# University of Pennsylvania Orthopaedic Journal

Volume 23 June 2013

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Denis S. Drummond, M.D.
Malcolm L. Ecker, M.D.
John M. Flynn, M.D.
Theodore J. Ganley, M.D.
B. David Horn, M.D.
Helen Meeks Horstmann, M.D.
J. Todd Lawrence, M.D., Ph.D.
Bong S. Lee, M.D.
Ines C. Lin, M.D.
Wudbhav N. Sankar, M.D.
David A. Spiegel, M.D.
Lawrence Wells, M.D.
Jennifer Winell, M.D.

## Pediatric Sports Medicine Specialists:

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Matthew Grady, M.D.
Christina L. Master, M.D.
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Michaela Moore, M.S.N., C.R.N.P.
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Roni Robinson, C.R.N.P.
Kelly Ryan, C.R.N.P.
Anna Simon, B.S.N., M.S.N.-C.P.
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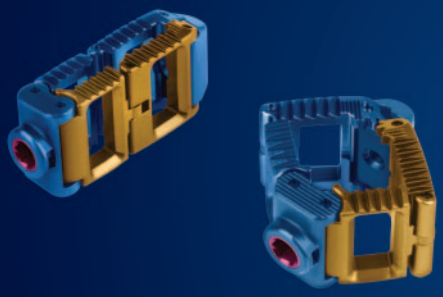

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# University of Pennsylvania Orthopaedic Journal

Volume 23, June 2013

## Editorial Board

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# University of Pennsylvania Orthopaedic Journal

## Volume 23, June 2013

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## CLINICAL ARTICLES

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## PROGRAMS FOR NEW SURGEONS

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# Letter from the Editors-in-Chief

It is our privilege to present the 23rd edition of the *University of Pennsylvania Orthopaedic Journal*. The legacy of the UPOJ began in 1985 under the auspices of former chairman Dr. Carl T. Brighton. Since that time, the UPOJ has been published annually, with the exception of a brief hiatus between 1993 and 1997. Thus, with the presentation of the 23rd edition of the UPOJ, we celebrate the 28th anniversary of the oldest resident-run orthopaedic journal in the nation.

We proudly dedicate this edition of the UPOJ to Dr. R. Bruce Heppenstall, who continues to serve as a member of the Penn orthopaedic faculty with the same vigor that he has maintained for an astounding 38 years. This year marks Dr. Heppenstall's retirement from the operating room, leaving a great void in the ORs at both Pennsylvania Hospital and the Hospital of the University of Pennsylvania. Throughout his long and storied career, Dr. Heppenstall has earned the respect and admiration of his colleagues, mentors, and students. There are few on the faculty who could run an OR with such confidence and good-natured candor. This edition is a small tribute to Dr. Heppenstall's sincere dedication to resident education and unremitting loyalty to Penn Orthopaedics.

This year marks a change in the structure and format of the UPOJ. With the hope of providing a more complete representation of the extensive ongoing research within our department, we have moved to an "extended abstract" format for all submissions. This format allows our authors to share their work with our readership without compromising the submission of future full-length manuscripts to other peer-reviewed scientific journals. Furthermore, we are now able to include abstracts submitted to the Orthopaedic Research Society and the American Society for Bone and Mineral Research by our colleagues in the McKay Orthopaedic Research Laboratory. It is our great pleasure to display this prestigious work within the UPOJ for the first time, and we hope that the new format increases both the breadth and readability of its contents.

Since 1997, the UPOJ has remained financially independent from the Department of Orthopaedic Surgery. The support from educational grants and advertisers allow us to bring this publication to print. We extend our greatest thanks to our industry sponsors for their contributions toward our mission of musculoskeletal research and education.

The publication of the UPOJ would not be possible without the tireless efforts of our chairman Dr. L. Scott Levin and program director Dr. Craig L. Israelite. We are further indebted to the invaluable mentorship of our faculty advisors Dr. Jaimo Ahn and Dr. Samir Mehta. The support, creative input, and oversight that these individuals have donated to the UPOJ throughout the academic year have been truly instrumental in making the 23rd edition a reality. We would further like to thank the following resident colleagues and subspecialty section editors for their hard work and enthusiasm: Dr. Ryan M. Taylor (Trauma), Dr. John G. Horneff, III (Shoulder and Elbow), Dr. Nicole S. Belkin (Sports Medicine), Dr. Adam T. Griska (Hand), Dr. Kevin J. McHale (Pediatrics), Dr. Stephen J. Torres (Adult Reconstruction), and Dr. Christos Photopoulos (Spine).

On behalf of our fellow authors and editors, we welcome you to the 23rd edition of the UPOJ. Within its pages are a vast array of ideas, experiments, and discoveries, and we trust that culture of innovation at Penn Orthopaedics will foster this tradition for many years to come.

Sincerely,
Andrew H. Milby, MD and Sarah M. Yannascoli, MD
Editors-in-Chief
*University of Pennsylvania Orthopaedic Journal*
Volume 23

# Dedication to Dr. R. Bruce Heppenstall

Andrew H. Milby, MD and Sarah M. Yannascoli, MD

We are proud to dedicate this 23rd edition of the UPOJ to a living legend in orthopaedic surgery who embodies the academic ideal of scholarship, education, and clinical excellence. Dr. R. Bruce Heppenstall has served Penn Orthopaedics with loyalty and distinction for no less than 38 years, and his achievements continue to inspire us in the operating room, at the bedside, and in the laboratory.

Dr. Heppenstall was born in Canada and completed his undergraduate and medical education at the University of Manitoba. He subsequently performed a rotating internship and residency in general surgery at the Winnipeg General Hospital in Manitoba. His interest in the care of patients with traumatic injuries motivated him to pursue a residency in orthopaedic surgery at the University of Pennsylvania under the tutelage of Dr. Edgar L. Ralston. Following a postdoctoral fellowship at the University of California in San Franscisco sponsored by the National Institutes of Health, Dr. Heppenstall returned to Penn, where he has remained as a keystone of the faculty in orthopaedic surgery since that time.

Early in his career, Dr. Heppenstall continued the tradition of scientific inquiry that was inspired by Dr. Ralston through extensive collaboration with surgeon-scientist, and later department chair, Dr. Carl T. Brighton. Together, they performed detailed investigations of bone electrobiology and the physiologic optimization of fracture healing. Along with an ongoing appreciation of the evolving techniques of internal fixation, this work culminated in publication in 1980 of the comprehensive text, *Fracture Treatment and Healing*. Incredibly, Dr. Heppenstall maintained this commitment to scientific inquiry alongside a busy clinical practice and duties as chief of the fracture service at the Hospital of the University of Pennsylvania and chief of orthopaedic surgery at the Philadelphia Veterans Affairs Medical Center.

In addition to his seminal contributions to fracture biology, Dr. Heppenstall was early to recognize the crucial importance of soft tissue management in traumatic injuries. A growing interest in the metabolic effects of tissue ischemia ultimately led to long and rewarding collaboration with eminent biophysicist Dr. Britton Chance. Using nuclear magnetic resonance spectroscopy, Dr. Heppenstall and Dr. Chance were able to able to describe the derangements of intracellular energy metabolism induced by ischemia in the setting of compartment syndrome or tourniquet use. An elegant animal model of compartment syndrome that allowed for careful simultaneous monitoring of blood pressure and compartment pressure gave rise to the term Delta pressure, or difference between the compartment pressure and mean arterial pressure; a value that is still relevant to diagnosis of compartment syndrome in daily practice. The recognition of the value of this work culminated in the receipt of the prestigious Kappa Delta Orthopaedic Research Award in 1986.

