

**Human Research Program
Human Health Countermeasures Element**

Evidence Book

Risk of Accelerated Osteoporosis

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I. PRD Risk Title: Risk of Accelerated Osteoporosis

Description: Bone mineral loss occurs in microgravity due to unloading of the skeletal system, with average loss rates of approximately 1% per month. It is unclear whether this bone mineral density will stabilize at a lower level, or continue to diminish. It is unknown if fractional gravity, present on the moon and Mars would mitigate the loss; crewmembers could be at greater risk of osteoporosis-related fractures in later life. Greater understanding of the mechanisms of bone demineralization in microgravity is necessary to frame this risk, as well as to understand how current and future osteoporosis treatments may be employed.

II. Executive Summary

By definition, osteoporosis (Op) 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 Op 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. Moreover, being female is a risk factor for Involutional Op, with a greater incidence of fractures occurring earlier in ageing women than in men. This risk factor is associated with menopause (at around age 50), in which estrogen deficiency, during the first decade after onset, induces an accelerated turnover of bone that eventually becomes unbalanced and results in bone loss. It is this earlier induction of postmenopausal bone loss that predisposes a greater number of females to fragility fractures at an earlier age. Similarly, this report proposes that there is enough evidence from crew members flown on space missions >30 days to suggest that the adaptations of the skeletal system to mechanical unloading predispose crew members to accelerated onset of Op after return to earth.

In brief, this report will provide detailed evidence indicating that long-duration crew members exposed to the weightlessness of space during an average 6-month mission.

- Display bone resorption that is aggressive, that targets normally weight-bearing skeletal sites, that is uncoupled to bone formation, and that results in deficits in areal bone mineral density (BMD) that can range from 3 to 9% of preflight BMD;
- Display compartment-specific declines in volumetric BMD in the proximal femur (a skeletal site of clinical interest), which significantly reduce its compressive and bending strength;
- Lose hip bone strength (i.e., force to failure);
- Recover BMD over a postflight time period that exceeds spaceflight exposure but for which the complete restoration of whole bone strength remains an open issue; and
- Display risk factors for bone loss – such as negative mineral (calcium) balance and down-regulated calcium-regulating hormones – that are compounded by mission operational constraints such as nutritional deficiencies and lack of UV sunlight for vitamin D conversion.

The full characterization of the skeletal response to mechanical unloading in space is not complete. Longitudinal measures of crew members after spaceflight are required. Knowledge gaps related to exploration missions are substantial. Those gaps will be addressed with prioritized research. To define the level of Risk for Accelerated Op following exploration

missions to the Moon and Mars, and to manage that risk with appropriate mitigation or treatment, it is important to understand the pattern of spaceflight-induced bone loss and its recovery.

This report is not suggesting that spaceflight-induced bone loss is similar to menopause-induced bone loss. On the contrary, mechanisms behind spaceflight-induced bone loss and menopause-induced bone loss are distinct. “Postmenopausal Op” is a metabolic bone disease while bone loss in space is driven by biomechanics. This report, rather, will highlight how spaceflight induces excessive bone loss and structural changes that could have a cumulative effect on the ageing-induced bone losses that occur years later – just as menopause does.

III. Introduction

A. Description of Osteoporosis

Osteoporosis (Op) 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. The most recognized hallmarks of osteoporosis are low bone mineral density and disrupted cancellous bone microarchitecture. This syndrome is more often associated with the elderly because of combined ageing-induced bone loss and the age-related co-morbidities that influence bone volume.

Op can be divided into two categories based on different etiologies of skeletal deterioration: Primary Op (or “Involutional Op”) is a consequence of the *ageing* process (Riggs, 1998) while Secondary Op is induced by external factors such as glucocorticoid medication.

While the weightlessness of space may be considered a causative factor for Secondary Op, there is no evidence from bone mineral density measurements (BMD) that would substantiate a diagnosis of Op by World Health Organization (WHO) guidelines (c. 1994) (Table 2-1). It is worth noting, however, that the WHO guidelines are for the purpose of identifying a BMD threshold for treatment intervention, which does not necessarily correspond to a diagnostic threshold for Op. In this case, BMD serves as a surrogate for whole bone strength and a reflection of bone deterioration for use in the elderly white female population. However, a complete reflection of whole bone strength in the younger astronaut population will require supplementation of dual-energy X-ray absorptiometry (DXA) measurements with technology such as quantitative computerized tomography (QCT), high resolution peripheral QCT, and MRI technology for non-invasive assessments of “bone quality” – indices such as bone geometry, compartment-specific volumetric BMD, and trabecular microarchitecture. Moreover, guidelines do not address the 10-year probability for fracture risk, which is dependent on age, BMD, and other factors (Kanis, 2007). These issues will be addressed in a separate Evidence Base Report on Fracture Risk.

Table 2-1. WHO Guidelines for diagnosis of Op by BMD. BMD is used to stratify individuals according to relative risk for fracture but is a poor predictor of who will fracture.

WHO Classification	T-score (SD from mean BMD of young Caucasian females)
Normal	-1 to + 1
Osteopenia	Between -1 and -2.5
Osteoporosis	-2.5 or less
Severe Osteoporosis	-2.5 or less and fragility fracture

Primary Op, moreover, can be subdivided into two types: *Postmenopausal Op* is a high bone turnover state that occurs in females with the onset of menopause because of the deficiency in estrogen. *Senile Op* is a low bone turnover state that occurs in both males *and* females at about the 7th decade of age because of an age-related decline in the capability to produce bone (Riggs, 1986; Riggs, 1998).

This report will present evidence that the *absence* of mechanical loading during spaceflight (i.e., weightlessness) induces a rate of bone loss that is reminiscent of, if not greater than, the accelerated bone loss induced by the *absence* of estrogen (i.e., estrogen deficiency). Specifically, measurable BMD deficits with menopause-induced bone loss occur in years while spaceflight-induced bone loss occurs in a matter of months. Essentially, this report asserts that spaceflight is a risk factor for the earlier onset of Op in crew members vs. their terrestrially-based peer group just as menopause is a risk factor for the earlier onset of Op in females compared to males. However, the characterization of spaceflight-induced bone loss is not as extensive as that of menopause-induced bone loss. As a consequence, comparisons will be drawn between the two pathophysiologies to help identify gaps in knowledge and in the evidence required to substantiate that spaceflight increases the risk for accelerated Op.

B. Bone Physiology Background Information

Remodeling is the process by which the adult skeleton renews and repairs itself; approximately one tenth of the skeleton is renewed annually. The remodeling of bone occurs 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 of this cellular process 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 (Riggs, 2005), a negative balance of bone in each unit can reduce skeletal mass over time and compromise the skeleton’s integrity under normal mechanical loading.

Furthermore, the skeleton is composed of two types of bone: cortical bone (also known as compact bone) and cancellous bone (also known as trabecular bone or “spongy” bone). Eighty percent of the skeleton is made up of cortical bone, with the 20 % balance made up of cancellous bone. Cortical bone is found, for example, in the shafts of the long bones and in the endplates of the vertebrae, while cancellous bone is found in the bone marrow compartments at the ends of long bones, within vertebral bodies, and in the pelvis. Ten percent of the skeleton is remodeled

each year, but only 3% of cortical bone is renewed compared to 25% of cancellous bone. This difference in metabolic activity is due to the highly porous, scaffold-like structure of cancellous bone, which provides 80% of all bone surfaces in the skeleton. The initiating step of the remodeling process is bone resorption, and the resorptive action of osteoclasts occurs on bone surfaces next to bone marrow. Thus, bone remodeling occurs predominantly in cancellous bone, on the inside (endocortical) surface of cortical bone, and within cortical bone in Haversian canals. There is recent evidence, however, of resorption occurring on the periosteal surface of cortical bone (Bliziotes, 2006).

Moreover, rates of skeletal remodeling are gender-specific. Figure 2-1 displays the different pattern of bone gain and loss in men and women as they age. This gender difference is primarily attributed to gonadal hormones, which influence multiple facets of bone volume regulation. Figure 2-1 depicts three phases of bone volume regulation (I-III) in the ageing population: bone mass gain (I) and bone mass loss (II and III).

