Space Biomedical Engineering
& Life Support

Bone Mechanics

Bone Changes in Weightlessness

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1. History of Bone Studies in Spaceflight and Earth-based Analogs

Given the right political motivation and an appropriate investment of resources, astronauts could be exploring the surface of Mars as early as 10 years from now. During the 6 to 12 month journey the astronauts could experience bone loss that would put them at serious risk of fracture upon return to a gravitational environment, either on Earth or on Mars. This section explores the history of studies on space flight bone loss and assesses what we know to date about the problem.

1.1 Background

1.1.1 Measurement of bone mineral density

The parameter that is most often used to describe loss of bone mass, stiffness, and strength, is bone mineral density (BMD). This is not a "density" in the traditional engineering sense, that is, total mass divided by volume (gm/cm3), but is instead an "areal density" of mineral mass (gm/cm2). Its value is derived from dual-energy X-ray absorptiometry (DXA), in which a two-dimensional projection of a bone is divided up into regions in which the bone-mineral content (BMC, calculated from the amount of X-ray absorptance) is divided by the projected area of the region to yield the BMD value for that region. This technique has several limitations in terms of assessing the strength of bone. Specifically, by collapsing the bone to two dimensions, information about its three dimensional geometry, and three dimensional density distribution are lost. It is thus difficult to reconstruct an engineering model of the bone that takes into account these three-dimensional attributes. To date, all of the measurements of bone mineral loss in the proximal femora of astronauts (and subjects in Earth-based space flight simulations) have used DXA as the sole imaging technique. To assess strength, the BMD values obtained from DXA are correlated with in vitro mechanical tests of cadaveric femora. Applying more accurate techniques of assessing bone strength, such as the three-dimensional finite element analysis described in this thesis, is greatly hindered in the case of space flight studies due to the absense of three dimensional bone information, such as can be obtained by computed tomography (CT), for instance. Many of the limitations of the work described in this thesis stem directly from this lack of three-dimensional data and it is hoped that future space flight bone studies will fill this information gap.

1.1.2 Bone Loss in Spaceflight and Earth-based Analogs

During space flights lasting longer than one month, astronauts undergo significant losses of bone mass and bone mineral density in the weight bearing areas of the skeleton, particularly the spine and lower limbs, as a result of the unloading produced by weightlessness in the microgravity environment (LeBlanc et al., 1998; Holick, 1998; Vico et al., 1998). Due to the relatively small number of human subjects who have flown in space, the limited duration of missions to date, and the inaccuracy of early measurement techniques, the problem of bone loss during weightlessness is not yet well quantified or well understood. Enough evidence has been gained, however, to raise concern about the risk of fracture, particularly in the hip, during skeletal loading following return to Earth (1 G), during activities on the surface of Mars (3/8 G), or even during strenuous activities performed in weightlessness, such as extravehicular (EVA) construction of the International Space Station (ISS).

The results of studies conducted during the space flights of the 1960's and early 1970's are highly variable due to poor measurement techniques employed in some cases. Following the Gemini 4, 5, and 7 missions, lasting from 4 to 14 days, investigators noticed a distinct increase in calcium excretion (Lutwak, 1966; Whedon et al., 1967) and initially thought that the astronauts had experienced a dramatic 10-20% loss in calcaneus and metacarpal bone density (Mack and Lachance, 1966; Mack et al., 1967). However, through reevaluation, these losses were reduced to about 2-4% for five astronauts and 9% for one astronaut (Vose, 1974). The 18-day Soyuz 9 mission produced a 8-10% decrease in heel bone density for both cosmonauts (Birykov and Krasnykh, 1970). Bone density measurement techniques were improved during the three-man Apollo flights, lasting up to 13 days, but in only one of these flights were investigators able to measure a significant amount of bone loss from the heel (Rambaut et al., 1975).

