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TITLE: Vitamin D Supplementation for Prevention of Post-Traumatic Osteoarthritis: Evaluation in Animal and Clinical Models

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Abstract

The goals of this translational study are to create an animal model of joint injury and evaluate the impact of Vitamin D in prevention and progression of PTOA. Concurrently, we will evaluate a clinical cohort of USMA cadets treated for ACL tear, with pre- and post-injury serum 25-hydroxy-Vitamin D levels and correlation with joint space narrowing and biomarkers of cartilage injury. If Vitamin D supplementation can prevent the onset of often rapid joint destruction that occurs with PTOA, this simple and safe intervention could potentially translate to pre-emptive treatment in high-risk military occupations. In addition, Vitamin D could be used at the time of injury to possibly mitigate ongoing articular cartilage damage.

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Introduction

The purpose of this study is to create an animal model of joint injury and evaluate the impact of Vitamin D supplementation in prevention and progression of post-traumatic osteoarthritis (PTOA). Concurrently, this funding supports an add-on study at the United States Military Academy, to evaluate a clinical cohort of USMA cadets treated for anterior cruciate ligament (ACL) tear, with pre- and post-injury serum 25-hydroxy-Vitamin D levels and correlation with joint space narrowing and biomarkers of cartilage injury. If Vitamin D supplementation can prevent the onset of often rapid joint destruction that occurs with PTOA, this simple and safe intervention could potentially translate to pre-emptive treatment in high-risk military occupations. In addition, Vitamin D could be used at the time of injury to possibly mitigate ongoing articular cartilage damage.

Keywords

Murine, post-traumatic osteoarthritis, military, ACL, knee, medial meniscus, femoral, tibial, 25-hydroxy-Vitamin D, supplementation

Overall Project Summary

This report represents the first annual summary of work for the 2014-15 year of funding for this project. Reporting will be organized by task as noted in the Statement of Work.

<u>Specific Aim 1: to evaluate the impact of systemic Vitamin D supplementation on the initiation and development of surgically induced OA in a murine model</u>

Objectives: Vitamin D Supplementation and Rodent Surgery
Imaging/Tissue Analysis of Surgical Model

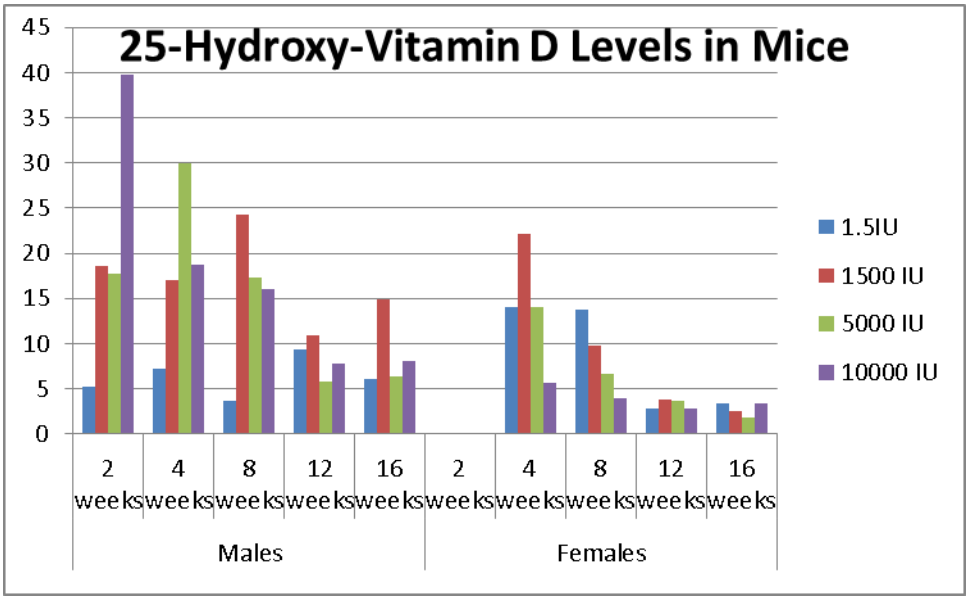
Progress

- Institutional IACUC and federal ACURO applications were submitted and approved, respectively, in May and June of 2014.
- We initiated the animal model using C57-Bl6 mice fed with four types of supplemented chow:
    - 1.5IU/kg Vitamin D (minimal Vitamin D - control)
    - 1,500 IU/kg Vitamin D (regular food)
    - 5,000 IU/kg Vitamin D
    - 10,000 IU/kg Vitamin D
- We pretreated mice with these feeding regimens for 2 weeks and obtained blood for 25-hydroxy-Vitamin D analysis.
- We then performed destabilization of the medial meniscus (DMM)[1] surgery (with sham surgery on the opposite leg as control) to surgically initiate osteoarthritis in each feeding subgroup, and sacrificed mice at 4, 8, 12, and 16 weeks.

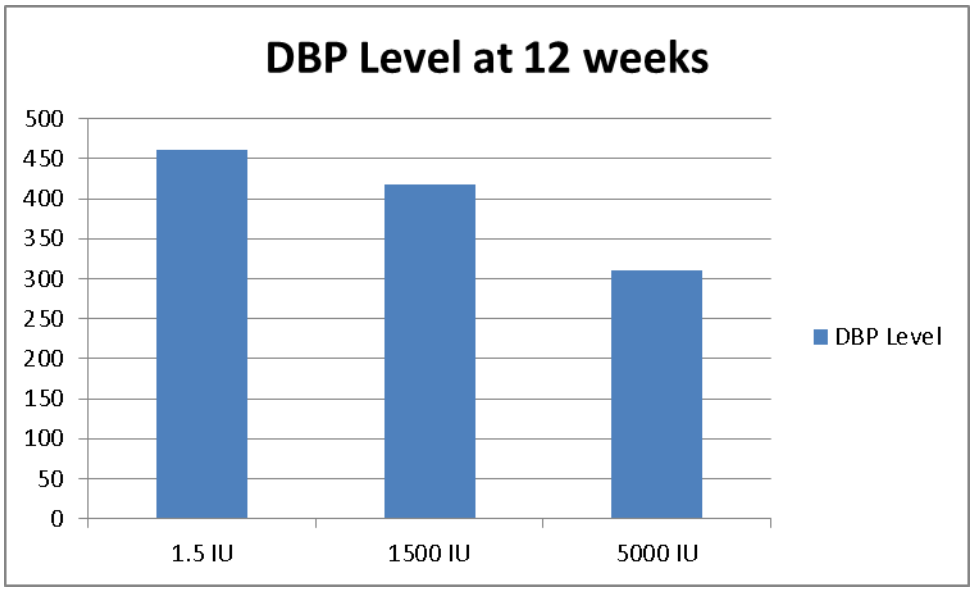
- We also obtained blood for 25-hydroxy-Vitamin D analysis in each group prior to sacrifice.
- We then performed histology, faxitron Xray imaging, and selected micro-CT analysis of the murine. We chose to perform histology as opposed to immunohistochemistry as the first round was to determine optimal timepoints and surgical technique to initiate OA reliably.
- A group of experienced animal histology investigators performed a blinded rating of the degree of osteoarthritis of the murine knee histology using the Glasson scale.[2]

Results

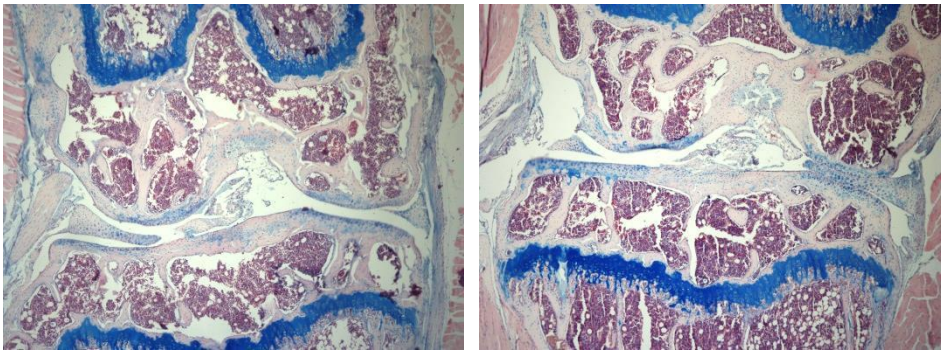
- Using ELISA, we evaluated differential levels of circulating 25-hydroxy-Vitamin D in each of the 4 groups of mice fed different levels of Vitamin D in feed over time, and noted initial increase in circulating 25-hydroxy-Vitamin D levels that differed by feeding dose, with metabolic equilibration over time. While high doses of Vitamin D have been previously shown to be well-tolerated in mice,[3] the findings of metabolic equilibration over time have not been previously reported. In males, the dose-response from minimal to high levels was shown best at 2 and 4 weeks; we did not have data on females in this group at 2 weeks.



- We also tested Vitamin-D binding protein (DBP), which binds Vitamin D metabolites in plasma up to a certain species-specific level. It has been shown that free Vitamin D metabolites are active, and thus once DBP binding is maximized, the free metabolite levels will increase.[4] Our results showed the highest levels of DBP in the mice given minimal Vitamin D, with DBP decreasing as supplementation increased.

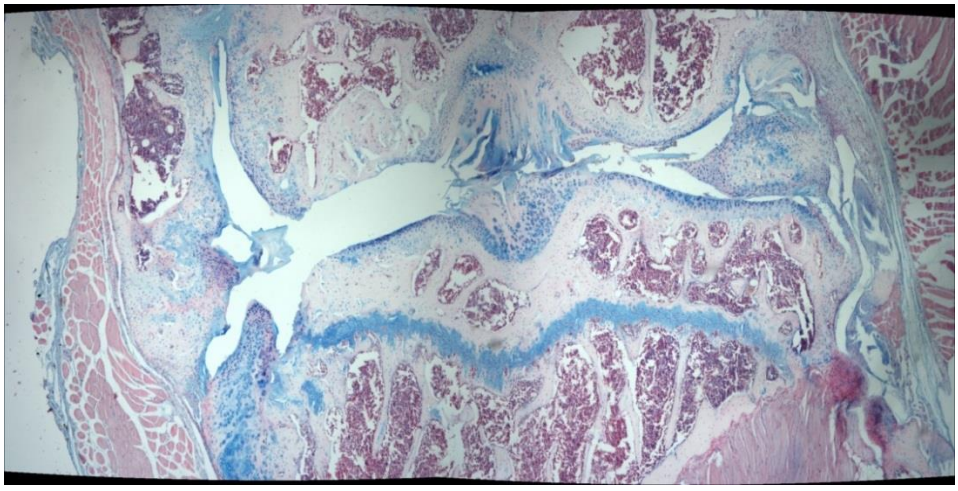


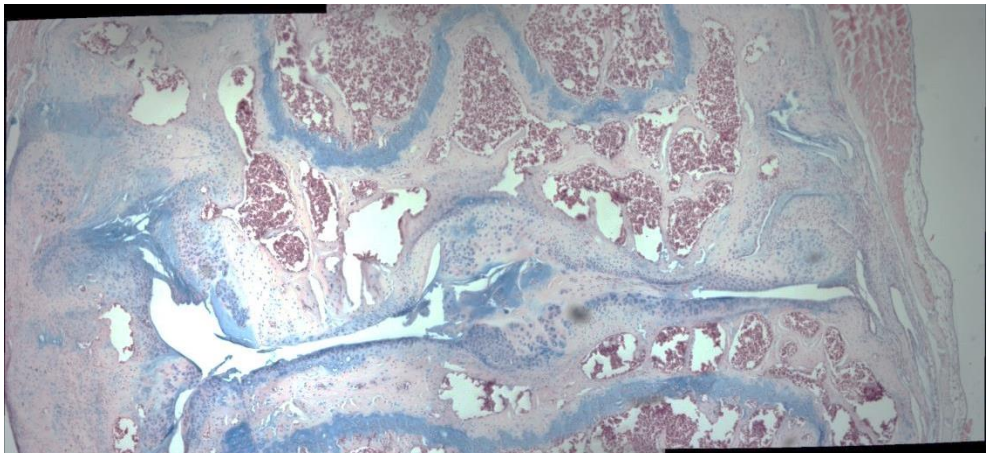
- Histology imaging with Glasson grading[2] showed minimal signs of osteoarthritis overall, but particularly at the 4 and 8 weeks timepoints. This calls into question the reliability of DMM alone to induce osteoarthritis.



1500 IU Vit D in female mouse at 4 weeks; 5000 IU Vit D in male at 8 weeks

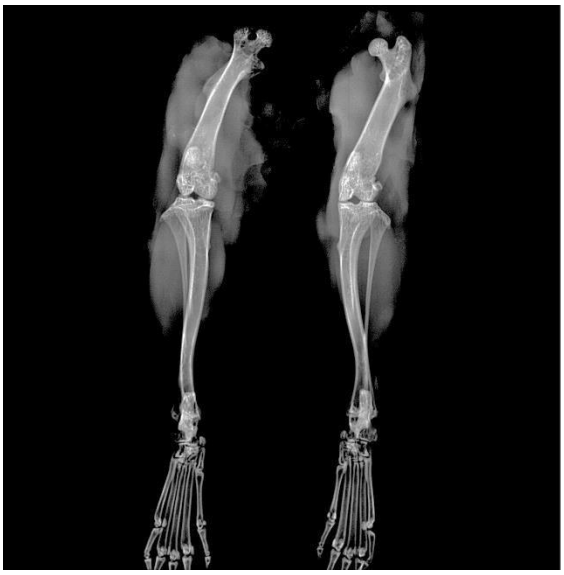
- At 12 and 16 weeks, we noted more consistent signs of osteoarthritis.