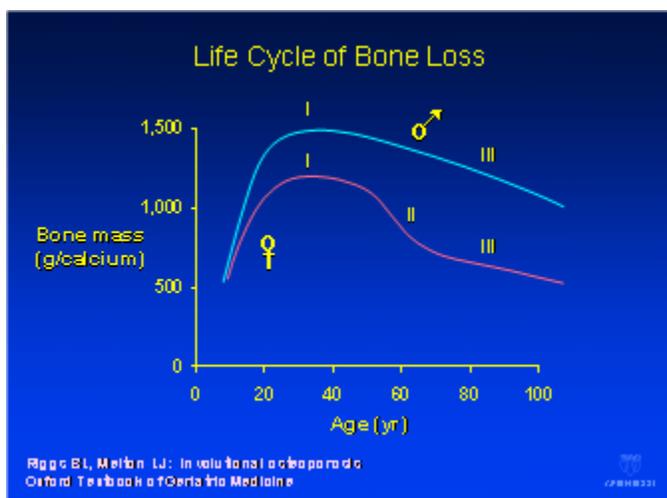


Figure 2-1. The involutional pattern of bone loss is displayed in this schematic of bone mass changes as the population ages. The pattern of bone loss diverges according to sex at around age 50 years; females undergo a biphasic loss while males experience a single phase of bone loss. After the onset of menopause, women lose bone at a rapid rate before experiencing senile bone loss, which occurs at a slower rate in men.

Phase I displays how puberty induces differential growth. The larger accretion of bone mass in males corresponds to androgen stimulation of radial bone growth, which results in bones with larger cross-sections. In contrast, estrogen in females suppresses radial growth, bone elongation, and expansion of the medullary canal. Age-related bone loss commences soon after peak bone mass is attained (~age 35) in both sexes. However, women undergo a biphasic loss of bone mass (II and III), while men experience only a single phase (III) (Riggs, 1986). Women are subjected to a rapid phase of bone loss (II) with the onset of menopause at around age 50.

Around age 70 women enter the second phase of bone loss (III), in which bone loss occurs in both men and women at the same rate and, in contrast to Phase II, the loss of bone mass is slower and a consequence of a pervasive under-filling of remodeling units (Riggs, 2002; Riggs, 1998).

When remodeling is accelerated, as in Phase II of menopausal bone loss, the “birth rate” of bone remodeling units is high. The increased number of bone remodeling units can lead to greater porosity in cortical bone and to the perforation of horizontal trabecular struts in cancellous bone microarchitecture. These changes to horizontal struts result in a loss of connectivity between trabeculae and to a reduction in the mechanical strength of the trabecular scaffold, not unlike the collapse of a building as individual floors are destroyed by an implosion.

Aside from invasive analyses, the loss of bone mass by increased remodeling can also be inferred by detection of increased levels of biomarkers for bone formation and bone resorption (Garnero 1999, Bonnicksen 2006) in blood and urine specimens, respectively. The relationship between biomarker levels and BMD is not strong enough for diagnosing Op in the individual (Melton, 1997), although assays of biomarkers are an established means of monitoring a response to Op therapy (Watts, 1999).

Furthermore, perturbations in the endocrine regulation of bone volume accompany each phase of age-related bone loss. The increased release of calcium during menopause-induced bone loss initiates a cascade of down-regulated calcium-regulating hormones starting with the suppression of parathyroid hormone and the reduced production of 1,25-dihydroxyvitamin D, and resulting in deficient intestinal absorption of calcium. Over time, factors contributing to senile bone loss, such as nutritional deficiencies and endocrinopathies, induce hyperparathyroidism, a primary reduction of 1,25-dihydroxyvitamin D, and poor calcium absorption (Riggs, 1986).

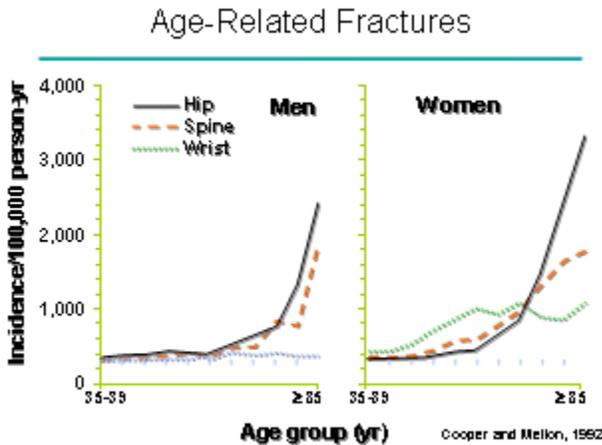


Figure 2-2. Age-related fractures in men and women. Women display an earlier and greater incidence of fractures at sites composed of predominately trabecular bone (Cooper & Melton, 1992).

Figure 2-2 shows how the two phases of age-related bone loss have specific characteristics that account for the different types and occurrence of fractures in men and women. Estrogen is a hormonal suppressor of osteoclastic resorption, and estrogen-deficient women display an accelerated turnover of bone with increased activation of bone remodeling units (a higher “birth rate” of remodeling units or “activation frequency,” as seen in Figure 2-3) and an unrestrained activity of osteoclasts (deeper and greater number of resorption lacunae, Figure 2-4).

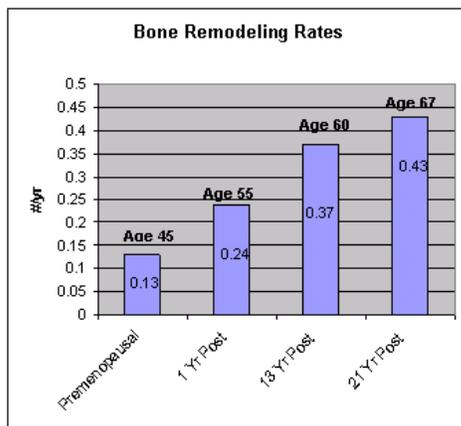


Figure 2-3. Bone remodeling rates, as determined by histomorphometric determination of activation frequency, increase with age (adapted from Recker, 2004).

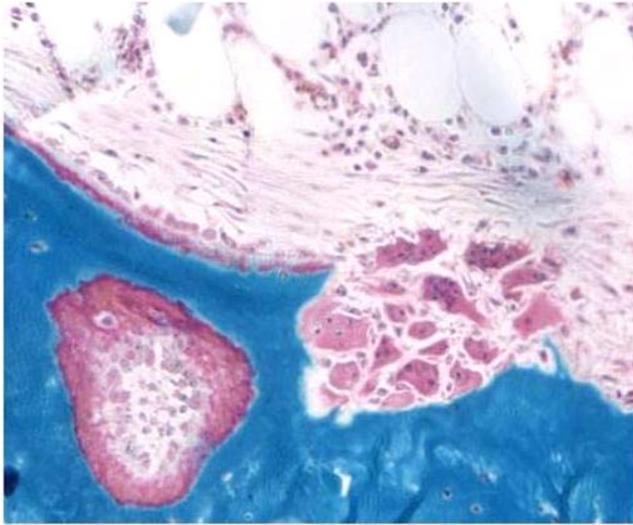
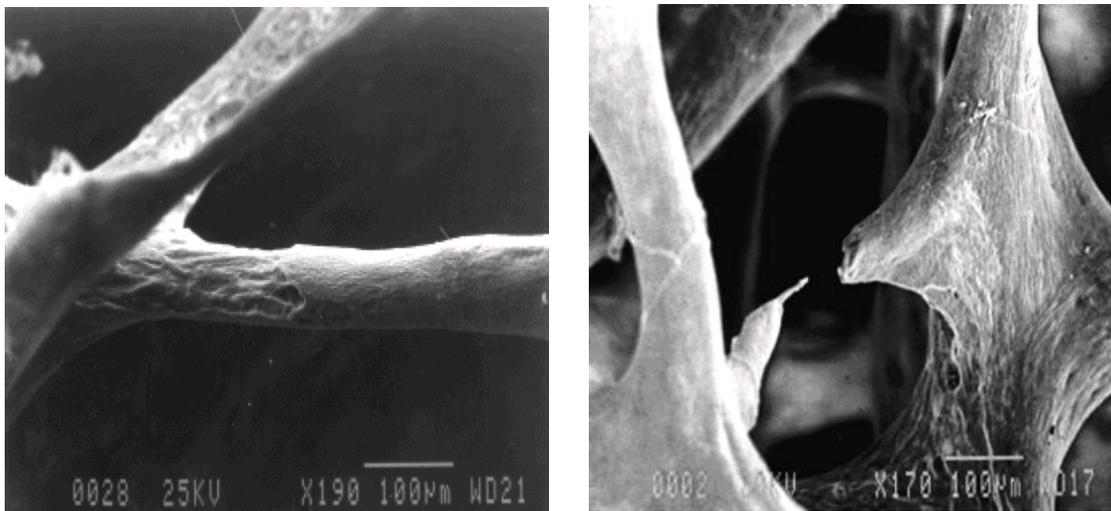


Figure 2-4. Unrestrained osteoclast recruitment and resorption of bone lacunae (slide courtesy of Mayo Clinic Bone Histomorphometry Lab).

As previously discussed, the rapid loss of bone with menopause preferentially occurs in the cancellous bone compartment (trabecular or spongy bone), where aggressive resorption 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 (Figure 2-5a), ii) perforation of trabecular struts (Figure 2-5b) and iii) loss of trabecular elements and connectivity (Kleerekoper 1985; Mosekilde, 2000; Seeman, 2002).



