Brett D. Crist, MD

**2nd Beth and Tom Smith
Visiting Professor**

**31st Annual Gary Poehling, MD
Resident Research Day**

**Department of Orthopaedic Surgery and
Rehabilitation**

Wake Forest School of Medicine

June 17, 2022

Brett D. Crist, MD
2nd Beth and Tom Smith Visiting Professor

Dr. Brett Crist is the Vice Chair of Business Development, Director of the Orthopaedic Trauma Service, Director of the Orthopaedic Trauma Fellowship, Director of the Limb Preservation Center, and Professor of Orthopaedic Surgery at the University of Missouri Health Care System.   He is a board-certified Orthopaedic Trauma, and Hip and Pelvis Reconstruction Surgeon. Dr. Crist specializes in orthopaedic trauma/fracture care, hip and pelvis reconstruction including total hip arthroplasty, young adult hip disorders/hip preservation, limb deformity correction, and fracture nonunions. His research interests in anterior total hip arthroplasty, fracture care including deformity, patient-centered outcomes, and hip preservation procedures.

Thirty-First Annual Gary Poehling, M.D. Resident Research Day
June 17, 2022

Second Annual Beth and Tom Smith Visiting Professor

Brett D. Crist, MD
Director, Orthopaedic Trauma Fellowship
Professor of Orthopaedic Surgery
Division Chief, Orthopaedic Trauma
Department of Orthopaedic Surgery
University of Missouri Health Care

8:30   Introduction: Eben A. Carroll, MD

8:35   Brett D. Crist, MD

9:15   **BREAK**

Emcee: Alex Jinnah, MD (PGY 4)

            Physician Scientists
9:30   Tameka Dean, MD
9:40   Nequesha Mohamed, MD

9:50   Discussion

10:00   **BREAK**

            PGY3
10:15   Anirudh Gowd, MD
10:25   Evan Miller, MD
10:35   Matthew Akelman, MD
10:45   Nicholas Andring, MD
10:55   Samuel Rosas, MD

11:05   Discussion

11:15   **LUNCH**

            PGY5
12:30   Nick Yetter, MD
12:40   Amy Trammel, MD
12:50   T. David Luo, MD

1:00   Discussion

1:10   **BREAK**

1:25   Awards Presentation

Risk of Osteoporotic Proximal Humerus Fractures is Decreased in Peripheral Vascular Disease

Tameka Dean DO MS, Nequesha Mohamed MD, Michael Suarez BS, Xue Ma MD PhD,
Holly Pilson MD

Introduction: Proximal humerus factures (PHF) are one of most common fractures attributed to osteoporosis. In previous studies, peripheral vascular disease (PVD) has been shown to accelerate bone demineralization and to increase the incidence of appendicular osteoporotic fractures. As PVD has a predilection for the lower extremity, studies have primarily investigated bone loss and fracture risk in the hip. However, PVD has been associated with both regional and total body bone mineral density loss, suggesting that fracture risk may not be limited to the lower extremity. This study will investigate whether PVD independently increases the risk of proximal humerus fractures in patients with osteoporosis.

Methods: A retrospective review of the National Inpatient Sample was performed between 2009-2015 to identify all patients diagnosed with osteoporosis (n=7,486,332). International Classification of Diseases (ICD) 9 diagnosis codes were utilized to classify proximal humeral fractures, approximating 71,469. A yearly stratification of PHF incidence and comparison of patient demographics were performed. Demographics consisted of age, sex, race (White, Black, Hispanic, Asian, American Indian/Alaskan Native and other), Charlson Comorbidity Index (CCI) (0, 1, 2, 3+), diabetes, smoking status, and PVD. Annual incidence and demographics were evaluated with t-test and chi-square analyses. Fracture risk factors were assessed with multivariate regression.

Results: PHF incidence slightly increased over the study period from 0.9% in 2009 to 1.0% in 2015 (p<0.001). Patients with a fracture were more likely older, White and female compared to patients without a fracture (p<0.001). Regression analyses for fracture incidence demonstrated a significantly higher PHF risk among diabetics and smokers (all p<0.001), but was not associated with CCI score. Fracture risk was significantly lower among patients with PVD (odds ratio: 0.648; 95% confidence interval: 0.622 – 0.676) and non-White races except American Indian/Alaskan Native patients (all p<0.001).

