Adaptation of the Skeletal System During Long-duration Space Flight

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Evidence from crew members who flew on space missions longer than 90 days suggests that adaptations of the skeletal system to mechanical unloading may predispose these crew members to an accelerated onset of osteoporosis after they return to Earth. By definition, osteoporosis is a skeletal disorder that is characterized by low bone mineral density and structural deterioration. It reduces the ability of bones to resist fracture under the loading of normal daily activities. Age-related osteoporosis is readily recognized as a syndrome afflicting the elderly because the insipid and asymptomatic nature of bone loss does not typically manifest as fractures until after approximately age 60. This review draws parallels between the rapid and earlier bone loss in females that occurs with menopause and the rapid bone loss in middle-aged crew members that occurs with space flight unloading, and how the cumulative effects of space flight and aging could be detrimental, particularly if skeletal effects are totally or partially irreversible.

On Earth, the adult human skeleton renews and repairs itself with approximately one-tenth renewed annually. The putative osteocytic cells signal the skeleton to initiate remodeling in discrete packets. In a well-orchestrated manner, bone-resorbing cells (osteoclasts) remove bone tissue while bone-forming cells (osteoblasts) replace it. When remodeling is accelerated, as occurs 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 aging female. 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., the trabecular or spongy bone) in which resorption preferentially occurs along the bone surfaces adjacent to bone marrow. This mechanism of bone loss leads to: (1) thinning of the cortical bone shell and the trabecular plates; (2) perforation of trabecular struts; and (3) loss of trabecular elements and connectivity. With menopause, there is a 20% to 30% reduction in cancellous bone compared to the 5% to 10% loss of cortical bone associated with the first decade after menopause. This bone loss accounts for a higher incidence of fractures in women (compared to men of the same age range) at skeletal sites predominantly composed of cancellous bone (i.e., wrist fractures and vertebral crush fractures). Increased remodeling can also be inferred by increased levels of biomarkers for bone formation and bone resorption.

The application of quantitative computed tomography [QCT] to a population study substantiated the earlier and persistent losses in cancellous bone occurring in both men and women (~33% and 50% of total lifetime loss, respectively). Likewise, substantial losses in cortical bone in women begin around midlife with menopause onset, while cortical bone loss in men does not accelerate until much later. Not only do women have smaller bones than men 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 space-flight-induced bone loss is limited in comparison to what is known about either the pathophysiology of primary osteoporosis or the cellular mechanisms of secondary osteoporosis in terrestrial populations. Space flight missions do not typically provide controllable experimental conditions that permit 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. Nevertheless, the limited data from space flight can be evaluated in the context of the extensive knowledge base for terrestrial osteoporosis.

We analyzed the perturbations in calcium homeostasis and bone remodeling detected with short-duration space flights (<90 days as defined herein, but typically <2 to 3 weeks based on mission durations) and the measurable decrements in bone mineral densities and bone structure in

"long-duration" crew members after space flight exposures of typically approximately 4 to 6 months (Tables 1 and 2).

Crew members exposed to the weightlessness of space for a typical long-duration (i.e., 4- to 6-month) mission on the Russian Space Station *Mir* or the International Space Station (ISS)

1) Display bone resorption that is aggressive, targets normally weight-bearing skeletal sites, is uncoupled to bone formation, and results in areal bone mineral density (BMD) deficits that can range between 6% and 20% of pre-flight BMD.

2) Exhibit compartment-specific declines in volumetric BMD in the proximal femur (a skeletal site of clinical interest) that significantly reduce its compressive and bending strength, and that 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 space flight exposure, but for which the restoration of whole bone strength remains an open issue and may involve structural alteration.

4) Present risk factors for bone loss – e.g., 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 (an inability to provide essential nutrients and vitamins).

Substantiating whether space flight increases the risk for accelerated osteoporosis ultimately centers on determining whether space-flight-induced skeletal changes are irreversible after a crew returns to Earth. If space-flight-induced bone loss is not restored and decrements in whole bone strength are not recovered in the post-flight period, crew members will experience the combined effects of space and aging on the skeleton, and will 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 space flight will be compounded by bone loss with menopause.

What determines whether bone loss and whole bone strength are restored? Pre- and post-flight measurements of bone 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. Longitudinal measures during the post-career lifetime of a crew member should also be conducted. Moreover, understanding the time course of bone turnover during space flight will improve our ability to evaluate the risk of longer exposures to skeletal integrity and its impact on recovery after a crew member returns to Earth. These additional indices will enhance the probabilistic risk assessments for crew members who are returning from long-duration space flight missions.

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. *BMD and body composition after 4 to 14.4 months of space flight.*

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. *QCT changes in volumetric BMD in 14 ISS crew members (% per month + SD [standard deviation]).*

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