Figures 2-5a, b. Trabecular thinning and trabecular perforation as displayed by electron microscopy (Mosekilde, L).

A reduction in trabecular number, vs. a reduction in trabecular thickness, is a microarchitectural change that is associated with reduced mechanical strength and fractures (Figures 2-6 and 2-7). Overall, the rate of reduction in cancellous bone mineral density is 3-5 times that of cortical bone density (3-4% BMD loss/year) and accounts for a higher incidence of fractures in women (compared to men of same age range) at skeletal sites predominantly composed of cancellous bone (wrist fractures and vertebral crush fractures) (Riggs, 1986).

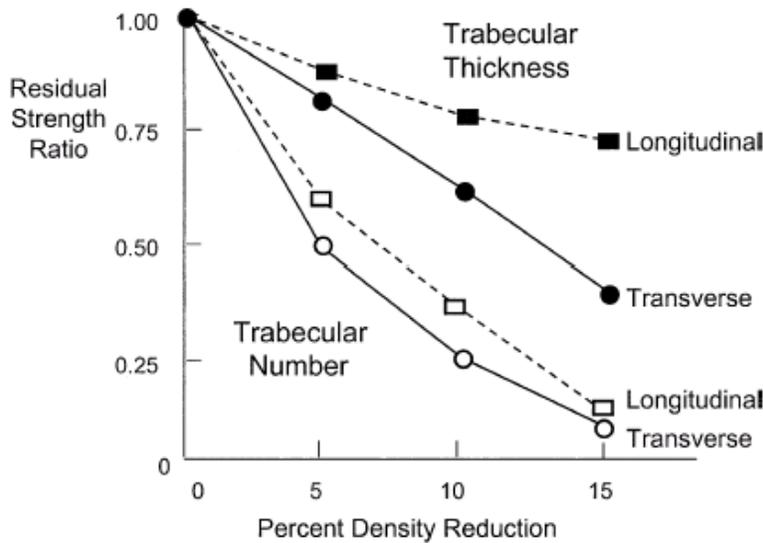


Figure 2-6. Changes in trabecular bone microarchitecture. Residual strength of cancellous bone compartment is less (“weaker”) when density loss occurs by reduction in trabecular number (“linear” density of trabeculae) than by trabecular thinning (Silva, 1997).

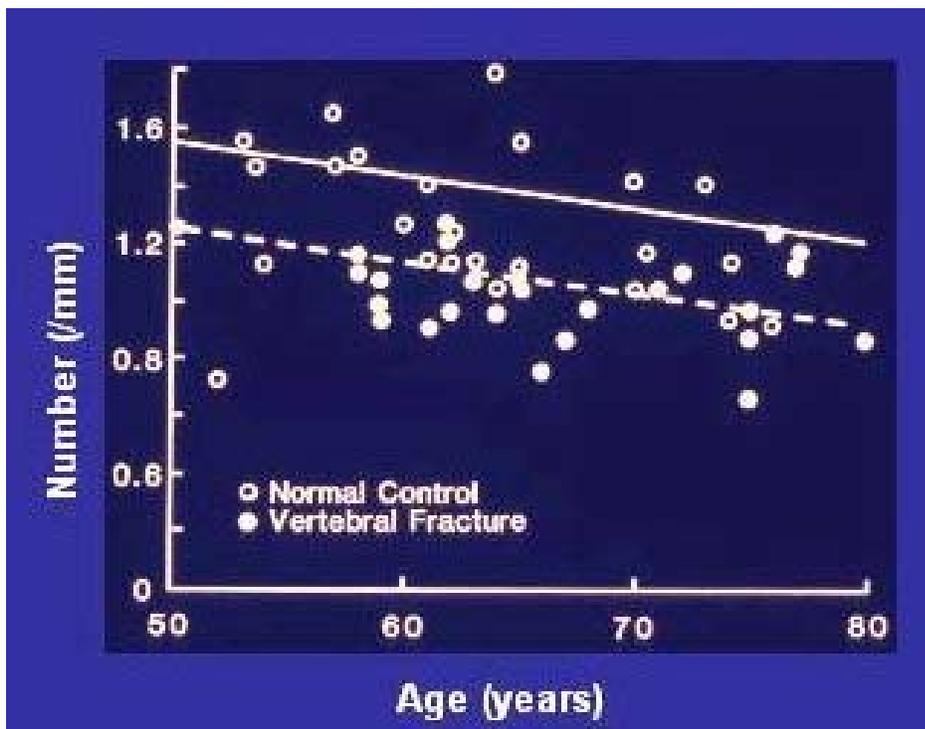


Figure 2-7. Reduction in trabecular number in bone microarchitecture is associated with fragility fractures (Kleerekoper, 1985).

On the other hand, the bone loss associated with Senile Op involves both cancellous and cortical bone compartments. With the under-filling of resorption cavities, cancellous bone has thinner trabeculae and cortical bone has a reduced thickness with increased porosity. This reduction in bone mass, in both elderly men and women, accounts for a greater incidence of fractures at the hip and of wedge fractures in vertebral bodies of the spine.

Additionally, as women age, the skeletal effects of Postmenopausal Op and Senile Op are combined. As shown in Figure 2-2, hip and vertebral fractures increase in both sexes after age 70, but the occurrence is slightly earlier and the prevalence is greater in women. Some of this

difference can be attributed to different rates of survival. More recently, however, the application of the more sensitive QCT to a population study (Riggs, 2004; 2007) substantiated that there are earlier and persistent losses in cancellous bone in both men and women (~33% and 50% of total lifetime loss, respectively). Likewise, substantial losses in cortical bone in women were initiated around mid-life 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 Op (and its associated fragility fractures) in women compared to men at the same age.

Interestingly, there are striking similarities between menopause-induced bone loss and spaceflight-induced bone loss, suggesting that the “deficiency” of mechanical loading may increase the risk for early onset Op in crew members who have been exposed to prolonged periods of spaceflight compared to their terrestrial peers.

Common characteristics of “deficiencies” in estrogen and mechanical loading include:

- Accelerated remodeling of bone
- Reductions in bone mineral density
- Reductions in bone volumetric densities and structure
- Preferential trabecular bone loss
- Reductions in bone strength
- Perturbed endocrine regulation

Discussion of these characteristics will be expanded in the Evidence section.

IV. Evidence

C. Reductions in Bone Mineral Density

1. Spaceflight Evidence

Evaluations of bone density following prolonged space exposures were first implemented with the 3-manned crew of the Skylab missions and demonstrated the regional specificity of bone loss in space. Measurements by single-photon absorptiometry failed to show any impact of spaceflight on measurements in the upper body (wrist), but detected significant losses in the lower extremity (calcaneus, in 3 of 9 astronauts) (Vogel, 1976). BMD changes in crews of different missions became more negative with increasing duration (28, 56, and 84 days) of Skylab flights (Figure 2-8) (Rambaut, 1979). Similarly, Oganov (1990) analyzed spine BMD with early application of computed tomography (CT). Evidence from four Russian cosmonauts, after 5- to 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 (Oganov, 1990).

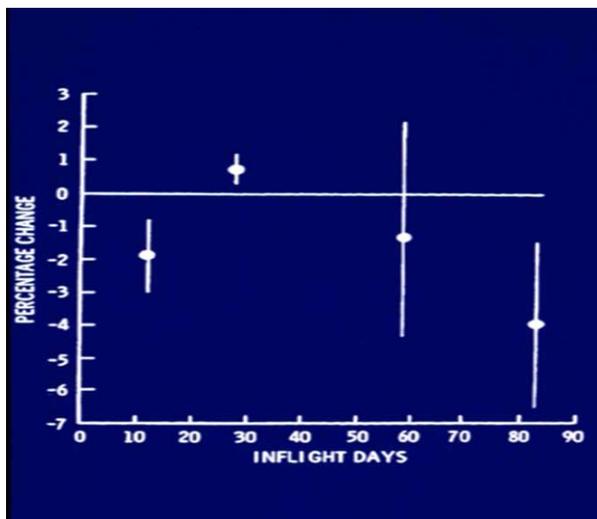


Figure 2-8. BMD measured with varying durations of Skylab missions and compared to a 14-day Apollo mission.

Furthermore, it was with the advent of DXA technology for measurement of areal BMD (g/cm^2) that BMD deficits were detected at skeletal sites that were normally weight-bearing on Earth. LeBlanc et al. (2000) conducted DXA BMD measurements of crew ($n=16-18$) before and after they served on the Mir spacecraft (~4 months) 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 as percent change per month to report an average loss of 1-1.5% on a monthly basis (Table 2-2). Further assessment revealed large variability in BMD losses of crew members, both intraskeletally and interskeletally, and that the BMD losses were greater in the lower limbs and the weight-bearing sites of the central skeleton. These sites included the hip and spine, sites that have a high incidence of osteoporotic fractures in the elderly population on Earth.