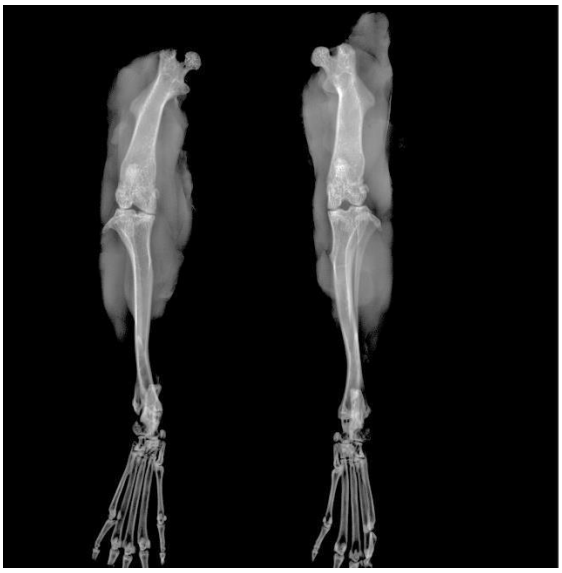




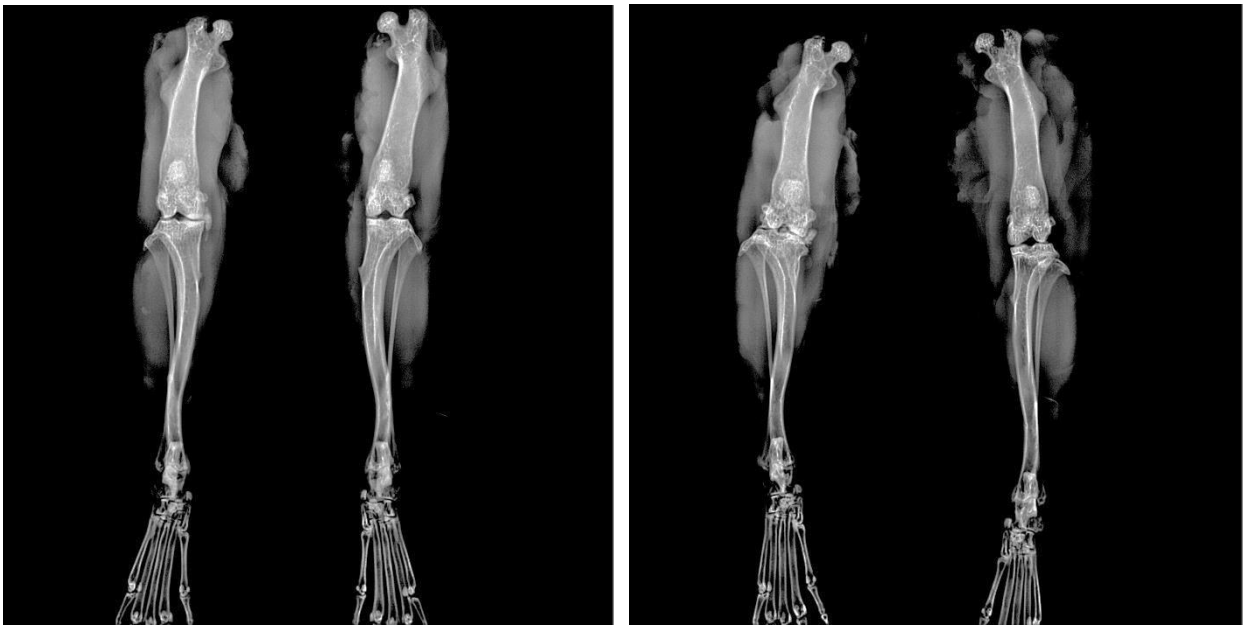
Both views above in 16 week mice, top 1.5IU Vitamin D; bottom 1500 IU Vitamin D supplementation.

Faxitron imaging showed progressive signs of osteoarthritis over time, but again increased most at 12 and 16 weeks:

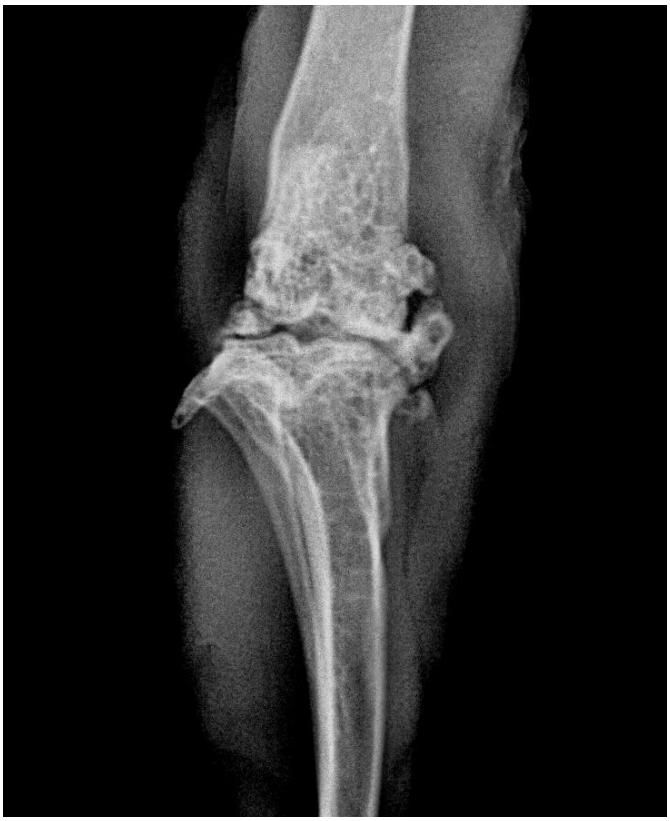




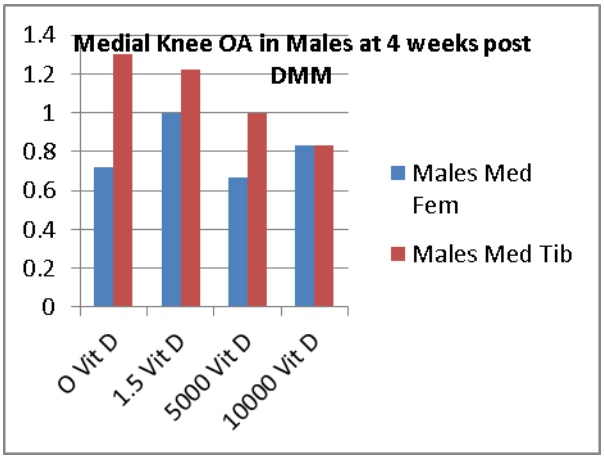
4 and 8 week views with DMM (surgical) limb on left, sham surgery on right; for comparison, all are of male mice with 1500 IU (normal) feed levels.

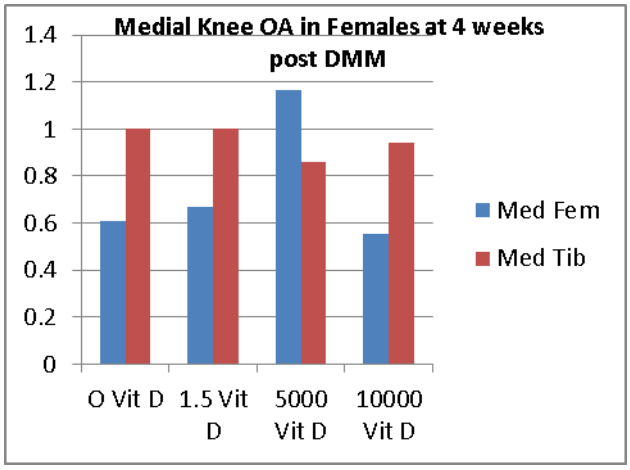


12 and 16 week radiographs on left and right respectively. Note the osteophytes on both left murine legs in these radiographs, as shown in this magnified example:

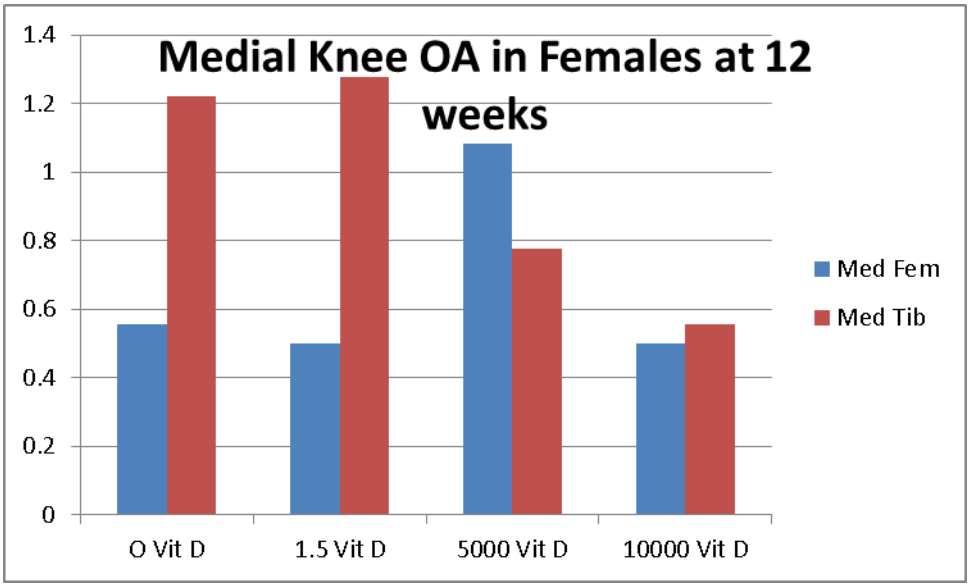


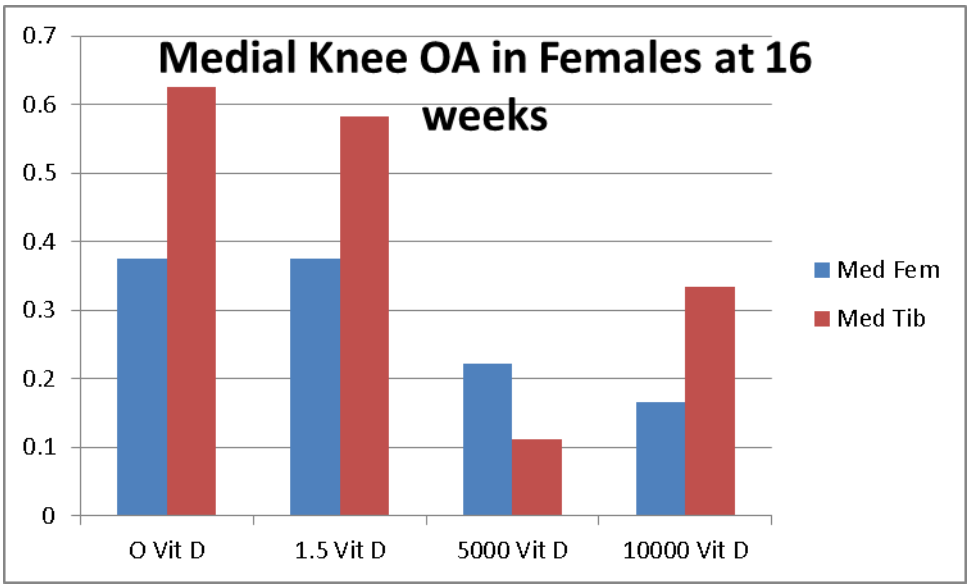
- In performing Glasson rating of osteoarthritis across all four groups with Vitamin D supplementation, results showed the following:
    - Overall minimal induction of osteoarthritis in the earlier timepoints
    - No correlation between Vitamin D supplementation and osteoarthritis in male or female mice at 4 or 8 weeks.



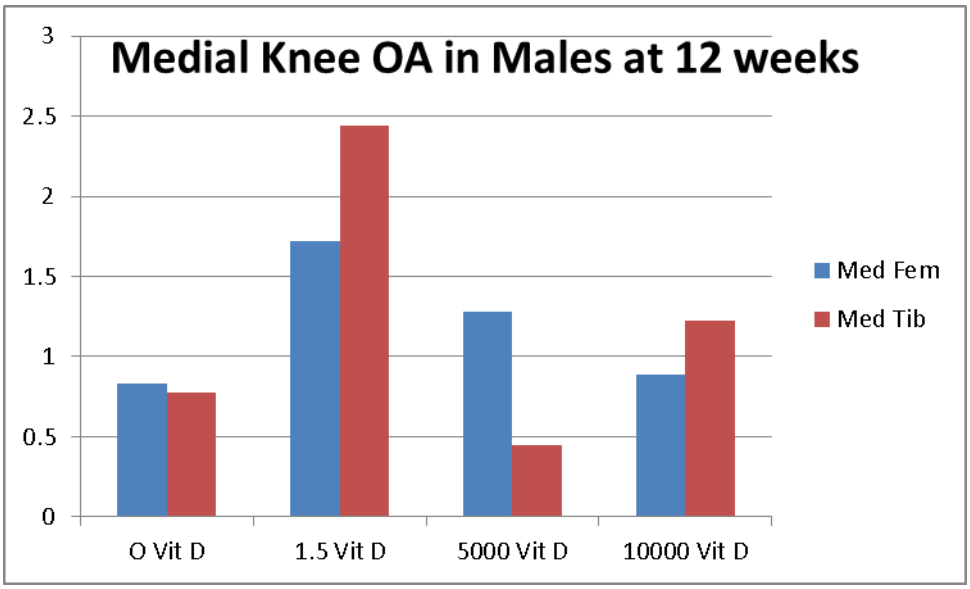


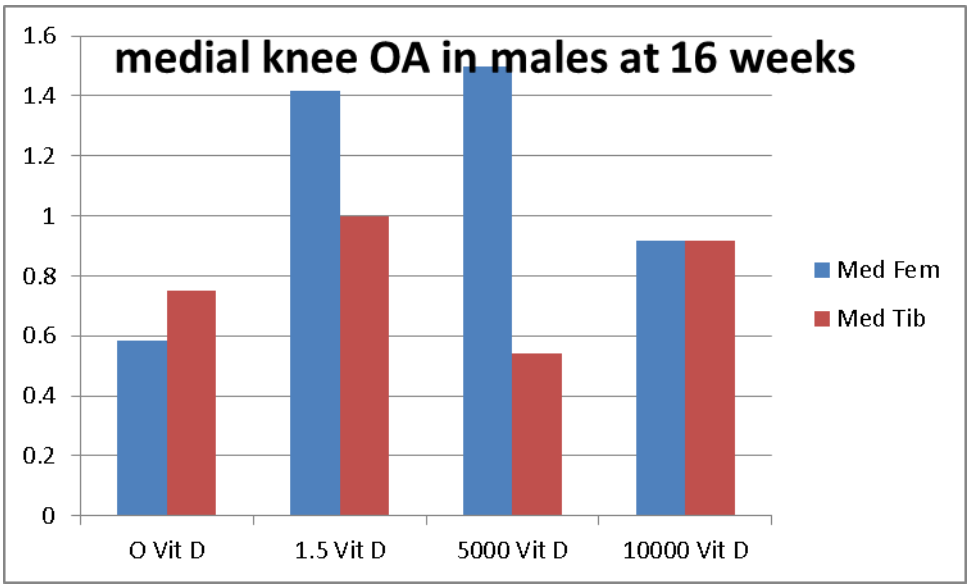
    - In female mice at 12 and 16 weeks, ratings showed decreased OA histologically on the tibial side at 12 weeks and on both the tibial and femoral sides at 16 weeks.



