Fiscal Year:	FY 2013	**Task Last Updated:**	FY 09/18/2013
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:	12/01/2010	**End Date:**	05/31/2013
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	2	**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: End date change to 5/31/2013 per NSBRI (Ed., 5/31/13) NOTE: NSBRI data submission 1/2013 has new start/end dates--now 12/1/2010-11/30/2013 (Ed., 1/15/2013) 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)		
Grant/Contract No.:	NCC 9-58-PF02304		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

POSTDOCTORAL FELLOWSHIP
SUPPLEMENTAL REPORTING SEPTEMBER 2013:

Reduced mechanical loading during bed rest or spaceflight produces rapid and severe bone loss. Recovery of this bone loss requires re-loading for at least twice the reduced loading period. One strategy for enhancing recovery with re-loading is to mitigate the initial osteopenia with a bisphosphonate treatment that suppresses bone resorption in postmenopausal osteoporosis. However, bisphosphonates also suppress bone tissue repair. This can lead to microdamage accumulation and degrade the tissue-level mechanical properties important to fatigue and fracture resistance. This project investigated whether the bisphosphonate risedronate (RIS) administered during long-term limb immobilization (IM) in an animal model would slow cortical bone loss, allowing enhanced recovery and maintenance of tissue-level mechanical properties upon remobilization (RM).

Tissue-level mechanical properties were measured on machined specimens under static and dynamic loads. Tissue-level mechanical properties were decreased and the sensitivity to fatigue crack propagation increased, compared to control. Toughness was positively correlated with post-yield, i.e. plastic strain to failure. The apparent decrease in tissue-level toughness was substantiated by observations of relatively smooth fracture surfaces and increased microcrack density in the IM bones versus control. RIS treatment during IM was effective in partially preserving bone mass by suppressing turnover. At the tissue-level, RIS completely preserved toughness, fatigue life and sensitivity to fatigue crack propagation at control levels. Combined, these results suggested that RIS given during long-term IM slowed bone loss and maintained tissue-level mechanical properties. Twelve-months of RM did not recover cortical bone morphology in the non-drug treated group. At the tissue-level, RM did not recover fatigue-life and partially recovered toughness, mainly due to increased post-yield strain to failure. In comparison, RM in the previously RIS-treated group completely recovered cortical area and width, primarily by endosteal infilling of the marrow space. However, RM of previously drug-treated bone dramatically affected the tissue-level mechanical properties. Reduced toughness and fatigue life, and increased sensitivity to fatigue crack propagation, were all significant versus control.

This investigation measured changes in tissue-level mechanical properties of IM bone treated with RIS and subsequent RM. The benefit of RIS is in slowing bone loss during long-term IM. There are potential benefits over long duration space flights. However, reduction in tissue-level mechanical properties with RIS treatment followed by RM, point to an increase in susceptibility towards crack propagation. This is a concern, and should be considered in the optimization of bone loss mitigation and post-flight recovery regimens.

REPORTING JANUARY 2013:

Astronauts suffer from rapid bone loss due to disuse in microgravity, which requires substantial rehabilitation on return to Earth's gravity. Bisphosphonate drugs can suppress disuse-related bone loss, and therefore, expedite recovery on Earth. However, there are safety concerns over recent reports of atypical' fractures in patients on long-term (>5 years) bisphosphonate treatment. Therefore, the effects of bisphosphonates on the tissue-level properties of bone during immobilization and with restoration of mechanical usage need further investigation. In this project, we are investigating whether risedronate (RIS), a bisphosphonate treatment, given during a long-term (6 months) limb immobilization (IM) in an animal model would 1) slow bone loss, 2) enhance the recovery with remobilization (RM, 12 months), and 3) maintain the tissue-level mechanical properties.

Aim 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 (saline control) and with risedronate modify cortical bone tissue's resistance to fatigue and fragility fracture.

Aim 2. Characterize tissue-level material properties to determine how remobilization and the discontinuation of risedronate treatment modify cortical bone tissue's resistance to fatigue and fragility fracture.