Table 2-2. Change in BMD (averaged change per month) in crew members serving on missions on the Mir spacecraft (LeBlanc, 2000).

BMD and Body Composition Changes 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

DXA measurement of BMD is used routinely only on crew members serving on spaceflight missions >30 days.

2. Comparison to Ageing Population

Compared to the averaged monthly loss of BMD in crew members, a 2-3% loss per year is observed in postmenopausal females during the rapid bone loss phase in the first decade after

menopause onset (Riggs, 1986). Additionally, Figure 2-9 provides a comparison of longitudinal changes in total hip BMD as a function of age for both men and women as reported by Warming (2002); 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 (Figure 2-9a, b), crew members in the age range 35-55 displayed a ~6-fold greater decrement after a 6-month spaceflight mission than 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; male crew members displayed large BMD variability in the lumbar spine and forearm (Figure 2-9c, d). The losses quantified in the pre-menopausal long duration crew members may be comparable to losses measured in the 50-59 population age group (Figure 2-9 e, f), but currently the number of subjects is small (n=3 females).

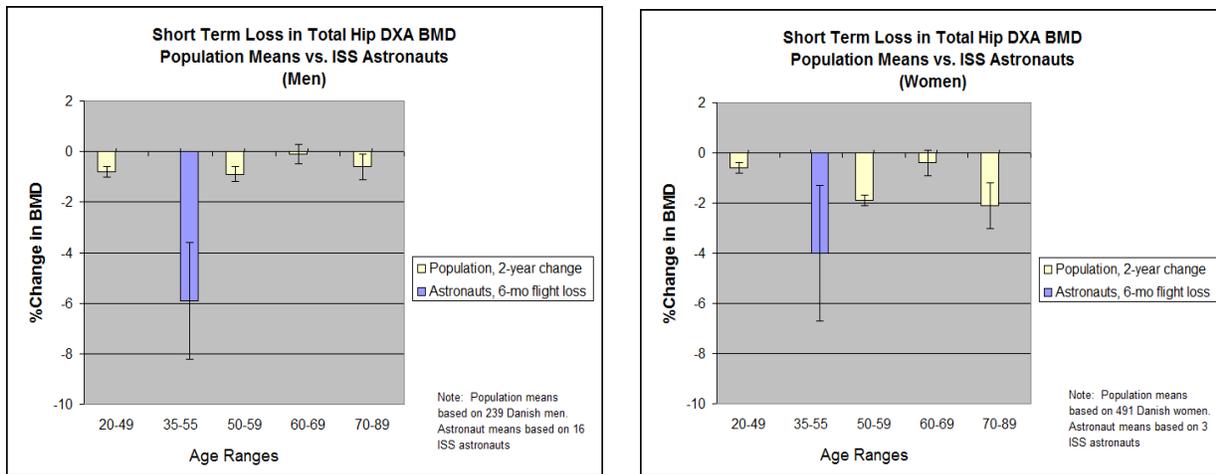


Figure 2-9 a, b. Comparison of BMD change for total hip in male (a) and female (b) crew members vs. population mean. ISS: International Space Station. (Adapted from Warming, 2002, and Johnson Space Center Bone Mineral Lab).

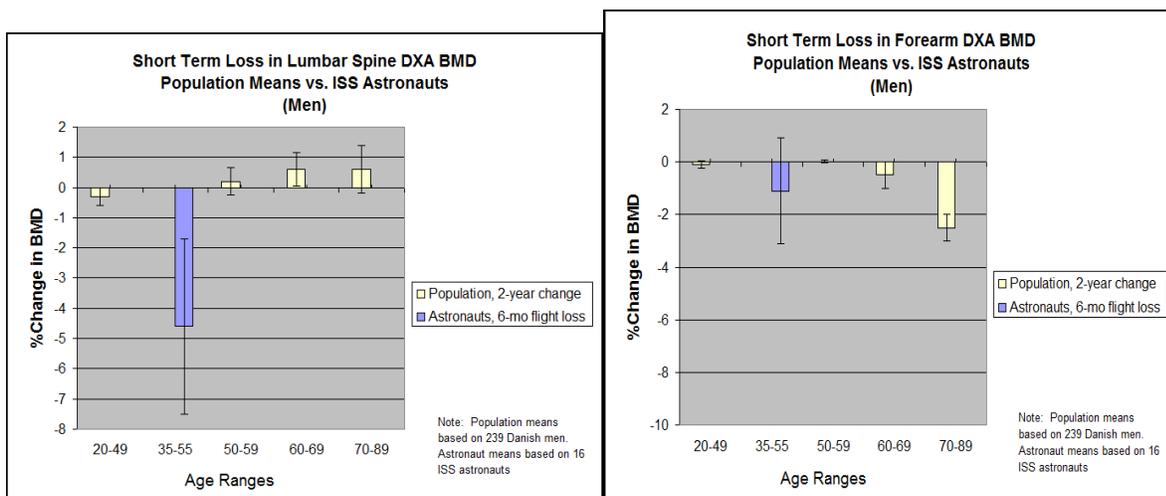


Figure 2-9 c, d. Comparison of BMD change for lumbar spine and forearm in male crew members vs. population mean. ISS: International Space Station. (Adapted from Warming, 2002, and Johnson Space Center Bone Mineral Lab).

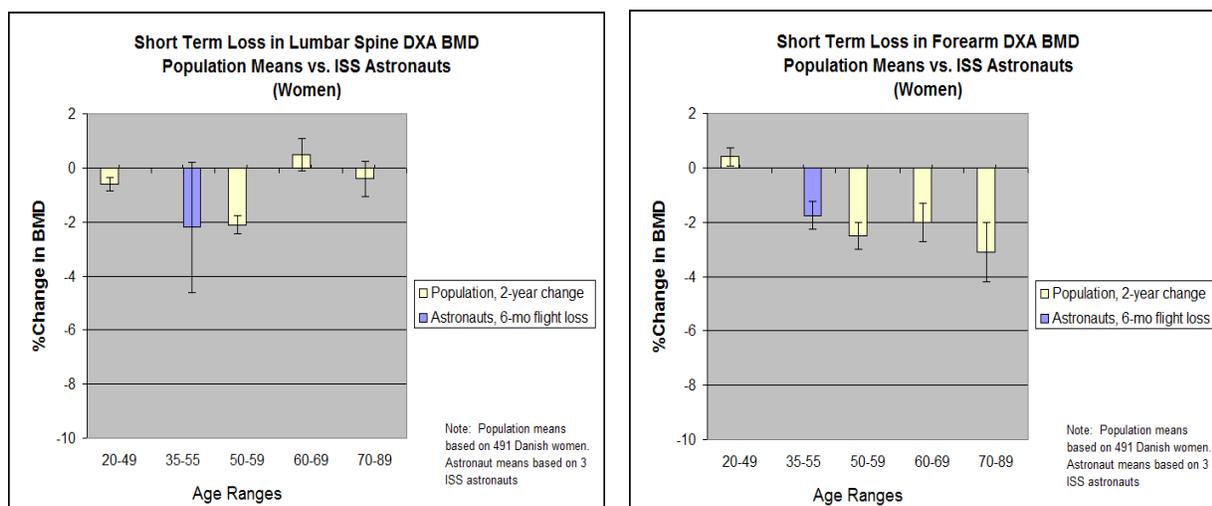


Figure 2-9 e, f. Comparison of BMD change for lumbar spine and forearm in female crew members vs. population mean. ISS: International Space Station. (Adapted from Warming, 2002, and Johnson Space Center Bone Mineral Lab).

This comparison between populations indicates that spaceflight induces a loss of BMD that is rapid and exceeds the normal loss in BMD in a similarly-aged terrestrial population. The loss over 6 months may be even greater than the BMD loss that occurs in females after the onset of menopause.

D. Reductions in Bone Volumetric Density, Size, and Structure

1. Spaceflight Evidence

There is evidence that spaceflight-induced remodeling is specific to separate bone compartments, which can be delineated with imaging by QCT. A preferential BMD loss in cancellous vs. cortical bone compartments (on basis of percentage) has been detected in both Russian and U.S. crew serving in long duration (>30-day to 6-month missions) as determined by QCT technology and peripheral QCT (Vico, 2000; Lang, 2004).

QCT scans performed on the spine and the total hip (femoral neck and proximal femur) of crew members serving on six-month missions on the International Space Station (ISS) quantified trabecular bone losses of 2.2-2.7% per month (Lang et al, 2004) in the hip and 0.7% per month in the lumbar spine as averaged to month of duration (n=14 crew members) (Table 2-3).

