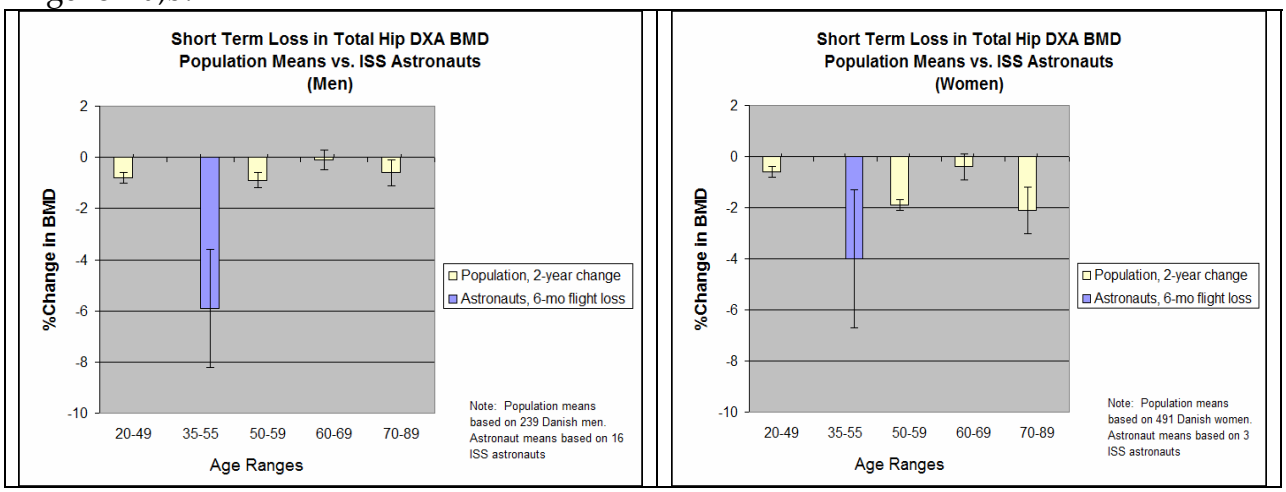


Figure 4 c ,d.

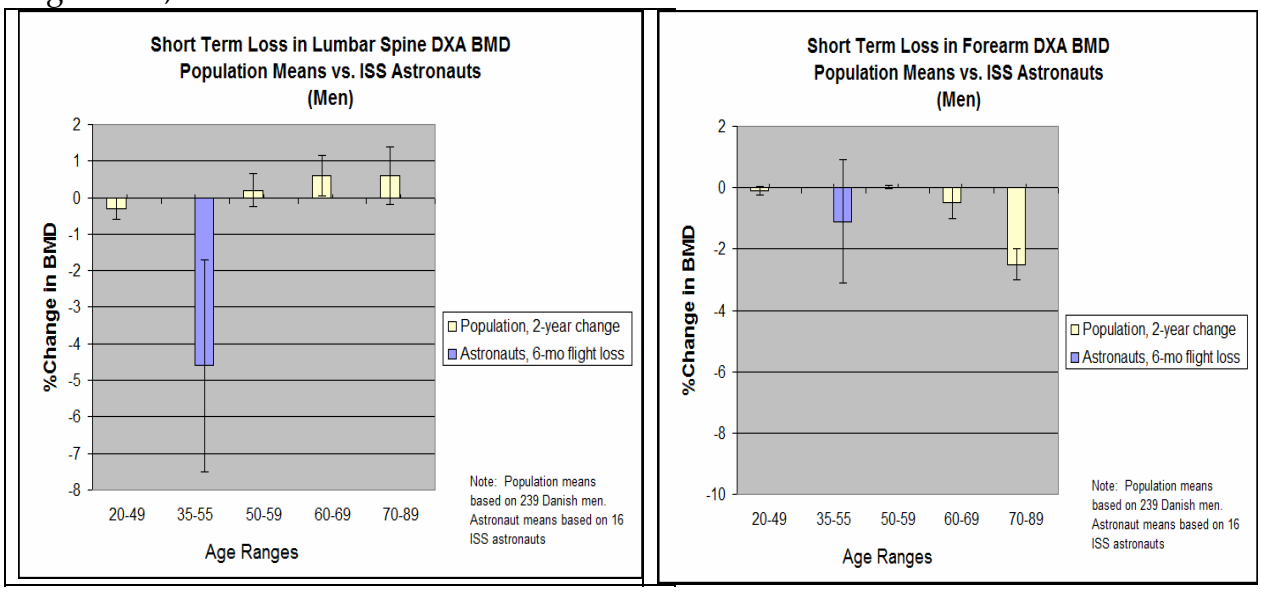


Figure 4 e, f.