Key findings: In year-1, we showed that 6-month IM resulted in significant bone loss at rate equivalent to 1% per month. RIS treatment slowed bone loss during IM and allowed better recovery with RM, especially for cortical bone, which was completely recovered at the end of 12-month RM. IM also decreased tissue-level mechanical properties, including strength, stiffness and toughness, which were preserved with RIS treatment. RM of previously RIS-treated bone completely recovered strength and stiffness but significantly reduced toughness (-29%) versus control. Fatigue studies conducted in year-2 showed that IM markedly decreased the fatigue-life i.e., cycles to failure (Nf) of cortical bone compared to control. In comparison, RIS-treatment during IM maintained fatigue-life, which decreased with RM, regardless of drug treatment. Fractographic analysis of beams showed tissue-level embrittlement for all treatment groups, which was evident from the relative differences in fracture surface roughness. Control beams exhibited greater surface roughness compared to treated groups, indicating treatment-related suppression of mechanisms that promote toughness and resistance against crack extension. Crack propagation studies are underway to further quantify and compare sensitivity to crack growth and rate of crack growth. Examination of tissue-level microarchitecture showed decreased osteonal composition in IM bone, regardless of bisphosphonate treatment (-25% versus control). However, the osteonal composition was completely recovered with RM of previously RIS-treated bones. Based on these observations, a 3rd year of funding has been secured to quantify ceullar activity and indices of bone turnover and bone formation. This work will be carried out in the subsequent aim (year-3) of this study and provide further insights into the relationships between tissue-level mechanical properties, microarchitecture, and turnover.

Aim 3. Characterize bone formation parameters, using dynamic histomorphometry, and micro-architecture, using histology, to determine how risedronate treatment during immobilization and recovery with remobilization influence the cellular activity.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:	SUPPLEMENTAL REPORTING SEPTEMBER 2013: Bisphosphonates are the most prescribed treatment for osteoporosis and offer attractive countermeasures to prevent bone loss during bed rest or space flight. However, there are concerns over recent reports of low-energy (atypical) fractures in patients on long-term bisphosphonate therapy. Results from this investigation have indicated that a bisphosphonate treatment is effective in preventing bone loss and preserving tissue-level mechanical properties during disuse. However, remobilization of drug-treated cortical tissue increases fragility under both sustained and cyclic loading conditions. This investigation has quantified, in an animal model, some of the major risks and benefits for bisphosphonates when used to combat the disuse osteoporosis experience by astronauts. The results should give guidance in properly assessing the risk-to-benefit of their clinical use for spaceflight. REPORTING JANUARY 2013: The significant bone loss that occurs with bed rest after disability increases the risks of fracture and death. Improving therapy for these patients and for astronauts who also experience this type of disuse osteoporosis during space flight deserves greater study. Results obtained thus far clearly show that treatment with a high-dose of bisphosphonate attenuates bone loss during long-term disuse. However, the current study further demonstrates that the combination of RIS treatment and recovery with remobilization may increase cortical bone fragility due to decreased toughness and fatigue-life. Completion of this investigation will allow for a proper risk-to-benefit clinical comparison of bisphosphonate therapy for use on Earth and beyond.
Task Progress:	SUPPLEMENTAL REPORTING SEPTEMBER 2013: All proposed aims and activities have been completed. REPORTING JANUARY 2013: Micro-damage Analysis (in-progress): After mechanical testing, one half of each fractured beam was bulk stained in 1% basic fuchsin and embedded in polymethy-methacrylate (PMMA) using standard staining and embedding protocols. The plastic blocks were then cut to obtain 200 µm thick sections, transverse to the beam length. The sections were grounded to approximately 70 µm thickness, fine polished using alumina slurries (particle diameters 1.0 µm and 0.05 µm) on cloth wheel and mounted on plastic slides for imaging. Beam cross-sections were then imaged under an optical microscope (AxioImager, Carl Zeiss) equipped with a multichannel fluorescence acquisition system (Axiovision, Zeiss). Sections (n=3/beam) from the fracture edge were used to quantify load-induced damage. Preliminary results obtained from monotonically tested beams show evidence of micro-cracks ranging from 30 to 70 µm in length with smaller cracks observed in the drug treated groups and at lower density. Work is underway to correlate toughness and fatigue-life with extent of microdamage in beams. Fatigue Crack Growth (in-progress): Miniature compact tension (CT) specimens (6x4x1 mm3) were prepared from the posterior cortex of the radius using slicing equipment (Buehler, Isomet 5000). The specimen also comprised of a sharp notch and two precision holes to mount the specimen on a set of loading fixtures using stainless steel pins. Specimens are prepared such that the direction of crack extension is parallel to the long-axis of the osteons. A special setup was designed to monitor crack length, comprised of a fixed lens (200X) digital microscope (ProScope HR) that is attached to a manual XYZ translation stage for accurate positioning of the microscope. The entire assembly is mounted on an aluminum base plate attached to a microscope boom. Crack growth is conducted under cyclic fatigue at a frequency of 5 Hz and a stress ratio (R=smin/smax) of 0.1. The specimen geometry and crack length are used to calculate stress intensity distribution around the crack tip and the results are modeled according to Paris' Law, da/dN=C(delta K)m, where da/dN = rate of crack growth, delta K = stress intensity range, C = crack growth coefficient and m = crack growth exponent (brittleness index). Experiments are currently underway to quantify and compare m and C between all groups.
Bibliography Type:	Description: (Last Updated: 10/30/2019)
Abstracts for Journals and Proceedings	Bajaj D, Belman R, Fritton JC. "Evaluation of spatial variation in tissue-level mechanical properties of small animal cortical bone under diametral compression." Orthopaedic Research Society Annual Meeting 2012, San Francisco, CA, February 4–7, 2012. Orthopaedic Research Society Annual Meeting 2012, San Francisco, CA, February 4–7, 2012. Poster 0359. , Feb-2012
Abstracts for Journals and Proceedings	Bajaj D, Palacio-Mancheno PE, Patel M, Reyes G, Cardoso L, Schaffler MB, Fritton JC. "Remobilization following anti-resorptive treatment with risedronate decreases cortical tissue toughness." First Annual Musculoskeletal Repair and Regeneration Symposium, Albert Einstein College of Medicine, Bronx, NY, October 4, 2012. First Annual Musculoskeletal Repair and Regeneration Symposium, Albert Einstein College of Medicine, Bronx, NY, October 4, 2012. , Oct-2012
Abstracts for Journals and Proceedings	Bajaj D, Palacio-Mancheno PE, Schaffler MB, Cardoso L, Fritton JC. "Effects of bisphosphonate treatment and remobilization on the tissue-level quality of immobilized bone." 2012 NASA Human Research Program Investigators' Workshop, Houston, TX, February 14-16, 2012. 2012 NASA Human Research Program Investigators' Workshop, Houston, TX, February 14-16, 2012. , Feb-2012
Abstracts for Journals and Proceedings	Geissler JR, Bajaj D, Allen MR, Burr DB, Fritton JC. "Alendronate treatment elicits a reduction in fatigue-life of canine cortical bone." Orthopaedic Research Society Annual Meeting 2012, San Francisco, CA, February 4–7, 2012. Orthopaedic Research Society Annual Meeting 2012, San Francisco, CA, February 4–7, 2012. Abstract #0089, , Feb-2012
Abstracts for Journals and Proceedings	Bajaj D, Patel P, Schaffler MB, Fritton JC. "Cortical bone structure is completely recovered with remobilization after risedronate treatment while tissue-level cyclic fatigue life is not." 2013 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-14, 2013. 2013 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-14, 2013. , Feb-2013
Abstracts for Journals and Proceedings	Bajaj D, Palacio-Mancheno PE, Patel M, Reyes G, Cardoso L, Schaffler MB, Fritton JC. "Decreased Cortical Tissue Toughness Upon Remobilization after Anti-Resorptive Treatment with Risedronate." Orthopaedic Research Society Annual Meeting 2013, San Antonio, TX, January 26-29, 2013. Orthopaedic Research Society Annual Meeting 2013, San Antonio, TX, January 26-29, 2013. Poster 0693. , Jan-2013