Discussion: This study found an increased fracture risk in patients who are older, female, diabetic and smokers, which is consistent with what has been previously reported. However, despite prior reports of PVD accelerating bone loss and subsequent fracture, we found an unexpected lower risk of fracture in this cohort of patients with proximal humerus fracture. We suspect that this may be related to medical management of PVD conferring additional protective prevention of fractures. However, treatment regimens were not available in this database. It is also important to note that proximal humerus fractures are known to have higher incidence in post-menopausal women, presumably due to their higher rate of osteoporosis. However, PVD is more common in men. Future studies are needed to decipher the protective factors involved in lowering proximal humerus fracture risk in osteoporosis and whether this association with PVD is sex-specific.

Diabetes is Associated with an Increased Osteoarthritis Incidence in Non-Human Primates

Nequesha Mohamed MD, Nicole A. Gagnon, John Olson, Johannes Plate MD PhD, Mark Cline DVM PhD, Jeffrey Willey PhD

Purpose: Cartilage breakdown in the joint, or osteoarthritis (OA), and diabetes share several risk factors including obesity and metabolic changes. Diabetes can also lower bone mineral density (BMD), making joints more fragile. Tracking these conditions in humans may be difficult, but non-human primates (NHPs) are a fully-translatable model longitudinally tracked at our institution with annual computed tomography (CT) scans. This study was designed to assess the relationship between OA, BMD, diabetes, and obesity in NHPs. We hypothesize that OA and low BMD will be significantly associated with the presence of diabetes.

Methods: 201 rhesus macaques were analyzed (mean age=11.6 years). 163 were irradiated prior to enrollment, while 38 were adopted as controls. A subcohort of 134 rhesus macaques TBI-exposed and 32 unexposed controls were assessed for BMD (n=168). Radiation was assessed as a potential contributor to OA and low BMD in the context of diabetes development. Osteoarthritis was determined from annual CT scans using a modified Kellgren-Lawrence (KL) grading system for the knee, hip, and shoulder joints, and spine. Diabetes and obesity were determined from health records. Proximal humeral head BMD was analyzed as a minimally weightbearing joint that displayed early OA. Descriptive statistics and chi-square analyses were performed using SPSS. All significance values were set at $p < 0.05$.

Results: No relationship was seen between radiation and overall OA status (p=0.208). However, OA was significantly higher in non-irradiated animals for the knee (p=0.049), hip (p=0.002), shoulder (p=0.003), and spine (p=0.003). Radiation was not associated with diabetes in this cohort (p=0.264), and obesity was more common in the non-irradiated cohort (p=0.008).
Diabetic animals had significantly higher incidences of OA of the knee (p=0.001), hip (p<0.001), shoulder (p<0.001), and spine (p=0.001), resulting in a higher incidence of overall OA in diabetic NHPs (p<0.001). Obesity was significantly higher among diabetics (p<0.001), and was significantly associated with all arthritic joints (all p<0.001).
Irradiated NHPs had lower cortical volume, lower cortical BMD, and shorter humeral length (all p<0.003). Trabecular BMD was higher (p=0.004) in irradiated NHPs. Cortical volume and BMD were higher in diabetic NHPs (both p<0.001), while trabecular BMD and humeral length were similar (p>0.05).

Conclusions: Osteoarthritis of all joints was significantly higher in diabetic and obese NHPs. Radiation decreased cortical volume and BMD, increased trabecular BMD, while diabetes increased cortical volume and BMD. There was no effect of radiation on OA or diabetes in this cohort, but there may be some effect on BMD. Diabetes appears to play a role in joint degeneration and maladaptive bone mineralization, providing a foundation for future investigative studies to determine the pathways that may potentiate these diseases.