Despite these achievements, Dr. Heppenstall could never be accused of resting on his laurels, and the countless students and residents that rotated with him were most likely to be impressed by his wit, candor, and work ethic. Dr. Heppenstall's direct approach to communication has demonstrated to generations of residents that there is truly no substitute for being honest with patients and their families. In the operating room, regardless of the case being performed, Dr. Heppenstall was always looking beyond the next step. It was a fatal mistake to be caught without a plan in Dr. Heppenstall's operating room, but as quickly as you were chastised, you would catch a glimpse of a smile from beneath his mask.

We can think of no individual who more fittingly captures the ideals of academic and clinical excellence put forth in this issue of the UPOJ than Dr. Heppenstall. Cathcart 8 and Founders 4 have lost one of their most colorful personalities and tireless educators, but we are truly grateful that Dr. Heppenstall is still seeing patients and remains available to us as a mentor. His legacy will continue to inspire surgeon-scientists at Penn Orthopaedics for many generations to come.

# Letter from Dr. R. Bruce Heppenstall

I first came to Penn as an orthopaedic resident in 1969. Dr. Edgar J. Ralston was the chairman and a fine gentleman who cared deeply for each resident. On rounds one Sunday, he related to me that I would probably not be performing the same operations that he was performing, due to rapid changes in the field of orthopaedic surgery. Boy, was he correct! (Just as one example: cup arthroplasty versus total joints!).

My next step at Penn was the completion of a research year under Dr. Carl T. Brighton. The year was incredibly productive. I spent much of my time documenting oxygen tension and studying the electrical effects of the growth plate. Following completion of the program, I traveled to the University of California, San Francisco for a trauma and wound healing fellowship. While in California, Dr. Richard Rothman flew out to persuade me to join him in practice at Pennsylvania Hospital as a part of the Penn faculty. Three years later, under some pressure from Dr. Brighton and Dr. William Fitts, chairman of general surgery, I was asked to return to HUP and the VA and start a trauma and joint program. The caveat for them was that they would give up treating fractures to honor my new position. In order to secure my post, Dr. Brighton and Dean Stemmler appointed me as the chief of orthopaedic surgery at HUP for the next ten-plus years. Following Dr. Fitzgerald, Dr. Richard Lackman became the chairman of our department. Dick, like Dr. Ralston, was very concerned about the welfare of the residents and continued to improve the program. Finally, Dr. L. Scott Levin was named chairman, bringing with him extensive plastic and orthopaedic surgical experience. Dr. Levin was obviously the correct choice, as evidenced by what is happening to the program: 1) an orthopaedic institute under construction; 2) numerous residents returning to the faculty; 3) nine new faculty appointments; 4) the Human Tissue Laboratory in Stemmler Hall available for dissections and scientific programs; 5) extensive publication of manuscripts to the AAOS, ORS, OTA, etc.; and 6) a powerful research department led by Dr. Louis Soslowsky. Need I say more? A great place to be!

Residency is a tough grind. You are required to give of yourself for the benefit of patients and the accumulation of knowledge. It is not easy to give up time with your family and children. However, there are fun-filled and exciting times as well. My wife and I enjoyed having the residents for a baseball game and a wild party in the Heppenstall house years ago. I also enjoyed attending 25 years of the Snowmass Colorado Trauma and Sports Medicine course. It was fun to support all chief residents for the week and ski with them. Many, many stories. All in all, it has been a blast that I will never forget. You are now a part of the Penn Orthopaedics family and have a chairman who loves to teach and loves to throw parties. Therefore, the beat goes on and the years flash by. Enjoy!

# Letter from the Chairman

L. Scott Levin, MD, FACS

The past academic year has marked a tremendous period of growth for Penn Orthopaedic Surgery. Of the 23 department chairs, I am no longer the "new kid on the block." My recruitment has been followed by new department chair recruits in ophthalmology, emergency medicine, oral surgery, dermatology, neurology, radiology, and physical medicine and rehabilitation. Despite the changes in health care economics, influence of the Federal and State Government on health care legislation and funding, reimbursement with third-party payers and insurance companies, Penn Medicine has remained strong, and Penn Orthopaedics is yet again stronger compared to this time last year.

The concepts of Jim Collins – hoping to bring a very good department to greatness – continue to influence my thoughts as leader of Penn Orthopaedics. This year has been a time of key faculty recruitment both in the McKay Orthopaedic Research Laboratory with the addition of a third PhD scientist since 2009, and the recruitment of Dr. Kristy Weber, former Professor of Orthopaedics at Johns Hopkins University who was recruited to Penn to become the new Director of Orthopaedic Oncology, Vice Chair for Faculty Affairs, and have a leadership role in the Sarcoma Program at the Abramson Cancer Center. With the support of the ACC and the Abramson family, we have been able to provide an endowed chair for Dr. Weber who is deserving of this honor.

Dr. Weber will be joined this academic year by Drs. Andrew Kuntz, Keith Baldwin, Derek Donegan and Neil Sheth. All of these faculty members were prior Penn orthopaedic residents. Drs. Kuntz, Baldwin and Donegan started their faculty positions this past August and have had a huge impact on teaching, education, and research within the department. Dr. Sheth started this past September and has already made an impact on our global health program. Neil has also been granted a senior scholar position at the Leonard Davis Institute and serves as Director of Joint Replacement Surgery at the VA Hospital.

Further growth in the department of spine surgery has occurred with the appointment of Dr. Harvey Smith. Just over a year after Dr. Vincent Arlet (Chief of Spine Surgery) arrived, we have been fortunate to recruit Dr. Smith, continuing our trend of appointing surgeon-scientists to join our faculty. Dr. Smith comes from the New England Baptist Hospital in Boston, MA, where he had a thriving practice. His desire to be in a more academic institution has allowed us to recruit him to Penn Medicine and he will assume the role of Assistant Professor on the clinical educator track, he will also serve as the Director of the VA Spine Service.

Our most exciting news is the initiation of construction of the Penn Center for Advanced Care, a facility which will house the Penn Musculoskeletal Institute. The new Penn Shock Trauma hospital is also under construction. Our Musculoskeletal Institute groundbreaking ceremony for this was held this past fall. These new homes of Penn Orthopaedics will provide bookends on the western and eastern part of the city with a full complement of orthopaedics at Pennsylvania Hospital and at the new facilities at PPMC.

This January 2013 marked a significant milestone in the history of the department. The 3B Orthopaedic Group, which had been part of the Penn Health System but not part of CPUP or the Department of Orthopaedics, has departed from the Penn health system to a different health system. Under Pennsylvania Hospital CEO Michael Buckley, we have been embraced. All orthopaedic specialties are represented at Pennsylvania Hospital, and we have expanded our operative and leadership roles there considerably. We have moved into the first floor Cathcart space, and transformed the clinic into a model for musculoskeletal medicine with implementation of our EPIC Medical Record System, providing efficient, cutting-edge clinical care.

Our Press Ganey scores within the health system, particularly at HUP, have gone "through the roof" in a positive way. I would like to recognize Lori Gustave, (COO), Fabian Marechal (Director of Service Line Operations), and Jasmine Kain, (Chief Operating Director and Practice Manager) for implementing quality care improvement measures along with our support staff. Our patients are greeted with a smile and courteous dialogue, which ultimately results in a better experience for them at Penn Medicine and Penn Orthopaedics.