Table 2-3. 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 occurred in volumetric BMD, expressed as loss averaged per month, for all sites with greater percentage deficit for trabecular bone of proximal femur (Lang, 2004).

QCT Changes in BMD in 14 ISS Crewmembers (%/Month±SD)	
Lumbar Spine, Integral	-0.9±0.5**
Lumbar Spine, Trabecular	-0.7±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**

For the total hip and femoral neck, the percentage BMD loss was greater in the trabecular compartment (the more metabolically-active site), although the BMD loss on a total mass basis was greater in the highly dense, cortical bone due to loss from the endocortical surface (Lang et al, 2004). 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 represented a reduction in both estimated axial compressive strength and bending strength (Lang 2004).

E. Comparison to Ageing Population

Age and sex differences in the vertebra and proximal femur, as determined by QCT, were conducted in a population of men (n=323) and women (n=373) aged 20-97 years (Riggs et al, 2004). Bone geometry and volumetric BMD were determined to characterize the changes in structure over time and how these structural changes influence Op fractures induced with ageing. This characterization underscored the complexity of age-related changes, with some of these age-related changes being detected before midlife or influenced by gender. The results, summarized below, enhanced the characterization of skeletal effects reported previously with more limited methodology, such as with DXA or histomorphometry.

- Increased porosity of cortical bone
- The thinning of the cortex by resorption at the endocortical surface
- Large reductions in trabecular volumetric BMD
- Increases in periosteal expansion for an outward displacement of cortical bone

In females the reduction in trabecular bone is 3-5 times greater than the loss of cortical bone and accounts for the greater incidence of fractures in the wrist and spine during the early years after menopause onset (see Figure 2-2). Histomorphometry of bone biopsies of postmenopausal females indicates that there is an increased number of osteoclasts with aggressive resorptive activity leading to the perforation of trabecular plates and loss of trabecular elements (i.e., loss of connectivity) (Parfitt, 1983). Reductions in trabecular elements are correlated with fractures and reduced whole bone strength, as previously mentioned (Kleerekoper, 1985; Van der Linden, 2001; Silva, 1997).

This comparison indicates that geometrical changes and trabecular bone losses observed with Postmenopausal Op and with normal ageing are qualitatively similar to those documented after long-duration spaceflight.

F. Delayed Recovery of Bone Loss

1. Spaceflight Evidence

There is evidence that the recovery of space-induced bone loss is delayed in the postflight period. Vico (2000) 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 recovers lost BMD, it would occur on Earth after a period longer than the mission duration (Vico, 2000). Additionally, Lang et al. (2006) repeated QCT scans at the proximal femur in 11 ISS crew members one year after landing. They demonstrated an increase in cross-sectional volume at the femoral neck, compared to the measurements soon after landing, but with a

persistent depression in volumetric bone mineral density. These data at one year postflight indicate that radial bone growth was stimulated on return to Earth’s gravitational field but that the increased volume remained under-mineralized. Furthermore, recovery of volumetric BMD in the trabecular bone compartment was not evident (Carpenter, re-submitted ms, 2009).

Recently, a novel method of analyzing areal BMD has been reported that characterizes skeletal recovery (Sibonga, 2007). BMD measurements were accumulated over a postflight 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 2-10).

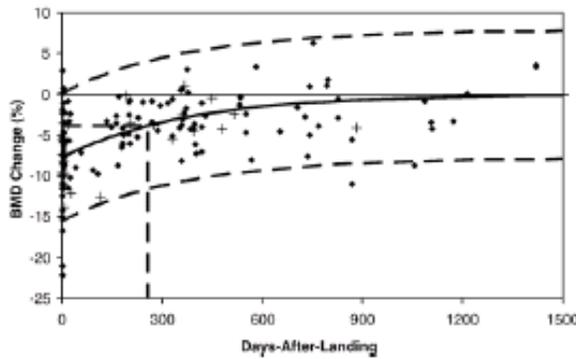


Figure 2-10. Changes in BMD at the trochanter after landing. The intercept of the fitted line shows where 50% recovery time for the 7.8% spaceflight-induced bone loss would occur after about 8.5 months (Sibonga, 2007).

The derivation of a “half-life” index provided a time point (days after landing) that represented the timing of 50% restoration of BMD. In spite of the large variability in the BMD measurements, and the uncertainty in half-life values (generally 3-9 months depending on skeletal site), the asymptotic increase in BMD over the postflight period was clearly apparent, and provided the basis for the assertion that substantial recovery occurs at >4 times the half-life (Table 2-4) (Sibonga et al, 2007).

Table 2-4. Fifty percent recovery time represents the number of days after landing at which there is a restoration of half of the bone mineral lost during spaceflight. L_0 represents BMD loss as a direct consequence of spaceflight. Confidence limits (95%) for the fitted values are provided in parentheses.

Summary of fitted data per skeletal site

Skeletal site	Loss (L_0) 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)

Furthermore, biochemical analyses of biomarkers indicate that with return to earth’s gravity, N-telopeptide (NTX) excretion in urine is suppressed, and there is a delayed increase in serum levels of osteoblast-specific proteins (bone specific alkaline phosphatase and osteocalcin) (Smith, 2005) (Figure 2-11). This trend in biomarkers precedes the positive change in BMD, which has also been observed in bed rest test subjects in the re-ambulatory period following bed rest (LeBlanc, 1990).

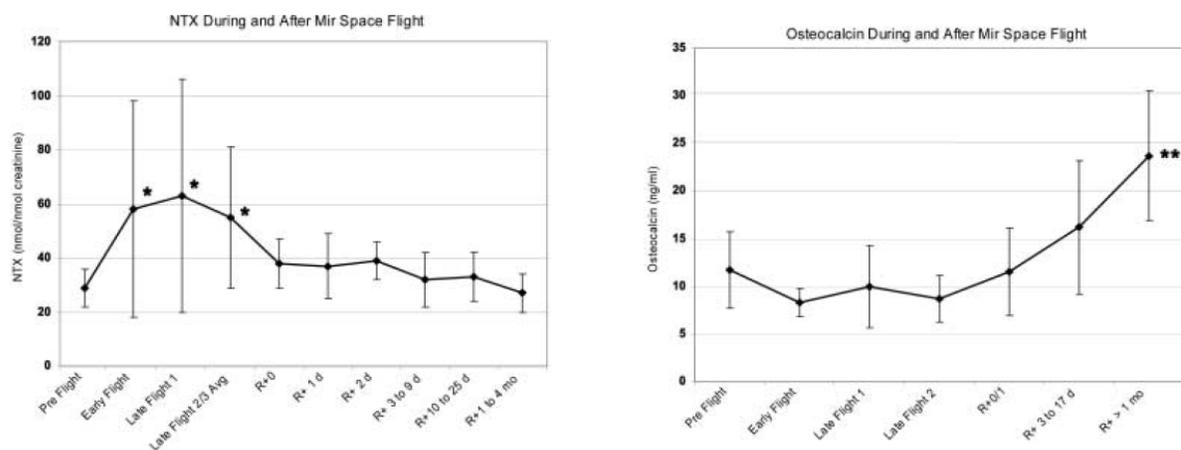


Figure 2-11 a, b. Bone turnover markers measured in specimens collected before, during, and after flight suggest that return to earth’s 1-G environment reverses the increased excretion of bone resorption marker NTX (amino terminus of cross-linked collagen degradation product) and eventually stimulates expression of bone formation markers (osteoblast-specific osteocalcin) (Smith, 2005).

2. Comparison to Ageing Population

The spaceflight-induced geometrical changes at the femoral neck appear similar to the adaptive response to cortical thinning and trabecular bone loss normally observed with age-related bone loss in the elderly (Mosekilde, 2000; Seeman, 2002), suggesting a compensatory physiological response of the skeleton to recover compressive and bending strength. QCT analysis of age and sex differences in bone geometry (Riggs, 2004) similarly documented apposition of bone at the periosteal surface (outer surface) in response to thinning of the cortex by age-related increases in bone resorption at the endocortical surface (inner surface to bone marrow). This comparison suggests that age-related changes in bone structure observed in the elderly are similar to those documented in younger crew members after long-duration spaceflight.

There are various therapies for involutional bone loss that improve bone mass by replacing deficient factors. Individuals with Senile Op are supplemented with calcium and vitamin D to treat calcium malabsorption and its associated secondary hyperparathyroidism – an endocrine risk factor for bone loss (Dawson-Hughes, 1997; Boonen, 2006). Alternatively, anabolic therapy (e.g., Trademark Forteo) can provide the stimulus for osteoblastic bone formation (Holick, 2005; Riggs, 2005). The prevention or mitigation of Postmenopausal Op, moreover, has historically centered on hormone replacement, or alternatively anti-resorptive agents such as bisphosphonates, since bone loss is induced by the deficiency of the anti-resorptive estrogen (Cauley, 2003; Black, 2000).