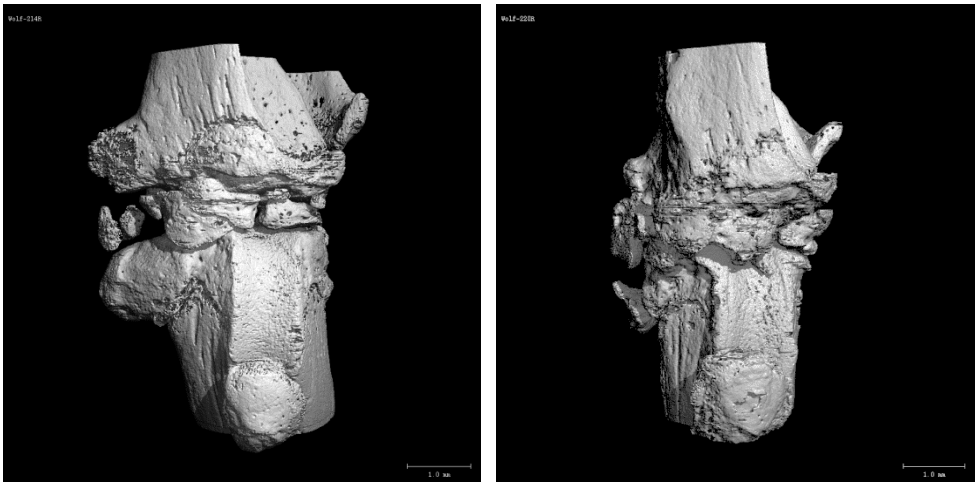


- We did not observe this effect in male mice, as shown below:





Micro-CT analysis was performed only in the 16 week subset to evaluate the qualititative degree of osteoarthritis visible. This modality is highly sensitive, as it shows osteophytes and joint irregularity clearly:



Accomplishments

- Established animal model with successful supplementation of Vitamin D via feed – **but need to refine surgical technique and timepoints to most accurately induce and measure osteoarthritis at baseline. We have submitted a proposal to IACUC and ACURO to drop the 4 and 8 week timepoints and use 12, 16, and 20 weeks; and to add ACL transection to a subgroup of mice (to be evaluated at 8 weeks) in addition to DMM technique.**
- Established reliable histology and Glasson measurement techniques

- We have some exciting potential evidence of Vitamin D mitigation of OA in female animals.

Specific Aim 2: To evaluate the serum 25-hydroxy-Vitamin D status of military cadets before and after ACL injury and reconstruction and correlate these findings with biomarkers of articular cartilage injury as well as radiographic joint space narrowing

Objectives: Initiation of Add-on to Existing Study
Subject Enrollment/Specimen and Data Collection

Progress

- We obtained Keller Army Hospital and UConn Institutional Review Board (IRB) approval in October 2014 to add-on to the existing study of ACL tears in United States Military Academy (USMA) cadets and biomarkers for initiation of PTOA. Our IRB approval allows us to also measure 25-hydroxy-Vitamin D levels in pre-injury, at-injury, at-surgery, and post-surgical serum samples from USMA subjects.
- To date, study participation is as follows per Dr. Cameron (USMA PI):
    - 63 ACL injured cadets screened
    - 36 ACL injured cadets enrolled in study; this is on target for 90-100 cadets to be enrolled over three years.
    - Matched control subjects are also enrolled for each ACL injured case.
- We will not perform Vitamin D testing until we have reached target enrollment, both for reliability of testing (batched testing is much more comparable) and budget costs.

Results/Accomplishments reporting is deferred pending further enrollment for this segment of the study.

Problems/Changes

- Based on the observations of minimal osteoarthritis in the early timepoints, we plan to address this with two changes:
    - Investigation of the impact of adding anterior cruciate ligament (ACL) transection to the DMM model on development of OA – to be evaluated at 8 weeks
    - Deleting early timepoints of 4 and 8 weeks, and addition of one additional timepoint in order to evaluate mice at 12,16, and 20 weeks after surgical induction of osteoarthritis.
    - We have received institutional IACUC approval for these changes
    - This proposed amendment has been submitted to ACURO and is pending approval.

Key Research Accomplishments

- The main accomplishment thus far is the preliminary finding of a correlation between increased Vitamin D supplementation and decreased OA histologically in the murine model. It is interesting to note that this was only seen in females, implying a possible sex-differential effect. Van Grootheest et al showed in a recent epidemiological study in the Netherlands that circulating Vitamin D levels were higher in women than men, particularly in the group under 35 years.[5] In contrast, Rabenberg et al showed no sex differences in 25-hydroxy-Vitamin D levels in an adult census study.[6] In our second and third rounds of the animal study, we can evaluate whether this is a consistent effect and whether the sex difference is still present.

Conclusion

This combined animal and clinical study is making progress on both fronts. We have successfully established a mouse model of surgical induction of PTOA and have demonstrated that we can effectively supplement with dietary Vitamin D in varying doses. Additionally, we have obtained some interesting preliminary evidence that Vitamin D in supraphysiologic doses mitigates the degree of PTOA in female animals. This will be further investigated as we refine the animal models in the upcoming rounds of animal surgery.

Our add-on to the clinical study has been successfully initiated and over one-third of subjects has been enrolled. Data from these subjects will be available for analysis once we perform batched serum Vitamin D testing, at the end of enrollment.

Publications, Abstracts, and Presentations - Nothing to report

Inventions, Patents, and Licenses – Nothing to report

Reportable Outcomes – Nothing to report

Other Achievements - Nothing to report

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Appendix

- PI CV

- Relevant clinical research from PI – recent publication about Vitamin D and bone turnover levels in patients with distal radius fractures

CURRICULUM VITAE
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EDUCATION

1987-1991	University of Maryland College Park, MD B.A., *magna cum laude* with General Honors
1991-1996	University of Pennsylvania School of Medicine Philadelphia, PA M.D., May 21, 1996

POST-DOCTORAL EDUCATION

1996-1997	Brown University Department of Surgery - **Internship** Providence, RI Director: Kirby I. Bland, MD
1997-2001	Brown University Department of Orthopaedic Surgery-**Residency** Providence, RI Director: Michael G. Ehrlich, MD
2001-2002	Brown University Division of Orthopaedic Trauma, Department of Orthopaedics – **Orthopaedic Trauma Fellowship** Providence, RI Director: Peter G. Trafton, MD
2002-2003	Mayo Clinic Division of Hand Surgery, Department of Orthopaedics – **Hand Surgery Fellowship** Rochester, MN Director: Robert D. Beckenbaugh, MD/Richard A. Berger, MD, PhD

CERTIFICATION

2005/2013	Board Certified (Diplomate) - American Board of Orthopaedic Surgery (Chicago, Illinois)
2006/2013	Certificate of Added Qualification (Hand Surgery) - American Board of Orthopaedic Surgery (Chicago, Illinois)

LICENSURE

Licensed in Connecticut, Colorado, Minnesota, Illinois and Georgia

ACADEMIC APPOINTMENTS

2003 – 2009	Assistant Professor, Department of Orthopaedic Surgery, University of Colorado Health Sciences Center
2009-2010	Associate Professor, Department of Orthopaedic Surgery, University of Colorado-Denver
2010-2015	Associate Professor, Department of Orthopaedic Surgery, University of Connecticut
2015-present	Professor, Department of Orthopaedic Surgery, University of Connecticut

TEACHING/EDUCATIONAL APPOINTMENTS

University of Colorado School of Medicine
- Co-Director, Musculoskeletal Block (required 3rd-year course) (2007-2010)
- Director, Orthopaedic Medical Student Courses/Sub-Internships (2007-2010)

University of Connecticut School of Medicine
- Curriculum Reform Clinical Education Committee (2015-2016)
- Admissions Interviewer (2014-2015)
- Instructor, Musculoskeletal Block (2010-present)

HOSPITAL APPOINTMENTS

2003-2010	University of Colorado Hospital
2004-2010	Denver Veterans Administration Medical Center
2004-2010	Denver Health Medical Center
2004-2010	The Children's Hospital of Denver
2005-2010	Rose Hospital (Denver)
2010-present	John Dempsey Hospital
2014-present	Connecticut Children's Medical Center

AWARDS & HONORS

2014	Connecticut Technology Council Women of Innovation Award
2013	American British Canadian Traveling Fellowship – American Orthopaedic Association
2010	Sterling Bunnell Traveling Fellowship –American Society for Surgery of the Hand
2008	Clinician Scientist Award – Orthopaedic Research and Education Foundation
2008	Leadership Fellows Program – American Academy of Orthopaedic Surgeons
2007	John J. Fahey North American Traveling Fellowship –American Orthopaedic Association
2006	American Society for Surgery of the Hand – Young Member Leadership Program
2006	Alexandra Kirkley Traveling Fellowship - Ruth Jackson Orthopaedic Society
2005	United States Bone and Joint Decade Young Investigator
2001	Haffenreffer Award for Resident Research
1996	William G. Munn Memorial Prize for Promise in Orthopaedics
1995	Alpha Omega Alpha Medical Honor Society

1990 Phi Beta Kappa
1987 Chancellor's Scholar (full four-year college merit scholarship)

PROFESSIONAL SOCIETY MEMBERSHIP

American Society for Surgery of the Hand (Active Member, 2007 - present)
American Academy of Orthopaedic Surgeons (Fellow, 2007 – present)
American Orthopaedic Association (Member, 2012-present)
American Association of Hand Surgeons (Member, 2003-present)
Orthopaedic Leadership Institute (2010-present)
Ruth Jackson Orthopaedic Society (2002-present)
Rocky Mountain Hand Surgery Society (2003-present)
Colorado Orthopaedic Society (2004-2010)
Connecticut Orthopaedic Society (2010-present)
New England Orthopaedic Society (2015-present)

JOURNAL REVIEW

Deputy Editor, *Journal of Hand Surgery* (2011-present)
Associate Editor, Scientific – *Journal of Hand Surgery* (2009-present)

Associate Editor, Hand and Microsurgery, *Journal of Bone and Joint Surgery Reviews* (2013-present)

Editorial Board, *Orthopedics* (2003-present)

Web Updates Editor, *Skeletal Trauma* (2008-2015)

Expert Contributor, *British Medical Journal Best Practice* website (2014-2015)

Consultant Reviewer
- *Journal of Bone and Joint Surgery* (2007-present)
- *Journal of Hand Surgery* (2008-2009)
- *Journal of Bone and Joint Surgery – British* (2009-present)
- *Clinical Orthopaedics and Related Research* (2007-present)
- *Orthopedics* (2003-present)
- *Hand (*2010-present)
- *British Journal of Sports Medicine* (2013-present)
- *International Journal of Sports Medicine* (2012-present)

Editor, Hand Module, *Orthopaedic Hyperguide* (2008-2011)

COMMITTEES/SERVICE

American Society for Surgery of the Hand
- Council Member at Large (2014-2017)
- Program Co-Chair, Annual Meeting (2014)
- CME Guidelines Task Force (2015)
- Commercial Support Committee (2012-2015)
- Touching Hands Project (2012-2015)

Bunnell Traveling Fellows Committee (2010-2014)
Products and Publications Committee (2005-2011)
Annual Meeting Scientific Displays Committee (Member, 2006-2015; Chair, 2009-2012)
Mentoring Task Force (2006)
Resident Education Committee (2007-2010)
Crucial Elements of Hand Surgery Committee (2007-2008)
Courses and Meetings Advisory Committee (2007-2010)
Young Members Steering Committee (Member, 2008-2010; Chair 2010-2011)
Diversity Committee (2008-2011)
Membership Task Force (2009)

American Foundation for Surgery of the Hand
Board Member-at-Large (2012-2014)
Complus Manus Committtee (2012-2014)
Nominating Committee (2012-2013)
Touching Hands Project (2012-2013)

American Academy of Orthopaedic Surgeons
Chair, Residents, Fellows, and Candidate Members Subcommittee (2008-2011)
Member (2006-2009)
Co-Editor, Residents' Monthly E-Newsletter (2007-2009)
Co-Chair, Leadership Development Endowment Fund Meeting Committee (2010-2012)

American Board of Orthopaedic Surgeons/National Board of Medical Examiners
Oral Boards Examiner (2015)
Joint Committee for CAQ Question-Writing Task Force (2011-2015)

Orthopaedic Research and Education Foundation
Grant Reviewer (2010-present)

Ruth Jackson Orthopaedic Society Governing Board
President (2014-2015)
Vice- President (2013-2014)
Secretary (2011-2013)

Orthopaedic Leadership Institute
Inaugural Meeting Program Coordinator (2011)

American Association of Hand Surgery
Research Committee (2008-2011)

Board of Directors, Rocky Mountain Hand Surgery Society (2008-2011)
Secretary/Treasurer (2008-2009)
Vice President (2009-2010)

New England Hand Society (2011-present)

Department of Orthopaedic Surgery, University of Connecticut
Research Committee (2011-present, Chair 2012-present)
Admissions Committee member (2010-present)
OR Lean Committee (2014-15)

Colorado Multiple Institutions Review Board (IRB) reviewer, 2004-2008

Faculty Advisor, Orthopaedic Student Interest Group, University of Colorado School of Medicine, 2008-2010

Department of Orthopaedics, University of Colorado
Finance Committee member, 2006-2010
Academic Council member, 2007-2010
Curriculum Committee member, 2006-2010

University of Colorado Hospital Trauma Committee member, 2004-2010

Active Women's Health Initiative, University of Colorado Hospital, 2004-2010

PEER-REVIEWED PUBLICATIONS

1. **Moriatis JM**, Gannon FH, Shore EM, Bilker W, Zasloff MA, Kaplan FS: Limb swelling in patients who have fibrodysplasia ossificans progressiva. *Clin Orthop Rel Res* 336: 247-253, 1997.

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18. **Wolf JM.** The influence of ligamentous laxity and gender – implications for hand surgeons. *J Hand Surg* 34(1): 161-163, 2009.

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21. **Wolf JM**, Athwal GS, Shin AY, Dennison DG. Instructional course lecture: Acute trauma to the upper extremity: what to do and when to do it. *J Bone Joint Surg Am* 91(5):1240-1252, 2009.

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23. **Wolf JM**, Dawson L, Mountcastle SB, Owens BD. The incidence of scaphoid fracture in a young, active population. *Injury*, (epub) Jun 2009.

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27. **Wolf JM,** Mountcastle SB, Burks R, Sturdivant RX, Owens BD. Epidemiology of lateral and medial epicondylitis in a military population. *Mil Med* 175(5): 336-339*,* 2010.

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72. Owens BD, **Wolf JM,** Clifton K, Svoboda SJ, Cameron KL. The association between serum relaxin and subsequent shoulder instability. Accepted, *Orthopedics,* 2015.

73. Rohde R, Adams JE, **Wolf JM.** Where are the women in orthopaedic surgery? Submitted, *Clin Orthop Rel Res,* 2015.

NON-PEER REVIEWED PUBLICATIONS

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2. **Wolf JM**: *Editorial:* The genetic key to a rare disease and its impact on orthopaedics. *Orthopedics* 29:1, 2006.

3. **Wolf JM**, Athwal GS, Hoang B, Mehta S, Owens BD. Report from the 2007 AOA North American Traveling Fellowship. *J Bone Joint Surg Am* 90(5):1160-1164, 2008.

4. **Wolf JM.** Web commentary on: Pyrolytic carbon resurfacing arthroplasty for osteoarthritis of the proximal interphalangeal joint. *J Bone Joint Surg Am*, 2011.

5. **Wolf JM.** *Editorial:* New iPad App for the Journal of Hand Surgery, *J Hand Surg,* 37 (9): 1763-1764, 2012.

6. **Wolf JM.** *Editorial:* Do we need to treat tennis elbow? *Orthopedics* 35(11): 921-922, 2012.

7. Scher DL, Ferreira JD, Cote ML, Abdelgawad A, **Wolf JM.** *Editorial:* The need for musculoskeletal education in primary care residencies. *Orthopedics,* 37(8): 511-513, 2014.