Machine Learning Prediction of Health Care Admissions Costs Following Select Orthopedic Procedures

Anirudh K. Gowd, MD, Avinesh Agarwalla, MD; Edward C. Beck, MD, MPH; Joseph N. Liu, MD; Brian R. Waterman, MD

Introduction: Supervised Machine Learning (SML) is becoming increasingly utilized within the field of Orthopedic Surgery for uses such as predictive modeling, image analysis, and outcomes research. With growing pressures to increase cost efficiency, SML may be used to help predict cost of admission and readmissions after orthopedic procedures.

Methods: The following orthopedic procedures were selected for study: anterior cervical discectomy and fusion (ACDF), open treatment of hip fractures, and total shoulder arthroplasty. The Nationwide Readmissions Database (NRD) was accessed in 2018. The database was queried for all primary procedures by International Classification foo Diseases (ICD-9) codes. Costs were calculated by utilizing the total hospital charge and each hospital's cost-to-charge ratio. Unplanned readmissions within 90 days were calculated using unique patient identifiers. Hospital characteristics, including annual volume of procedures performed, size, region, and differences in wage were incorporated into the model in addition to patient demographics, diagnoses, and comorbidities. Training and testing data subsets were created for each procedure and model performance was determined by receiver operating characteristic, area under the curve (ROC-AUC). Machine learning algorithms were used to predict patients with immediate postoperative admission costs greater than the fourth quartile of total cost. Factors associated with high cost were determined.

Results: Within the combined dataset, 42,485 cases of ACDF, 63,494 cases of hip fractures, and 49,354 cases of TSA were separately studied. Total admissions costs were $26,977 +/- 28,947, $23,439.6 ± 19,250.4, and $13,871 ± 14,301.06, respectively. SML models using logistic regression were top performing for TSA (AUC=0.83) and gradient boosting trees for ACDF (AUC=0.86) and hip fractures (AUC=0.88). Wage index, representative of regional differences in hospital workers' income, was the highest weighted variable in all three datasets. For ACDF, diagnosis severity, annual volume of procedures performed, and readmissions were the next weighted variables. For hip fractures, readmissions, age, and annual volume of procedures were the next weighted. Lastly, for TSA, annual volume of procedures, readmissions, and diagnosis severity were the next weighted.

Conclusion: SLM is successful in providing accurate models of healthcare expenditure for ACDF, open treatment of hip fracture, and TSA. Broadly, regional and patient health largely drive cost, but there is heavy influence on hospital volume and readmission rates.

Contributions of the Axial Spine to Kicking Biomechanics in the Dipping Kick Among Elite Soccer Players

Evan M. Miller, MD; Garrett Bullock, PT, DPT, DPhil; Brian R Waterman, MD; Kristen F Nicholson, PhD; Tadhg J. O'Gara, MD

Introduction: A direct free kick within 25 yards of the goal is a unique scoring opportunity, with a conversion rate of 6-13%. Because the opposing team attempts to block the free kick by standing 10 yards in front of the ball, successful free kicks often incorporate the dipping technique to go over the wall of players and then dip beneath the crossbar. The goal of the present study was to develop normative data for thoracic, lumbar and pelvic range of motion (ROM) during a soccer dipping kick among an elite NCAA division I soccer population, compare successful and unsuccessful kicks, and evaluate these findings in the context of existing biomechanical literature.

Methods: A repeated measures, cross-sectional study was conducted in a sample of asymptomatic, NCAA Division I College and professional soccer players at the Wake Forest McCreary Field House. Kinematic three dimensional (3D) motion data were collected using 52 reflective markers. Players made twenty attempts. An official standard match ball was placed twenty yards in-line with the near post of a FIFA and NCAA standardized goal. The near post upper corner was labeled as the 90 by 90 cm corner in-line with the player. Five 182.88 centimeter Rogers Athletic Titan Pop Up Dummies were placed ten yards between the goal and the player. A successful attempt was defined as when the ball cleared the defender barrier and passed into the designated upper corner.