Studies conducted during the longer-term Skylab, Salyut and Mir space station missions allowed for better measurement of calcium homeostasis and bone density, but were confounded by other factors such as variable compliance with prescribed exercise countermeasures intended to minimize bone loss. Skylab metabolic data indicate that over a three month period, the total negative calcium balance from excess urine and fecal excretion is as much as 25 grams (Rambaut et al., 1979b; Rambaut et al., 1979a), but later estimates reduced this value to 12.8 grams or 1% of the 1250 grams in the average skeleton (Cann, 1993). Reduced losses during the Skylab 4 mission have been attributed to increased exercise by the astronauts. Both US and Soviet investigations estimated that the average bone loss from the calcaneus was 1% per month (Stupakov et al., 1984). A combined US / USSR study of long-term spaceflight, in which quantitative computed tomography (QCT) scans were taken of the spine found no significant loss of density in the vertebral bodies (Oganov et al., 1990), apparently validating the exercise countermeasures. Closer inspection, however, revealed that there was an 8% loss of density in the posterior elements of the vertebrae, which correlated with a 4% loss of volume in the attached muscles, perhaps demonstrating the limited effectiveness of exercise countermeasures in space. Further evidence of this limitation came from QCT scans of one cosmonaut after a 366-day Mir mission, which showed a 10% loss of trabecular bone mass in L1, L2, and L3 vertebrae (Grigoriev et al., 1991). When investigators started looking at other regions in the body, they found even more distressing losses. Most significantly, a quantitative digital radiography (QDR, equivalent to DXA) study of cosmonauts after 4.5—6 month long missions on Mir found bone mineral density (BMD) losses of as much as 14% in the femoral neck and greater trochanter of the hip (Oganov et al., 1992). A study of US astronauts found that even in relatively short flights (1 to 2 weeks), the vertebrae L2-4 could lose as much as 3% of baseline BMD (Miyamoto et al., 1998).

Spaceflight Bone Loss in Humans

Flight / Study	Finding	References
Gemini 4,5, and 7	4-14days; Calcaneus and metacarpal bone density losses of 2-4% for 5	Vose, 1974
Soyuz 9	18 days; 8-10% decrease in calcaneus density for both cosmonauts	Birykov and Krasnykh, 1970
Skylab 2 Mission	No significant bone mineral content changes in arm; calcaneus loss returned to	Rambaut, et al. 1975
Long Term Follow-Up of Skylab Bone	Statistically significant loss of os calcis mineral in nine Skylab crewmembers, 5	Tilton, et al. 1980
Combined U.S. / U.S.S.R Study of Long	QCT of spine; Up to 8 months; No loss in vertebral bodies, but 8% loss in	Oganov, et al. 1990
Mir 366-Day Mission	One cosmonaut averaged 10% loss of trabecular bone from L1, L2, L3; measured by	Grigoriev, et al.
Mir 4.5 - 6 Month Flights	QDR assessment of BMD; total body mineral losses averaged 0.4%; most marked	Oganov, et al. 1992
Mir 1 and 6 Month Flights	pQCT; noticeable loss of trabecular and cortical bone in the tibia after 6 months	Collet, et al. 1997
NASDA Study of 2 NASA Astronauts	42 year old femaleand 32 year old male; short flight; negative calcium balance;	Miyamoto, et al. 1998
of 2 NASA Astronauts	year old male; short flight; negative calcium balance; 3.0% loss of BMD in L2-4	al. 1998

The seriousness of the losses in BMD during spaceflight is evident when compared with the losses attributed to aging. On average, the rate of BMD loss for the proximal femur and lumbar vertebrae in men and women over 55 years of age has been estimated to be around 0.5—1% per year (Burger et al., 1998; Greenspan et al., 1996; Ensrud et al., 1995; Jones et al., 1994). These rates of loss are believed to increase the risk of hip fracture in elderly individuals at the rate of about 4% per year and beyond age 75 the risk of hip fracture increases exponentially. As mentioned above, the rates of loss from the same skeletal areas during spaceflight are about 1 - 2% per month, 10 or more times greater than the rate occurring in normal aging. From another perspective, an estimated loss of 20% in femoral neck BMD during a year of spaceflight would correspond to the average BMD loss in the femoral neck of a woman aging from 50 years to almost 80 years (Looker et al., 1995). While the mechanisms responsible for bone loss in ageing and spaceflight are probably different (LeBlanc and Schneider, 1991), the similarities in the observed changes may be of mutual benefit to the study of either case (Hughes-Fulford, 1991).