8. Wolf JM. *Editorial:* Raising the bar: the use of standardized reporting outcomes. *J Hand Surg* 39(10):1905-1906, 2014.

ELECTRONIC MEDIA

1. **Wolf JM**, Lawson AB, Mallette P, Leppek N, Spitzer VM: Wrist and Carpal Anatomy section, *The Fractured Wrist*, Instructional DVD-video, American Academy for Orthopaedic Surgeons, 2008.

2. **Wolf JM**. Injection of the digital flexor. WebMD article, www.emedicine.com, 2008.

3. Owens BD, **Wolf JM**, Murphy T. Lateral epicondylitis. WebMD article, www.emedicine.com, 2008.

4. Scher DL, **Wolf JM**: Lateral elbow tendinopathy. American Academy of Orthopaedic Surgeons Web site: Orthopaedic Knowledge Online 2011;9(9): http://orthoportal.aaos.org/oko/abstract.aspx?article=OKO_HAN031.

TEXTBOOK CHAPTERS

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2. **Wolf JM,** Weiss APC: Arthroplasty of the hand. *In* Operative Orthopaedics, 3rd edition.Chapman MW, ed. J.B. Lippincott Company, 2000.

3. Hayes E, Carney K, **Wolf JM,** Smith J, Akelman E: Carpal tunnel syndrome. *In* Rehabilitation of the Hand and Upper Extremity, 5th edition. Mosby, Inc, 2002.

4. **Wolf JM.** Dupuytren's disease. *In* Hand Surgery, 1st edition. Berger RA, Weiss APC, eds. New York: Lippincott, Williams & Wilkins, 2004.

5. **Wolf JM,** Shin AY: Proximal row carpectomy. *In* Operative Techniques in Hand and Wrist Surgery. Chung KC, ed. Philadelphia: Elsevier, 2007.

6. **Wolf JM,** Shin AY: Carpal anatomy. *In* Distal Radius Fractures and Carpal Injury: The Cutting Edge. Slutsky D, ed. Philadelphia: Elsevier, 2008.

7. D'Ambrosia P, **Wolf JM:** Metacarpophalangeal and carpometacarpal fractures and dislocations. *In* Master Skills: Fractures. Budoff JE, ed. American Society for Surgery of the Hand, 2008.

8. **Wolf JM,** Shin AY: Radius/Carpus/DRUJ - Bones and ligaments. *In* Principles and Practice of Hand Surgery. Slutsky D, ed. Philadelphia: Elsevier, 2008.

9. **Wolf JM.** Cross-finger flaps. *In* Flap Reconstruction of the Upper Extremity: A Master Skills Publication. Rayan GH, Chung KC, eds. American Society for Surgery of the Hand, 2009.

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11. **Wolf JM.** Options in failed tendon transfers. *In* Reoperative Hand Surgery. Duncan S, ed. New York: Springer, 2011.

12. Scher DL, **Wolf JM.** Ligament injuries in the hand and wrist. *In* Musculoskeletal Examination of the Elbow, Wrist and Hand. Culp RW, Katolik LI, eds. Philadelphia: SLACK Inc., *in press.*

13. Gerhardt D, **Wolf JM.** Lateral epicondylitis. *In* Evaluation and Management of Common Upper Extremity Disorders. Rohde RE, Millett P, eds. Philadelphia: SLACK Inc., 2011.

14. Young L, **Wolf JM.** Carpometacarpal arthrodesis. *In* Arthritis of the Hand and Upper Extremity. Glickel SZ, Bernstein RA, eds. Chicago: ASSH, 2011.

15. Scher DL, **Wolf JM.** Lateral elbow tendinopathy. *In* Orthopaedic Knowledge Update/Online. Rayan GH, Grana W, eds. Chicago: AAOS, 2011.

16. **Wolf JM.** The perionychium: anatomy and pathophysiology. *In* The Hand: Examination and Diagnosis, 4th edition. Rayan GH, Akelman E, eds. Chicago: ASSH, 2011.

17. **Wolf JM.** History taking and examination of the hand. *In* The Hand: Examination and Diagnosis, 4th edition. Rayan GH, Akelman E, eds. Chicago: ASSH, 2011.

18. **Wolf JM.** Hand and finger contracture. *In* The Hand and Upper Extremity Surgery Textbook. Weiss APC, Berger RA, Slutsky D, Goldfarb CA, eds. Chicago: ASSH, 2013.

19. Scher DL, **Wolf JM.** General medical conditions. *In* The Hand and Upper Extremity Surgery Textbook. Weiss APC, Berger RA, Slutsky D, Goldfarb CA, eds. Chicago: ASSH, 2013.

20. **Wolf JM.** Elbow Tendinopathies and Bursitis. *In* DeLee and Drez: Sports Medicine. Miller M, ed. Philadelphia: Elsevier Inc, 2014.

21. Pensak M, **Wolf JM.** Soft tissue problems. *In* Orthopaedic Revision, Della Rocca G, ed. Springer, *in press,* 2014..

22. Scher DL, **Wolf JM,** Nesti L. Hand, wrist, and elbow injuries. *In* Musculoskeletal Injuries in the Military. Owens BD and Cameron KL, eds. Springer, *in press,*2014.

23. Dukas A, **Wolf JM.** Management of complications of periarticular fractures of the DIP, PIP, MCP, and CMC joints. *In* Complications of Hand Fractures. Chung KC, ed. Philadelphia: Springer Inc, *In press*, 2014.

24. Marchese J, **Wolf JM.** Closed pinning of metacarpal neck/shaft fractures. *In* Case Competencies in Orthopaedic Surgery. Frank R, Provencher MT, Forsythe B, eds. Philadelphia: Elsevier Inc, *in press,* 2014.

25. Yoshida R, **Wolf JM.** Benign tumors of the skin. *In* Tumors of the Hand and Upper Extremity. Kakar S, Murray P, eds. American Society for Surgery of the Hand. *In press,* 2015.

26. **Wolf JM.** Distal radius fractures: fixation of intraarticular fracture with volar plate. *In* Distal Radius Fractures. Lawton J, ed. Philadelphia: Springer Inc, *in press,* 2015.

27. **Wolf JM.** Lateral and medial epicondylitis. *In* Advanced Reconstruction Series: Elbow. Ring D, ed. Chicago: AAOS, *in press,* 2015.

28. Yoshida R, **Wolf JM.** Thumb CMC arthroplasty. *In* Hand Surgery Update IV. Murray PM, Hammert WR, eds. Chicago: ASSH, *in press,* 2015.

29. Kozlowski R, **Wolf JM.** Basilar thumb arthritis. *In* Chapman's Comprehensive Orthopaedics, 4th edition. Chapman MW, James M, eds. Philadelphia: JP Medical Publishers, *in press,* 2015.

30. Suh N, **Wolf JM.** Hand and wrist reconstruction. *In* Orthopaedic Knowledge Update 12. Ring DR, ed. Chicago: American Academy of Orthopaedic Surgeons, *in press,* 2015.

TEXTBOOKS

1. Cannada L, **Wolf JM,** co-editors: *Guide for Women in Orthopaedic Surgery*. Ruth Jackson Orthopaedic Society, 2015.

2. Wolf JM, Editor, *Tennis Elbow: Clinical Management*. Springer: New York, 2015.

RESEARCH SUPPORT

PEER-REVIEWED

CURRENT

1. Wolf (PI) 9/1/14-8/31/15 $20,000 3% effort
   American Foundation for Surgery of the Hand
   Conditional Deletion of Relaxin Receptor in Ligament: In Vivo Model
   We will create a transgenic mouse with inducible deletion of relaxin receptor at the level of tendon and ligament using a cross of relaxin null and scleraxis-Cre mice.

2. Wolf (PI) 10/7/14-10/6/17 $750,000 10% effort
   Department of Defense/Congressionally Directed Medical Research Program
   Supplementation of Vitamin D in Prevention of Post-Traumatic Osteoarthritis: Animal and Clinical Models
   This project will study the impact of oral Vitamin D in prevention of surgically induced arthritis in a murine model, as well as evaluate Vitamin D levels in military cadets prior to and after ACL injury.

3. Wolf (PI) 7/1/14-6/30/15 $50,000 5% effort
Orthopaedic Research and Education Foundation/Goldberg Arthritis Grant
Animal Model of Vitamin D Supplementation for Prevention of Osteoarthritis
This project evaluates the potentially preventive impact of Vitamin D oral supplementation on the initiation and development of surgically induced osteoarthritis in mice.
Awarded but declined due to overlap with DOD/CDMRP grant above

4. Wolf (PI) 9/14/13-09/13/15 $20,000 3% effort
American Foundation for Surgery of the Hand
Impact of local and systemic relaxin in a murine osteoarthritis model
This study uses a murine model to examine the impact of locally and systemically delivered relaxin on the development of surgically induced osteoarthritis.

5. Chung (PI) 06/01/2011-05/30/2016 $22,500 3% effort
NIH/NIAMS RO1. WRIST Study Group
A clinical trial for the surgical treatment of elderly distal radius fractures
This multicenter randomized trial compares 3 different methods of fixation in surgically treated distal radius fractures in elderly patients.
Role: Co-investigator, PI on subcontract

COMPLETED

1. Rozental (PI) 05/01/2012-04/30/2013 $45,000 3% effort
Orthopaedic Research and Education Foundation/RJOS/DePuy
Markers of bone turnover and Vitamin D in patients with distal radius fractures
This study expands the smaller pilot study to evaluate biomarkers of bone turnover and 25-hydroxy-Vitamin D in patients with distal radius fractures, compared to controls.
Role: Co-Investigator

2. Wolf (co-PI) 09/01/11-08/31/12 $20,000 3% effort
American Foundation for Surgery of the Hand
25-Hydroxy-Vitamin D and bone turnover marker levels in patients with distal radius fractures
This study will evaluate Vitamin D and biomarkers of bone turnover in patients with wrist fractures and controls.
Role: co-PI

3. Wolf (PI) 08/20/10-06/01/11 $20,000 3% effort
University of Connecticut GCRC/CICATS Pilots and Feasibility Funds-2010
Correlation of serum relaxin with joint mobility and ligament injury and analysis for gender differences
This study will correlate serum relaxin with a prospective injury database in military cadets.
Role: PI

4. Wolf (PI) 09/01/08-08/31/10 $20,000 3% effort
American Foundation for Surgery of the Hand
Effect of relaxin on gender differences in laxity and arthritis of the thumb base

This study will evaluate hormonal effects on gender differences in thumb laxity and osteoarthritis.
Role: PI

5. Wolf (PI) 07/01/08-06/30/11 $300,000 15% effort
Orthopaedic Research and Education Foundation Clinician-Scientist Award
Does relaxin mediate gender differences in joint laxity and osteoarthritis of the thumb carpo-metacarpal joint?
This study's goal is to correlate serum relaxin levels and joint laxity in normal subjects as well as to evaluate this relationship in patients with surgically treated thumb CMC osteoarthritis.
Role: PI

6. Wolf (PI) 10/01/06-09/30/08 $20,000 3% effort
American Foundation for Surgery of the Hand
A prospective, randomized, controlled trial of autologous blood injection vs. corticosteroid injection for the treatment of lateral epicondylitis.
This is a prospective, blinded, multicenter trial to evaluate the efficacy of autologous blood injection for lateral epicondylitis.
Role: PI

7. Dawson (PI) 2/01/08-1/31/09 $1000 2% effort
Southwest Orthopaedic Trauma Association
Incidence of scaphoid fractures in a young, active population.
This study uses a military database of healthcare visits coded by ICD-9 to calculate the incidence of scaphoid fracture in a young, active population as well as analyze potential demographic risk factors for this injury.
Role: Co-investigator

8. Sobky (PI) 07/01/04-06/30/05 $5,000
Department of Orthopaedics, University of Colorado Health Sciences Center
Comparison of bending strength and load to failure of multiple volar plates.
This was a biomechanical study of the strength and stiffness of multiple plates used for fixation in distal radius fractures.
Role: Co-investigator

9. Wolf (PI) 07/01/94-06/30/95 $20,000
American Heart Association
Sequencing of bone morphogenetic proteins and effects on human osteoblast-like cells.
This was a project to evaluate the effect of BMP-2 and BMP-4 on osteoblasts in culture.
Role: PI

NON-PEER-REVIEWED

1. Wolf (PI) 01/01/04-04/01/06 $20,000
Orthologic, Inc., Phoenix, Arizona
A double-blind, randomized, placebo-controlled Phase III study to evaluate the efficacy and safety of Chrysalin on the rate of healing in distal radius fractures.
This was a multicenter trial of an injectable substance with the goal to increase healing in distal radius fractures.
Role: PI

INVITED PRESENTATIONS and LECTURES (National/International)

1. Metacarpal and Phalangeal Fractures: *Operative Treatment of Phalangeal Fractures.* Instructional Course Lecture, AAOS Annual Meeting. February 2007, San Diego, CA.

2. Trapeziometacarpal Arthritis and Other Degenerative Arthropathies of the Hand: *Evidence-Based Treatment.* Instructional Course Lecture, ASSH Annual Meeting, September 2007, Seattle, WA.

3. Kienbock's Disease: *Cases and Discussion.* Interactive Case Review, ASSH Annual Meeting, September 2007, Seattle, WA.

4. Lateral Epicondylitis: Evidence-Based Treatment in 2007. *North American Traveling Fellowship Lecture*. University of Maryland, October 5, 2007. Dalhousie University, Halifax, October 10, 2007. University of Rochester, October 17, 2007. Boston University Medical Center, October 22, 2007. Brown University, October 24, 2007. Emory University, November 1, 2007.

5. Current Trends in the Fixation of Distal Radius Fractures. *North American Traveling Fellowship Lecture*. McGill University, Montreal, October 12, 2007. Dartmouth-Hitchcock Medical Center, October 17, 2007. Massachusetts General Hospital, October 17, 2007. University of Miami Medical Center, October 29, 2007.

6. The Visible Hand: Anatomy and Virtual Surgery. *North American Traveling Fellowship Lecture*. Carolinas Medical Center, October 1, 2007. Rothman Institute, October 8, 2007. Sacre-Coeur Hospital, University of Montreal, October 16, 2007. University of Rochester, October 18, 2007.

7. Dupuytren's Disease: Outcomes and Evidence. *North American Traveling Fellowship Lecture*. Maisonneuve-Rosemont Hospital, University of Montreal, October 18, 2007. University of Florida-Jacksonville, October 31, 2007.

8. Current Trends in the Fixation of Distal Radius Fractures. Howard Rosen Tri-State Trauma Symposium, Hospital for Joint Diseases, New York, New York, October 19, 2007.

9. Acute Trauma to the Upper Extremity: What to Do and When to Do It: *The Wrist.* Instructional Course Lecture, AAOS Annual Meeting, San Francisco, California, March 2008.

10. Metacarpal and Phalangeal Fractures: *Treatment of Metacarpal Shaft Injuries and Carpometacarpal Fracture-Dislocations.* Instructional Course Lecture, AAOS Annual Meeting, March 2008, San Francisco, California.

