Fiscal Year:	FY 2012	**Task Last Updated:**	FY 12/09/2011
PI Name:	Bajaj, Devendra Ph.D.		
Project Title:	Pharmaceutical Countermeasure Effects on Tissue-Level Quality of Immobilized Bone		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Musculoskeletal Alterations Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Bone Fracture**:Risk of Bone Fracture due to Spaceflight-induced Changes to Bone (2) **Osteo**:Risk Of Early Onset Osteoporosis Due To Spaceflight		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	07103-2785	**Congressional District:**	10
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2010 NSBRI-RFA-10-01 Postdoctoral Fellowships
Start Date:	11/01/2010	**End Date:**	11/30/2012
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	1	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: change in end date to 11/30/2012 per NSBRI; previously 10/31/2012 (Ed., 6/11/2012)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Fritton, James (MENTOR/University of Medicine and Dentistry of New Jersey)		
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Task Description:	POSTDOCTORAL FELLOWSHIP Introduction: Astronauts suffer from rapid bone loss due to disuse in microgravity. Recovery of such bone loss requires substantial rehabilitation on return to earth's gravity. Bisphosphonate drugs are being considered as potential countermeasures to suppress bone loss in microgravity and therefore, expedite recovery on earth. However, there are concerns over long-term safety of the drug and its effects on bone fragility. In this project we are investigating whether risedronate (RIS), a bone anti-resorptive (bisphosphonate) treatment, given during a long-term (6 months) limb immobilization in an animal model would 1) slow bone loss, 2) enhance the recovery by restoration of mechanical usage with remobilization (for 12 months), and 3) maintain the tissue-level mechanical properties. The project aims are: 1) Characterize tissue-level material properties (microdamage, mineralization, fatigue life and fatigue crack growth resistance) in the distal forelimb (radius) to determine how immobilization without pharmaceutical intervention (vehicle control) and with risedronate modify cortical bone tissue's resistance to fatigue and fragility fracture. 2) Characterize tissue-level material properties to determine how remobilization, with or without previous risedronate treatment, modifies cortical bone tissue's resistance to fatigue and fragility fracture. Key Findings: Results obtained thus far suggest that RIS-treatment slows bone loss during long-term immobilization (IM), and also allows for better recovery during remobilization (RM). However, 12 month RM may be insufficient for complete recovery of trabecular bone lost during IM. On the contrary, 12 month RM was sufficient to restore cortical width by new bone formation in the marrow cavity. Immobilization also resulted in an increase in cortical bone porosity, which regardless of RIS-treatment and RM remained significantly elevated compared to control. The deleterious effects of this cortical bone loss during IM were most evident by decreased strength, stiffness and toughness. However, RIS-treatment during IM preserved tissue-level mechanical properties and RM completely restored cortical bone stiffness. RM also resulted in partial recovery of strength at least in the strongest structural orientation (i.e. stress applied perpendicular to bone length). However, RM of previously RIS-treated bone resulted in a significant reduction in toughness versus control (-30% to -40%). Overall, RIS-treatment during immobilization preserved bone and tissue-level mechanical properties. However, restoration of mechanical usage by remobilization reduced the cortical bone toughness. Current work is quantifying the extent of microdamage accumulation and the mechanical properties of cortical bone beams under fatigue loading. This investigation has allowed for measurement of changes in tissue-level mechanical properties of immobilized bone treated with risedronate and subsequent remobilization. The outcomes thus far have shown the benefit of RIS in slowing bone loss during long-term IM and thus highlight potential benefits over long duration space flights. However, reduction in tissue-level toughness may point to an increase in susceptibility towards crack propagation with RIS and RM, is a concern, and requires further investigation. This work will be carried out in the subsequent aim (year-2) of this study.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Bisphosphonates, including alendronate and risedronate are used to treat osteoporosis and offer attractive countermeasures to prevent bone loss in space. However, bisphosphonates reduce the tissue remodeling capacity of bone and this may result in increased accumulation of flaws in the form of microdamage. Consequently, there are concerns over the long-term safety of bisphosphonates as unrepaired flaws can propagate through fatigue, a process of progressive degradation that results from cyclic loading, and can lead to fractures. As such, results thus far have indicated a decrease in toughness with Risedronate treatment and remobilization. Completion of this investigation will allow for a proper risk-to-benefit clinical comparison of bisphosphonate. The final outcomes of this investigation are expected to help put an end to the debate over the long-term safety of bisphosphonates and the implications for bone fragility.
Task Progress:	MicroCT: Bone loss due to IM adversely affected cortical and trabecular morphology. As a percentage loss within bone type, loss was greatest in the trabeculae where, compared to control, bone volume (BV) was reduced by over 60% as a result of 28% thinner trabeculae (Tb.Th) and complete loss of trabeculae; trabecular separation (Tb.Sp) was 25% greater. Cortical area (Ct.Ar) was reduced by 22% as a result of periosteal bone loss that reduced cortical width (Ct.Wi) by 18%. RIS was effective in slowing bone loss. Nonetheless, trabecular BV diminished by 38% during IM with RIS treatment. RM of previously Veh- or RIS-treated bone restored trabecular BV to within 35% of control. While Ct.Wi recovered completely with RM of previously RIS-treated bone, Ct.Ar and polar moment of inertia did not, indicating that most bone was added by endosteal infilling of the marrow space. This is supported by a smaller Ma.Ar. Reflecting the greater bone turnover of trabeculae, tissue mineral density (Tb.TMD) was 10% less after IM and Ct.TMD was not affected by any treatment. Deficits in Tb.TMD were partially prevented with RIS and partially recovered with RM to within 5% of control. Increased bone resorption due to IM also increased cortical tissue porosity by 40% over control. RIS treatment did not prevent the increased porosity which continued to be greater than control by 37 - 58% with all treatments. The effects of increased porosity on whole-bone mechanical behavior could be partially compensated by new bone formation in the marrow cavity with RIS and RM. Monotonic Testing: A total of 60 beams were prepared and tested under monotonic bending in two different orientations. IM resulted in an approximately 10% decreased E. RIS maintained E in both orientations. RM of the previously Veh-treated bone partially recovered E in the stronger orientation. However, RM of previously RIS-treated bones completely restored the stiffness in both orientations. Similarly, IM also resulted in decreased strength in both orientations and RIS treatment maintained strength in both orientations. Surprisingly, in the weaker orientation, RM of previously Veh-treated bone did not recover strength and for RIS-treated bone, RM resulted in decreased strength. The most significant changes were observed in the energy required to fracture, an apparent measure of toughness. IM resulted in greater than 25% reductions in toughness in both orientations. Similar to strength and stiffness, RIS treatment maintained toughness in both orientations. In the stronger orientation, RM of the Veh-treated bone recovered toughness to within 10% of control. However, in both orientations RM of RIS-treated bone resulted in an approximately 30% reduction in toughness compared to control. This was largely attributed to a reduction in post-yield deflection in both orientations, indicating an increased brittleness of the cortical tissue with RM after RIS-treatment.
Bibliography Type:	Description: (Last Updated: 10/30/2019)