Modeling Space Radiation Induced Bone Changes in Rat Femurs through Finite Element Analysis

Dale Johnson, Summer E. Lawrence, Eric W. Livingston, Robert D. Hienz, Catherine M. Davis, Anthony G. Lau

Abstract— **As the duration of manned missions outside of the Earth's protective shielding increase, astronauts are at risk for exposure to space radiation. Various organ systems may be damaged due to exposure. This study investigates the bone strength changes using finite element modeling of Long Evans rats (n=85) subjected to graded, head-only proton (0, 10, 25, and 100 cGy, 150 MeV/n) and ^{28}silicon (0, 10, 25, and 50 cGy, 300 MeV/n) radiation. The strength of the femoral neck will be examined due its clinical relevance to hip fractures. It has been shown in previous studies that bone mineral density was not reduced at the site of fracture. These findings question whether measurements of bone mineral density may be used to assess risk of hip fracture. The mechanisms leading to the irregular relationship between bone density and strength are still uncertain within literature and investigated to greater extent in clinical applications. Finite element analysis within this study simulated physiological loading of the femoral neck. No significant changes in femoral neck strength were found across doses of proton or ^{28}silicon head-only radiation. Future work includes performing mechanical testing of the bone samples. Moving from mouse to larger animal models may also provide the increased lifespan for assessing the long-term outcomes of radiation exposure.**

I. Introduction

Sending a manned mission to Mars is a long-term goal of the National Aeronautics and Space Administration (NASA). This journey poses many risks, including exposure to space radiation. Once outside of the radiation shielding effects that the Earth's magnetosphere provides, astronauts are subject to the consequences of the foreign environment. Space radiation is accumulated due to the combined effects of galactic cosmic radiation and solar particle events, leaving astronauts at risk for negative consequences to bone health and various organ systems. Since astronauts will accumulate 0.5-1.0 Gy of heavy ion radiation over this two-year mission, long-term effects of astronaut bone structure must be considered [1]. The radiological mechanisms that cause this to occur are still uncertain within literature as well as the implications of long term exposure [2], [3]. Previous studies have shown the relation between clinical radiation and reduced bone strength; however, those pertaining to space relevant radiation remain inconclusive. In the vertebrae and femoral neck, bone losses due to clinical radiation may range from 0.8-1.5% per month, while other bone sites can see losses up to 2% per month [2]. From an oncologic perspective, cancer patients are exposed to approximately 2 Gy photon (gamma/X ray) and electron radiation [2]. Therapeutic irradiation used to treat pelvic tumors in women has been shown to increase risk of hip fracture by 65% postradiotherapy [3]. It has also been shown that typical measures of bone mass fail to predict hip fractures induced by radiation therapy [4]. Therefore, testing beyond the parameters of bone mineral density is essential. Computational finite element modeling can provide close approximations of structural integrity and strength along with site specific material properties. Femoral strength and load-to-strength ratios obtained using finite element models have been shown to be highly predictive of incident hip fractures in men [5]. This study will focus on evaluating the long term effects of space radiation on bone strength changes in the femoral neck region for head-only, proton and ^{28}silicon radiation through finite element models constructed from high resolution micro-CT imaging.

II. Methods

A. Study Design

All live animal work was performed at Johns Hopkins and Brookhaven National Labs. The animal protocol and all procedures were approved by the Institutional Animal Care and Use Committees of the Johns Hopkins University and NASA's Brookhaven National Labs. The data set presented is the first cohort of a larger study investigating various doses and types of space radiation exposure. In this study, male Long Evans rats (n=85) were exposed to head-only proton (150 MeV/n) and ^{28}silicon irradiation (300 MeV/n) at 0, 10, 25, 50, or 100 cGy doses at the NASA Space Radiation Laboratory (Brookhaven National Lab) before being euthanized 14-months post exposure. Sample sizes for each treatment are tabulated below in Table 1.

