Bone Loss during Spaceflight: Available Models and Counter-Measures

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There is ongoing concern for human health during spaceflights. Of particular interest is the uncoupling of bone remodeling and its resultant effect on calcium metabolism and bone loss. The calculated average loss of bone mineral density (BMD) is approximately 1-1.5% per month of spaceflight. The effect of decreased BMD on associated fractures in astronauts is not known. Currently on the International Space Station (ISS), bone loss is managed through dietary supplements and modifications and resistance exercise regimen. As the duration of space flights increases, a review of the current methods available for the prevention of bone loss is warranted. The goal of this project is to review and summarize recent studies that have focused on maintaining BMD during exposure to microgravity. Interventions were divided into physical (Table 1), nutritional (Table 2), or pharmacologic (Table 3) categories. Physical modalities included resistance exercise, low level vibration, and low intensity pulsed ultrasound. Nutritional interventions included altering protein, salt, and fat intake; and vitamin D supplementation. Pharmacologic interventions included the use of bisphosphonates and beta blockers. Studies reported outcomes based on bone density determined by DXA bone scan, micro-architecture of histology and microCT, and serum and urine markers of bone turnover. The ground analog models utilized to approximate osseous physiology in microgravity included human patients previously paralyzed or subjects confined to bedrest. Ground analog animal models include paralysis, immobilization and ovariectomies. As a result of the extensive research performed there is a multi-modality approach available for the management of BMD during spaceflight that includes resistance training, nutrition and dietary supplements. However, there is a paucity of literature describing a formalized tiered protocol to guide investigators through the progression from animal models to human patient ground analogs to experiments on the ISS. With regards to testing, further evaluation to determine the association between non-invasive tests and fracture during and after spaceflight needs to be performed.

Physical Interventions					
Intervention	**Reference**	**Model**	**Number of Partcipipants**	**Outcome Measures**	**Results**
Resistance Exercise	Shackelford *et al*., 2004	Human Bed Rest	5 male, 4 female	Serum Markers	Resistance training exercise associated with increased bone turnover and formation markers vs control showing increase in resorption only
Low Level Vibration	Rubin *et al*., 2004	Human Post Menopausal	70 female	DXA	Intention-to-treat showed no change, however increased compliance associated with protective effect
LIPUS	Ferreri *et al*., 2011	Ovariectomized Rats	6 Groups of 5 animals each	MicroCT, FEA, Histology	Local improvement in microstructure, modulus of elasticity, strength, and bone volume with 100 mW/cm^2

Table 1. Studies examining physical interventions for the management of BMD. DXA = DXA Bone Scan, FEA = Finite Element Analysis, LIPUS = Low Intensity Pulsed Ultrasound

Nutritional Interventions					
Intervention	**Reference**	**Model**	**Number of Partcipipants**	**Marker**	**Results**
Decrease Sulfur containing Amino Acids	Breslau	Human Ambulatory	15 healthy Individuals	Urine and Serum Markers	Increased sulfur containing amino acids associated with increased urince calcium
Limit NaCl intake	Buehlmeier *et al*., 2012	Human Ambulatory	8 healthy male	Urine and Serum Markers	Increased NaCl intake associated with increase in urine calcium excreted and NTX; counteracted with Potassium Bicarbonate
Omega-3-Fatty Acids	Zwart *et al*., 2010	Bedrest, Short-duration Space Flight, Long Duration Space Flight	10 Short Duration, 24 Long Duration, 16 Bedrest	Serum Markers	Increased fish intake assocaited with less bone loss in space
Vitamin D	Izawa *et al*., 1981	Immobilized Rats	48 animals	Bone length, Cortical thickness, Calcified bone mass	After 6 weeks Vitamin D analogs diminished the effect of immobilization in the development of osteoporosis

Table 2. Studies examining nutritional interventions for the management of BMD

Pharmacologic Interventions					
Intervention	**Reference**	**Model**	**Number of Partcipipants**	**Marker**	**Results**
Bisphosphonates: Aldendronate	LeBlanc *et al*., 2002	Human Bedrest	21 males	DXA, Serum Markers	Alendronate 70mg weekly showed positive effect of BMD
Bisphosphonates: Zoledronic Acid	Shapiro *et al*., 2004	Spinal Cord Injury Patients	15 patients	DXA	Single infusion of Zoledronic acid associated with protective effect on hip at 10 weeks
Bisphosphonates: Pamidronate	Watanabe *et al*., 2004	Human Bedrest	25 males	DXA, Serum Markers	Pamidronate vs Exercise vs Bedrest: Exercise increased bone formation, did not prevent bone loss; Pamidronate prevented bone loss
Propanolol	Khajuria *et al*., 2013	Immobilized Rats	5 groups of 6 animals each	Bone Porosity, Mechanical Properties, Electron Microscopy	Propanolol was comparable to Zoledronic acid and Alfacalcidol in regards to bone porosity, mechanical properties, and cortical microarchitecture

Table 3. Studies examining pharmacologic interventions for the management of BMD