The strength of our institution, and moreover our department, is that we maintain a passionate commitment to our research mission. While many academic departments and private enterprises are hiring physicians for the purpose of providing primarily patient care; we are able to hire individuals who not only provide superb patient care, but have dedicated time to contribute to our educational and research missions in our operating rooms, our conference rooms and most importantly promote orthopaedic science in our research laboratories. Drs. Sheth, Kuntz, and Baldwin have all submitted research grants to the VA and to the OREF for faculty development, which has been encouraged by Dr. Soslowsky and myself in order to support their academic careers and the research mission of the department. Despite declining rates for reimbursement, our clinical enterprise remains strong.

As testimony to our robust academic orthopaedic mission, our ORS performance remains outstanding. There were 35 ORS abstracts presented at this year's ORS meeting amongst Dr. Lou Soslowsky, Dr. Rob Mauck, Dr. Ling Qin and Dr. Sherry Liu. Dr. Lou Soslowsky was also honored for his Spotlight presentation, and Dr. Qin's group received a New Investigator Recognition Award. The McKay Orthopaedic Research Laboratory and Dr. Lou Soslowsky, are currently ranked #5 in the nation in terms of NIH funding, with four additional VA Merits, and four more in review. Our further academic performance at the 2013 AAOS included several instructional courses lectures and multiple podium presentations by faculty and residents. We have further hired a database information technology manager, Dexin Li, to continue to help our clinical research efforts with a Penn Orthopaedic database.

This year in the Human Tissue Laboratory we have hosted the Foundation of Orthopaedic Trauma course, the hip International Congress for Joint Reconstrcution course, the Face and Hand Transplant course for the American Society of Reconstructive Transplantation, and a number of other CME and industry sponsored courses. These education programs only begin to demonstrate the huge educational boom to Penn Orthopaedics provided by the Human Tissue Laboratory. Next May, we are proud to host an AAOS course within the Penn Human Tissue Laboratory facilities.

Our hand program continues to expand with development of new technologies for vascular disorders of the upper extremity, microsurgery, brachial plexus, and modern non-operative management of conditions such as Dupuytren's disease as well as other disorders. Highlights within our divisions include international presentations by Dr. David Bozentka, Dr. David Steinberg and myself at the International Federation of Societies for Surgery of the Hand in India. The hand transplant program continues to thrive with our team effort and national leadership in this unique focus of transplant medicine, and was recently highlighted on ABC Nightline. We have further instituted a number of new clinical programs based on our surgical innovations in order to give us an edge both regionally and nationally. We have performed our first vascularized fibular graft to the hip for avascular necrosis. This procedure was popularized by my mentor Dr. James Urbaniak at Duke, and has allowed our microsurgical armamentarium to expand. Dr. Urbaniak was present for our inaugural case in a 26-year-old lawyer who had Stage III AVN and was treated with a vascularized fibula and continues to do quite well.

Our sports medicine department has recently been granted approval by our Dean, Dr. Larry Jameson, to establish a Type I center - the Penn Cartilage Center under the direction of Dr. Jim Carey. This provides a tremendous opportunity for us to have a recognized center of excellence within our ranks. The department is dedicated to cartilage disorders and this center will link our tissue engineering research led by Dr. Robert Mauck and others, to our clinical enterprise. We will be hosting our second annual cartilage symposium with international faculty this spring.

Our spine program continues to flourish under Dr. Vincent Arlet and is now attracting patients from the Caribbean as well as the Middle East because of Dr. Arlet's international reputation. The collaboration with CHOP and our neurosurgery colleagues has been outstanding. This clinical recognition and multi-disciplinary cooperation will only continue to flourish with the addition of Dr. Harvey Smith.

Our adult reconstructive program has expanded and we have recruited Dr. David Nazarian to join us. Dr. Nazarian is a regional expert in hip and knee replacement and has a well established practice. His role in education and clinical care will add a tremendous amount to our adult reconstruction group. My tenure began with three total joint surgeons and now we have seven.

The foot and ankle division continues to thrive under Keith Wapner's direction. Over the past eight months the program has had two peer-reviewed publications, five book chapter publications, nine national lecture presentations and international lecture presentations in China, Thailand, Germany, England and the Netherlands. Dr. Wapner and Dr. Chao serve as reviewers for Foot and Ankle International, the official journal of the American Foot and Ankle Society. Furthermore, Dr. Wapner serves as a reviewer for the JAAOS, JBJS, CORR and the American Journal of Sports Medicine, as well as serving as the past president of the American Orthopedic Foot and Ankle Society, a member of the Managerial Board of Foot and Ankle International, and a member of the American College of Surgeons Advisory Council for Orthopaedic Surgery. Dr. Chao acts as the Foot and Ankle consultant for the Philadelphia Ballet Company.

The orthopaedic trauma and fracture service recently added Dr. Derek Donegan to its complement, bringing the number of operative orthopaedic trauma and fracture surgeons to four. Dr. Donegan has quickly developed a robust trauma and fracture practice at Pennsylvania Hospital. The trauma and fracture service continues to serve all three missions via outstanding clinical, research, and educational contributions. The trauma faculty serves in leadership roles in several orthopaedic academic organizations including MSIS, OTA, AOA, AAOS, as well as several journals including JBJS, CORR, JOT, COP, JAMA and NEJM. The practice continues to expand to include a wider breadth of clinical services including deformity correction, limb lengthening, surgical hip dislocations, and complete periprosthetic fracture management. In addition, the service continues to participate in several multi-center, multi-national prospective studies and has obtained federal and foundation funding for its own studies.

Our relationship with CHOP both on the research side, under the direction of Dr. Maurizio Pacifici, as well as the clinical side with Dr. John Dormans has never been stronger. CHOP's orthopaedic faculty continues to expand and is currently comprised of 21 providers, including 18 specialty trained pediatric orthopaedic surgeons (13 operative and 5 non-operative), and 3 pediatricians with sports medicine training. The CHOP faculty addition this year is Keith Baldwin, MD, MSPT, MPH, who completed his clinical fellowship at CHOP in 2011-2012. CHOP has also recently developed a partnership with Virtua Hospital to provide pediatric services at Virtua's facilities in Voorhees and Mount Holly. CHOP Orthopaedics currently has 4 clinical fellows, 4 research fellows, 2 medical students doing a year-long research fellowship, and multiple visiting international scholars. The CHOP Division of Orthopaedic Surgery is currently conducting 93 ongoing, active clinical research and basic science projects. Investigators within the division have been awarded funding from both internal and external sources to conduct these studies. In the past two years, the division has published over 100 articles in major orthopaedic journals. In addition to clinical research, the Orthopaedic Basic Research Program, led by Maurizio Pacifici, PhD, has contributed to research initiatives related to a number of skeletal pathologies, including Multiple Hereditary Exostoses (MHE).

Since Dr. Keith Baldwin's appointment, he has rekindled the legacy of Dr. Mary Ann Keenan in the unique field of neuro-orthopaedics. Dr. Baldwin is dividing his time between CHOP and the adult service at HUP, and is providing excellent care for patients with spasticity, spinal cord injury and traumatic brain injury.

Our shoulder and elbow group has been joined by Dr. Andrew Kuntz who is leading shoulder research efforts both clinically and experimentally. The service has 10 publications and 14 abstracts

presented nationally and internationally. Dr Huffman was inducted into the ASES and served as a moderator for the AAOS and served as member of the AAOS Shoulder and Elbow Subcommittee. Dr. Huffman also had the privilege of participating in the Japanese Traveling Fellowship program this past year. Dr. Glaser served as the AAOS course chair, as well as a moderator for the AOA and AAOS.

