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

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Fort Detrick, Maryland 21702-5012

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

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**Sponsoring/Monitoring Agency:**
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Fort Detrick, Maryland  21702-5012

**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, immunohistochemistry, 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 histologic changes in animals given one of two supraphysiologic doses of oral Vitamin D. Micro-CT demonstrates greater osteophyte volume in females but no consistent correlation with supplementation level. In the clinical portion, we have enrolled 70/100 (70%) of the required military cadets 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, 25-hydroxy-Vitamin D, supplementation

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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

ACCOMPLISHMENTS

This report represents the third annual summary of work for the 2016-17 year of funding for this project. It should be noted that we have requested and received a no-cost extension due to the transfer of funding from the University of Connecticut to the University of Chicago, with a 6 month lag pending administrative transfer. Reporting will be organized by task as noted in the Statement of Work.

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

Major Goals

1. Vitamin D Supplementation and Rodent Surgery
2. Imaging/Tissue Analysis of Surgical Model

Accomplishments

Major Activities

- We have completed the all three rounds of animal experimentation with C57-BL6 mice fed to supplement with four levels of Vitamin D:
  - control (1.5 IU/kg - minimal Vitamin D)
  - 1500 IU/kg (normal dietary level of Vitamin D)
  - 5000 IU/kg
  - 10,000 IU/kg
- A total of 300 mice underwent surgical initiation of osteoarthritis using destabilization of the medial meniscus and MCL sectioning. A small subgroup was treated with anterior cruciate ligament (ACL) sectioning to evaluate the degree of osteoarthritis induction.

- We changed the timepoints to evaluate mice at 8, 12, 16, and 20 weeks as we noted minimal induction of osteoarthritis at 4 and 8 weeks.

- Initial testing using mouse Vitamin D ELISA confirmed graduated levels of Vitamin D in the sera of treated mice groups.

- We then performed histology, faxitron X-ray imaging, and selected micro-CT analysis of the murine knees.

- 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, for rounds 1 and 2 of murine experimentation. We have repeated this rating at the University of Chicago, using data from rounds 2 and 3. These groups of surgically treated mice are thought to represent more consistent induction of osteoarthritis due to increased familiarity with the DMM technique.

**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 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, 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. Our results showed the highest levels of DBP in the mice given minimal Vitamin D, with DBP decreasing as supplementation increased.

Histology Analysis

In analysis of the histology from round 2, performed by the same three blinded examiners for consistency, we noted improved consistency of arthritic change at the 8, 12, 16, and 20 week timepoints. Histological analysis again showed some evidence in female mice of mitigation of post-traumatic osteoarthritis in the ACL group, as well as in females at 12 weeks, but no trends in male mice.

On the left, 20-week female with 0 Vitamin D supplementation with thinned cartilage and joint narrowing. On the right, female with 5000IU/kg supplementation, showing normal staining of the cartilage with less articular change. Note that in both, tibial squaring and osteophyte formation are visualized.
20 week histology samples from male mice with 5000 IU/kg Vitamin D. Note osteoarthritic changes on the left, with lesser changes on the right. Supplementation again seems to be more effective in female sex of mice.

Histology analysis is ongoing, with the first two rounds showing promising data. A group of three experienced investigators rated histology slides in a blinded fashion using the Mankin scoring system for severity of murine joint osteoarthritis, with the findings of:

- 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:

In a subset of mice treated with ACL transection in combination with destabilization of the medial meniscus, we observed faster onset and more severe osteoarthritic changes. Note the near complete loss of cartilage on the left side of the knee, with fibrillation and displacement of the meniscus.

Evaluation of these mice showed a protective effect of Vitamin D supplementation, although all of these mice developed osteoarthritis at 8 weeks. However, there was a trend toward less severe involvement in the supraphysiologically dosed female mice, as shown below.
We are repeating this histologic evaluation at the University of Chicago using slides from rounds 2 and 3 of DMM surgery in mice, based on the assumption that the surgical technique was better and the induction of osteoarthritis more consistent in these rounds.

**Bone Imaging**

**Faxitron imaging** showed progressive signs of osteoarthritis over time.

8, 12, and 16 week views with DMM (surgical) limb on left, sham surgery on right; all are of male mice with 1500 IU (normal) feed levels.

**Micro-CT analysis** has similarly shown signs of progressive osteoarthritis with aging in the murine model. We completed the analysis of rounds 2 and 3 through a subaward with the University of Connecticut.
Examples of micro-CT imaging with segmented views.