11. Trends and Outcomes in the Fixation of Distal Radius Fractures & Gender Differences in Thumb Carpometacarpal Arthritis. *Visiting Professor:* Grand Rounds, Texas Tech University/William Beaumont Army Medical Center, July 9, 2008, El Paso, Texas.

12. The Minimum Surgical Experience. Resident Educators' Workshop, American Society for Surgery of the Hand Annual Meeting, Chicago, Illinois, September 2008.

13. Tendinopathies of the Hand and Dupuytren's Contracture. Hand Review Course, American Association of Hand Surgeons Annual Meeting, January 9, 2008, Maui, Hawaii.

14. Elbow Dislocations: Back to the Basics: *Simple Elbow Dislocations.* Instructional Course Lecture, AAOS Annual Meeting, February 2009, Las Vegas, Nevada.

15. Acute Trauma to the Upper Extremity: What to Do and When to Do It: *The Wrist.* Instructional Course Lecture, AAOS Annual Meeting, February 2009, Las Vegas, Nevada.

16. Hormonal Influences inThumb Arthritis. Research Lecture, University of Virginia, April 18, 2009, Charlottesville, Virginia.

17. Tendon Biology. ASSH Master Skills Course: Tendon Repair and Reconstruction. Chicago, Illinois, October 16-17, 2009.

18. Current Treatment Strategies in Arthritis of the Basilar Thumb Joint: *Nonoperative Treatment* and *Pantrapezial Osteoarthritis.* Symposium, AAOS Annual Meeting, March 2010, New Orleans, Louisiana.

19. Elbow Dislocations: Back to the Basics: *Simple Elbow Dislocations.* Instructional Course Lecture, AAOS Annual Meeting, March 2010, New Orleans, Louisiana.

20. The Influence of Joint Laxity and Hormones on Gender Differences in Thumb Carpometacarpal Arthritis. Grand Rounds Speaker, Columbia University Dept. of Orthopaedic Surgery, May 27, 2010, New York, New York.

21. The Use of Steroid and Hyalgan Injections for Trapeziometacarpal Arthritis. ASSH Precourse, ASSH Annual Meeting, October 7, 2010, Boston, Massachusetts.

22. Lateral Epicondylitis Treatment in 2010, Grand Rounds Speaker, University of Michigan Dept. of Plastic Surgery, November 2, 2010, Ann Arbor, Michigan.

23. Hormonal Influences on Gender Differences in Basilar Thumb Arthritis. Grand Rounds Speaker, Stanford University Dept. of Orthopaedic Surgery, January 19, 2011, Palo Alto, California.

24. Gender and Hormones in Carpometacarpal Joint Arthritis of the Thumb. Grand Rounds Speaker, University of Massachusetts Dept. of Orthopaedic Surgery, January 26, 2011, Worcester, Massachusetts.

25. Acute and Chronic Management of Mallet Injuries. ASSH Specialty Day, AAOS Annual Meeting, February 19, 2011, San Diego, California.

26. Thumb CMC Arthritis: A Survey of US Hand Surgeons. Japanese Society of Hand Surgery Annual Meeting (held online), May 2011, Aomori, Japan.

27. Hormonal Influences on the Development of Trapeziometacarpal Arthritis. Department of Rheumatology Rounds, Landspitalinn Hospital/University of Iceland, June 7, 2011, Reykjavik, Iceland.

28. Acute and Chronic Scapholunate Ligament Injury. Invited Speaker, Department of Orthopaedic Surgery, Landspitalinn Hospital/University of Iceland, June 8, 2011, Reykjavik, Iceland.

29. Lateral Epicondylitis: Treatment of a Difficulty Problem. Invited Speaker, Orkuhusid Orthopaedic Clinic, June 8, 2011, Reykjavik, Iceland.

30. Limited Incisions – Volar and Radial for Distal Radius Fractures. Wrist Injuries: State-of-the-Art, Orthopaedic Learning Center, June 24, 2011, Rosemont, Illinois.

31. Decision-Making in Post-Traumatic Arthritis of the Wrist. Wrist Injuries: State-of-the-Art, Orthopaedic Learning Center, June 25, 2011, Rosemont, Illinois.

32. Upper Extremity Trauma. Hassleholm Hospital Orthopaedic Conference, August 22, 2011, Hassleholm, Sweden.

33. Hormonal Influences on Basilar Thumb Joint Laxity. Lund University Hand Conference, August 23, 2011, Lund, Sweden.

34. Hormones as Etiology for Thumb Arthritis. The Thumb CMC Joint: Anatomy, Hormones, Biomechanics - and a Surgery Wish List. Symposium, AAOS Annual Meeting, February 2012, San Francisco, California.

35. Hormonal Influences on the Basilar Thumb Joint. Sex, Bones, and Women. Symposium, AAOS Annual Meeting, February 2012, San Francisco, California.

36. Fragility Fractures of the Upper Extremity: What Every Hand Surgeon Should Know. Instructional Course Lecture, American Society for Surgery of the Hand Annual Meeting, September 2012, Chicago, Illinois.

37. Lateral Epicondylitis: Doing Something vs. Nothing. Symposium Moderator, American Society for Surgery of the Hand Annual Meeting, September 2012, Chicago, Illinois.

38. Evidence Based Medicine 2012 - The Use of Evidence in Daily Practice. Symposium, American Society for Surgery of the Hand Annual Meeting, September 2012, Chicago, Illinois.

39. Fast and Furious: Thumb CMC Arthritis in 5-Minute Bullets. Symposium, American Society for Surgery of the Hand Annual Meeting, September 2012, Chicago, Illinois.

40. Highlighting the Achievements of the American Foundation for Surgery of the Hand (AFSH). Symposium, American Society for Surgery of the Hand Annual Meeting, September 2012, Chicago, Illinois.

41. Hand Fractures: Techniques and Complications. Current Concepts in Upper Extremity Injury and Reconstruction Course, November 2012, Atlanta, Georgia.

42. CMC and MCP Instability. Current Concepts in Upper Extremity Injury and Reconstruction Course, November 2012, Atlanta, Georgia.

43. Hypermobility and Orthopaedic Surgery.*ABC Traveling Fellowhip Lecture*. Royal National Orthopaedic Hospital, Stanmore, UK, April 25, 2013. Nuffield Orthopaedic Centre, Oxford, UK, April 27, 2013. Lancashire and Wigan Infirmary, Wrightington, UK, May 1, 2013. Sheffield NHS Trust, Sheffield, UK, May 3, 2013. Jubilee National Hospital Centre, Glasgow, UK, May 7, 2013.

44. Lateral Epicondylitis: To Treat or not to Treat in 2013? *ABC Traveling Fellowship Lecture.* Royal Orthopaedic Hospital, Birmingham, UK, April 29, 2013. Edinburgh Royal Infirmary, May 5, 2013. Newcastle/Northumbria NHS Trust, May 6, 2013. University of Pretoria, Pretoria, South Africa, May 14, 2013. Kwazilu-Natal University Hospital, May 16, 2013. University of Cape Town/Stellenbosch University Combined Program, May 22, 2013.

45. Simple Elbow Dislocations: Epidemiology and Treatment. *ABC Traveling Fellowship Lecture.* Medunsa Orthopaedic Hospital, Limpopo, South Africa, May 15, 2013. Bloemfontein University Hospital, Bloemfontein, South Africa, May 21, 2013.

46. Failed Thumb CMC Arthroplasty. Israeli Society for Surgery of the Hand, November 27, 2013, Tel Aviv, Israel.

47. Current Trends in Thumb CMC Arthroplasty. Israeli Society for Surgery of the Hand, November 27, 2013, Tel Aviv, Israel.

48. Lateral Epicondylitis & Mallet Finger Deformity, Electives in Hand Surgery, New Orleans, Louisiana, February 7-8, 2014.

49. Thumb CMC Arthritis: Epidemiology, Hormones, Treatment. Grand Rounds Speaker, University of Rochester. Rochester, New York, August 24, 2014.

50. Owning Osteoporosis Care in Your Practice. Instructional Course Lecture, American Academy of Orthopaedic Surgeons Annual Meeting, New Orleans, LA, February 2015.

51. Hand and Wrist Injuries in Gymnasts. Italian Society for Surgery of the Hand. Viterbo, Italy. October 8-10, 2015.

52. Quality Is in the Eye of the Beholder: What's Measured, What Matters, and How Do We Reconcile This? Symposium, American Academy of Orthopaedic Surgeons Annual Meeting, March 10, 2016, Orlando, Florida.

NATIONAL/INTERNATIONAL PRESENTATIONS

1. **Wolf JM**; Gannon FH; Shore EM; Bilker W; Zasloff MA; Kaplan FS: The prevalence, natural history, and pathogenesis of limb swelling in patients who have fibrodysplasia ossificans progressiva. Adult Bone and Mineral Working Group, American Society for Bone and Mineral Research Annual Meeting; September 10, 1995, Baltimore, Maryland. (podium)

2. **Wolf JM**; Gannon FH; Shore EM; Bilker W; Zasloff MA: Kaplan FS: Limb swelling in patients who have fibrodysplasia ossificans progressiva. Second International Symposium on Fibrodysplasia Ossificans Progressiva; October 30-31, 1995, Philadelphia, Pennsylvania. (podium)

3. **Wolf JM**; Weiss APC: Complications of wrist arthroscopy. American Academy of Orthopaedic Surgeons Annual Meeting; March 4, 1999, Anaheim, California. (podium)

4. **Wolf JM**; Weiss APC: A new technique of intercarpal arthrodesis. Adrian Flatt Residents and Fellows Conference, American Society for Surgery of the Hand; October 4, 2000, Seattle, Washington. (podium)

5. Wyman JJ; Greisberg J; **Wolf JM**; Zou L; Terek R: "The effects of gadodiamide on proteoglycan production, cell proliferation, and apoptosis in chondrocytes." Symposium of the International Cartilage Repair Society, June 16, 2000, Gotebörg, Sweden. (podium)

6. **Wolf JM**; Weiss APC; Akelman E: Mini-open carpal tunnel release using a new protective guide and blade system. American Association of Hand Surgery Annual Meeting, January 10-13, 2001, San Diego, California. (poster)

7. **Wolf, JM**; Green A: The effect of co-morbidity on pain, function, and general health status (GHS) associated with idiopathic adhesive capsulitis (IAC). American Academy of Orthopaedic Surgeons Annual Meeting, February 28-March 4, 2001, San Francisco, California. (poster)

8. Greisberg J; **Wolf JM**; Wyman JJ; Terek R: "The effects of gadolinium chelates on articular cartilage." Orthopaedic Research Society, February 25-28, 2001, San Francisco, California. (poster)

9. **Wolf JM;** Meitner PA; Terek RM: The effect of hydrogen peroxide on chondrosarcoma cells: an *in vitro* analysis. Musculoskeletal Tumor Society Annual Meeting, April 25-27, 2002, Toronto, Canada. (podium)

10. **Wolf JM;** DiGiovanni CW: Thromboembolic prophylaxis in patients with foot and ankle trauma. American Orthopaedic Foot and Ankle Society Annual Meeting, July 14-16, 2002, Traverse City, Michigan. (podium)

11. **Wolf JM,** Meitner PM, Terek RM: Hydrogen peroxide as a potential adjuvant therapy for chondrosarcoma. Orthopaedic Research Society Annual Meeting, February 2-5, 2003, New Orleans, Louisiana. (poster)

12. Tashjian RZ, Ritter M, **Wolf JM,** Weiss APC, Green A: Functional outcomes and general health status after ulnohumeral arthroplasty for primary degenerative elbow arthritis. American Shoulder and Elbow Surgeons Focus Meeting, November 14-16, 2003, Las Vegas, Nevada. (podium)

13. Tashjian RZ, Ritter M, **Wolf JM,** Weiss APC, Green A: Ulnohumeral arthroplasty affects functional outcomes and general health status. Ninth International Congress of Shoulder Surgeons, May 3, 2004, Washington, DC. (podium)

14. **Wolf JM,** Shin AY, Moran S, Beckenbaugh RD: Complications of silastic metacarpophalangeal joint arthroplasty. American Society for Surgery of the Hand Annual Meeting, September 9-11, 2004, New York, New York. (poster)

15. **Wolf JM**, Sobky K, Baldini T, Thomas K, Bach J**:** Biomechanical comparison of different volar plates for fixation of distal radius fractures. American Association for Hand Surgery Annual Meeting, January 11, 2007, San Juan, Puerto Rico. (podium)

16. **Wolf JM,** Scott F, Gordon M, Ozer K, Williams A: Preliminary results of a randomized prospective trial of autologous blood injection for lateral epicondylitis. American Society for Surgery of the Hand Annual Meeting, September 20, 2008, Chicago, Illinois. (podium)

17. **Wolf JM,** Boyer MI. Evaluation of knowledge of common hand surgery problems in internal medicine residents. American Society for Surgery of the Hand Annual Meeting, September 18, 2008, Chicago, Illinois. (poster)

18. **Wolf JM**, Dawson L, Mountcastle SB, Owens BD. Incidence of scaphoid fracture in a young, active population. Orthopaedic Trauma Association Annual Meeting, October 11, 2008, Denver, Colorado. (poster)

19. **Wolf JM,** Athwal GS, Hoang BH, Mehta S, Williams A, Owens BD. Resident knowledge of levels of evidence criteria. American Academy of Orthopaedic Surgeons Annual Meeting, Las Vegas, Nevada, February 25, 2009. (podium)

20. **Wolf JM,** Blonna D, O'Driscoll SW. Prevention of nerve injuries using a safety-driven step-wise technique for arthroscopic capsulectomy of the elbow. American Shoulder and Elbow Society Open Meeting, Las Vegas, Nevada, February 28, 2009. (podium)

21. **Wolf JM**, Williams A, Boyer MI. Prospective Outcomes Assessment in Dupuytren's Contracture Comparing Palmar and Palmo-Digital Fasciectomy. Joint Meeting of the American and British Societies for Surgery of the Hand, London, UK, April 30, 2009. (podium)

22. **Wolf JM**, Athwal GS, Hoang BH, Mehta S, Williams A, Owens BD. Knowledge of levels of evidence criteria in orthopaedic residents. Special Emphasis Poster. American Orthopaedic Association Annual Meeting, Bonita Springs, Florida, June 2009. (poster)

23. Sturdivant R, Burks R, Owens B, **Wolf J**, and Cameron K. Epidemiological studies in the military. Joint Statistical Meeting, Washington, DC, August 5, 2009. (podium)

24. Posner MA, **Wolf JM,** Belmont PJ, Owens BD. Epidemiology of Major League Baseball Injuries. American Academy of Orthopaedic Surgeons Annual Meeting, New Orleans, Louisiana, March 2010. (poster)

25. Van Tassel DC, Owens BD, Pointer L, **Wolf JM.** Incidence and Demographics of Scaphoid Fracture in the United States Population. American Academy of Orthopaedic Surgeons Annual Meeting, New Orleans, Louisiana, March 2010. (poster/alternate podium)