On a personal note, I have had the opportunity to visit a number of institutions as a visiting professor this past year including: St. Luke's Hospital in Bethlehem, PA; Mount Sinai in NYC; UC Irvine, CA; Penn State Hershey Bone and Joint Institute, PA; Medical University of South Carolina, SC; UC San Francisco, CA; and the University of Utah, UT as the graduation speaker. I am currently serving as World Society for Reconstructive Microsurgery president and was elected to the Board of Regents of the American College of Surgeons. I served as the American Society for Reconstructive Transplantation president and was reelected to the American Society for Surgery of the Hand counsel and to the AOA nominating committee.

We have embedded non-operative physicians, Dr. Kate Temme and Dr. John Vasudevan into our Sports Medicine and Spine Clinics creating an integrative musculoskeletal care delivery model, which will be essential in our new institute. Our orthopaedic anesthesia colleagues have also continued to provide excellent regional care, and a number of outstanding initiatives and peer-reviewed papers have occurred in collaboration with the anesthesia department.

Our senior faculty have always deserved recognition. Dr. Marvin Steinberg continues to be an effective senior statesman for Penn Orthopaedics and is involved in a number of projects that include his continued interest in osteonecrosis. He has presented papers regionally and internationally on this topic. Dr. Steinberg is active in local and international medical organizations. He is the Chairman Elect of the Girdlestone Orthopaedic Society and Program Chair for the Annual Meeting of the Association for Research on Circulation in Bone (ARCO). He is a consultant reviewer for JBJS and other medical journals and member of the Grant Evaluation Committee of the OREF. Lastly, he still continues to participate in medical student education and teaching on a monthly basis. Dr. Bruce Heppenstall has stepped down in his operative role and continues to practice non-operatively. Dr. Heppenstall has been part of Penn Orthopaedics for 40 years and we will be raising an orthopaedic endowed chair for him to recognize his contributions and legacy.

As I look at almost four years of my tenure, I do believe that we are going from "good to great." The strength of our faculty, the commitment to our research mission and our educational efforts has never been stronger. We have recently added Drs. Samir Mehta and Jaimo Ahn as our educational program directors consortium under the leadership of Dr. Craig Israelite. We are further growing our educational program with the addition of two ACGME Sports Fellows starting in July and an additional joint fellowship position. This year we had over 800 applicants and we interviewed 84 for the match. Our current interns who matched into our program last June 2012 are as follows: Jason B. Anari, MD, (UNDNJ/RW Johnson), Tyler R. Morris, MD, (Drexel University) Alexander L. Neuwirth, MD, (UNDNJ/RW Johnson), Philip A. Saville, MD, (University of Leicester), Michael T. Talerico, MD, (Saint Louis U. SOM), Nathan A. Wigner, MD, (Boston University) and Chase Woodward, MD, (Northwestern University).

Our June 2013 graduating residents all matched into fellowship programs at the following institutions: Dr. Eileen Crawford (Sports Medicine) at the University of Michigan; Dr. Andre (Nic) Gay (Foot and Ankle) with Roger Mann, MD, in Oakland, CA; Dr. Jason Hsu (Shoulder and Elbow) Washington University, St. Louis, MO; Dr. Tae Kim (Orthopaedic Oncology) Memorial Sloan-Kettering Cancer Center; Dr. Amun Makani (Sports Medicine) Massachusetts General Hospital; Dr. Min Park (Hand and Upper Extremity) Robert A. Chase Hand Center at Stanford University; Dr. Amy Sewick (Sports Medicine) University of California, Los Angeles; and Dr. Roshan Shah (Reconstructive Arthroplasty) Rush University.

As we approach the end of my fourth year of my first six-year term, I have never been professionally happier. It is humbling to lead such an erudite and distinguished group of men and women in our quest for excellence in musculoskeletal care and orthopaedic surgery. Across all missions, our institution is strong, our leadership determined, and to quote Dr. Amy Gutmann, "Penn is going from excellence to eminence." I feel part of this quest and hope you believe after what I have shared with you, that we continue our evolution from Good to Great and from Excellence to Eminence!

# Letter from the Program Director

Craig L. Israelite, MD

The University of Pennsylvania orthopaedic surgery residency program continues to be one of the top programs in the nation. The program's reputation has grown to the point where we receive over 800 applications to our program yearly. This year our program was more competitive than ever. The selection committee comprised numerous individuals who spent hours devising a scored ranking system that was an outstanding selection tool; this ranking methodology is in the process of publication. We are fortunate that we have matched some of the top candidates in the entire country.

The new interns starting in 2013 will be Keith P. Connelly (University of Central Florida), Cody D. Hill (Baylor College of Medicine), James M. Friedman (Duke University), Daniel P. Lim (Keck School of Medicine/University of Southern California), Joshua C. Rozelle (Drexel University), Joshua T. Steere (Stritch School of Medicine/Loyola University Chicago), Chia H. Wu (Perelman School of Medicine/University of Pennsylvania), and Zachary R. Zimmer (Stony Brook University). These are all exceptional individuals who are extraordinarily talented and diverse, and they will continue to strengthen the residency program.

We are pleased to inform that our outgoing senior residents have, again, done exceptionally well in the fellowship match, with many matching their first choices in their respective subspecialities. Eileen Crawford will be doing sports medicine at the University of Michigan; Andre (Nic) Gay will be doing foot and ankle at Oakland Bone and Joint Specialists; Jason Hsu will be doing shoulder and elbow at Washington University in St. Louis; Tae Won B. Kim will be doing orthopaedic oncology at Memorial Sloan-Kettering in New York; Amun Makani will be doing sports medicine at Massachusetts General Hospital; Min Jung Park will be doing hand surgery at Stanford University; Amy Sewick will be doing sports medicine at University of California-Los Angeles; and Roshan Shah will be doing total joint replacement at Rush University in Chicago. Although this has become routine that our graduating residents attend some of the finest and most sought-after fellowships in the country, we congratulate them, wish them well, and hope that they will continue to be part of the Penn Orthopaedics family.

The accomplishments of our current residents have been unprecedented. Numerous peer-reviewed journal publications as well as local, national, and international meeting presentations have brought the banner of Penn Orthopaedics to the forefront. We can be proud of all of the scholarly activity at the University of Pennsylvania, which has truly become a leader in academic orthopaedic surgery.

Although it is with mixed emotions that we bid farewell to our graduating residents, we have no doubts that they will all be extraordinary leaders in the field of orthopaedic surgery. This year we were again led be two exceptionally gifted, talented, and energetic academic chief residents. Dr. Eileen Crawford and Dr. Jason Hsu have inspired the entire orthopaedic residency to become extraordinarily well-organized and efficient. Under their leadership, numerous improvements have been implemented, including the development of a strong and balanced two-year core curriculum. This will serve to enhance the educational opportunities given to the residents and enhance their core orthopaedic knowledge. Additionally, the day-to-day management of resident assignments could not be accomplished without the stellar efforts of these two dedicated individuals. The academic chief residents for next year, Dr. Mara Schenker and Dr. Chancellor Gray, have already begun the transition and have shown extraordinary leadership skills. Finally, the entire faculty at the University of Pennsylvania continues to give selflessly and teach at a level that is the envy of orthopaedic residency programs throughout the country. Under the strong leadership of our chairman, Dr. L. Scott Levin, the faculty are amongst the most dedicated and approachable in the country. It is an absolutely wonderful mix of academic, clinical, and social interaction to which any program could aspire.