Results: Data from a total of 20 kicks with 2 successful and 2 unsuccessful kicks from each of the 5 participants were analyzed. The average lumbar flexion, tilt, and rotation were $39.8\pm13.2°$, 3.5 ± 8.5 °, and $7.5\pm12.9°$ respectively. Thoracic flexion, tilt, and rotation were $7.3\pm6.0°$, $-2.4\pm7.3°$, and $8.1\pm34.8°$ respectively. Pelvic anterior/posterior tilt was $-32\pm9.5°$ and obliquity was $4.1\pm4.2°$. For successful kicks, the average maximum lumbar flexion, tilt, and rotation were $59.5\pm14.6°$, $22.3\pm5.2°$, and $26.8\pm5.2°$ respectively. Thoracic flexion, tilt, and rotation were $40.7\pm16.3°$, $13.7\pm8.7°$, and $31.1\pm26.5°$ respectively. Pelvic anterior/posterior tilt was $13.5\pm9.2°$ and obliquity was $6.4\pm2.6°$. Successful kicks had a lower thoracic rotation at ball contact and average maximum thoracic rotation at $31.1\pm26.5°$ compared to the average maximum value for unsuccessful kicks at $43.7\pm28.6°$, although not statistically significant.

Conclusion: Among successful and unsuccessful attempts, there were no statistical differences between spinal and pelvis segment range of motion when comparing these values at ball contact and their maximums. Yet, two of the main findings of this study was that total spine range of motion does not differ when comparing the results of the current study to previous reports and there is a trend for less thoracic rotation when comparing successful to unsuccessful attempts.

Costs And Predictors Of 90-Day Readmissions After Shoulder Arthroplasty With A Hospitalist Comanagement Model

Matthew R. Akelman MD, T. David Luo MD, Luke P. Hedrick BS, Samuel Rosas MD PhD MBA, Anastasios Papadonikolakis MD PhD, Benjamin R. Graves MD, Ethan R. Wiesler MD, Michael T. Freehill MD, Christopher J. Tuohy MD

Introduction: Readmission rates of patients undergoing shoulder arthroplasty have a significant effect on the cost and revenue of shoulder arthroplasties. Orthopaedic-hospitalist co-management care (OHC) services have been implemented to improve the quality of care provided during the initial procedural admission and decrease readmissions, however there is a gap in the literature regarding the cost-effectiveness of the OHC model with respect to shoulder arthroplasty. The purpose of this study was to assess the costs and predictors of 90-day readmission in patients undergoing shoulder arthroplasty with a hospitalist comanagement model. This study also aimed to determine if there was a significant difference in readmission rates and overall costs following shoulder arthroplasty for patients managed with and without OHC. We hypothesized that patients managed with OHC would have significantly higher 90-day costs and equivalent rates of 90-day readmissions compared to patients managed without OHC.

Methods: This was a single-center retrospective analysis using data from the Atrium Health Wake Forest Baptist center. All patients aged 18 and older who underwent primary shoulder arthroplasties, including total shoulder arthroplasty (TSA), hemiarthroplasty (HA), and reverse shoulder arthroplasty (RSA) between June 2013 through February 2017 were reviewed. Demographics, preoperative American Society of Anesthesiologists (ASA) score, Charlson Comorbidity Index (CCI), medical history, operative notes, hospital charges and unplanned readmissions within 90 days of discharge were reviewed. Indications for consulting OHC included multiple medical comorbidities and postoperative medical complications during a patients stay.

Results: 325 patients underwent shoulder arthroplasty and were included in this study. 126 patients received total shoulder arthroplasty, 45 received hemiarthroplasty, and 154 received reverse shoulder arthroplasty. 57 patients were comanaged with OHC and were more likely to have a higher ASA (p<.001) or CCI score (p<.001), longer length of stay (p<.001), and have a hospital complication during their initial admission (p<.001). 24 patients were readmitted within 90 days, and were more likely to a history of myocardial infarction (p=0.041), congestive heart failure (p=0.009), higher preoperative ASA and CCI (p<0.039), and longer initial length of (p<0.001). OHC was not associated with increased readmission (p=0.206). Initial length of stay (OR 1.229, p=.004) was the strongest predictors of readmission. The average total 90-day cost for a patient undergoing shoulder arthroplasty was $24,441 ± 8,903. Length of stay (beta weight 0.294, p<.001), readmission within 90 days (beta weight 0.26, p<.001), OHC (beta weight 0.168, p=.001), congestive heart failure (beta weight 0.123, p=0.014), and implant type (beta weight 0.107, p=.030) were the strongest predictors of increased cost.

