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PI Name:	Puttlitz, Christian Ph.D.		
Project Title:	Fracture Healing in Haversian Bone under Conditions of Simulated Microgravity		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Biomedical countermeasures		
Joint Agency Name:	TechPort:	No	
Human Research Program Elements:	(1) HHC: Human Health Countermeasures		
Human Research Program Risks:	(1) Fracture: Risk of Bone Fracture due to Spaceflight-induced Changes to Bone (IRP Rev F)		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	puttlitz@engr.colostate.edu	Fax:	FY
PI Organization Type:	UNIVERSITY	Phone:	970-224-9743
Organization Name:	Colorado State University		
PI Address 1:	1374 Campus Delivery		
PI Address 2:	Department of Mechanical Engineering and School of Biomedical Engineering		
PI Web Page:			
City:	Fort Collins	State:	CO
Zip Code:	80523-1374	Congressional District:	4
Comments:			
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Contact Monitor:	Maher, Jacilyn	Contact Phone:	
Contact Email:	jacilyn.maher56@nasa.gov		
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COI Name (Institution):	Browning, Raymond (Colorado State University) Haussler, Kevin (Colorado State University) McGilvray, Kirk (Colorado State University) Ryan, Stewart (Colorado State University) Santoni, Brandon (Foundation for Orthopaedic Research and Education)		
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	<p>There is a need for information regarding hard and soft tissue healing in microgravity environments, and if impaired healing exists, what countermeasures can be called upon to enhance healing. Research on fracture healing using the rodent hindlimb suspension model shows healing is impaired in simulated microgravity, while clinical research shows that moderate, early mechanical loading caused by weight bearing induces osteogenesis and aids in repair of bone fracture. Further research is needed to determine what loads, if any, should be applied during spaceflight to promote fracture healing.</p> <p>Most ground-based microgravity models utilize rodent hindlimb suspension to simulate how reduced loading affects isolated physiologic systems. Unfortunately, results derived from these studies are difficult to directly translate to the human condition due to major anatomic and physiologic differences between rodents and humans. Specifically, the differences in rodent and human bone structures become increasingly important when studying orthopaedic issues such as bone maintenance and healing during spaceflight. For example, the basic microstructure of rodent bone, known as “plexiform” bone, lacks the osteons (Haversian systems) that are the main micro-architectural feature of human cortical bone. Furthermore, it is known that the osteogenic and healing potential of rodent bone far exceeds that of adult human tissue.</p> <p>Due to these limitations in current ground-based microgravity models, there exists a need to develop a ground-based, large animal model of fracture healing in simulated weightlessness that more closely approximates the human condition as has been done in the first year of this study. This animal model should be capable of simulating a wide spectrum of microgravities and able to investigate exercise protocols that may aid in the optimization of the fracture healing cascade. Four specific aims were defined to meet these goals: 1) Develop a ground-based large animal model of bone unloading in order to simulate full weightlessness; 2) interrogate the effects of a simulated microgravity environment on bone fracture healing in a large animal model; 3) develop a computational model of weightbearing in ovine bone under different experimental conditions in order to characterize the loads experienced by the fracture site; and 4) develop treadmill protocols that enhance bone fracture healing in the presence of simulated microgravity.</p>
<p>Rationale for HRP Directed Research:</p>	<p>The data collected during the first year of this study clearly demonstrate that the ovine model of ground-based microgravity effectively simulates the bone loss experienced by astronauts in space and ground-based rodent hindlimb suspension. This model has a major advantage over rodent hindlimb suspension models in that the mature ovine bone structure is nearly identical to that of humans, and future studies utilizing this large animal model (i.e., how hard and soft tissues heal in a microgravity environment which will be executed in year two of this grant) will be easily translated to the human condition. Furthermore, the study of fracture healing will benefit from the use of a large animal model rather than a rodent model since the healing potential of sheep more closely matches that of humans than rodents. The ground-based experiments utilizing this large animal (ovine) model directly addresses the need to know how varying microgravity environments affect fracture healing, as well as determining the applied loads at the fracture healing site through inverse dynamics and finite element simulations. The fracture rehabilitation protocols explored within this study will also aid in determining which mechanical environment leads to enhanced bone healing under microgravity conditions. The data produced during this study will significantly advance the basic mechanobiology of fracture healing by discerning which mechanical signals and environments facilitate enhanced bone healing.</p>
<p>Research Impact/Earth Benefits:</p>	<p>Solid progress has been made in establishing the efficacy of the ground-based large animal model of simulated microgravity. In order to simulate microgravity on a large animal model, a transarticular external fixation device was created to reduce the load experienced by the metatarsal bone of the sheep hindlimb. Characterization of the external fixation device was performed by altering the number, material, and diameter of the fixation pins and connecting rods on the device and measuring the resultant decrease in load transferred through the metatarsal bone. The results of the characterization study show that a variety of microgravities may be studied by altering the design of the external fixation device. These data demonstrate that the study of other lunar gravities (Moon, Mars, etc.) is possible with this model. In order to test the in vivo efficacy of the model, two microgravity devices were implanted in an animal model for 8-weeks. Dual energy x-ray absorptiometry results demonstrated losses of 30%-50% in BMD between the treated and contralateral controls in the microgravity groups over 8 weeks, while no differences were observed in the sham group. These changes are further substantiated through micro-computed tomography (μCT) and histomorphometry results which display decreases of 18%-28%, 34%-38%, and 39%-48% in trabecular number, trabecular thickness, and bone volume respectively. Four-point bending tests displayed decreases of 41% in bending modulus between the treated and contralateral metatarsal bones, while diametral compression experiments demonstrated decreases between 25%-30% in diametral failure load indicating that mechanical as well as radiographic changes occurred due to the simulated microgravity environment. The alterations in BMD with the current ovine microgravity model are similar to changes previously reported by Bloomfield et al. (Bone 2002) of 21% in 28 days and Vico et al. (Bone 1998) of 40% in 6 weeks using hindlimb unloading in skeletally mature male rats.</p> <p>Computational models of the sheep hindlimb have also been created to assess the loading generated by the musculature and the stresses in the individual bones. A CT scan of a sheep hindlimb was utilized to construct the geometry of a musculoskeletal and finite element model. Appropriate muscles, tendons, and ligaments were attached to the musculoskeletal model, and validation will be performed via ground reaction forces and three-dimensional motion capture data acquired on a custom-built force measuring treadmill. The three-dimensional surfaces from the CT scan were then meshed and imported the finite element solver software. Material properties were assigned, and ligaments were attached. Mesh optimization and model validation will be performed via in vivo strain and kinematic measurements. The muscle and joint reaction forces from the musculoskeletal model will serve as inputs to the finite element model to quantify strain levels experienced in the metatarsal bone at various microgravity levels.</p> <p>The remaining three months in Year 1 will complete the sample size of the in vivo animal model development, and computational model validation. Based upon the data generated to date, it is expected that these animal specimens will conclusively and statistically demonstrate that the current ovine microgravity model effectively simulates the decline in bone tissue (and associated mechanical properties) that accompanies long-term spaceflights. The architectural and physiological similarities between ovine and human bone will allow future results regarding bone fracture healing in various simulated microgravity environments using this model directly applicable to human spaceflight.</p>
<p>Task Progress:</p>	

Bibliography Type:	Description: (Last Updated: 03/25/2020)
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