Disuse Op and Postmenopausal Op have different etiologies, with cellular mechanisms that remain to be completely defined. The deficiency of an osteogenic stimulus (such as the lack of mechanical loading in space) initiates a rise in bone resorption in accordance with Wolff’s Law (Forwood, 1995); the deficiency of an anti-catabolic factor (such as the lack of estrogen with menopause) accelerates bone turnover by increasing the activation of remodeling sites. In spite of different etiologies, BMD losses in both cases are attributed to increased and unbalanced bone resorption.

G. Perturbed Remodeling

1. Spaceflight Evidence

Evidence from bone turnover markers suggests that the remodeling process is uncoupled in space, leading to an unbalanced remodeling of bone and a deficit in bone mass. Albeit indirect measures of turnover at the level of the entire skeleton, levels of these biomarkers suggest that bone resorption is increased and bone formation is 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 and peptides that are synthesized and released by osteoblasts during bone formation. Historical data document:

- i) An increased excretion of hydroxyproline (a post-translationally modified amino acid specific to collagen) relative to preflight level in all 3 Skylab missions (Rambaut, 1979).
- ii) An increase (100-150%) in cross-linked collagen fragments at the amino terminus (NTX) during flight, determined in a retrospective analysis of in-flight urine specimens collected from Skylab crew members (Smith, 1998).
- iii) Increases in NTX during flight with minimal influence on serum osteocalcin (an osteoblast-specific protein) in Mir crew members (Smith, 2005), and
- iv) Suppression of procollagen type I C-terminal peptide, bone-specific alkaline phosphatase, and osteocalcin (osteoblast-specific protein and peptide) concurrent with increased bone resorption markers (Caillot-Augusseau , 1998)

Collectively, these indirect, systemic assays of bone turnover suggest that remodeling is uncoupled from mechanical unloading and that the volumes of resorbed bone and formed bone are consequently not balanced.

2. Comparison to Ageing Population

Menopausal bone loss is the result of rapid bone remodeling that has been quantified by the increases in activation frequency, a histomorphometric index that reflects the initiation of bone remodeling units (Recker, 2004). This increase in bone remodeling is also implied by increases in bone turnover markers (Sornay-Rendu, 2005; Garnero, 2005).

This comparison indicates that bone remodeling is not balanced during both spaceflight and menopause because the resorption of bone exceeds the formation of bone.

H. Related Risk Factors for Bone Loss

Bone loss can be a reflection of several processes, and thus the extensive variability observed with skeletal measures (e.g., BMD) is not unexpected. Several risk factors contribute to bone loss. Endocrine co-morbidities contribute to spaceflight-induced bone loss and may further influence the Risk for Accelerated Op.

1. Spaceflight Evidence

Evidence from short duration (< 90 days) spaceflight missions suggests that a negative calcium balance occurs during spaceflight missions due to both a reduction in calcium intake and an increase in calcium excretion. Mineral metabolism studies that were conducted during the Skylab missions enabled Whedon and colleagues (1976; 1976; 1977; Smith, 1977) to characterize the negative calcium (and mineral) balance during spaceflight.

Data were obtained from the 3 astronauts flying on each of three Skylab missions having durations of 28, 56, and 84 days. In spite of the large variability in mean values, collectively the data suggest that the deconditioning of the skeleton increases with the duration of spaceflight (LeBlanc, 2007). Other results were a rapid and sustained elevation in urine calcium, a gradual increase in fecal calcium, and a negative calcium balance averaging – 5 g/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 demonstrate that the negative calcium balance is likely due to bone atrophy (increased excretion) and to calcium malabsorption (decreased intake), and these Skylab results were corroborated with subsequent kinetic and metabolic studies on a 3-month joint NASA-Mir flight (Smith, 1999). Furthermore, the stimulation of bone resorption during spaceflight was re-affirmed with state-of-the-art assays for multiple cross-linked collagen biomarkers, conducted on stored Skylab specimens (Smith, 1998).

With the observed signs of increased bone resorption during spaceflight, measurements of calcium-regulating hormones failed to document a change in parathyroid hormone (PTH) or 1,25-dihydroxyvitamin D in astronauts serving on Mir missions (Smith, 1999; 2005).

Together with the delayed reduction in serum PTH, these data suggest that increased demineralization of bone will mildly increase serum calcium and phosphorus and lead to a reduction in the hormones responsible for increasing serum calcium (PTH and 1,25-dihydroxy vitamin D). These deficits likely suppress intestinal absorption of calcium and re-absorption of calcium by the kidney, thereby contributing to the negative calcium balance seen with spaceflight.

2. Comparison to Ageing Population

In the elderly population, calcium absorption is poor due to inadequate conversion of vitamin D by sunlight and reduced enzymatic conversion to 1,25-dihydroxyvitamin D. Renal insufficiency and nutritional deficiencies are causal and contributing factors. Collectively, these co-morbidities result in hypocalcemia, and the resulting secondary hyperparathyroidism induces bone loss in the aged.

This comparison indicates that crew members on space missions incur risk factors for bone loss similar to those that can be incurred with ageing. However, it must be noted that bone loss during spaceflight induces calcium malabsorption in crew members, while calcium malabsorption in the elderly induces the bone loss of ageing. Poor calcium absorption in both of these cases does not suggest that treatment would be the same, as documented by Heer et al (1999).

I. Decreased Bone Formation

1. Spaceflight Evidence

Spaceflight impairs the mineralization of bone in space. Histomorphometry of iliac crest bone biopsies that have been labeled with tetracycline (a bone fluorochrome) is the standard method for evaluating mineralization rates and mineralizing surfaces in skeletal tissue. However, no biopsies have been obtained from astronauts during or after a spaceflight mission. Histomorphometry data, though, have been obtained from bone biopsies of non-human primates that were administered tetracycline prior to launch to space (Zerath, 1996; 2002). Compared to biopsies obtained before 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 after landing. Histomorphometric data were accompanied by a reduction in bone mineral content with flight.

2. Ground-based Evidence

The following reports from spaceflight analogs corroborate and enhance the limited spaceflight evidence because of the use of invasive analytical methods and the controlled experimental conditions in which to evaluate mechanical unloading:

1. Immobilization or mechanical unloading by prolonged bed rest down-regulates calcium-regulating hormones (Stewart, 1982; Arnaud, 1992; LeBlanc, 1995).
2. Mechanical unloading by prolonged bed rest uncouples remodeling, as reflected by bone turnover markers (Leuken, 1993; LeBlanc, 2002; Smith, 2003; Shackelford, 2004).
3. Mechanical unloading uncouples osteoclastic and osteoblastic mediation of bone remodeling, as determined in bone biopsies (Minaire 1974; Vico, 1987; Zerwekh, 1998).
4. Mechanical unloading by 120 days of bed rest (Thomsen, 2006) and during >two years following spinal cord injury (Modlesky, 2004) deteriorates connectivity of trabecular microarchitecture.
5. Skeletal unloading in non-human primates immobilized in a spaceflight analog impairs mineralization, accelerates bone resorption, and reduces bending strength (Young, 1983; Mechanic, 1986; Young, 1986).

The collective histomorphometric data from humans and non-human primates indicate i) that skeletal unloading uncouples bone remodeling, ii) that the level of bone resorption exceeds the extent of bone formation, and iii) that mineralization is impaired.

3. Comparison to Ageing Population

Involitional bone loss in the elderly is associated with impaired bone formation (Riggs, 1986). Resorption lacunae may be of normal depth, but osteoblasts have reduced capability to sufficiently replace resorbed bone (Lips, 1978). More recent characterization of age-related differences in iliac crest biopsies from males reveals that reductions in bone formation are due to a reduction in matrix production and mineralizing activity of osteoblasts (Clarke, 1996; Sibonga,

submitted manuscript). This comparison indicates that both spaceflight and ageing reduce the activity of osteoblasts.

Histomorphometry of iliac crest biopsies of *healthy* individuals substantiates that the leading contributor to age-related bone loss in males is the reduction in bone formation while an increase in bone turnover more likely influences bone loss in the ageing female (Recker, 1988, Clarke, 1996). Post-menopausal women with spinal cord injury had 34% greater index of trabecular separation than pre-menopausal women with spinal cord injury, suggesting interaction between mechanical unloading by paralysis and estrogen insufficiency (Slade, 2005).

This comparison suggests that the system, tissue, and cellular responses to mechanical unloading resemble the combined response of skeletal cells and tissue to involutional bone loss in both sexes, i.e., increased resorption and suppressed formation. Moreover, the effects of menopause may accentuate the effect of mechanical unloading on bone microarchitecture.