Conclusion: Patients managed with OHC had increased medical comorbidities, equivalent readmission rates, and increased costs compared to patients without OHC. OHC may be an effective way to decrease readmission rates for more medically complex patients, but is associated with increased cost.

Early Results Using a Novel Femoral Neck Implant in Adults

Nicholas Andring, MD, Hunter Yancey, MD., Gabriel Sowards, MD, Sharon Babcock, MD,
Holly Pilson, MD, Jason Halvorson, MD, Eben Carroll, MD

Purpose: Femoral neck fractures are common injuries with multiple treatment options. For patients not undergoing arthroplasty, a myriad on fixations constructs have historically been used. Newer implants seek to improve on historically high rates of implant failure reported in the literature. One such implant is the Depuy Synthes Femoral Neck System (FNS). The primary purpose of this study is to determine the reoperation rate in adult patients treated with the FNS compared to published reoperation rates of sliding hip screws and cannulated screws.

Methods: This is a retrospective chart review at a level 1 academic trauma center of adult patients who underwent operative fixation of a femoral neck fracture with the FNS implant and at least three months radiographic follow up. After institutional approval, charts were identified with CPT codes 27236, 27235, 27244, and 27245. Charts were reviewed for demographics, fracture characteristics, implant selection, surgical complications, reoperation, and medical comorbidities. Older patients with valgus impacted AO/OTA31-B1 type injuries were made weight bearing as tolerated, whereas younger patients with mostly 31-B2 and 31-B3 fracture types were non-weightbearing at least six weeks.

Results: Fifty-eight patients with femoral neck fractures were identified treated with the FNS implant with at least three months of radiographic follow up. Reoperation rate across all injury patterns was 5.17%. Average age was 61 +/- 26 years, with 50% female patients. Thirty-five patients had low energy, nondisplaced or valgus impacted femoral neck fractures whereas twenty-three sustained high energy Pauwel's II or III injury patterns. There were two reoperations in the high energy group for nonunion or AVN and one reoperation in the geriatric low energy group for nonunion. Overall, blood loss was 186 +/- 193 ml, however, only 128 +/- 54 ml in patients of the low energy mostly stable fracture patterns who did not require direct open reduction but almost three times higher in the high energy group who required open reduction 74% of the time. Operative time was 115 +/- 112 minutes overall but only 35.0 +/- 13.8 minutes in the low energy group that did not require open reduction versus 205 +/- 108 minutes in the high energy group that included eleven patients with ipsilateral femur fractures.

Conclusion: Early results of the FNS implant are promising and seem non-inferior to implants currently used to stabilize femoral neck fractures. More research with a larger number of patients and longer follow duration are needed to confirm these early results.

Patients With Previous COVID-19 Infection Can Safely Undergo Total Joint Arthroplasty

Samuel Rosas, MD, PhD, MBA, David C. Pollock, MD, Martin Roche, MD, Farideh Najafi, MD, Leonard Buller, MD, Chad Krueger, MD

Introduction: Covid 19 has affected many. Therefore, the purpose of this study was to evaluate whether Covid-19 would impact outcomes of TJA.

Methods: A retrospective review of the Mariner Dataset was conducted. Patients who underwent TKA or THA between 2019 and 2020 and had a previous diagnosis of Covid and were 50 - 85 were selected. TKA and THA were independently studied, and patients were propensity score matched based on age, gender, Charlson comorbidity index, year of surgery, US state of surgery, and 28 comorbidities at a 1:1 ratio. Comorbidities were compared before and after matching and 90-day outcomes were compared using descriptive statistics, t-tests, Chi squares and Cox regressions. We hypothesized that 90-day outcomes in those with a history of Covid would be similar to matched controls.