The next year will be as challenging as ever, as additional rules and regulations from our University and the government continue to shape the training and development of our residents. However, the strength, diversity, and dedication of Penn Orthopaedics should not only be able to weather these transitions, but continue to be a national leader in education.

Again, it has been my great pleasure to be associated with this program and I truly cherish the relationships that it has fostered throughout these years.

# Bilateral Hand Transplantation, a "Life-Saving" Operation?: A Case Report and Commentary

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## Introduction

The first hand transplant was performed in South America almost fifty years ago. Unfortunately, azathioprine and prednisone were unable to prevent acute rejection and the transplanted limb was amputated about 3 weeks later.[1,2] It was thirty-four years until the next hand transplant was performed in Lyon, France, and this was closely followed by the Louisville group who performed the first transplant in the United States in 1999.[2-4] The first bilateral hand transplantation occurred just two years later in Lyon, France.[2] These early successes began the modern era of hand transplantation. Since that time, hand transplantation has dramatically grown. Worldwide, more than 70 hand transplants have been performed, and there are at least seven centers in the United States that have performed a hand transplant. As time and experience have been gained, indications for transplantation have migrated proximally, and the first forearm transplant in the United States was performed in 2009. More recently teams have transplanted above the elbow, with early success as proximal as the deltoid region.[5,6] In this article, we present our experience with a 27-year-old female quadrimembral amputee who underwent bilateral proximal forearm-level hand transplantation at the University of Pennsylvania.

## Case Presentation

A 27-year old female quadrimembral amputee with bilateral proximal forearm amputations and bilateral transtibial amputations performed in the setting of sepsis presented to the hand surgery clinic one year following her illness. Prior to listing the patient for hand transplantation, the patient underwent an extensive preoperative screening process that included psychological, physical, financial, medical (to include infectious disease and cardiology), and surgical (plastic surgery, transplant surgery, hand surgery) evaluation. The patient presented with a chronic right knee wound that required a free scapular flap for below knee salvage and prosthesis fitting. After the patient's lower extremity function was improved and she was optimized medically and psychologically, the patient was determined to be a hand transplant candidate and was listed for transplantation (Figures 1A and 1B).

Three weeks after listing the patient a suitable donor was identified. The donor was found to match the recipient in terms of ABO compatibility, age (within 10 years), gender, race, skin tone, viral status (CMV negative), and

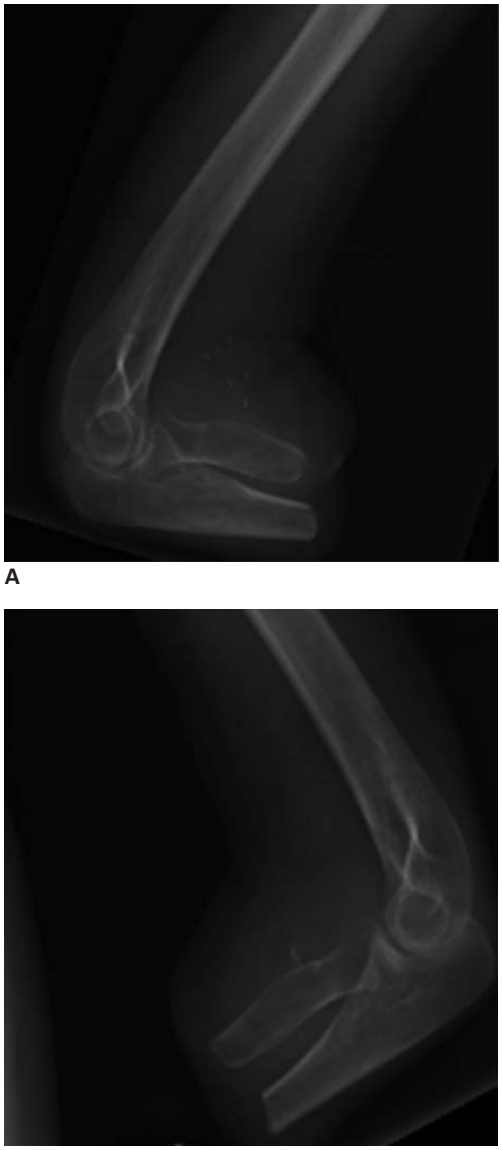

**Figure 1A and B.** Preoperative radiographs demonstrating bilateral proximal-level transradial amputations.

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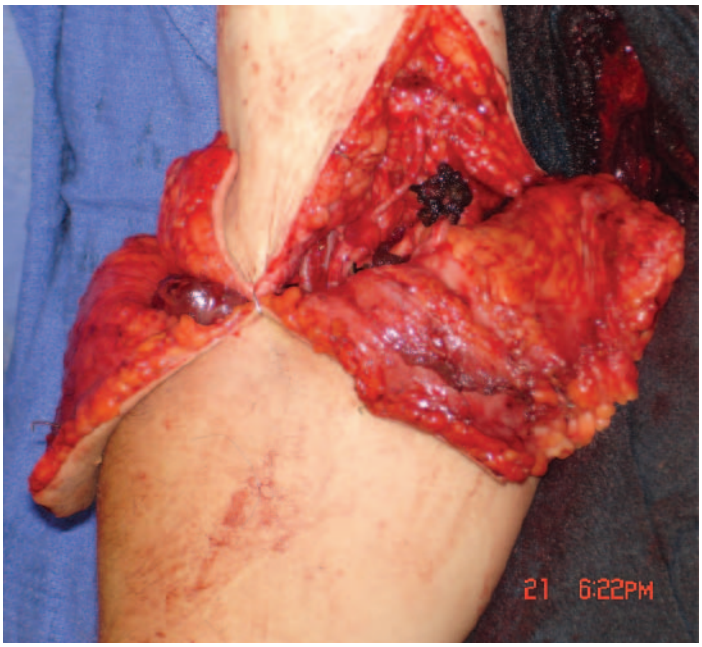


**Figure 2.** 90/90 flaps were developed for the insetting of the transplanted limbs.

limb size (within 15% of the recipient). A procurement team from the University of Pennsylvania was sent to the donor's location while the patient was simultaneously transported to the University of Pennsylvania. The donor upper extremities were procured at the proximal humerus level and the limbs were immediately perfused with University of Wisconsin preservation solution, wrapped in sterile moistened towels, placed in extremity drapes, and placed on ice for transportation.

The patient traveled to the University of Pennsylvania and the timing of surgery was planned to coincide with receipt of the donor limbs to the operating room. The donor and recipient limb dissections were performed simultaneously by four distinct surgical teams. Skin flaps from both the donor and recipient arms were raised in a 90/90 fashion so that inter-digitation of the flaps occurred at the time of closure (Figure 2). The neurovascular structures, including all named cutaneous nerves and veins were identified and labeled with pre-fashioned aluminum tags (Figure 3). The recipient proximal ulna and radius were identified and the distal osteopenic bone