Table 1: Sample sizes for radiation type and dosage

Radiation Type	Dosage (cGy)				
	0	**10**	**25**	**50**	**100**
Proton	3	8	9	0	10
^{28}Silicon	10	14	15	16	0

*Research supported by The New Jersey Space Grant Consortium, The College of New Jersey Mentored Undergraduate Research Experience, and NASA Cooperative agreement NCC 9-58 with the National Space Biomedical Research Institute (NBPF04201, NBPF01604, EO00010), and NASA NNX15AC71G

F D. Johnson (corresponding author) and A. G. Lau are with the Department of Biomedical Engineering at The College of New Jersey, Ewing Township, NJ 08638 USA email: johnsd22@tcnj.edu; Anthony.Lau@tcnj.edu

S. Lawrence and E. Livingston are with the Joint Department of Biomedical Engineering at the University of North Carolina, Chapel Hill, NC 27599 (email: Eric.Livingston@unc.edu)

R. D. Hienz and C. M. Davis are with the Department of Psychiatry and Behavioral Sciences, Division of Behavioral Biology, Johns Hopkins University School of Medicine, Baltimore, MD, 21218 USA (email: cdavis91@jhmi.edu)

B. MicroCT Imaging

Scans of the femurs were conducted by micro computed tomography, or micro-CT, at 18µm isotropic resolution (Scanco µCT80). Micro-CT methods are similar to that of an X-ray but provide higher resolution and in three dimensions. This image data not only provides the geometric structure of the sample but also the material densities once referenced to a phantom control. Scans of the superior region of the femur allow for the three-dimensional microstructural properties of the femoral neck to be examined. Image data was then exported as a composition of DICOM images.

C. Image Processing

Micro-CT scan data were rotated to align the diaphysis of the femur vertically. Three-dimensional alignment was necessary to ensure loading would be applied anatomically accurate and uniform across all samples. Bone was segmented from surrounding tissue using a threshold based on pixel intensity. Pixel intensity is correlated with material density, e.g. fewer incident x-rays traverse bone than surrounding soft tissue. Samples were then reduced to the region of interest beginning superior to the ball of the femur and extending 500 slices, 9.0 mm, inferior. Previous studies in our lab were conducted with hexahedral models of mice femora and tibiae that had received simulated space irradiation. Due to the large size and computational demand of rat bones at this resolution, software was used to apply a scaled reduction. Three-dimensional models were then created using advance edge detection (Mimics 18.0). This model was then refined through adaptive remeshing and contained approximately 3 million tetrahedral elements. Adaptive remeshing was used to allocate higher resolution areas to the more complex geometries of the model. Excluding the inferior surface, smoothing was applied to further reduce computational cost. Models still required roughly 80 GB of RAM for processing upon being converted to volume meshes of tetrahedral elements. The use of tetrahedral elements in modeling the proximal femur has been shown to allow for closer approximations to theoretical results of simplified models, though, exhibit a lack of stability in the degree of refinement when compared to hexahedral elements [6]. Other studies have concluded that application determines which element type will provide a closer approximation to experimental values [7]. Due to the effects of radiation on the microarchitecture of bone, the use of tet4 elements may be justified in their greater ability to approximate key differences in trabecular structure. (3-Matic 10.0).

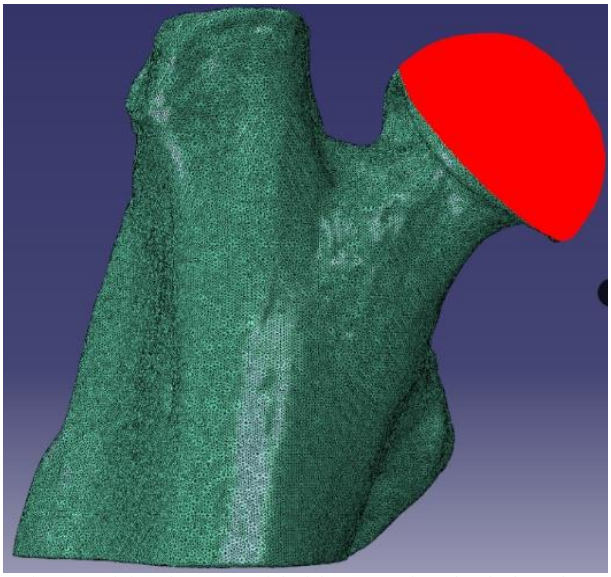

Figure 1: Finite Element Model of the Femoral Neck. The boundary condition at the femoral head (shown in red) is displaced downward to simulate physiological loading.