26. Posner MA, **Wolf JM**, Belmont PC, Owens BD. Epidemiology of Major League Baseball injuries. Society of Military Orthopaedic Surgeons Annual Meeting, Honolulu, Hawaii, December 2009. (poster)

27. Posner MA, **Wolf JM**, Belmont PC, Owens BD. Epidemiology of Major League Baseball injuries. Mid-America Orthopaedic Association Annual Meeting, Austin, Texas, April 22, 2010. (podium)

28. Posner MA, **Wolf JM,** Mountcastle S, Belmont PC, Owens BD. Epidemiology of Major Leage Baseball Injuries. American Orthopaedic Society for Sports Medicine Annual Meeting, Providence, Rhode Island, July 18, 2010. (podium)

29. Schreier S, Williams AE, **Wolf JM.** Relationship between Generalized Hypermobility and Carpometacarpal Radiographic Laxity. American Society for Surgery of the Hand Annual Meeting, Boston, Massachusetts, October 7, 2010. (poster)

30. Stoneback J, Owens BD, Athwal GS, Pointer L, **Wolf JM.** Incidence of Elbow Dislocations in the United States Population. American Academy of Orthopaedic Surgeons Annual Meeting, San Diego, California, February 18, 2011. (poster)

31. Stoneback JW, Owens BD, Sykes JB, Athwal GS, Pointer L, **Wolf JM**. Incidence of Elbow Dislocations in the United States Population. Canadian Orthopedic Association Annual Meeting. St John's, Newfoundland. July 7-9, 2011. (poster)

32. **Wolf JM,** Scott F, Delaronde S, Williams AE, King KB. Relaxin Upregulates Relaxin Receptor and MMP in the Anterior Oblique Ligament. American Society for Surgery of the Hand Annual Meeting, Las Vegas, Nevada, September 9, 2011. (podium)

33. Mir H, Cannada L, Black KP, Murray J, **Wolf JM.** Orthopaedic Resident and Program Director Opinions of Resident Duty Hours – A National Survey. American Orthopaedic Association Annual Meeting, Washington, DC, June 2012. (special emphasis poster)

34. **Wolf JM,** Scott F, Williams AE, Delaronde S, King KB. Serum Relaxin is Correlated with Relaxin Receptors and MMP-1 in the Anterior Oblique Ligament. 2012 World Congress on Osteoarthritis, Barcelona, Spain, April 26-29, 2012. (poster)

35. Clifton K**,** Rodner CM, Drissi H, **Wolf JM.** Relaxin Receptors in the Dorsoradial Ligament and Synovium of the Trapeziometacarpal Joint. American Society for Surgery of the Hand Annual Meeting, Chicago, Illinois, September 7,2012, (podium)

36. **Wolf JM**, Turkiewicz A, Atroshi I, Englund M. Prevalence of Symptomatic Basilar Thumb Joint Osteoarthritis in the General Population. American College of Rheumatology Annual Meeting, Washington, DC, November 12, 2012. (poster)

37. Judson CR, Cote M, Bernstein J, **Wolf JM.** Outcomes of Conservative Therapies for the Treatment of Lateral Epicondylitis with Minimum One Year Follow-up. American Society for Surgery of the Hand Annual Meeting, San Francisco, California, Oct 3-5, 2013. (e-poster)

38. **Wolf JM.** Measuring trapeziometacarpal mobility using stress radiography and its association with generalized hypermobility. International Thumb Osteoarthritis Workshop, Newport, Rhode Island, Oct 23-25, 2013 (podium)

39. Judson C, Cote M, Coyle KM, **Wolf JM.** Outcomes of conservative therapies for the treatment of lateral epicondylitis with minimum one year follow-up. American Society for Surgery of the Hand Annual Meeting, Seattle,Washington. September 8-12, 2014 (poster)

40. Webber T, Patel SP, Pensak M, Fajolu O, Rozental TD, **Wolf JM.** Correlation between distal radius cortical thickness and bone mineral density. Hand Wrist Biomechanics International Meeting, Milan, Italy, June 16, 2015. (podium)

41. Rohde RS, **Wolf JM,** Adams JE. Where are the Women in Orthopaedic Surgery? Special Interest Poster, American Orthopaedic Association Annual Meeting, Providence, Rhode Island, June 24-27, 2015. (poster)

42. Rozental TD, Walley K, Herder L, Coyle K, Bouxsein M, **Wolf JM.** 25-Hydroxy-Vitamin D and bone turnover marker levels in patients with distal radius fractures. American Society for Surgery of the Hand Annual Meeting, Seattle, Washington. September 8-12, 2015 (poster)

COURSE FACULTY

1. Co-director: Hand Anatomy for Hand Therapists Course, May 23, 2004, Englewood, Colorado.

2. Co-director: Hand Anatomy for Hand Therapists Course, April 21, 2006. Englewood, Colorado.

3. Co-Director: Hand Anatomy for Hand Therapists Course, May 10, 2008, Englewood, Colorado.

4. Moderator, Instructional Course Lecture. Acute Trauma to the Upper Extremity: What to Do and When to Do It. American Academy of Orthopaedic Surgeons Annual Meeting, March 6, 2008, San Francisco, California.

5. Moderator, Instructional Course Lecture. Acute Trauma to the Upper Extremity: What to Do and When to Do It. American Academy of Orthopaedic Surgeons Annual Meeting, February 27, 2009, Las Vegas, Nevada.

6. Instructor, ASSH Master Skills Course: Flexor Tendon Repair and Reconstruction. SERC Institute, October 16-17, 2009, Burr Ridge, Illinois.

7. Co-Chair, ASSH Annual Meeting Precourse: Controversies in Hand Surgery: What Works, What Doesn't. ASSH Annual Meeting, October 7, 2010, Boston, Massachusetts.

8. Moderator, ASSH Specialty Day: Finger Fractures Section. AAOS Annual Meeting, February 19, 2011, San Diego, California.

9. Instructor, Orthopaedic Learning Center: Wrist Injuries: State-of-the-Art. AAOS Course Faculty, June 24-25, 2011, Rosemont, Illinois.

10. Moderator, New England Hand Society Annual Meeting: Radial Fracture and Thumb Arthritis Section. December 3, 2011, Sturbridge, Massachusetts.

11. Instructor, Hand Surgery Comprehensive Review Course: Osteoarthritis and Atypical Arthridities. July 15, 2012, Chicago, Illinois.

12. Moderator, ASSH Annual Meeting Symposium: Tennis Elbow: Doing Something vs. Nothing. September 2012, Chicago, Illinois.

13. Instructor, 4th Annual Current Concepts in Upper Extremity Restoration Conference. November 2-3, 2012, Atlanta, Georgia.

14. Co-Moderator, AFSH Grants Symposium. American Society for Surgery of the Hand. October 2013, San Francisco, California.

15. Co-Chair, Interactive Case Reviews, American Society for Surgery of the Hand, October 2013, San Francisco, California.

16. Moderator and Instructor, International Thumb Osteoarthritis Workshop. Clinical vs Research Questions in Thumb Arthritis. October 2013, Newport, Rhode Island.

17. Program Co-Chair, Annual Meeting, American Society for Surgery of the Hand, September 2014, Boston, Massachusetts.

18. Instructor, Hand Surgery Comprehensive Review Course: Osteoarthritis and Atypical Arthridities. July 2015, Chicago, Illinois.

19. Faculty, Hand Section, New England Orthopaedic Society, May 2015, Rockland, Maine.

20. Faculty, 2nd Annual Course on Wrist Arthroscopy and Arthoplasty, October 10-12, Arezzo, Italy.

REGIONAL/LOCAL PRESENTATIONS

1. A new technique of open carpal tunnel release. New England Hand Society Annual Meeting, December 1, 2000, Sturbridge, Massachusetts.

2. Access and use of the Internet in a hand surgery population. New England Hand Society, December 7, 2001, Sturbridge, Massachusetts.

3. Osteoporosis and Orthopaedics. Sargent School of Physical Therapy, Boston University, November 6, 2001, Boston, Massachusetts.

4. Foot and Ankle Injuries. Sargent School of Physical Therapy, Boston University, November 13, 2001, Boston, Massachusetts.

5. Triceps Rupture and Reconstruction: Case Report and Review of the Literature. Packard Lecture Presentation, May 19, 2004, Denver, Colorado.

6. Advances in Wrist Arthroscopy. Fall Orthopaedic Summit on Minimally Invasive Surgery, September 15, 2005, Keystone, Colorado.

7. Pyrocarbon in Small Finger Joints. Hand SIG Society, Denver Medical Library, October 19, 2005, Denver, Colorado.

8. Scapholunate Ligament Tears. Doctors Demystify the Wrist 2006, October 21, 2006, Denver, Colorado.

9. Common Problems in Hand Surgery. Physical Medicine and Rehabilitation Conference, February 8, 2007, Denver, Colorado.

10. Ulnar Collateral Ligament Injuries of the Thumb. Doctors Demystify the Thumb 2007, April 21, 2007, Denver, Colorado.

11. Top 10 Issues in Hand Surgery for Primary Care Physicians. Webcast, January 22, 2007, Denver, Colorado.

12. Common Hand Surgery Diagnoses. Physical Medicine and Rehabilitation Conference, January 16, 2008, Denver, Colorado.

13. Hand Surgery as Related to Rheumatology. Rheumatology Teaching Conference, March 23, 2008, Denver, Colorado.

14. Lateral and Medial Epicondylitis. Doctors Demystify the Elbow 2008, April 19, 2008, Denver, Colorado.

15. Issues in Hand Surgery for Primary Care. Physician Assistants Curriculum, April 24, 2008, Denver, Colorado.

16. New Treatments for Dupuytren's Contracture. Hand SIG Society, Denver Medical Library, April 15, 2009.

17. My Aching Hand: Discovery Series. University of Connecticut Health Center, November 9, 2010.

18. Lateral Epicondylitis: Current Treatment in 2012. Clinical Research Center Conference, University of Connecticut Health Center, March 14, 2012.

19. Texting Tendinitis: Discovery Series. University of Connecticut Health Center, December 4, 2012.

20. Common Issues in Hand Surgery: Grand Rounds. Department of Medicine Grand Rounds, University of Connecticut Health Center, April 16, 2015.

21. Lateral Epicondylitis in 2015. New England Orthopaedic Society, May 29, 2015, Rockport, Maine.

25-Hydroxyvitamin-D and Bone Turnover Marker Levels in Patients with Distal Radial Fracture

Tamara D. Rozental, MD, Lindsay M. Herder, BA, Kempland C. Walley, BSc, David Zurakowski, PhD, Kathleen Coyle, RN, BSN, Mary L. Bouxsein, PhD, and Jennifer M. Wolf, MD

Investigation performed at the Department of Orthopaedic Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts, and the Department of Orthopaedic Surgery, University of Connecticut Health Center, Farmington, Connecticut

Background: Fragility fractures are a major public health issue with substantial socioeconomic cost. Vitamin-D deficiency and increased bone turnover are associated with higher rates of bone loss and an increased risk of fracture. We hypothesized that patients with a distal radial fracture would have lower levels of 25-hydroxyvitamin D (25[OH]D) and increased levels of serum bone turnover markers than controls without a fracture.

Methods: Postmenopausal women with a recent distal radial fracture (fracture group, n = 105) were prospectively recruited and were compared with individuals without a fracture (control group, n = 150). Outcome variables included serum levels of 25(OH)D and markers of bone formation, including N-terminal extension propeptide of type-I collagen (P1NP), parathyroid hormone (PTH), bone-specific alkaline phosphatase (BSAP), and osteocalcin, as well as a marker of resorption (C-terminal telopeptide of type-I collagen [CTX-1]). Bone mineral density was measured with dual x-ray absorptiometry.

Results: The fracture group was slightly older than the control group (mean and standard deviation [SD], 66.8 ± 10.8 years versus 63.3 ± 9.0 years, p = 0.008), had a lower body mass index (26.4 ± 5.9 kg/m^2 versus 28.0 ± 6.2 kg/m^2, p = 0.05), and more commonly had had a prior fracture (52% versus 31%, p < 0.001). Bone mineral density at the hip was lower in the fracture group than in the control group (0.831 ± 0.130 g/cm^2 versus 0.917 ± 0.139 g/cm^2, p < 0.001). The mean 25(OH)D levels were similar in the fracture and control groups (44.4 ± 14.6 ng/mL versus 41.3 ± 14.5 ng/mL, p = 0.08). Levels of serum markers of bone formation were significantly higher in the fracture group than in the control group (P1NP: 70.4 ± 33.2 ng/mL versus 53.2 ± 25.6 ng/mL, p < 0.001; osteocalcin: 22.3 ± 9.9 ng/mL versus 20.2 ± 9.2 ng/mL, p = 0.017). Levels of BSAP, PTH, and CTX-1 were similar in the two groups. Multivariable logistic regression showed independent associations between a distal radial fracture and low total hip bone mineral density (odds ratio [OR] = 2.02 for each decrease of 1 SD, 95% confidence interval [CI] = 1.38 to 3.01, p < 0.001) and a high P1NP level (OR = 2.17 for each 1-SD increase, 95% CI = 1.52 to 3.06, p < 0.001).

Conclusions: In this cohort, 25(OH)D levels were not associated with distal radial fracture and do not appear to affect the risk assessment for distal radial fracture in postmenopausal women. Patients with a distal radial fracture, however, had increased bone turnover as evidenced by high P1NP and osteocalcin levels. Women with both a high P1NP level and low bone mineral density were at particularly high risk for fracture.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Peer Review: This article was reviewed by the Editor-in-Chief and one Deputy Editor, and it underwent blinded review by two or more outside experts. The Deputy Editor reviewed each revision of the article, and it underwent a final review by the Editor-in-Chief prior to publication. Final corrections and clarifications occurred during one or more exchanges between the author(s) and copyeditors.