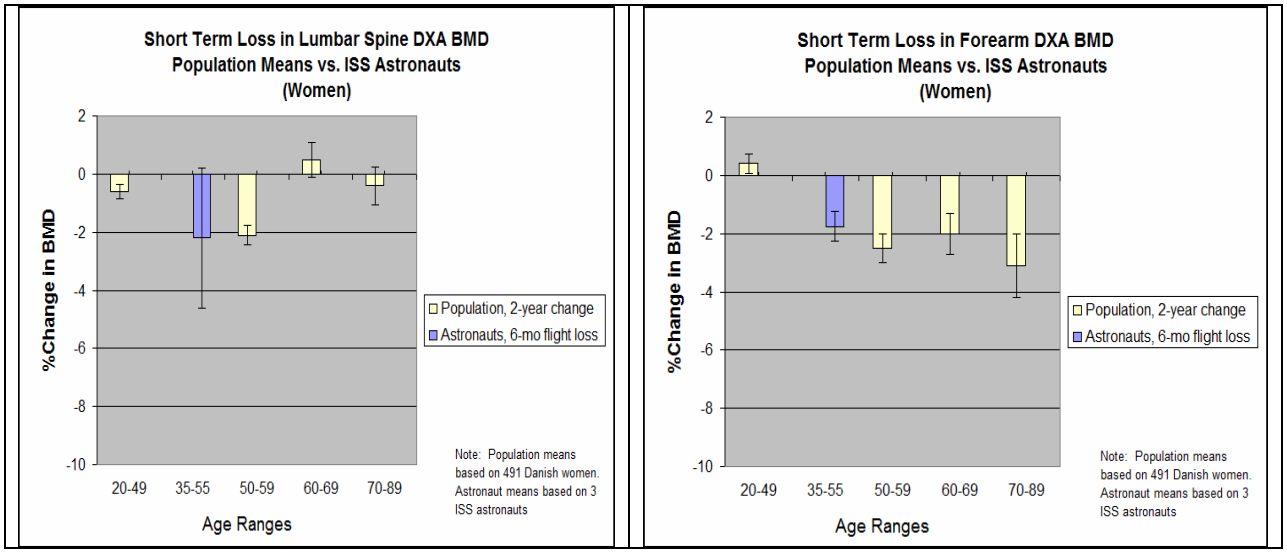


Figure 5.