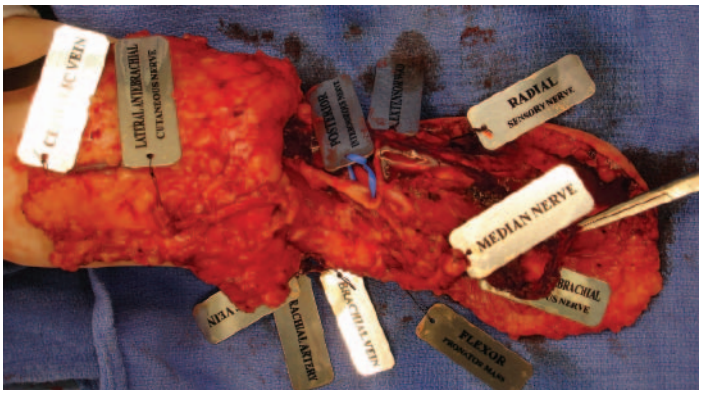


**Figure 3.** Labeling of important structures in both the recipient and the donor limbs was performed.

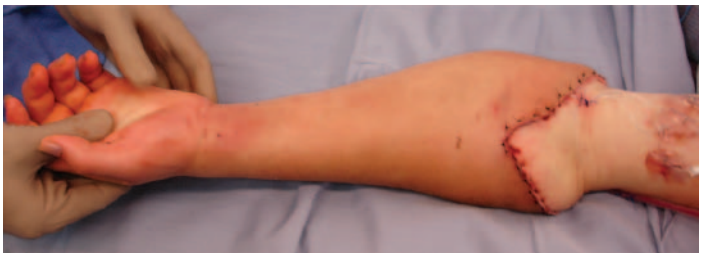

**Figure 4.** Transplanted forearm immediately following surgery with Cook-Swartz implantable Doppler leads in place.

was removed. Approximately 9 cm of residual radius and ulna remained for fixation. Bone was removed from the donor arms to match the amount of residual bone left on the recipient's radius and ulna. The sequence of transplantation proceeded with open reduction and internal fixation of the ulna and radius using 3.5 dynamic compression plates, arterial repair, venous repair, neural repair, followed by muscle fixation of the flexor/pronator mass, and the extensors, to the distal humerus with the suture anchors. The patient's upper extremities were placed into posterior long-arm splints and the allotransplant was monitored with the use of internal Cook-Swartz Doppler probes (Cook Medical, Bloomington, IN; Figure 4).

## Results

Twenty-one months following transplantation, our patient has regained her independence. She currently lives alone and can perform activities of daily living with little modification. She has regained 4/5 strength of elbow flexion/extension, finger flexion and extension, thumb flexion/extension. She has also recently begun to regain intrinsic muscle function and is able to oppose her thumbs. There is evidence of early ulnar nerve function in the hand and protective sensation has returned. Two episodes of acute rejection have occurred which have been treated successfully with short-term steroid dose increases. She continues to have transplant biopsies performed on a regular basis and is maintained on triple drug therapy consisting of tacrolimus, mycophenolate mofetil, and methylprednisolone.

## Discussion

Our patient has had excellent motor and sensory recovery thus far. The long term follow up of patients in the International Registry on Hand and Composite Tissue Transplantation has demonstrated that these allotransplants will continue to improve in function for as long as five years from the time of transplantation.[7] We anticipate the possibility of improved intrinsic function as well as potentially discriminatory sensation as time goes on.

The admonition "primum non nocere" remains critical as the field of allotransplantation continues to progress. In Dr. Cooney's position statement on hand transplantation for the American Society for Surgery of the Hand (ASSH) in 2002, he echoed this sentiment and indicated that the society recommended "great caution and a measured approach to the patient requesting limb transplant."[8] Additionally,

**Figure 5.** Bilateral hand transplants at 18 months from the time of transplantation.

the society advised that the procedure be limited until "immunosuppressive advances minimize the risk benefit ratio." While significant success has been achieved in the field of allotransplantion and improvements in immunosuppression have been realized, a survey of the ASSH in 2010 still reflected this cautious outlook on hand transplantation.[9] The survey indicated that only 24% of responders were in favor of hand transplantation, while 45% were against, and 31% were undecided. The least controversial situation, however, was the bilateral upper extremity amputee, as 78% of the responders indicated that this was the ideal indication for transplantation.

The risk to benefit ratio guides us as surgeons and influences our decision to offer patients various procedures. This is no different in hand transplantation. It is critical that we define exactly the potential benefits of the procedure. The intermediate risks are relatively well-defined,[7] and long term risks may be extrapolated from the solid organ transplantation data. The benefits, however, may not be easily articulated, and are currently not fully understood. The depths of the psychological distress and depression that amputees face should not be underestimated. In one study evaluating the cause of death of amputee patients, the authors found significantly higher rates of suicide and accidental death rates in this patient population.[10] This study did not specifically look at multiple limb amputees or quadrimembral amputees, though one might expect even higher rates of these unfortunate outcomes in patients with increasing functional impairment. The risk to benefit ratio must be carefully considered by the surgeon and the patient on a case-by-case basis. While it has been stated that hand transplantation is a quality of life-giving transplant,[11] in our opinion, it is not unreasonable that hand transplantation also be considered life-saving when performed for the proper indication (Figure 5).

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# Interfacility Transfer Utilization in the Management Pediatric Hand Injuries

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## Introduction

Emergent interfacility transfer is a means of ensuring that patients with complex injuries obtain tertiary evaluation in timely and seamless fashion; however, there are significant costs associated with its use. In addition, many patients undergoing transfer do not ultimately require the tertiary services suspected at initial triage.[1,2] More accurate characterization of the factors driving the decision to transfer patients to a higher level of care may improve resource allocation and reduce healthcare expenditures.

Accidental injuries are the most common reason for presentation of pediatric patients to the ED,[3] with hand injuries representing nearly two percent of all visits to one pediatric tertiary referral center.[4] Severe injuries, such as traumatic amputations, may result in substantial and permanent functional and emotional impairment.[5-7] Optimal outcomes require a multidisciplinary team of emergency physicians, hand surgeons, and anesthesiologists with expertise in the care of the pediatric trauma patient. As a result, many patients with such injuries that are initially triaged at regional hospitals subsequently undergo interfacility transfer for definitive evaluation and treatment. By analyzing our series of patients undergoing interfacility transfer for hand injuries, we sought to identify factors that may be associated with disproportionate rates of transfer utilization to better facilitate educational outreach and resource allocation.

## Materials and Methods

Children's Hospital of Philadelphia is a pediatric level one trauma center and academic tertiary referral center receiving a large volume of interfacility transfers. Institutional review board approval was obtained prior to commencement of this study. Electronic medical records were reviewed from the two-year period from July 1st, 2009 to June 30th, 2011 to identify all patients that were transferred to our institution, as well as the subset of these patients that were transferred for evaluation or treatment of a traumatic injury to the hand or wrist. Data regarding age, gender, diagnosis, site of injury, acuity, arrival time, admission status, and procedures performed during the hospitalization were collected. In addition, a list of facilities referring at least one hand injury was generated, and these facilities were organized into four categories based on the following capabilities: 1) hand surgery and pediatric admission/anesthesia, 2) hand surgery but no pediatric admission/anesthesia, 3) pediatric admission/anesthesia but no hand surgery, and 4) neither hand surgery nor pediatric admission/anesthesia.

The list of referring facilities was used to identify all transfers originating from these facilities for comparison of the hand injury transfer rate to the category-specific transfer rates using the chi-square test. The cohort of patients undergoing transfer for hand trauma was subsequently stratified by site of injury, time of transfer, admission status, and need for surgical intervention. The distributions of patients in each of these subcategories were compared to the expected distributions from the overall cohort using the chi-square test. P values less than 0.05 were considered significant.