**MicroCT Image Analysis of Femoral and Tibial Epiphyses**

Changes in epiphyseal bone density often accompany joint instability, which are often observed and reported as subchondral thickening. Although a subchondral cortical “shell” is sometimes discernible in human studies by limiting inspection to a mid-sagittal cutting plane, trabeculation patterns in rodents greatly limit the selection of a region that defines and partitions a subchondral region (Figure X). Our approach for quantifying epiphyseal bone was to measure the bone volume of the entire epiphysis, thus objectively capturing all bone without subjective, manual interpretation of subchondral boundaries in a single plane of section. Moreover, because the spatial resolution and discretization of microCT imaging is very high, this objective definition provides for tremendously robust quantitation of bone volume and/or mass. In this study, spatial resolution and discretization to 16 micrometer cubic volume elements (i.e., voxels) is equivalent to 244,140 discrete voxels per cubic millimeter.
Figure X: Sagittal “slice” of volumetric rendering of a mouse knee joint, showing segmentation of the femoral epiphysis as a whole. Bone volume was quantified within the entire epiphysis as an objective measure of bony changes accompanying joint instability created by destabilization of the medial meniscus (DMM).

Isolation of the trabecular compartment within each epiphysis also was performed via manual selection (Figure Y), as is applied routinely in rodent studies. This approach quantifies the “volume fraction” of bone within the selected region, dividing bone volume (BV, obtained via Gauss filter and thresholding) by the total volume (TV) of the selected region (i.e., BV/TV).

Figure Y: Sagittal “slice” of volumetric rendering of a mouse knee joint, showing segmentation of the trabecular compartment within the femoral epiphysis. Bone volume fraction (BV/TV) was quantified within the entire volumetric trabecular compartment of each epiphysis by dividing bone volume (BV) obtained via Gaussian threshold filter by the total volume (TV) of the selected region.

When we evaluated total bone volumes looking at epiphyseal volume increases, we expected to see consistent increase in the volume based on increased bone formation with osteoarthritis, and evaluated to see if there was an effect with varying Vitamin D supplementation. We did not see definite change in epiphyseal bone volumes when comparing the surgical induction of OA side to the sham surgical left, but did note differences in osteophyte formation between sides. Thus, we focused our in-depth analysis on osteophyte volume using micro-CT.
In the evaluation of osteophyte volume with micro-CT at 16 and 20 weeks post surgery, total and bone volumes in osteophytes showed similar trends in male and female mice – specifically, that in the absence of Vitamin D very little osteophyte formation was seen. In the mice given supplementation of greater than physiologic levels (5000 IU compared to 1500 IU), there was a decrease in osteophyte volume. However, with 10,000 IU supplementation, osteophyte volume increased similar to the physiologic levels. These findings were consistent across time points and across mice sex. We interpreted this as an absence of specific correlation between Vitamin D supplementation and decreased osteophyte volume or total bone volume, but have noted a difference in osteophyte volume overall between male and female mice. Female mice have nearly 3 times higher volume of osteophyte formation than males at all timepoints. This is an interesting sex difference and may be reflective of previously noted trends in osteoarthritis in humans.³

Alternatively, a difference in Vitamin D dosage might explain these findings – specifically, that 5000 IU of Vitamin D might have a mitigating effect, but 10000 IU of Vitamin D was too high and activated further bone formation and other pathways in the osteoarthritic cascade. This will be investigated further with the validation through histology to see if there is a large difference between doses.
References

5. Rabenberg M, Scheidt-Nave C, Busch MA, Rieckmann N, Hintzpeter B, Mensink GB. Vitamin D status among adults in Germany--results from the German Health Interview and Examination Survey for Adults (DEGS1). *BMC Public Health.* 2015;15:641.

Summary of Aim 1 Accomplishments

- Completed animal surgeries at UConn before PI change of location.
- Established reliable histology ratings techniques using Mankin scoring rubric.
- Completed histology testing and in process of validating histology analysis.
- Completed micro-CT analysis. The findings of no specific correlation of osteophyte volume or bone volume with Vitamin D supplementation level using micro-CT are noted,
although there was a consistent effect of lower osteophyte volume with 5000 IU supplementation. The lack of further volume change with more Vitamin D supplementation, however, may indicate that this observation is just due to chance. Again, the sex difference with female mice showing higher volumes of osteophyte formation is notable and we plan to continue analyzing this finding. Further sub-analysis is needed to definitively translate these results.