Osteoporosis and fragility fractures are major public health issues with substantial socioeconomic costs[1-4]. Currently, fracture risk assessment is based on bone mineral density measurements with dual x-ray absorptiometry combined with clinical risk factors. However, bone mineral density does not always accurately reflect fracture risk as up to

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TABLE I Demographic Characteristics and Lifestyle Activities of the Two Study Groups

Characteristic	Distal Radial Fracture (N = 105)	Controls (N = 150)	P Value
Age* *(yr)*	66.8 ± 10.8	63.3 ± 9.0	0.008†
Race *(no. [%])*			0.16
Caucasian	91 (87%)	124 (83%)	
African American	5 (5%)	19 (13%)	
Hispanic	7 (7%)	6 (4%)	
Asian	2 (2%)	1 (1%)	
Weight* *(kg)*	68.8 ± 15.6	73.0 ± 17.2	0.05†
BMI* *(kg/m^2)*	26.4 ± 5.9	28.0 ± 6.2	0.05†
Hand dominance *(no. [%])*			0.63
Left	8 (8%)	16 (11%)	
Right	97 (92%)	134 (89%)	
Age at menarche* *(yr)*	12.9 ± 1.5	12.8 ± 1.4	0.89
Gravida‡	2 (1-4)	2 (1-3)	0.55
Para‡	1 (0-3), n = 77	2 (0-3), n = 96	0.58
History of fracture *(no. [%])*	55 (52%)	47 (31%)	<0.001†
Smoking *(no. [%])*	4 (4%)	8 (5%)	0.77
Calcium supplements *(no. [%])*	52 (50%)	91 (61%)	0.10
Vitamin-D supplements *(no. [%])*	50 (48%)	66 (44%)	0.93
Alcohol *(no. [%])*			0.24
0 drinks/wk	54 (51%)	75 (50%)	
1-3 drinks/wk	23 (22%)	47 (31%)	
4-7 drinks/wk	19 (18%)	21 (14%)	
≥8 drinks/wk	9 (9%)	7 (5%)	
Caffeinated beverages *(no. [%])*			0.95
0 cups/day	19 (18%)	28 (19%)	
1 cup/day	32 (30%)	50 (33%)	
2-3 cups/day	46 (44%)	62 (41%)	
≥4 cups/day	8 (8%)	10 (7%)	
Physical activity level *(no. [%])*			0.27
Inactive	11 (10%)	26 (17%)	
Active	82 (78%)	118 (79%)	
Unknown	12 (11%)	6 (4%)	

*The values are given as the mean and standard deviation. †A significant difference between groups. ‡The values are given as the median with the interquartile range in parentheses.

50% of those with a fragility fracture do not have osteoporosis as demonstrated by bone mineral density testing[5-7]. Recent efforts have thus focused on other means of identifying patients who are at greatest risk for future fracture.

Low serum levels of vitamin D are associated with higher rates of bone loss and increased risk of fracture[8-12]. Circulating levels of serum 25-hydroxyvitamin D (25[OH]D) are currently considered the most reliable marker for vitamin-D status[13]. The optimal level of 25(OH)D has not yet been established, although several thresholds have been suggested[14]. The Institute of Medicine defines vitamin-D deficiency as a serum level of 25(OH)D of <25 ng/mL[15,16].

High bone turnover has also been associated with increased rates of bone loss[17-19] and with an increased risk of fracture independent of bone mineral density[18,20-22]. The most commonly used bone turnover markers are those that reflect bone formation, including N-terminal extension propeptide of type-I collagen (P1NP), bone-specific alkaline phosphatase (BSAP), and osteocalcin, and those that reflect bone resorption, including C-terminal telopeptide of type-I collagen (CTX-1)[19].

TABLE II Univariate Comparison of Bone Density Between the Fracture and Control Groups

Variable	Distal Radial Fracture* (N = 105)	Controls* (N = 150)	Area Under Curve	P Value
Lumbar spine				
Bone mineral density *(g/cm²)*	0.976 ± 0.187	1.108 ± 0.814	0.602	0.11
Bone mineral density T-score	−1.15 ± 1.18	−0.56 ± 1.25	0.632	<0.001†
Femoral neck				
Bone mineral density *(g/cm²)*	0.756 ± 0.153	0.798 ± 0.261	0.621	0.18
Bone mineral density T-score	−1.48 ± 1.06	−0.81 ± 1.08	0.694	<0.001†
Total hip				
Bone mineral density *(g/cm²)*	0.831 ± 0.130	0.917 ± 0.139	0.679	<0.001†
Hip bone mineral density T-score	−1.12 ± 1.06	−0.45 ± 1.10	0.680	<0.001†

*The values are given as the mean and standard deviation. †A significant difference between groups as shown by the Student t test.

Vitamin D and bone turnover markers have not been extensively studied in patients with fracture of the distal part of the radius[23-25]. To our knowledge, no studies have explored the association between vitamin-D levels and wrist fracture in a North American population. Similarly, although prior studies have demonstrated that increases in levels of bone turnover markers could be used to identify osteopenic women at high risk for fracture[19,21], biochemical markers in postmenopausal women with a distal radial fracture have not been specifically studied. In the present study, we sought to determine the relationship between distal radial fracture and levels of 25(OH)D and bone turnover markers. We hypothesize that postmenopausal women with a distal radial fracture would have lower circulating levels of 25(OH)D and higher levels of bone turnover markers than women of similar age with no fracture.

Materials and Methods

Patient Identification

Following approval by our institutional review boards, postmenopausal women over the age of fifty years were recruited at Beth Israel Deaconess Medical Center (Boston, Massachusetts) and University of Connecticut Health Center (Hartford, Connecticut) by their treating orthopaedic surgeon. Consecutive patients with a distal radial fracture were screened for inclusion. All subjects gave written informed consent prior to participation. Subjects were eligible for inclusion into our fracture group if they had a history of a distal radial fracture within three weeks before presentation for treatment. Only fractures occurring from low-energy falls were included. Patients with no history of fractures in adulthood who were presenting for treatment of other conditions were recruited for our control group. Potential subjects were excluded if they had endocrinopathies (insulin-dependent diabetes mellitus or thyroid disease) or metabolic bone disease (osteomalacia, osteoporosis, Paget disease, or primary hyperparathyroidism). Exposure to glucocorticoids and immunosuppressive medications were also exclusion criteria, as was treatment with hormone replacement therapy, bisphosphonates, parathyroid hormone (PTH), selective estrogen receptor modulators, or aromatase inhibitors. Of 533 patients screened, 407 were eligible for inclusion. Seventy-two patients were lost to follow-up, twenty-four patients refused to participate, and fifty-six patients either withdrew consent or elected not to participate in at least one study component.

Demographic Information and Medical and Medication History

At the time of enrollment, standardized questionnaires were used to record prior fractures; reproductive, menstrual, and smoking history; alcohol and caffeine intake; physical activity; and calcium/vitamin D supplementation[26].

TABLE III Univariate Comparison of Biomarker Levels Between the Fracture and Control Groups

Serum Biomarker	Distal Radial Fracture (N = 105)	No Distal Radius Fracture (N = 150)	Area Under Curve	P Value
25(OH)D* *(ng/mL)*	44.4 ± 14.6	41.3 ± 14.5	0.435	0.08
No. (%) with 25(OH)D <32 ng/mL	23 (22%)	36 (24%)	0.490	0.78
CTX-1* *(ng/mL)*	0.51 ± 0.28	0.46 ± 0.27	0.546	0.21
P1NP* *(ng/mL)*	70.4 ± 33.2	53.2 ± 25.6	0.667	<0.001†
BSAP* *(μg/L)*	19.5 ± 6.3	19.8 ± 6.9	0.493	0.85
PTH* *(pg/mL)*	41.0 ± 16.8	42.0 ± 17.3	0.484	0.66
Osteocalcin* *(ng/mL)*	23.3 ± 9.9	20.2 ± 9.2	0.589	0.017†

*The values are given as the mean and standard deviation. †A significant difference between groups as shown by the Student t test.

TABLE IV Independent Multivariable Risk Factors Associated with Distal Radial Fracture in Women Fifty Years of Age and Older

Predictor	Adjusted OR	95% CI	P Value
Age	1.05	1.02-1.08	0.03*
BMI	1.00	0.94-1.05	0.97
History of fracture	3.00	1.51-5.78	<0.001*
Calcium supplements	0.40	0.23-0.85	0.014*
25(OH)D (per 1-SD decrease)	0.88	0.65-1.25	0.48
CTX-1 (per 1-SD increase)	0.80	0.47-1.24	0.39
P1NP (per 1-SD increase)	2.17	1.52-3.06	<0.001*
Osteocalcin (per 1-SD increase)	1.14	0.78-1.77	0.50
Total hip bone mineral density (per 1-SD decrease)	2.02	1.38-3.01	<0.001*

*Significant independent predictor of fracture in multivariable logistic regression analysis with backward selection with use of the likelihood ratio test to assess significance.

Height and weight were measured on a stadiometer and calibrated scale, respectively. Hand dominance, mechanism of injury, and type of treatment (surgical or nonsurgical) were tabulated.

Vitamin-D Levels and Bone Turnover Markers

To minimize the potential effect of fracture-healing on bone metabolism[27], levels of serum markers were assessed at three months after injury. Blood was drawn in the morning after an overnight fast to reduce the effects of diurnal variation and eating[28,29]. Markers of bone formation included P1NP, BSAP, and osteocalcin. P1NP reflects an early phase of bone formation. BSAP is present in pre-osteoblasts and osteoblasts, and osteocalcin is made by mature osteoblasts. CTX-1 was used to measure bone resorption and is most reliable for this purpose[30]. PTH levels were measured to identify secondary hyperparathyroidism associated with vitamin-D deficiency. Serum samples were kept frozen at −70°C, and assays were performed in batch by the Maine Medical Center Research Institute (Scarborough, Maine). Assays were analyzed with the IDS-iSYS automated analyzer (Immunodiagnostic Systems [IDS]) with detectable ranges of 25(OH)D, P1NP, BSAP, osteocalcin, PTH, and CTX-1 levels of 5 to 140 ng/mL, 2 to 230 ng/mL, 1 to75 μg/L, 2 to 200 ng/mL, 5 to 5000 pg/mL, and 0.033 to 6.0 ng/mL, respectively. Intra-assay variability for 25(OH)D, P1NP, BSAP, osteocalcin, PTH, and CTX-1 were 8.3%, 2.9%, 1.6%, 2.5%, 2.0%, and 3.2%, respectively.

Bone Mineral Density

Areal bone mineral density (g/cm^2) of the spine, total hip, and femoral neck was measured with dual x-ray absorptiometry (QDR 4500; Hologic, Waltham, Massachusetts) in the array (fan beam) mode.

Statistical Methods

The distal radial fracture and control groups were compared by using Pearson chi-square and Fisher exact tests for proportions and the Student t test for normally distributed continuous data. All serum biomarker values were found to be normally distributed and were not subject to log transformation. The area under the curve was calculated as a measure of discrimination between fractures and controls. Non-parametric data were compared by using the Mann-Whitney U test and were presented as the median and interquartile range (IQR). Power analysis indicated that the sample sizes targeted provided 90% power ($\alpha = 0.05$, $\beta = 0.10$) to detect 10% mean differences in 25(OH)D levels, bone turnover marker levels, and bone mineral density between groups with use of a two-tailed Student t test (version 7.0; nQuery Advisor, Statistical Solutions, Boston, Massachusetts). Multivariable logistic regression analysis of ten candidate variables[31] was applied to determine independent factors associated with fracture. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were derived as measures of association with biomarkers expressed per unit change in standard deviation (SD)[32]. The relationship between the probability of fracture and levels of predictive biomarkers was estimated by maximum likelihood with precision based on 95% CIs[33]. Statistical analysis was performed with use of IBM SPSS Statistics version 22.0 (IBM, Armonk, New York). A two-tailed $p < 0.05$ was considered significant.

Source of Funding

This work was supported by the Orthopaedic Research and Education Foundation and the American Foundation for Surgery of the Hand.

Results

Patient Characteristics

One hundred and five patients with a distal radial fracture (fracture group) and 150 patients without a fracture (control group) were prospectively enrolled. The fracture-group patients were slightly older (66.8 ± 10.8 years versus 63.3 ± 9.0 years, $p = 0.008$), had a lower body mass index (BMI) (26.4 ± 5.9 k/m^2 versus 28.0 ± 6.2 k/m^2, $p = 0.05$), and had more commonly sustained a prior fracture (52% [n = 55] versus 31% [n = 47], $p < 0.001$). The race distribution, percentage of patients who smoked and took calcium and vitamin-D supplements, caffeine and alcohol consumption, and physical activity level were similar in the two groups (Table I).

Thirty-eight patients sustained a fracture of the dominant extremity. Fifty-five fractures were treated with a cast and fifty, with operative fixation with a volar plate. All fractures healed without complications.

Bone Mineral Density

Bone mineral density as measured with dual x-ray absorptiometry was similar between the fracture and control groups at the lumbar spine and at the femoral neck but it was lower at the hip in the fracture group (0.831 ± 0.130 g/cm^2 versus 0.917 ± 0.139 g/cm^2, $p < 0.001$) (Table II). Thirty patients in the fracture group were classified as having osteopenia and

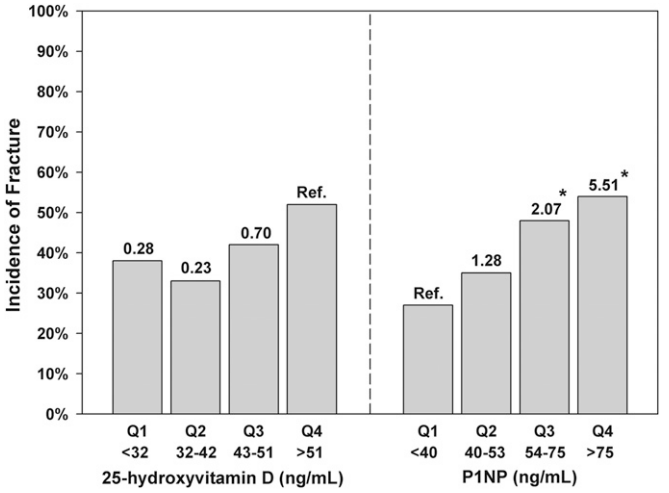

Fig. 1

Prevalence of distal radial fractures by quartiles of 25(OH)D and P1NP levels. The fracture prevalence was 39% for patients with a 25(OH)D level in quartile 1 (Q1) (<32 ng/mL), 31% for those with a level in Q2 (32 to 42 ng/mL), 46% for those with a level in Q3 (43 to 51 ng/mL), and 48% for those with a level in Q4 (>51 ng/mL). For P1NP, the respective values were 26% for Q1 (<40 ng/mL), 32% for Q2 (40 to 53 ng/mL), 41% for Q3 (54 to 75 ng/mL), and 66% for Q4 (>75 ng/mL). The asterisks denote significance. The odds of fracture were significantly greater for P1NP levels in the highest two quartiles (Q3 and Q4).

eleven were classified as having osteoporosis at either the hip or the spine according to the World Health Organization (WHO) classification. Thirty-seven of the controls were osteopenic, and five were osteoporotic.

25(OH)D and Bone Turnover Markers

Serum 25(OH)D levels were similar in the fracture and control groups after we controlled for age and BMI (44.4 ± 14.6 ng/mL versus 41.3 ± 14.5 ng/mL, $p = 0.08$) and after we excluded individuals who were taking over-the-counter supplementation (40.0 ± 14.8 ng/mL versus 40.1 ± 14.7 ng/mL, $p = 0.97$). After we adjusted for age and BMI, levels of markers of bone formation were higher in the fracture group than in the control group (P1NP: 70.4 ± 33.2 ng/mL versus 53.2 ± 25.6 ng/mL, $p < 0.001$; osteocalcin: 23.3 ± 9.9 ng/mL versus 20.2 ± 9.2 ng/mL, $p = 0.017$). Levels of BSAP, PTH, and CTX-1 were similar in the two groups (Table III). There was no significant correlation between the 25(OH)D and P1NP levels in the entire cohort ($r = -0.3$, $p = 0.29$) or in the fracture group ($r = -0.06$, $p = 0.57$). P1NP levels correlated with osteocalcin levels ($r = 0.18$, $p = 0.004$) in the entire cohort and in the fracture group ($r = 0.65$, $p < 0.001$). PTH levels correlated with osteocalcin levels ($r = 0.18$, $p = 0.004$) in the entire cohort and in the fracture group ($r = 0.29$, $p = 0.003$). There was no correlation among PTH levels, P1NP, and 25(OH)D levels.