## Results

A total of 13,193 patients were transferred to Children's Hospital of Philadelphia during the two-year study period. Of these, 169 patients were transferred for evaluation or management of an injury to the hand or wrist. Demographic data and injury characteristics for this cohort are reported in Table 1. No significant deviations from expected values occurred based on day of week or time of transfer. Hospital admission was required in 59 (35%) patients, of which 51 (86%) underwent a surgical procedure within 24 hours of presentation. Of the remaining 110 (65%) patients who were discharged from the emergency room, 27 (25%) underwent elective surgical intervention within two weeks of discharge.

Hand injury transfers originated from a total of 48 surrounding hospitals; patients from these institutions were responsible for 81.2% of the total transfer volume during the study period (Table 2). Hand injuries were responsible for 1.6% of patients transferred from these hospitals. Hand surgical coverage and pediatric admission/anesthesia capability was available at 16 hospitals, hand surgical coverage only at 12, pediatric admission/anesthesia capability only at 5, and neither hand surgical coverage nor pediatric admission/anesthesia capability at 15. Hospitals in these four categories were responsible for 41%, 18%, 11%, and 30% of all

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**Table 1. Demographics and diagnoses of study population**

| | no. | (%)* |
|---|---|---|
| No. patients transferred with hand injuries | 169 | (100) |
| Age (years)** | 8.4 ± 5.1 | |
| Gender | | |
| Male | 116 | (69) |
| Female | 53 | (31) |
| Diagnosis | | |
| Fracture | 73 | (43) |
| Amputation | 44 | (26) |
| Laceration | 22 | (13) |
| Infection | 18 | (11) |
| Dislocation | 5 | (3) |
| GSW | 3 | (2) |
| Blast | 1 | (1) |
| Burn | 1 | (1) |
| Congenital | 1 | (1) |
| Vascular | 1 | (1) |
| Contusion | 0 | (0) |
| Injury site | | |
| Finger | 71 | (42) |
| Wrist | 68 | (40) |
| Hand | 26 | (15) |
| Arm | 4 | (2) |

GSW, gunshot wound
*Percent of total transfers due to hand injuries (n=169).
**Values=Mean±SD.

transfers, and 36%, 7%, 22%, and 36% of hand injury transfers, respectively. A highly-significant difference ($p>0.001$) in the proportions of transfers originating from hospitals in these four categories was present if an equal 25% per category expected rate of hand injury transfers was assumed; however, this was reduced to a trend toward significance ($p=0.07$) if the expected hand injury transfer rate by category was assumed to be proportional to the volume of overall transfers received in each category (Table 2). The trend toward higher-than-expected rates of transfers was seen from hospitals with no pediatric admission/anesthesia capability, whether or not hand surgical coverage was present.

## Discussion

Although hand injuries represent a relatively small proportion (1.6%) of the total volume of patients transferred during the study period, only 35% required admission after evaluation. Of those admitted, 86% underwent a procedure within 24 hours (30% of total). The majority (65%) of patients transferred were able to be discharged from the ED with outpatient followup and elective surgical intervention, if required. In a series of 24,905 transfers, Li *et al* found that 24.7% of patients transferred to academic pediatric EDs were discharged directly from the ED.[8] The authors noted a higher rate of discharge from the ED (48.5%) among patients with orthopaedic diagnoses, with only 25.4% requiring admission longer than 24 hours. While the authors do not report separately on hand or wrist injuries, our findings support the conclusion that orthopaedic complaints represent a disproportionate number of transfers that do not ultimately require acute hospitalization or intervention.

We hypothesized that the presence of hand surgical coverage and/or pediatric admission/anesthesia capability at the referring institution may influence the decision to pursue transfer, as demonstrated by disproportionate distribution of transfers from institutions lacking these capabilities. The overall volume of transfers received from each institution by category was used to determine the expected proportions of hand injury transfers in each category. A trend toward a greater number of hand injury transfers was observed originating from institutions without pediatric admission/anesthesia capability (97 patients) versus the volume-weighted expected value (81 patients). This finding suggests that concerns regarding pediatric sedation or anesthesia may play a role in the decision to initiate transfer in patients with hand injuries. Cimpello *et al* reviewed the analgesia and sedation practice patterns of pediatric and general emergency physicians and found a similar hesitation on the part of both groups to administer analgesic medications during encounters for extremity injuries in children.[9] The authors noted that pediatric ED physicians were more likely to utilize sedatives and analgesics in combination for procedural sedation than were general ED physicians, though large proportions of patients in this and other series receive no analgesia whatsoever for even reductions of severely-displaced fractures.[10] Given the well-characterized safety profile of pediatric procedural sedation and analgesia,[11] even in a community ED setting,[12] these findings may be a result of the variable exposure to and comfort with use of these medications on the part of ED physicians.[13] Transfers of pediatric patients for the purposes of procedural sedation or anesthesia alone may represent an under-recognized contribution to the overall cost burden of the practice of defensive medicine.

While the limited number of hand injury transfers seen during the study period precludes the formulation of firm treatment recommendations, several areas can be identified for further study that may result in improved resource utilization. First, the value of educational outreach by physicians at tertiary referral centers cannot be overstated. While only diagnostic and decision-making services are practical with current teleconferencing technology, future advances may make additional remote services feasible and cost-effective. Perhaps the most important and practical initiative on the part of tertiary centers treating a large volume of upper extremity

**Table 2. Transfer rates by institution characteristics**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Total transfers (7/1/2009-6/30/2011) | 13193 | | | | | | | | |
| Total no. institutions referring hand injuries | 48 | | | | | | | | |
| Total transfers from institutions referring hand injuries | 10707 | | | | | | | | |
| No. patients transferred with hand injuries | 169 | | | | | | | | |
| Overall hand injury transfer rate | 0.016 | | | | | | | | |
| | Both | | Hand/No Peds | | Peds/No Hand | | Neither | | P value |
| No. institutions referring hand injuries by category | 16 | | 12 | | 5 | | 15 | | |
| Total transfers from institutions referring hand injuries by category | 4355 | (41) | 1880 | (18) | 1210 | (11) | 3262 | (30) | |
| Actual hand injury transfers by category | 60 | (36) | 37 | (22) | 12 | (7) | 60 | (36) | |
| Expected hand injury transfers by category (25% proportions) | 42.25 | (25) | 42.25 | (25) | 42.25 | (25) | 42.25 | (25) | 0.001 |
| Expected hand injury transfers by category (volume-weighted) | 69 | (41) | 30 | (18) | 19 | (11) | 51 | (30) | 0.073 |

P values calculated by the chi-square test.

injuries is to ensure the availability of short-term outpatient appointments for patients that may require subacute surgical intervention. A closed-feedback system that notifies referring providers when patients have been seen and evaluated in a timely fashion helps build trust among community ED physicians, and may reduce interfacility transfers in cases where there are concerns regarding access to care.

There are a number of important limitations to the conclusions that may be drawn from this study First, the study was conducted at a single center in a densely-populated area with a large number of referring hospitals of varying size and capabilities. Our findings have the potential to be affected greatly both by increased travel time and lesser subspecialization seen in less densely-populated regions, which limit their generalizability. Second, the availability of detailed data on hand injury transfers alone, as opposed to the entire cohort, limits the forms of statistical analysis that could be performed, and the power of these comparisons. Lastly, limited data were available regarding referring institutions with multiple locations or decentralized specialty centers. Our best attempts were made to approximate the overall capabilities of each discrete referring hospital based on geographic proximity and knowledge of regional institutional affiliations.