D. Image Processing

Volume meshes were imported into a numerical solver and assigned fixed boundary conditions at the flat, inferior surface. Homogenous, isotropic material properties with Poisson's ratio=0.3 and elastic modulus=10 GPa were applied to the model meaning that each of the elements within would respond to loading under these defined properties. A downward displacement of 0.5% of the bones length was then applied to the elements within the femoral head to simulate physiological loading of the femoral neck, shown in Figure 1 above. The reaction force to the displacement was collected from each sample as an indicator of bone strength (ABAQUS CAE 6.9).

E. Statistical Analysis

Statistical significance ($\alpha<0.05$) was determined by 2-way ANOVA for radiation type and 1-way ANOVA for radiation dose (Origin Pro 2015).

III. Results

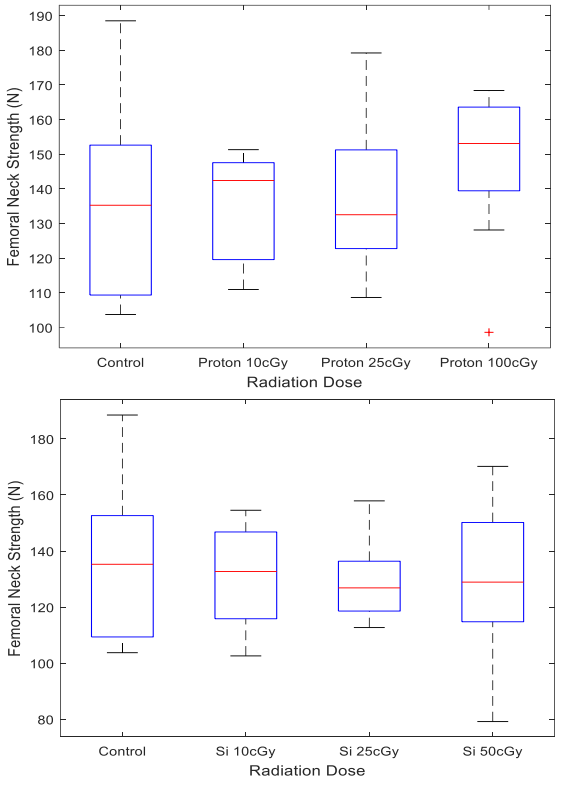

Figure 2: Femoral neck strength at various doses of irradiation for proton (top) and ^{28}silicon (bottom). Values reported as mean + or – standard deviation with box plots representing 25th and 75th percentiles.

There was no difference found between proton and ^{28}silicon radiation (p=0.055). There were no statistically significant changes in femoral neck strength from head-only proton (p=0.191) and ^{28}silicon (p=0.973) radiation. Analysis of this partial data set may be amended through additional samples. Due to equivalent treatments, controls from proton and ^{28}silicon cohorts were grouped together in statistical analysis. As part of a larger study, control group variability may be increased due to slight differences in cohorts of animals. Increasing dose of head-only proton and ^{28}silicon radiation increased the quantity of low femoral neck strength bones as shown in Fig. 2, above. This is shown by the outlier, denoted by the red plus, in the 100cGy proton plot and increased lower range in the 50cGy ^{28}silicon plot. Each suggests the presence of a sensitivity at greater doses of radiation exposure.

IV. Discussion

A. Time Dependency

Using rat subjects, this study is the first to investigate the long-term changes in bone strength from space radiation through finite element analysis. This extended time scale could have led to confounding effects of aging in conjunction with exposure. The time course of damage to bone health caused by radiation is an important consideration when attempting to correlate conclusions derived from murine models to human subjects. In mice exposed to clinical doses of therapeutic X-ray radiation, an increase in bone volume and strength was found 2 weeks post radiation while 12 weeks post-treatment a loss of strength was exhibited despite an increase in volume [4]. In mice exposed to space relevant doses (2 Gy) of proton radiation, deleterious effects on trabecular bone were exhibited 4 months post-exposure [8].