Results: Our query identified a total of 661 patients who underwent TKA and 635 THAs. Propensity scores satisfactory matched (>99%) both cohorts with demographics after matching being similar (p>0.05 for mean age, gender, age distribution, region of surgery). Moreover, comorbidity rates were similar after matching for 23/28 for THA and 25/28 for TKA. Outcomes of TKA with previous Covid were similar except for greater pneumonia (2.2% vs 1.2%, p=0.04) and LOS (ave 3.1 vs 2.57, p=0.027). For THA, pneumonia was also greater 6.9% vs 3.5, p<0.001) as hematomas (0.4% vs 0%, p=0.04), LOS (ave 4.5 vs 3.6) and reimbursements (p<0.001).

Discussion: Our study found that patients with a history of Covid can safely undergo TJA albeit a greater risk of 90-day pneumonia should be considered. Anticoagulation used after surgery should carefully be selected as to avoid thromboembolic events but also consideration should be taken towards hematoma formation.

Conclusion: 90-Day outcomes of TJA in those with Covid are similar to a propensity matched cohort albeit pneumonia rates are almost twice the amount.

Pectoralis Major Transfer for Winged Scapula via a Transaxillary Approach

William Yetter, MD, Tara Nagaraja, MD, Zhongyu Li, MD

Introduction: Medial scapular winging (MSW) is a problem that most commonly results from serratus anterior paralysis from long thoracic nerve injury leading to scapular dyskinesis. Transfer of the Sternal head of the pectoralis major tendon to the inferior pole of the scapula is a well-known intervention for symptomatic winging. Majority of reports show that repair is done through an anterior deltopectoral incision and posterior incision. Using a transaxillary approach for harvest of the pectoralis major tendon is not well described in the literature, but offers similar results with improved cosmetics. We performed a retrospective case series to look at patients that underwent pectoralis major transfer for MSW to look at outcomes using this approach.

Methods: This retrospective case series review included 7 patients with serratus anterior dysfunction leading to medial scapular winging. All patients underwent transfer of the sternal head of the pectoralis major to the inferior medial edge of the scapula after failing conservative treatment. Harvest of the pectoralis major tendon was obtained via a transaxillary approach instead of the traditional Deltopectoral approach.

Results: Mean preoperative to postoperative active forward flexion increased from 96.6 to 136.6 (one patient excluded because preoperative measurement was not available). 6/7 patients had improvement in active forward flexion (AFF) vs pre-op and only one patient required an additional surgery. 5/7 patients reported improvement in pain after surgery at one year of follow up. 4 patients did not have any winging post-op. 2 patients had mild scapular winging and only one patient had recurrence of winging. None of the patients had complications from the transaxillary incision site post-op.

Conclusion: Transfer of the sternal head of the pectoralis major tendon to the inferior pole of the scapula via a transaxillary approach is a viable option with similar results to transfer utilizing a deltopectoral approach. The transaxillary approach allows for adequate visualization of the pectoralis major tendon and a more direct path to the inferior pole of the scapula.

Outcomes of Trauma Patients with Orthopedic Injuries Unaffected by Orthopaedic Surgeons as Part of the Primary Trauma Codes Team

Amy Trammell, MD, Pallavi Juneja, Chukwuweike Gwam, MD, Rachel Bordelon, Nina Videau, MD, Jason Halvorson, MD

Introduction: The current United States healthcare system has no standard protocol for the physicians who should be included in the initial 'trauma team' responding to leveled trauma codes. In military combat hospitals, it was determined that multidisciplinary trauma care systems improved patient outcomes by increasing communication, providing efficient, high-quality care, and increasing expeditious disposition of casualties. However, to date, no analysis has been done after the implementation of the multi-disciplinary system to measure the potential benefit to patient care.

Methods: At the current institution, a Level I trauma center, a retrospective chart review was performed to compare patient care outcomes when an orthopaedic surgeon was present (Group A, March 15, 2017 to March 14, 2018) and was not present (Group B, May 1, 2018 to April 30, 2019) at trauma codes. Patient care outcomes were measured by the number of missed orthopaedic injuries, the time until antibiotics are administered for open or dirty wounds, and the time until emergent orthopaedic injuries are posted for and brought to the operating room (OR).