Articles in Peer-reviewed Journals	Bajaj D, Geissler JR, Allen MR, Burr DB, Fritton JC. "The resistance of cortical bone tissue to failure under cyclic loading is reduced with alendronate." Bone. 2014 Jul;64:57-64. Epub 2014 Apr 1. http://dx.doi.org/10.1016/j.bone.2014.03.045 ; PubMed PMID: 24704262; PubMed Central PMCID: PMC4041841 , Jul-2014
Articles in Peer-reviewed Journals	Geissler JR, Bajaj D, Fritton JC. "American Society of Biomechanics Journal of Biomechanics Award 2013: Cortical bone tissue mechanical quality and biological mechanisms possibly underlying atypical fractures." J Biomech. 2015 Apr 13;48(6):883-94. Epub 2015 Feb 2. Review. https://doi.org/10.1016/j.jbiomech.2015.01.032 ; PubMed PMID: 25683519; PubMed Central PMCID: PMC4380555 , Apr-2015
Awards	Bajaj D. "2nd Place, Poster Competition, 3rd Annual National Postdoc Appreciation Day Symposium. UMDNJ-RWJMS, Piscataway, NJ, September 2011." Sep-2011
Awards	Bajaj D. "USRA New Investigator Award for Outstanding Bone Research, Houston, Texas, February 2012." Feb-2012
Books/Book Chapters	Subramanian G, Bajaj D, Iyer S, Fritton JC, Quek SYP. "Osteonecrosis of the Jaw: A Spectrum Disorder?" in "Osteonecrosis: Diagnosis, Treatment and Management." Ed. G.I. Bianchi, P.C. Giordano. Hauppauge, NY : Nova Science Publishers, Inc., 2012. p. 1-44., Dec-2012