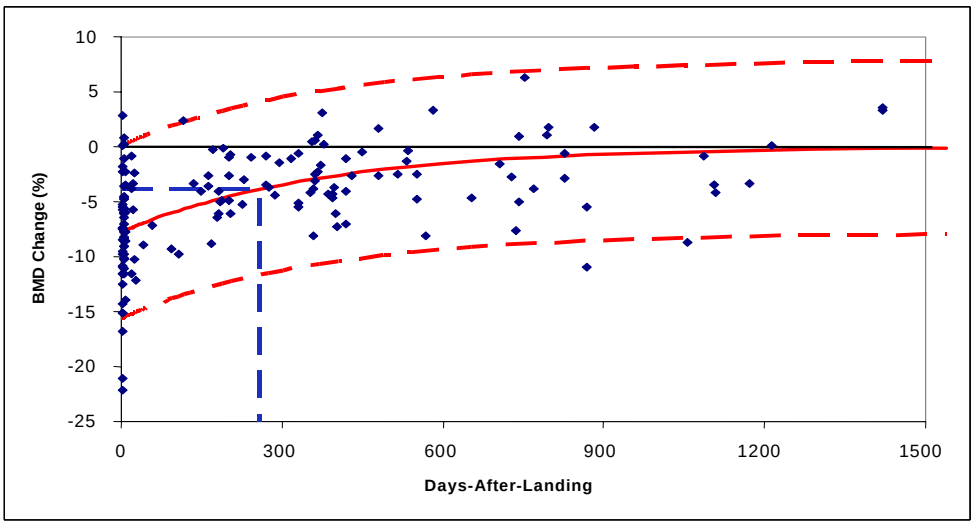


Figure 6

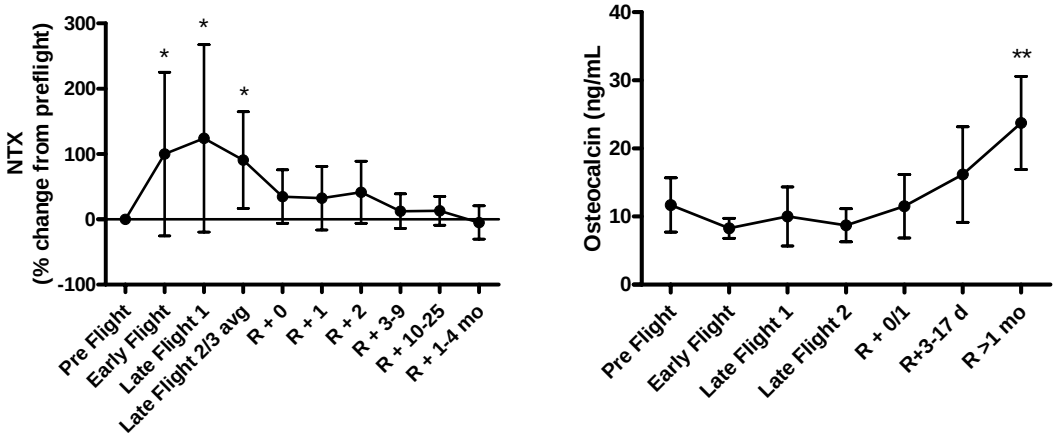
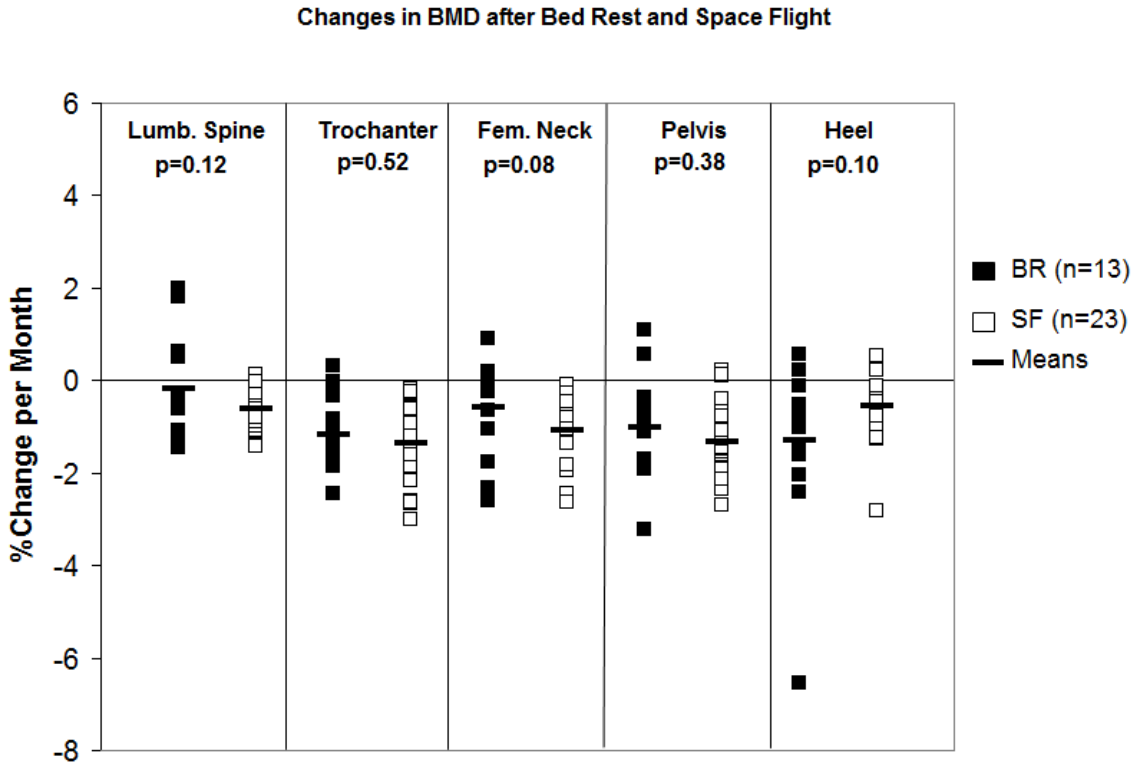

NTX
(% change from preflight)
300
200
100
0
-100
*
*
*
Pre Flight
Early Flight
Late Flight 1
Late Flight 2/3 avg
R + 0
R + 1
R + 2
R + 3-9
R + 10-25
R + 1-4 mo
Osteocalcin (ng/mL
40
30
20
10
0
**
Pre Flight
Early Flight
Late Flight 1
Late Flight 2
R + 0/1
R+3-17 d
R >1 mo

Figure 7.


Changes in BMD after Bed Rest and Space Flight
Lumb. Spine
p=0.12
Trochanter
p=0.52
Fem. Neck
p=0.08
Pelvis
p=0.38
Heel
p=0.10
%Change per Month
6
4
2
0
-2
-4
-6
-8
BR (n=13)
SF (n=23)
Means

BMD and Body Composition after 4-14.4 Months of Space Flight			
Variable	N	%/Month Change	SD
BMD Lumbar Spine	18	-1.06*	0.63
BMD Femoral Neck	18	-1.15*	0.84
BMD Trochanter	18	-1.56*	0.99
BMD Total Body	17	-0.35*	0.25
BMD Pelvis	17	-1.35*	0.54
BMD Arm	17	-0.04	0.88
BMD Leg	16	-0.34*	0.33

Table 1.

QCT Changes in volumetric BMD in 14 ISS Crew members (% per Month ± SD)	
Lumbar Spine (Integral)	-0.9±0.5*
Lumbar Spine (Trabecular)	-1.7±0.6*
Total Hip (Integral)	-1.4±0.8*
Total Hip (Trabecular)	-2.3±0.8*
Femoral Neck (Integral)	-1.2±0.7*
Femoral neck (Trabecular)	-2.7±1.9*

Table 2

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 3.