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

• The main accomplishment 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. In contrast, Rabenberg et al showed no sex differences in 25-hydroxy-Vitamin D levels in an adult census study. In our second round of the animal study, this appeared to be a consistent effect. We need to complete the pooled analysis of rounds 2 and 3 to validate this effect.

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

Major Goals

1. Initiation of Add-on to Existing Study
2. Subject Enrollment/Specimen and Data Collection

Major Activities:

• 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):
  o 119 ACL injured cadets screened
  o 70 ACL injured cadets enrolled in study; this is on target for 90-100 cadets to be enrolled over three year period.
  o 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.

Opportunities for Training and Professional Development – Nothing to report

Results Dissemination – Nothing to report

Plans for Next Reporting Period

- We are about to begin immunohistochemistry to look at markers within articular cartilage and molecules upregulated with osteoarthritic degeneration. Specifically, the expression of extracellular matrix proteins (type 1, II, IX, collagens, aggrecan), chondrocyte hypertrophy markers (Runx2, type X collagen, MMP13), enzymatic degradation products for aggrecan and collagens (aggrecan NITEGE, collagen C1 and C2 neoepitopes) and differentiation markers (Runx1, Sox9) will be examined by immunohistochemistry (IHC).
- Completion of pooled analysis of histology
- Preparation of manuscript regarding Vitamin D supplementation in murine model
- Preparation of manuscript(s) regarding impact of Vitamin D supplementation on murine osteoarthritis
- Completion of USMA cadet enrollment and batched Vitamin D analysis
- Initiation of imaging study analysis in USMA cadets

IMPACT

Impact on Development of Principal Disciplines
The fact that we are studying the effect of a common molecule on a devastating musculoskeletal injury in young people has stimulated interest in this topic. The military studies of Vitamin D supplementation in recruits are related in scope.

Impact on Other Disciplines – Nothing to Report

Impact on Technology Transfer – Nothing to Report

Impact on Society Beyond Science and Technology – Nothing to Report - yet. The results of this study could potentially impact public health and knowledge about the importance of Vitamin D for bone and joint health as well as routine surveillance for circulating blood levels.
CHANGES/PROBLEMS

Changes in Approach – Nothing to report

Actual Problems or Delays and Actions to Resolve

- The delay in funding transfer after PI change of institution slowed progress on the grant for 6 months.
  - work on the grant and set up of subaward at the University of Connecticut to complete micro-CT did not occur for 6 months.
  - With the change in institution and delay in funding transfer, cadet enrollment continued but payment for research assistant was threatened; fortunately, USMA was able to support his salary while awaiting grant transfer.
- We have received a no-cost extension to allow work on both specific aims 1 and 2 to be completed within the year.

Changes with Significant Impact on Expenditures – Nothing to report

Significant Changes in Use or Care of Human Subjects/Animals – Nothing to Report

USMA/Keller Army Hospital IRB is current – originally approved in October 2013, reviewed October 2017.

PRODUCTS

Publications, Conference Papers, and Presentations


Website/Internet – Nothing to report

Inventions, Patents, and Licenses – Nothing to report

Other Products – related research work:


Dr. Oliveira (above) and I have also begun a prospective project to look at Vitamin D levels in patients with specific tendinopathies – including Achilles tendinitis, lateral epicondylitis, and rotator cuff bursitis.
## PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

<table>
<thead>
<tr>
<th>Name</th>
<th>Project Role</th>
<th>Researcher Identifier</th>
<th>Person Month Worked</th>
<th>Contribution to Project</th>
<th>Funding Support</th>
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<tr>
<td>Jennifer Moriatis Wolf, MD</td>
<td>PI</td>
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<tr>
<td>Kenneth Cameron, PhD, ATC</td>
<td>USMA site PI</td>
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<td>Tong-Che He, PhD</td>
<td>Co-Investigator</td>
<td>0001-7721-3934</td>
<td>6</td>
<td>Assistance with histology review, immunohistochemistry, project planning</td>
<td>University of Chicago cooperative funding with Chinese government</td>
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<tr>
<td>Wei Jiang</td>
<td>Postdoctoral student</td>
<td></td>
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<td>Histology grading, slide preparation</td>
<td>University of Chicago postdoctoral support fund</td>
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<td>Douglas Adams, PhD</td>
<td>UConn site PI</td>
<td></td>
<td>5</td>
<td>Micro-CT analysis of murine knees</td>
<td>Connecticut Institute for Clinical and Translational Science</td>
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<td>Matthew Posner, MD</td>
<td>USMA Co-Investigator</td>
<td></td>
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<tr>
<td>Steven Svoboda, MD</td>
<td>USMA Co-Investigator (until USMA retirement)</td>
<td></td>
<td>6</td>
<td>Enrollment of patients, consent process</td>
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Change in Active Other Support of PD/PI or Key Personnel – Nothing to report