Some investigators have used bed rest as an analog for the skeletal unloading experienced in spaceflight. One early study put 90 healthy young men through 5-36 weeks of bed rest and found that not only was there an average 5% loss of calcaneal mineral each month, but that mechanical and biochemical countermeasures were unsuccessful at preventing this loss (Schneider and McDonald, 1984). During another 17 week bed rest study, subjects lost an average of 0.21 +/- 0.05% per week of bone mineral density in the femoral neck, and 0.27 +/- 0.05% per week in the trochanteric area (LeBlanc et al., 1990). Other studies have shown similar mineral losses, slowing of mineralization, and limitations of countermeasures. Some studies have also encountered contradictory results demonstrating the difficulties of bed rest as an analog for spaceflight (Vico et al., 1987; Zaichick and Morukov, 1998). The combined results of space flight and bed rest studies, in terms of measured BMD loss, are summarized in Table 1.1. The last column is a normalized parameter indicating the actual or projected BMD loss per year.

Bedrest / Hypokinesia Studies Models for Weightlessness of Spaceflight

Study	Finding	References
5-36 Weeks Bedrest	90 healthy young men; 5% loss of calcaneal mineral each month; mechanical and biochemical countermeasures not successful	Schneider and McDonald, 1984
120-Day Bedrest	Mineralization rate slowed; contradictory results demonstrate difficulties of bedrest as space analog	Vico, et al. 1987
17-Week Bedrest	6 healthy young males; 6 months of reambulation; BMD % change (p<0.5): femoral neck (FN) -3.6 trochanter (t) -4.6; % /week (p<0.5): FN -.21 +/- .05, T-.27 +/- .05; Reambulation % recovery: FN 0.00 +/- .06, T 0.05 +/- .05 (prox. femur did not recover well)	LeBlanc, et al. 1990
370-Day Antiorthostatic Hypokinesia Test	Highest losses in foot bones; remedial measures delay osteoporosis but do not completely exclude it; results obtained by different methods often conflicting	Zaichick and Morukov, 1998

Results from animal studies of bone mineral loss in spaceflight and immobilization have been highly variable due to differences in study design, duration, and measurement techniques. In addition, much of the variability may be due to the age of the animals, since many of the early studies were carried out on rats that were still growing (less than 5-6 months old). Rats were flown on eight Russian Cosmos biosatellite missions, lasting from 5 days to 22 days, as well as on the US Spacelab 3 mission (7 days). Juvenile male rhesus monkeys were flown on five Cosmos missions and an adult nemestria macaque monkey was flown on an early US mission (Biosatellite 3). Additional studies were carried out on rats and monkeys in various forms of suspension and hypokinesia. Bone formation was found to be reduced in the metaphyses of long bones during the first Cosmos mission (Yagodovsky et al., 1976). The Cosmos 782 and 936 missions resulted in a 40% reduction in the length of the primary spongiosa (Asling, 1978) and a 30% decrease in the femoral breaking strength (Spector et al., 1983). In addition, these missions revealed that an arrest line separating normal bone from defective and hypomineralized bone formed during spaceflight (Turner et al., 1985) and that osteoblast differentiation in non-weight bearing bones was suppressed during weightlessness (Roberts et al., 1981), thus yielding evidence that other bones in the body might be affected in long term flight. Rats flown for 5 days aboard the Cosmos 1514 biologic satellite incurred no measurable change in bone mass (Vico et al., 1987), while calcium excretion studies on monkeys on the same flight showed evidence of increased resorption (Cann et al., 1986). After the slightly longer Cosmos 1667 mission, the flight rats showed a greater loss of trabecular bone in the proximal metaphyses of the tibia than rats undergoing tail suspension for the same duration on earth (Kaplansky et al., 1987; Vico et al., 1991). Rats undergoing tail suspension of their hindlimbs for 15 days showed reductions in calcium content to 86.2 ± 2.5% for the tibia, and 75.5 ± 3.5% for vertebrae (Globus et al., 1984), while those exposed to hypokinesia and head-down suspension for periods of 35 to 60 days exhibited osteoporosis in the tibial and vertebral spongiosa (Durnova et al., 1986). Other tail suspension studies revealed a reduction of osteoblast number and growth and mineralization rates in the unloaded bones (Morey-Holton and Globus, 1998). Rhesus monkeys flown for 13 days on Cosmos 1887 and 2044, and 11.5 days aboard Cosmos 2229, showed reduced bone mineralization and growth and a significant decrease in whole body bone mineral content (BMC), with only partial recovery by one month post-flight (Cann et al., 1990; Zerath et al., 1996). In addition, during the Cosmos 2044 mission it was shown that the fracture repair process was impaired in rats (Kaplansky et al., 1991).