B. Radiation Therapy

The mechanisms that are associated with changes in bone structure are proposed to be similar when comparing clinical and space relevant doses of radiation [2]. Comparable to the delivery of radiation in this study, focus beam radiation therapy can deliver high doses to a specific tumor site while surrounding tissue may receive a lower dosage on the order of cGy. When patients receive radiation therapy, tissue outside of the treatment field also exhibits an inflammatory response [3], [9]. The innate immune system then appears to interpret this process based on the genetic background of the host [9]. Other studies have suggested that the inflammatory response may represent the mechanism by which bone formation is suppressed and strength is lost when clinical radiation is administered [3]. When considering head-only proton radiation, the effects of localized irradiation may extend to consequences systemically. One study has shown that applying 35 Gy of radiation to the mid-thigh region of Sprague-Dawley rats did not result in significant decreases in bone strength of the contralateral leg [10]. Acknowledging differences in dosage due to application, further research is necessary to understand the potential systemic implications of local irradiation.

C. Computational Modeling

Low bone mineral density is often associated with increased risk of hip fracture. However, in one study reductions in bone mineral density were not exhibited at fracture sites [11]. Evaluating subjects risk of hip fracture must therefore extend beyond measures of bone density, utilizing finite element models as a potential preferred assessment. Recent studies assessing the effects of resolution on micro-CT images of cortical bone from the tibia of Sprague-Dawley rats concluded that resolutions coarser than 2 μm did not adequately distinguish changes in small architectural features [12]. Consequently, scans at this scale are at the material level and require increased time and reduce the volume of bone that may be examined. With a micro-CT resolution of 18 μm focusing on microstructural properties in this study, these findings may support the great variation exhibited within treatment groups as material properties and microarchitecture contribute to overall bone strength. Differences in initial model alignment and variability among the animal models have also been recognized as potential sources for variability within the study.

D. Simulated Space Radiation

It has been well documented that the combination of unloading due to microgravity and space radiation may interact to enhance bone loss [2], [13]–[15]. When analyzing the effects of proton radiation alone, studies have shown dose dependent affects associated with bone strength. Low doses of heavy ion radiation, 0.5 Gy, have also been shown to not have a significant effect on bone quality unlike higher doses [14]. Krause et al. reported that 50 cGy of proton radiation did not have a significant effect on bone quality. Examining the effects of whole body proton irradiation on tibia and femora, a 2 Gy dose was shown to have significant effects on trabecular bone while 1 Gy and 0.5 Gy doses resulted in insignificant, unnoticeable changes in trabecular bone structure [8]. This supports the results of the study, where 0, 10, 25, and 100 cGy of head-only, proton radiation were found to have an insignificant effect on femoral bone strength.

E. Radiation Sensitivity

Femur samples were obtained through a tissue sharing program that allowed for a variety of studies to be conducted under the same experimental set up. Collaborators on this study were examining the neural and behavioral changes that may later be correlated to changes in bone strength. Previous work found that approximately 40% showed cognitive changes at similar type and dosage (100 cGy) of radiation used within this study [16]. This finding suggests individual sensitivities to the deleterious effects of radiation that may account for the outlier in the proton plot; and greater quantity of low strength bones in the silicon plot at higher doses of radiation. For a particular dose, this sensitivity may lead to deleterious effects on bone strength in some animals while others have minimal to no effect on bone strength. These animals were the initial cohort to establish baseline response to radiation and do not have corresponding cognitive assessment data.

F. Future Work

Mechanical tests of 3-point bending and femoral neck loading may be used to further evaluate the finite element methods that were implemented. Alternative skeletal sites may also be considered for a comparative analysis. Future

models may employ methods that incorporate both material and microstructural properties. Delineating the effects of radiation and aging may be achieved when examining shorter time periods or younger, skeletally mature rats. While this study focused on assessing femoral neck strength using FEA, future studies may examine microarchitectural changes through image processing techniques.

G. Limitations

Limitations of the study include small control groups for both proton and ^{28}silicon treatments, due to samples representing an initial cohort of a larger animal study. Radiation being delivered in an acute manner to the head alone may be less representative of conditions in space. However, these conditions may be a model for clinical radiation therapy. Within the finite element analysis, assuming linear elastic and homogenous material properties causes only structural changes to be evaluated.