V. Computer-based Simulation Information

There is no ethical method of accurately testing the mechanical strength of the skeleton in the human. Hence, estimations of whole bone strength are derived from computer modeling using the 3-dimensional imaging of bone geometry and virtual mechanical loading (Crawford, 2003; Keyak, 2005)

A. Spaceflight Evidence

Computer modeling was conducted on QCT hip scans of 11 long duration crew members (Figure 2-12). A finite element analysis (FEA) had been previously developed from 3-d 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 posterolateral falls) and the axial direction (associated with Stance) (Keyak 2005). This FEA was applied to the QCT scans previously performed in crew members who served on the space station to determine compartmental bone effects (Lang, 2004). The FEA determined a significant reduction in the failure load (i.e., hip strength), after the six-month mission, relative to prelaunch determination.

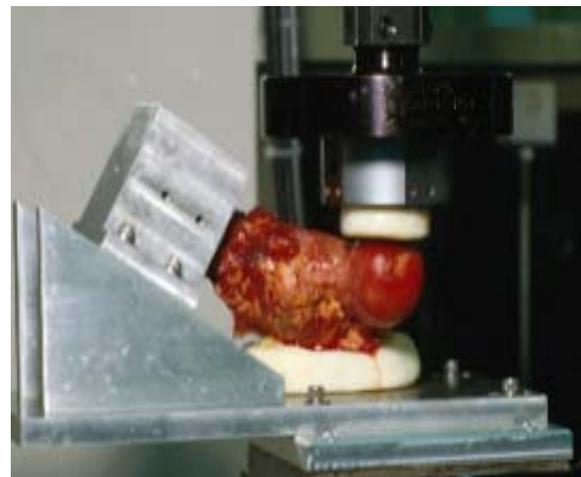
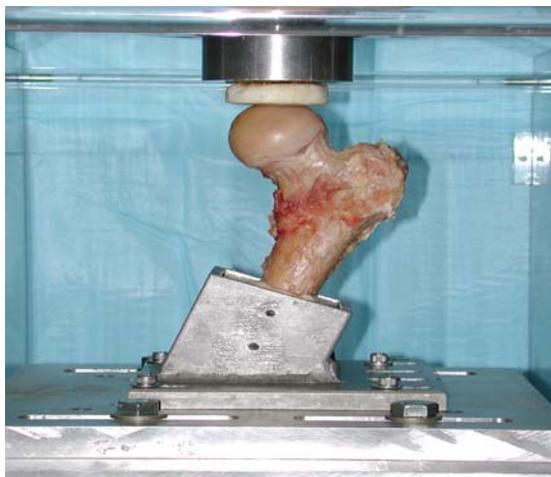


Figure 2-12 a, b. Finite element analysis was applied to estimate mechanical strength of hip as previously validated for two loading conditions: Stance (left image) and fall loads (right image) (Keyak, 2007).

Of the 11 crew members evaluated (Figure 2-13), up to two crew members lost up to 24-30% hip strength for either stance or fall loads. Roughly speaking, when loss of strength was averaged on a monthly basis, there was a two-fold reduction in the median hip strength (Stance loads 2.2%,; fall loads 1.9%) for each one- fold reduction in mean areal BMD (1.2% femoral neck; 1.6% trochanter) (LeBlanc, 2000) Table 2-5.

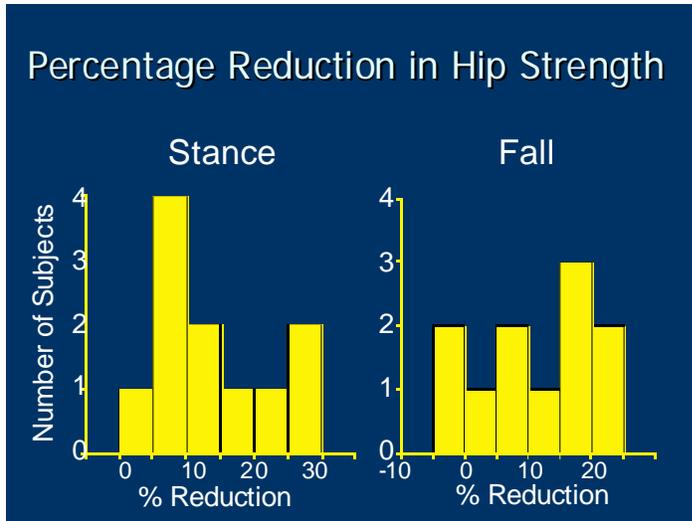


Figure 2-13. Number of crew members per quantified reductions in hip strength. Up to two long-duration crew members experience 20-30% reduction in hip strength for both loading scenarios (Keyak, 2007).

The FEA was applied to QCT scans performed in five crew member subjects 1 year after return 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, 2007). However, QCT does not have the resolution for trabecular microarchitecture and consequently FEA (Keyak, 2005) may underestimate hip bone strength.

Table 2-5. Significant reduction in failure loads of hip after ~6 month spaceflight mission for n= crew members (Keyak, 2007).

Loading Condition	Mean (SD) Preflight	Mean (SD) Postflight	<i>p</i>
Stance	13,200 N (2300 N)	11,200 N (2400 N)	<0.001
fall	2,580 N (560 N)	2,280 N (590 N)	0.003

B. Comparison to Ageing Population

The same FEA was applied in a cross-sectional comparison of hip strength in young vs. elderly women (N=128 postmenopausal [70 – 80 yr] females versus n=30 pre-menopausal [35-45 yr] females). The mean percentage reductions observed with ageing in a cross-sectional study of females was 7% for Stance loads while it was 24% for fall loads (Table 2-6). The median percentage reduction in hip strength for the 11 crew members serving on 6-month flight missions was 13.1% for Stance loads and 13.7% for fall loads.

Table 2-6. Perspectives on hip strength loss (Keyak, 2007).

Loading condition	Lifetime loss in ageing female, mean	Loss after ~6 mo in space, median (range)
Stance	6.9%	13% (4 to 30%)
fall	24.4%	14% (0 to 23%)

This comparison indicates that the reduction in hip strength after 6 months of weightlessness was comparable (~50%) to lifetime reduction in hip strength (for fall loads) in an ageing female. The hip strength of crew members was even “weaker” with the loading in the Stance orientation (compared to elderly females). Just as with the regional losses in BMD during spaceflight, the greater deficit in hip strength occurred at the site within the bone that is weight-bearing on Earth. The hip normally resists and adapts to axial loading while walking and standing on Earth but has fewer opportunities on Earth to adapt to loads incurred with falling.

VI. Exploration Mission Operational Scenarios

How do exploration missions, with the prolonged exposure to hypogravity, relate to the risk for Accelerated Op? As NASA prepares for exploration missions to planetary surfaces, the prolonged transit in weightlessness and the performance of activities in a partial gravity environment are expected to influence the bone mass of the skeleton. However, there is not enough evidence to fully address the occupational hazards of Exploration Missions on the long-term health of the astronaut because the characterization of skeletal adaptation to more than ~6 months of weightlessness (such as with transit) and of skeletal re-adaptation to fractional or 1 G (such as with surface stays) is incomplete.

The evidence in this report centers on how the effects of space compromise the skeleton prior to the diminishing effects of ageing. However, most of this evidence is from DXA scans performed in crew members after serving on space crafts in low earth orbit (~6 months of weightlessness) and monitored over a limited period after return to earth. Full understanding of how skeletal integrity is compromised requires expanded (e.g., bone size, turnover, compartmental BMD) and longitudinal measures of crew members (i.e., during varying degrees of mechanical loading – during and after mission) to characterize the adaptive changes in the skeleton over time. This evaluation not only applies to the skeletal structures but to the regulatory processes for mineral metabolism.

Nevertheless, the skeletal impact of an exploration mission to Mars, for example, can be estimated based on the existing trochanter BMD database after ~6 months in space and ~1 year back on earth. These projections (#1-4) described below are based on a mission scenario of a 6-

month outbound transit, an 18-month surface stay in a fractional earth gravitational field (1/3 G) and a 6-month return transit, as demonstrated in Figure 2-14.

Estimated Average Bone Loss During Long Mars Mission

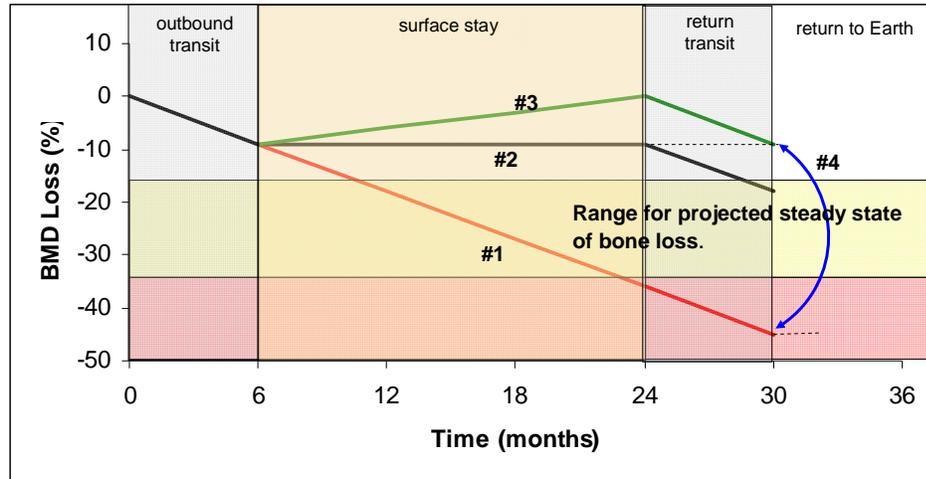


Figure 2-14. Figure of projected BMD changes per Mars mission architecture (adapted from Dr. Bill Paloski, JSC NASA).