Organizational Partners – Nothing to report

**SPECIAL REPORTING** – Quad Chart for October 2017 attached

**APPENDICES**
- Quad chart
- PI CV
CURRICULUM VITAE
Jennifer Moriatis Wolf, MD

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Department of Orthopaedic Surgery and Rehabilitation
Section of Hand and Upper Extremity Surgery
5841 S. Maryland Avenue, MC 4079
Chicago, Illinois 60637
Phone: 773-702-5384
Fax: 773-702-4384
Email: jwolf@bsd.uchicago.edu

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

2016-present Lund University Faculty of Medicine – PhD in Hand Surgery
Lund, Sweden
Supervisors: Isam Atroshi, MD, PhD; Martin Englund, 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
Licenses active in Connecticut, Colorado, Minnesota, Illinois, Georgia, and Indiana

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
2015-2016  Professor, Department of Orthopaedic Surgery
             University of Connecticut
2016-present  Professor, Department of Orthopaedic Surgery
             The University of Chicago

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)
   Medical School Admissions Committee (2014-2016)
   Instructor, Musculoskeletal Block (2010-present)
The University of Chicago
   Program Director, Hand Surgery Fellowship (2016-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)
2010-2016  John Dempsey Hospital
2014-2016  Connecticut Children’s Medical Center
2016-present  The University of Chicago Hospitals

AWARDS & HONORS

2016  Office of Faculty Initiatives Grant Award – The University of Chicago
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
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)
Connecticut Orthopaedic Society (2010-present)
New England Orthopaedic Society (2015-present)

JOURNAL REVIEW

Deputy Editor-in-Chief, Journal of Hand Surgery (2016-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 (2003-2016)

Web Updates Editor, Skeletal Trauma (2008-2016)

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

Consultant Reviewer
  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)
BMC Musculoskeletal Disorders (2014-present)
Osteoarthritis Cartilage (2015-present)
Arthritis Care and Research (2015-present)

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

COMMITTEES/SERVICE

American Society for Surgery of the Hand
Council Member-at-Large (2014-2017)
Treasurer (2017-2020)
Lead, Innovation Task Force (2017-2018)
Program Co-Chair, Annual Meeting (2014)
Liaison, AOA Own the Bone (2016)
Annual Meeting Committee (Co-Chair, 2016)
Publications and Products Committee (2015-2016)
Membership Application Task Force (2015)
Commercial Support Committee (2012-2017)
Touching Hands Project (2012-2015)
Bunnell Traveling Fellowship Committee (2010-2013; Chair, 2013-2014)
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 Committee (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
Joint Committee for CAQ Question-Writing Task Force (2011-2015)
American Orthopaedic Association  
Nominating Committee – alternate (2017-18)

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)  
Chair, Nominating Committee (2015)

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


46. Wolf JM, Cameron KL, Clifton K, Owens BD. Serum relaxin values in young athletic males are similar to females. *Orthopedics* 36(2):128-31, 2013.


NON-PEER REVIEWED PUBLICATIONS


ELECTRONIC MEDIA


TEXTBOOK CHAPTERS


TEXTBOOKS

RESEARCH SUPPORT

PEER-REVIEWED

CURRENT

1. Wolf (PI) 9/1/14-4/1/17 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 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 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.

COMPLETED

1. Chung (PI) 06/01/2011-05/30/2016 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

2. Wolf (PI) 9/14/13-09/13/15 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.

3. Rozental (PI) 05/01/2012-04/30/2013 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

4. Wolf (co-PI) 09/01/11-08/31/12 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

5. Wolf (PI) 08/20/10-06/01/11 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

6. Wolf (PI) 09/01/08-08/31/10 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

7. Wolf (PI) 07/01/08-06/30/11 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

8. Wolf (PI) 10/01/06-09/30/08 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

9. Dawson (PI) 2/01/08-1/31/09 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

10. Sobky (PI)  07/01/04-06/30/05
   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

11. Wolf (PI)  07/01/94-06/30/95
   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
   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)


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


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


53. Ulnar Collateral and Radial Collateral Ligament Repair and Reconstruction. AAOS Complex Wrist and Hand Trauma Course, April 15, 2016, Rosemont, Illinois.