V. Conclusion

Differences in strength of the femoral neck were found to be insignificant between varied doses of proton and ^{28}silicon radiation when assessed with subject specific finite element models. Future studies may recognize the limitation of head-only irradiation compared to whole body in terms of simulating the space environment.

References

[1] H. Matsumoto, A. Takahashi, and T. Ohnishi, "Radiation-induced adaptive responses and bystander effects.," Biol. Sci. Space., vol. 18, no. 4, pp. 247–54, 2004.

[2] S. a Hamilton et al., "A murine model for bone loss from therapeutic and space-relevant sources of radiation.," J. Appl. Physiol., vol. 101, no. 3, pp. 789–793, 2006.

[3] J. S. Willey, S. A. J. Lloyd, G. A. Nelson, and T. A. Bateman, "Space Radiation and Bone Loss," Gravitational Sp. Biol. Bull., vol. 25, no. 1, pp. 14–21, 2011.

[4] J. D. Wernle, T. A. Damron, M. J. Allen, and K. A. Mann, "Local irradiation alters bone morphology and increases bone fragility in a mouse model," J. Biomech., vol. 43, no. 14, pp. 2738–2746, 2010.

[5] E. S. Orwoll et al., "Finite Element Analysis of the Proximal Femur and Hip Fracture Risk in Older Men," J. Bone Miner. Res., vol. 24, no. 3, pp. 475–483, 2009.

[6] A. Ramos and J. A. Simões, "Tetrahedral versus hexahedral finite elements in numerical modelling of the proximal femur," Med. Eng. Phys., vol. 28, no. 9, pp. 916–924, 2006.

[7] M. Viceconti, L. Bellingeri, L. Cristofolini, and A. Toni, "A comparative study on different methods of automatic mesh generation of human femurs," Med. Eng. Phys., vol. 20, no. 1, pp. 1–10, 1998.

[8] E. R. Bandstra et al., "Long-Term Dose Response of Trabecular Bone in Mice to Proton Radiation," Radiat. Res., vol. 169, no. 6, pp. 607–614, 2008.

[9] S. Formenti and S. Demaria, "Systemic effects of local radiotherapy," Lancet Oncol., vol. 10, no. 7, pp. 718–726, 2009.

[10] M. Maeda, M. H. Bryant, M. Yamagata, G. Li, J. D. Earle, and E. Y. Chao, "Effects of irradiation on cortical bone and their time-related changes. A biomechanical and histomorphological study.," J. Bone Joint Surg. Am., vol. 70, no. 3, pp. 392–399, Mar. 1988.

[11] A. Konski and M. Sowers, "Pelvic fractures following irradiation for endometrial carcinoma.," Int. J. Radiat. Oncol. Biol. Phys., vol. 35, no. 2, pp. 361–367, May 1996.

[12] L. Cardoso, D. Ph, S. P. Fritton, and D. Ph, "3D Assessment of Cortical Bone Porosity and Tissue Mineral Density Using High-Resolution Micro-CT: Effects on Resolution and Threshold Methods," J Bone Miner Res., vol. 29, no. 1, pp. 1–16, 2015.

[13] H. Kondo et al., "Oxidative stress and gamma radiation-induced cancellous bone loss with musculoskeletal disuse," J. Appl. Physiol., vol. 108, no. 1, pp. 152–161, 2010.

[14] J. S. Alwood et al., "Heavy ion irradiation and unloading effects on mouse lumbar vertebral microarchitecture, mechanical properties and tissue stresses," Bone, vol. 47, no. 2, pp. 248–255, 2010.

[15] A. R. Krause, T. L. Speacht, Y. Zhang, C. H. Lang, and H. J. Donahue, "Simulated space radiation sensitizes bone but not muscle to the catabolic effects of mechanical unloading," PLoS One, vol. 12, no. 8, pp. 1–16, 2017.

[16] C. M. Davis, K. L. DeCicco-Skinner, and R. D. Hienz, "Deficits in sustained attention and changes in dopaminergic protein levels following exposure to proton radiation are related to basal dopaminergic function," *PLoS One*, vol. 10, no. 12, pp. 1–17, 2015.