Multivariable logistic regression analysis identified four independent factors associated with distal radial fracture after adjustment for age and BMI: a history of fracture (OR = 3.00, 95% CI = 1.51 to 5.78, $p < 0.001$), use of calcium supplements (OR = 0.40, 95% CI = 0.23 to 0.85, $p = 0.014$), elevated P1NP levels (OR = 2.17 for each 1-SD increase, 95% CI = 1.52 to 3.06, $p < 0.001$), and lower total hip bone mineral density (OR = 2.02 for each 1-SD decrease, 95% CI = 1.38 to 3.01, $p < 0.001$) (Table IV). Serum levels of 25(OH)D ($p = 0.48$), CTX-1 ($p = 0.39$), and osteocalcin ($p = 0.50$) were not associated with distal radial fracture.

Few (ten) patients in our cohort had a vitamin-D deficiency, and there was no association between vitamin-D deficiency (<25 ng/mL) and distal radial fracture ($p = 0.74$). When 25(OH)D levels were divided into quartiles, and with quartile 4 (highest 25[OH]D level) used as the reference, the odds of fracture were lower in quartiles 1, 2, and 3 but not significantly so ($p = 0.12$, $p = 0.06$, and $p = 0.3$, respectively) (Fig. 1).

Analysis of patients with a P1NP level higher than the reported reference median in premenopausal women (>37.3 ng/mL)[34] revealed a significant association between that factor and distal radial fracture ($p < 0.05$). Quartile analysis with use of quartile 1 (lowest P1NP level) as the reference revealed a 5.5-fold higher risk of fracture in quartile 4 (OR = 5.51, 95% CI = 2.58 to 11.83, $p < 0.001$) and a twofold higher risk in quartile 3 (OR = 2.07, 95% CI = 1.20 to 4.19, $p = 0.05$). There was no significant difference in fracture risk between the two lowest quartiles ($p = 0.52$) (Fig. 1).

There was a significantly greater likelihood of distal radial fracture in women with lower bone mineral density at the hip (likelihood ratio test = 20.58, $p < 0.001$) and a higher serum P1NP level (likelihood ratio test = 20.67, $p < 0.001$) (Fig. 2). Furthermore, women with both low bone mineral density and a high P1NP level were at particularly high risk for fracture (Fig. 3). Women with low bone mineral density and a P1NP level in the highest quartile had a probability of fracture of >50% (Fig. 4).

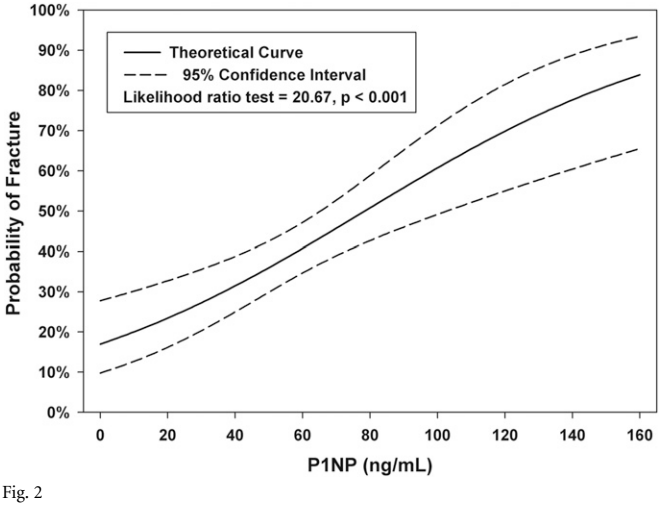

Fig. 2

Probability of distal radial fracture by levels of P1NP. The odds of fracture increase as levels of P1NP rise.

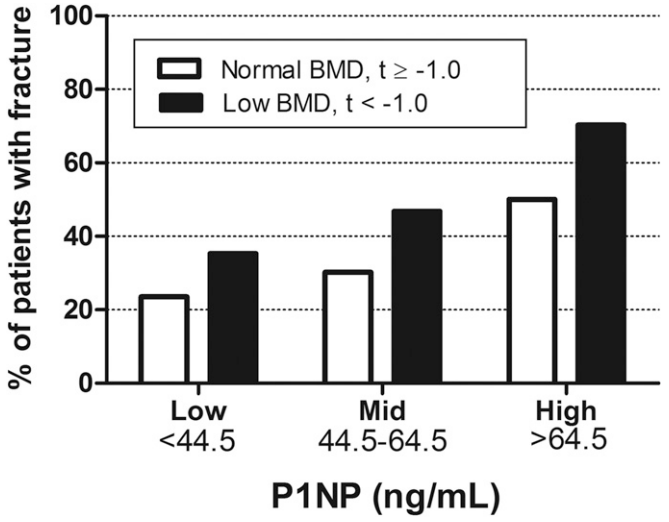

Fig. 3

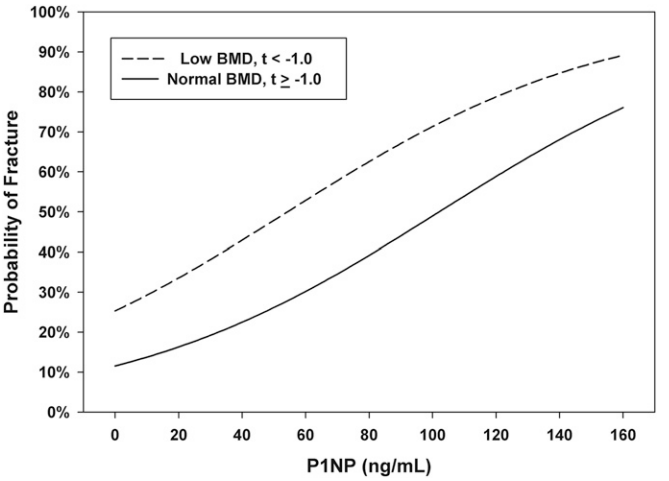

Fig. 4

Fig. 3 Percentage of patients with a distal radial fracture when stratified by normal total hip bone mineral density (BMD) (T-score ≥−1.0; white bars) and low total hip bone mineral density (T-score <−1.0; black bars) and levels of P1NP. The P1NP levels are stratified by study population tertiles, with low, mid, and high tertiles corresponding to <44.5, 44.5 to 64.5, and >64.5 ng/mL, respectively. More patients with low bone mineral density and a high P1NP level sustained a distal radial fracture. **Fig. 4** Probability of distal radial fracture for patients with normal bone mineral density (BMD) (T-score ≥−1.0) and low bone mineral density (T-score <−1.0) according to serum levels of P1NP. Patients with low bone mineral density and a high P1NP level had a >50% probability of sustaining a distal radial fracture.

Discussion

We found that postmenopausal women with a recent distal radial fracture have significantly poorer bone mineral density at the hip. Contrary to our hypothesis, 25(OH)D levels were similar between our fracture group and non-fracture control group both in unadjusted analyses and after controlling for age, BMI, and hip bone mineral density. The patients in the fracture group had increased levels of bone formation markers, and this increase remained significant after adjustment for age, BMI, and hip bone mineral density.

The prevalence of distal radial fracture increases markedly with age[27,35-37], and independent predictors of distal radial fracture include decreased bone mineral density, a history of falls, and a prior fracture after the age of fifty years[37,38]. Our study confirmed that a history of fracture and low bone mineral density are strongly associated with distal radial fracture. Although low bone mineral density has been associated with distal radial fracture, it does not explain all of the fracture risk[39-42]. Øyen et al. noted that only one-third of men and half of women presenting with a low-energy distal radial fracture met the WHO criteria for osteoporosis[37]. In our study, only 4% of the women with a distal radial fracture met the criteria for osteoporosis and 37%, for osteopenia. Clearly other factors besides low bone mineral density play a role in the etiology of these fractures.

Vitamin-D levels have been explored as a risk factor for fracture, primarily at the hip[8,9]. In one study, 96% of patients with a hip fracture were vitamin-D deficient[12]. The Women's Health Initiative reported that 25(OH)D levels of <8 ng/mL were associated with an increased risk of fracture[43]. Another study showed that 25(OH)D levels in women with concomitant hip and upper-extremity fractures were significantly lower than those in women with an isolated hip fracture[44]. Vitamin-D deficiency has not been extensively studied among patients with distal radial fracture. In one report, 49% of thirty-seven patients with a forearm fracture had vitamin-D deficiency, defined as <10 ng/mL[23]. Another study showed that 43% of 100 patients with a wrist fracture had 25(OH)D levels of <12 ng/mL[24]. In an analysis comparing 25(OH)D levels between patients with a distal radial fracture and non-fracture controls[25], Øyen et al. found that a level of 25(OH)D of <20 ng/mL was associated with an increased risk of fracture in women and men after they controlled for bone mineral density and BMI. They concluded that low 25(OH)D levels predicted fractures independently of bone mineral density. Contrary to these results, our study did not show an association between low 25(OH)D levels and distal radial fracture. There was no significant difference between groups after exclusion of women taking vitamin-D supplementation. Furthermore, our cohort did not display the high PTH values that are expected with vitamin-D deficiency. Together, these results suggest that low 25(OH)D levels are not associated with distal radial fracture in this cohort. Potential reasons are that our study exclusively enrolled postmenopausal women, whose awareness of the problem of vitamin-D deficiency is typically higher: 44% of the subjects enrolled and 48% of those with a fracture were taking supplementation prior to injury. Most notably, few patients in our cohort had a very low 25(OH)D level, likely reflecting recent attention given to treatment of this deficiency. We also applied a stringent set of inclusion criteria by excluding all patients taking prescription medications known to affect bone metabolism.

Our study revealed that patients with a fracture had higher levels of markers of bone formation than controls. Garnero et al. compared serum levels of bone turnover markers in healthy postmenopausal women with those in women with a fracture[45]. After adjustment for bone mineral density, women with levels of resorption markers in the highest quartile had a twofold increase in hip fracture risk compared with women with levels in the lowest quartile. Sornay-Rendu et al. also found that markers of bone formation and resorption could be used to identify osteopenic women at a high risk for fracture[21]. Similarly, others have documented that the association between fracture risk and increased levels of markers of bone formation is stronger than the association between fracture risk and increased levels of markers of bone resorption[46,47].

The effects of fracture repair must be distinguished from underlying abnormalities in bone metabolism. The Malmö Osteoporosis Prospective Risk Assessment (OPRA) study showed that fractures affect bone formation and levels of resorption markers up to one year following injury[28]. In patients with a wrist fracture, however, levels of bone formation and resorption markers were unchanged immediately following fracture and four months postinjury. In contrast, a study of ankle fractures showed that P1NP and osteocalcin levels remained elevated up to a year after fracture whereas levels of resorption markers were stable[48]. We elected to examine bone turnover markers at three months after injury to minimize the effects of the fracture itself on bone turnover marker levels; however, it is possible that measurements performed at later time points would have yielded different results.

The mechanism by which increased bone turnover influences skeletal fragility is important to elucidate and may be related to altered bone microarchitecture. Deficits in trabecular structure have been documented in patients with higher levels of bone turnover markers[49,50]. Similar to our results, a prior study of patients with a hip fracture showed a negative correlation between P1NP levels and bone mineral density and an increased risk of fracture with high levels of P1NP[51]. At present, levels of bone turnover markers are not routinely used in the evaluation of osteoporosis and fracture risk. Our study revealed that the P1NP level may be of clinical relevance in identifying patients at risk for distal radial fracture. There are potential advantages to using P1NP levels in routine clinical analysis: measurements are not substantially altered by food intake or by circadian rhythms[22,52], and they are stable at room temperature and −70°C. P1NP may thus be a useful clinical marker of an increased fracture risk, particularly when combined with low bone mineral density.

Study limitations include a predominantly Caucasian patient population and a cross-sectional design, which does not allow prospective fracture risk prediction. We excluded patients with known comorbidities known to affect bone metabolism, which limits our ability to generalize results. We elected to obtain 25(OH)D and bone turnover marker levels at three months after injury to minimize the effects of fracture repair on measured bone formation and resorption. As a result, our study does not reflect 25(OH)D levels on the day of injury; however, no new vitamin-D supplementation was started until after the blood was drawn. When bone turnover markers are used to assess bone metabolism, consideration must be given to day-to-day variability; circadian rhythmicity; and, for CTX-1, considerable change in response to eating. To account for these factors, we collected all specimens after the patient had fasted overnight, and at the same time of day, and analyzed them together with the same reagents. We believe that these steps minimized potential measurement variations.

The study's strength lies in its focus on distal radial fracture. Although central fractures are associated with greater morbidity, distal radial fractures are the earliest presenting fragility fractures in postmenopausal women[53-56] and thus offer a unique opportunity to initiate treatment for underlying abnormalities in bone structure and metabolism. We were able to obtain all measurements relatively soon after fracture, and we limited the number of potential confounders by applying strict inclusion and exclusion criteria. Finally, this study is unique in that it focused on 25(OH)D and bone turnover markers specifically in postmenopausal women with a distal radial fracture.

In conclusion, we found that postmenopausal women with a distal radial fracture have similar vitamin-D levels but increased levels of bone formation markers when compared with women without a fracture. Women with a high P1NP level and low bone mineral density were at particularly high risk for fracture. Although limited by the cross-sectional study design and the fact that few subjects in our study had a low vitamin-D level, our results suggest that routine monitoring of vitamin-D levels in our region does not appear to be necessary in patients with a distal radial fracture. P1NP may be a useful clinical marker of bone fragility. ■

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14. ABSTRACT

The purpose of this study is to evaluate the impact of Vitamin D in prevention and progression of post-traumatic osteoarthritis (PTOA). The animal portion of this study involves surgical induction of osteoarthritis in mice, with supplementation of varying levels of Vitamin D, and evaluation using histology and micro-CT. The clinical portion is an add-on study at the United States Military Academy, evaluating a clinical cohort of USMA cadets treated for anterior cruciate ligament (ACL) tear, with pre- and post-injury serum 25-hydroxy-Vitamin D levels and correlation with joint space narrowing and biomarkers of cartilage injury. Findings from the animal model show preliminary evidence that Vitamin D supplementation may decrease OA in female animals, with less severe histologic grading in animals given supraphysiologic doses of oral Vitamin D. In the clinical portion, we have enrolled 36/100 (36%) of the required patients for the clinical study, but will evaluate serum 25-hydroxy-Vitamin D once the entire cohort is enrolled. Our findings provide preliminary support for the concept that Vitamin D supplementation could prevent the onset of often rapid joint destruction that occurs with PTOA, with important implications for high-risk military occupations.

15. SUBJECT TERMS
Murine, post-traumatic osteoarthritis, military, ACL, knee, medial meniscus, femoral, tibial, 25-hydroxy-Vitamin D, supplementation

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