54. Radial Tunnel Syndrome. AAOS Complex Wrist and Hand Trauma Course, April 15, 2016, Rosemont, Illinois.


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)


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)


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)


COURSE FACULTY


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


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


22. Faculty, 2nd Annual Course on Wrist Arthroscopy and Arthroplasty, October 10-12, 2015, Arezzo, Italy.


27. Co-Chair, Interactive Case Reviews, ASSH Annual Meeting: Thumb CMC Arthritis. October 2016, Austin, Texas.


REGIONAL/LOCAL PRESENTATIONS


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.


PERSONAL
Married to Douglas S. Wolf
2 children
Hobbies: rowing, hiking, running, travel, exploring restaurants
Volunteer physician at overnight camp (2006-present)
Medical Director, Ramah Rockies Summer Camp (2009-10)
Vitamin D Supplementation for Prevention of Post-Traumatic Osteoarthritis: Evaluation in Animal and Clinical Models
OR130096/Peer Reviewed Orthopaedic Research Program/Translational Research Award

PI: Jennifer Moriatis Wolf, MD Org: University of Chicago Award Amount: $750,000

Study/Product Aim(s)
• to evaluate the impact of systemic Vitamin D supplementation on the initiation and development of surgically induced OA in a murine model
• 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.

Approach
• Oral vitamin D supplementation of mice at 4 doses, followed by induction of surgical osteoarthritis using destabilization of medial meniscus. Evaluation using micro-CT, histology and immunohistochemistry
• Add-on to existing clinical trial at United States Military Academy with measurement of Vitamin D levels prior to and during and after ACL injury and treatment, with postoperative imaging evaluation.

Goals/Milestones
CY14 Goal
- Establishment of animal model, initiation of add-on for ongoing clinical trial
  ✓ Initiation of animal study with Vitamin D murine supplementation – 100 mice underwent OA initiation surgery 1/9/15 after 2 weeks pre-feeding at 4 Vitamin D doses – experiment completed; histology and imaging analysis complete
  ✓ Initiate clinical study add-on with consent, obtaining pre-injury serum from DODSR – confirmed add-on to existing study

CY15 Goal
- Validation of model, tissue analysis, clinical trial
  ✓ Repeat animal studies to validate animal findings, micro-CT analysis – complete 2nd and 3rd round of 100 mice with 12, 16, 20 week timepoints as well as ACL transection addition with 8 week sacrifice; histology and micro-CT evaluation to be set up
  ✓ Begin tissue analysis of murine knees with histology and immunohistochemistry
  ✓ Continue clinical study with specimen and data acquisition (total 70 subjects enrolled)

CY16 Goal – Experimental completion and data analysis
- Complete histology and micro-CT analysis of murine data
- Finalize clinical subject enrollment and determine followup needs
- Data analysis/Comments/Challenges/Issues/Concerns: No consistent pattern of osteophyte formation related to dose using micro-CT

Timeline and Cost

<table>
<thead>
<tr>
<th>Activities</th>
<th>CY 14</th>
<th>CY 15</th>
<th>CY 16</th>
<th>CY 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation/Vitamin D Supplementation, Measurement and Rodent Surgery</td>
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<tr>
<td>Tissue Analysis of Surgical Model</td>
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<tr>
<td>Clinical Subject Enrollment and Specimen/Data/Imaging Acquisition</td>
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<tr>
<td>Data Analysis/Organization</td>
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Estimated Budget ($K)
- $250,000
- $250,000
- $250,000

Updated: 10/10/2017

Budget Expenditure to Date
Projected Expenditure: $1,062,293.00 (including indirects) – Univ Chicago total $337,479.49
Actual UCMC expenditure to date: 180,149.40 (additional $184,619 committed to subcontracts with USMA (Geneva Foundation) and UConn

Micro-CT analysis did not show a consistent pattern of osteophyte formation when measured by bone volume; however, females consistently showed osteophyte volumes twice as high as male mice at all time points measured (8, 12, 16, and 20 weeks). This sexual dimorphism bears further evaluation. In analysis of overall bone volumes, knees in mice treated with Vitamin D show a consistent trend of lower bone volumes.