1. Bone loss continues at same rate as out-bound transit throughout the entire mission duration with no abatement during fractional G surface stay.
2. Bone loss occurs during out-bound, ceases in fractional G surface stay, and resumes during return transit.
3. Bone loss occurs during out-bound transit, is partially recovered in fractional G surface stay, and resumes during return transit.
4. Bone loss occurs during out-bound transit but plateaus (dashed lines) at some to-be-determined asymptote roughly between 6-36 months after launch (as represented by blue arrow) depending on measured bone index.

The scenarios were formulated with the following presumptions:

1. Losses in trochanter BMD during 6-month transit (outbound and return) would occur at an average 1.5%/month as reported by Lang (2004) where no effective countermeasures for bone loss were available in spite of the provision of mechanical loading by exercise hardware on the International Space Station.
2. Unidentified asymptote occurring anywhere from 6 -36 months after a spinal cord injury depending on bone site and analysis for bone measurement (Minaire, 1974; Chantraine, 1986; Vestergaard, 1998; Lazo MG, 2001; Eser, 2004).

It should be noted that BMD changes with spaceflight and on earth are highly variable and influenced by risk factors for bone loss that are specific to each crew member. These projections

moreover are based on averaged bone loss and not maximal bone loss. There is the presumption that the crew for exploration missions would be selected for minimal bone loss in the mechanically unloaded environment based on exclusion criteria for bone loss risk factors as determined from epidemiological analyses of crew medical data and histories. However, risks should be defined in terms of maximal bone loss to formulate management strategies for the worse-case scenario.

Additionally, it would appear that the high level of uncertainty related to Mars missions is the response of the skeleton in fractional G. However, based on the previous discussions in this report, a greater uncertainty lies with the disruption of trabecular architecture during the 6-month transit under weightless conditions. Larger percentage losses in trabecular bone (Lang 2004) and inability to recover trabecular bone mass with 1 year after return (Lang, unpublished data), suggest that irreversible loss to trabecular connectivity has been induced to cancellous bone microarchitecture. Not only is this disruption to microarchitecture associated with the incidence of fractures (Kleerekoper, 1985) and a reduction in mechanical strength (Silva, 1997; Van der linden, 2001), the recovery of trabecular bone mass with mechanical loading (Tromp 2006; Lai, 2006) or pharmaceutical agents (e.g., Forteo) is yet to be clinically substantiated. Thus, research priorities are directed toward i) developing technologies for use during flight to determine the time course of skeletal changes, ii) evaluating the effects of spaceflight or mechanical unloading on human bone microarchitecture and iii) characterizing the effects of fractional G environment on human physiological systems.

In a recent presentation, Lang (2006) had estimated the Factor of Fracture Risk for crew members on a Mars mission based on scenario #2 and on QCT hip scans of 11 crew members who served on the ISS. Factor of Risk is calculated from the ratio of Applied Load to Bone Failure Load using the estimation of loads reported by Riggs et al (JBMR, 2006). Based on these estimations, Lang calculated a greater than 50% increase in the Factor of Fracture Risk for at least half of the subjects after return to Earth. The averaged Factor of Fracture Risk for returning crew members was comparable to a Factor of Fracture Risk determined for 70-80 year old women in a cross-sectional study. This comparison suggests that long duration spaceflight induces a risk in a middle-aged crew member that is comparable to the risk induced by ageing in females (Lang, 2006).

Finally, the scope of this report does not involve the risk for fracture which is addressed in a separate Evidence Base report. The probability of fracture is also dependent on applied forces -- some of which (i.e., gravitational force) are reduced in space. The definition of osteoporosis, however, is based on an increased risk for fracture under normal loads indicating a severe deterioration of skeletal integrity to reduce Bone Failure Load. Consequently, this report focused on whether the integrity of the skeleton had been irreversibly affected by prolonged exposure to space such that crew members would be at risk for an earlier onset of Op than would be predicted by natural ageing. There are still gaps in the knowledge base to substantiate this risk.

VII. Gaps

Gaps have been described throughout as they appear in the description of the evidence base, but they are relisted here in one section for summary purposes.

Risk of Accelerated Osteoporosis

GAP: An 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 geometry, bone thickness or microarchitecture – indices which influence whole bone strength.

GAP: Longitudinal measures over the lifetime of crew members are not extensively conducted. Cross-sectional comparisons, such as those conducted with the ageing population, are limited in the ability to define patterns of lifetime bone loss for different sites (Melton, 2000) and would not provide meaningful information for the management of astronaut long-term health.

GAP: Impact of spaceflight on balance, coupling and rate of remodeling has not been quantified at the level of the bone remodeling unit.

GAP: The multiple factors (including genetic) that influence the large variability in BMD loss during spaceflight have not been investigated.

GAP: QCT technology does not have the resolution to assess how loss of volumetric BMD in the trabecular compartment affects the microarchitecture. How spaceflight-induced losses in trabecular bone influence trabecular microarchitecture (trabecular thinning or loss of trabecular connectivity) is unknown.

GAP: The timing, extent and variability of volumetric BMD recovery in bone compartments are still not established.

GAP: The impact of multiple long-duration flights on cortical bone thinning and subsequent periosteal expansion is not known.

GAP: With DXA technology, the location (i.e., cortical bone, cancellous bone) of increased BMD is not discernable. Likewise, bone turnover markers are weakly correlated to changes in bone mass. Since changes to bone geometry, bone size and microarchitecture influence whole bone strength, and those measurements have not been fully characterized in crew members, the restoration of whole bone strength with the recovery of BMD is not known. (For further discussion of evidence, see section on Whole Bone Strength).

GAP: The multiple factors that influence the differential rate of BMD recovery after spaceflight have not been assessed.

GAP: There is insufficient power (small n) to evaluate the impact of multiple flights on BMD loss and BMD recovery.

GAP: Data collection is required - longitudinal measures in crew members both preflight and postflight to confirm that selected crew are replete in vitamin D prior to launch and that they are sufficiently supplemented during flight to prevent decrements.

GAP: The efficacy of anti-resorptive agents under weightless conditions of spaceflight has not been validated.

GAP: Validation that suppressing bone demineralization in space will abate the down-regulation of calcium-regulating hormones (and maintain calcium balance) has not been performed.

GAP: The factors or mechanisms, e.g., genetic variability, that contribute to the differential losses of BMD with spaceflight have yet to be identified (a repeat GAP).

GAP: Depressed cellular function and number with spaceflight have not been confirmed in humans immediately after flight or during the postflight period.

GAP: Estimations of whole bone strength for other skeletal sites (arm, wrist, spine) with large n of crew member subjects need to be performed.

GAP: A more complete understanding is still required for how countermeasures - resistive exercise, bisphosphonates, and other bone turnover modulators - may attenuate the aforementioned declines, induced by spaceflight, on bone mineral composition and strength.

VIII. 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 (BMD) during the typical 6-month mission in low earth orbit is 1-2% of the preflight measure. The changes in BMD are specific to regional sites of the skeleton and are highly variable amongst crew members. Geometrical changes in the proximal femur, moreover, have been associated with decrements in hip strength. 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 to manage any associated skeletal health risks by mitigation or treatment.

Substantiating whether spaceflight increases the risk for accelerated osteoporosis ultimately centers around 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 postflight period, then crew members will experience the combined effects of space and of ageing on the skeleton and be theoretically predisposed to an earlier diagnosis of osteoporosis and incidence of 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? Preflight and postflight 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. The time course of bone turnover during spaceflight moreover 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 probability risk assessments for crew members returning from long duration spaceflight missions.

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XI. List of Acronyms

BMD	Bone mineral density
DXA	Dual-energy x-ray absorptiometry
FEA	Finite element analysis
MRI	Magnetic resonance imaging
NTX	N-Telopeptide Cross-Links
Op	Osteoporosis
PTH	Parathyroid hormone
QCT	Quantitative computerized tomography
UV	Ultraviolet
WHO	World Health Organization

Risk of Accelerated Osteoporosis