Spaceflight Bone Loss in Animals

Flight / Study	Finding	References
Cosmos 605	Rats; Bone formation reduced in metaphyses of long bones	Yagodovsky, et al. 1976
Cosmos 782	Rats; 40% reduction in length of primary spongiosa due to reduced formation and increased resorption	Asling, 1978
Cosmos 782?	Rats; Osteoblast differentiation in non-weight-bearing site suppressed during weightlessness	Roberts, 1981
Cosmos 936	Rats; 30% decrease in femoral breaking strength of femora with recovery of	Spector, et al. 1983
Cosmos 782 & 936	Rats; Arrest line separating bone formed during and post-spaceflight; defective and hypomineralized bone	Tumer, et al. 1985
Rat Tail Suspension, 1984	Up to 15 days; Calcium content: tibia = 86.2 +/- 2.5%, vertebra = 75.5 +/- 3.5% of control	Globus, et al. 1984
Cosmos 1514	Primates; 5 days; resorption increased during flight	Cann, et al. 1986
Cosmos 1667, 1887, 2044	Primates; 13 days; lower mineralization rate and less bone mineralized; longitudinal growth slowed	Cann, et al. 1990
Cosmos 1667	Rats; 7 day spaceflight vs. 7 day tail-suspension; loss of trabecular bone in prox tibial	Vico, et al. 1991
Cosmos 2044	Rats; fracture repair process impaired during flight	Kaplansky, et al. 1991

Cosmos 2229	Primates; 11.5 days, tendency toward decreased BMC during flight; only partial recovery 1 month after	Zerath, et al. 1996
Rat-Tail Suspension 1998	Unloaded bones display reduced osteoblast number, growth, and mineralization rate in trabecular bone	Morey-Holton and Globus, 1998

1.1.3 Summary of findings from spaceflight and immobilization studies

The findings of these spaceflight and immobilization studies, conducted over the past 35 years, may be summarized as follows:

- Significant bone loss occurs in humans and animals exposed to weightlessness during spaceflight
- Urine and fecal calcium excretion is increased resulting in a negative calcium balance

  – Calcium resorption from bone is increased and absorption from gut is decreased

- Bone mineral density decreases

  – Critical weight-bearing areas lose density most rapidly and the rate of loss is approximately 1-2% per month

  – Non-weight-bearing areas are affected in the long term

- Osteoblast proliferation and activity are reduced while osteoclast activity either remains the same or increases slightly
- Bone growth is slowed
- Fracture repair is impaired
- Bone strength is reduced

1.2 Significance

Several conclusions may be drawn regarding the significance of these skeletal changes in terms of human spaceflight.

- Astronauts and cosmonauts spending a significant period in weightlessness (> 1 month) will experience a loss of bone strength and a subsequent increase in fracture risk during:

  – Activities on Earth (walking / running, falls)

  – Intravehicular / extravehicular activity (IVA / EVA) on Mars or in weightlessness

- A fracture occurring on Mars (3/8 G) has serious consequences to the individual and crew due to:

  – remoteness (limited medical resources)

  – possible inhibition of fracture repair and immune respones associated with weightlessness

  – loss of functionality in terms of the crew member's skills and duties (increased workload on remaining crew members)

To date, hip fracture has risk has generally been estimated based on correlations between bone mineral density (BMD) and failure load for a given loading condition (usually associated with an specific activity, including traumatic activities such as falls). In the vast majority of cases, the failure load in this context is obtained through mechanical testing of cadaveric femora. Thus, while BMD correlates reasonably well with bone strength in vitro, actual fracture risk is harder to calculate due to in vivo factors (e.g. body mass). Consequently, there exists a need to better assess the in vivo fracture risk for astronauts performing normal and traumatic activities following a significant period of weightlessness (i.e., more than a month).

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