Results: The first group (Group A) totaled 603 patients; the second group (Group B) totaled 769 patients. The average time to antibiotics was 51 minutes in Group A and 59 minutes in Group B. The average time it took to post emergent cases was 147 minutes for Group A and 176 minutes for Group B. The average time to the OR was 300 minutes for Group A and 401 minutes for Group B. No statistically significant differences were appreciated in any metrics of patient outcomes as stated above. Regarding missed injuries, there were 17 missed injuries in Group A and 23 missed injuries in Group B. There was also no statistical difference in missed injury between the two groups.

Conclusion: There is no significant difference in measured patient outcomes between Group A (with an orthopaedic resident at trauma codes) and Group B (without an orthopaedic resident at trauma codes). Based on these results, we recommend that the orthopaedic surgeons be involved in trauma codes by consult only. This allowed for a more streamlined approach in the management of trauma patients.

Ascorbic Acid as a Potential Radioprotectant in a Simulated Soft-Tissue Sarcoma Model

Tianyi David Luo, MD, Andy Kwok, Kerry Danelson, PhD, Cynthia Emory, MD, Jeffrey Willey, PhD

Introduction: Radiation exposure has well-documented deleterious effects on the musculoskeletal system that result in potentially devastating clinical consequences, including muscle fibrosis, degenerative joint damage, and substantial bone loss. L-ascorbic acid (AA), also known as vitamin C, exerts an anabolic effect on bone by promoting osteoblast differentiation and osteoclast apoptosis *in vitro*. Its safety profile and antioxidant properties make for an ideal therapeutic to prevent radiation-associated bone loss. The purpose of this study was to elucidate the *in vitro* and *in vivo* effects of AA using a clinically relevant model of sarcoma radiotherapy.

Methods: Osteoblast (MC3T3-E1) and osteoclast (RAW 264.7) precursors were cultured in conditions of increasing AA doses, then irradiated at 2-Gy after 24 hours. Cell differentiation, and resorption activity was quantified using established methods. ELISA and PCR were performed to assess the levels of osteoprotegrin (OPG) and receptor activator of nuclear factor kappa-β ligand (RANKL) production from osteoblasts. An *in vivo* study was performed in 68 adult female Sprague-Dawley rats divided into four groups: irradiated (n=18), non-irradiated (n=15), irradiated+AA treatment (n=17), and non-irradiated+AA treatment (n=18). AA supplementation (2mg/mL) was provided in drinking water to animal subjects for the entire study duration. Using an established model of extremity soft-tissue sarcoma radiotherapy, the irradiated groups underwent radiation to the right hindlimb, which were harvested after four weeks for biomechanical and micro-computed tomography (microCT) analysis.

Results: Osteoblast differentiation and mineralization was significantly lower after radiation in untreated control (p=0.002) and low-dose AA groups (p=0.049). Higher doses of AA resulted in similar mineralization between irradiated and non-irradiated cells. OPG production from osteoblasts increased significantly with AA treatment compared to untreated control regardless of radiation. Conversely, RANKL production increased significantly compared to non-irradiated control conditions. Osteoclast differentiation (p=0.013) and resorption (p<0.01) significantly increased after radiation. AA treatment decreased osteoclastogenesis and resorption activity in a dose-dependent fashion. Neither radiation nor AA treatment exerted an effect on biomechanical properties in rat cortical bone. Trabecular number significantly decreased on microCT after radiation (p<0.001), but did not recover in AA-treated rats.

Conclusion: Ascorbic acid attenuated the effects of radiation on osteoblast differentiation and mineralization, as well as osteoclastogenesis and bone resorption. Additionally, radiation increased production of RANKL from osteoblast, which promotes osteoclastogenesis. The addition of AA promoted the production of OPG, which blunts the effects of RANKL. Conversely, early prophylactic oral AA treatment in rats was not effective in reversing the deleterious effects of radiation on trabecular bone compared to non-irradiated controls.

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Acknowledgments

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