## Conclusion

The appropriate use of emergent interfacility transfers may represent an opportunity for improved healthcare resource utilization. Children sustaining injuries to the hand or wrist make up a disproportionate number of patients undergoing transfer but not ultimately requiring admission or urgent surgical intervention. While the availability of hand surgical or pediatric admission/anesthesia capabilities at the referring institution may play a role in the decision to initiate transfer, these and other patient factors were not strongly associated with increased numbers of hand transfers from hospitals in each of these subcategories. Improvements in inter-institutional provider communication and the consistent availability of short-term outpatient followup may help reduce rates of transfers for subacute conditions. Further study is necessary to better characterize the decision-making behind initiation of emergent transfer for pediatric hand injuries and to identify factors that may improve quality, access, and cost-effectiveness.

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# The Genetic Nature of Osteochondritis Dissecans: A Systematic Review and Call for Improved Studies

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## Introduction

Osteochondritis dissecans (OCD) is a focal, idiopathic, alteration of subchondral bone structure with risk for secondary damage to adjacent articular cartilage and premature osteoarthritis. These changes can manifest as early articular cartilage separation, partial detachment of an articular lesion, and osteochondral separation with loose bodies.[1-8]

OCD is a relatively common cause of knee pain and dysfunction in adolescents, with a predominance of cases in adolescent males.[2] The incidence of OCD has been estimated at 1.2% of the population based on knee arthroscopy.[9] OCD of the knee is subcategorized into a juvenile form and an adult form, depending on the status of the distal femoral physis. Juvenile OCD has a much better prognosis than adult OCD, with greater than 50% of cases showing healing within six to 18 months from non-operative treatment. The other 50% of patients with juvenile OCD, and most patients with adult OCD, frequently require operative intervention to achieve healing.[8]

The etiology of OCD remains unclear, and no theory regarding the cause of OCD is universally accepted.[9] Leading thoughts on the cause of OCD include repetitive microtrauma, secondary effects associated with vascular insufficiency, avascular necrosis, inherited factors, and genetic predisposition.[9] While a genetic factors have been proposed to play a role in OCD, surprisingly few genetic studies have been carried out to determine the underlying etiology. The purpose of this systematic review was to evaluate the present evidence supporting a genetic predisposition to OCD.

## Methods

We searched the Medline and EMBASE computerized literature databases for articles from January 1946 to September 2012 satisfying the following logic: "osteochondritis dissecans" OR "OCD" AND "genetic" OR "genetics" OR "family" OR "families" OR "familial" OR "twin" OR "triplet". Reference lists from the articles retrieved were further scrutinized to identify any additional studies of interest. All studies from the above-mentioned searches were then reviewed. Studies were included if they met the following criteria: 1) the language was English; 2) the main subjects were human. Studies were excluded if: 1) the above inclusion criteria were not met; 2) they were a review, editorial, or commentary. One author (I.G.) performed the initial search; another author (T.G.) then independently reviewed the results and selected the appropriate studies on the basis of the above criteria. Details of the search are highlighted in Figure 1.

We reviewed 35 studies that reported on a total of 232 patients with OCD: 8 familial series with at least 5 subjects,[10-17] 2 genetic linkage studies,[18,19] 18 familial case series with less than 5 subjects,[20-37] 5 monozygotic twin reports,[38-42] and 1 dizygotic twin report.[43] None of the data was extractable in a usable form to be compared or combined with other studies for further meta-analysis.

## Results

Alongside theories that OCD was caused by repetitive trauma and avascular necrosis, theories regarding the genetic nature of OCD were first proposed in the early 20th century. Bernstein[33] was the first to describe OCD lesions in multiple members of a family and to suggest a genetic component to its etiology.

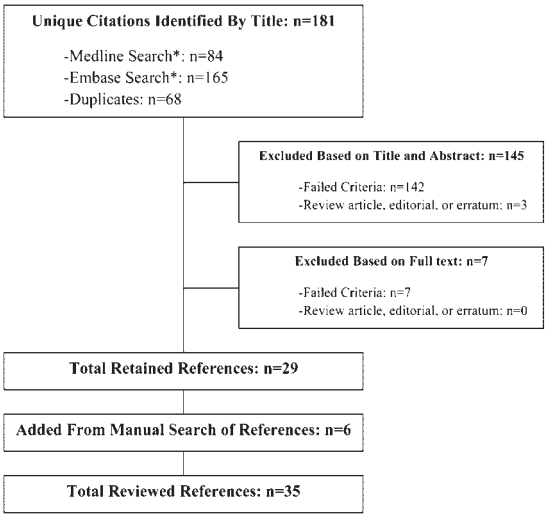


**Figure 1.** Details of the search methodology.

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Shortly thereafter, Wagoner and Cohn[37] described OCD in a son, father, and paternal uncle as well as in two brothers. In a series of 1,000 radiographs of asymptomatic men, Nielsen[44] noted an incidence of OCD of 4.1%. Interestingly, 14.6% of the male relatives of affected men also showed unmistakable radiographic evidence of OCD, thus strengthening the argument for a genetic predisposition to OCD.

In addition, multiple case reports and series have been published discussing findings of OCD in multiple members of a family. Novotny[34] and Lively[26] each described families with two siblings affected by OCD, and Gardiner[23] described a family with three affected siblings. Additionally, Fonseca[22] reported a family with two siblings and a maternal cousin affected with OCD. Pick[29] described a family in which a mother and three of four children were affected, and Tobin[31] described a family in which a father and all three children were affected by OCD. Hammett[38], Mackie[39], Mei-Dan[40], and Onoda[41], Woods[42], and Kenniston[43] all described families with twins both affected by OCD, often in the same location, and usually unrelated to repeated stress, implying a genetic component to the development of OCD.

Contrary to the above reports, in 1977, Petrie[17] conducted a study in 34 patients with OCD to establish if symptomatic first degree relatives were affected. Of 86 first degree relatives analyzed clinically and radiographically, only one was affected. The authors concluded that OCD is not a familial disease.

There have been multiple reports of syndromic OCD, in which patients are affected by other disease processes, indicating a genetic predisposition that the two diseases occur together. Stickler's syndrome, an autosomal dominant disease linked to mutations in both type II and XI collagen, has been reported in multiple cases to be associated with OCD.[20,35,45] In a series looking at patients with Stickler syndrome, 30% of patients have been shown to present with polyarticular OCD.[40] Dwarfism, or short stature $< 5^{th}$ percentile for age, has been reported to be associated with the development of multiple OCD lesions implying a genetic component.[11,12,14,28,29,32,46,47] Additionally, some endocrine factors, including thyroid disorders and cryptorchidism, have been postulated to have a genetic linkage to OCD based on familial occurrence.[1,24,36]

Atypical familial OCD lesions also increase support for a genetic component to OCD. Numerous reports of simultaneous polyarticular OCD lesions exist.[24,25,27,28,48] Repetitive trauma is intuitively thought to be less of a contributing factor to the occurrence of such lesions. Additionally, Anderson and Lyne[21] and Woods and Harris[42] described sisters and monozygotic twins, respectively, with lesions of the medial talus. While lesions of the lateral talus are often seen when a history of trauma is reported, medial talar OCD is typically not associated with trauma,[49] implying a possible genetic component to this lesion pattern. Lee *et al*[13] reported ten cases of bilateral femoral head OCD within a three generation family, unrelated to trauma. Since this rare diagnosis occurred in multiple members of the same family, the authors concluded that a genetic influence was likely.

While small case series have been at the forefront of the published literature, large family reports of OCD have also been well documented. Lee *et al*[13] and Stougaard[16] each reported on 3 generation families, Andrew *et al*[11] and Mubarak and Carroll[14] each reported on 4 generation families, and Andren *et al*[10] and Stattin *et al*[15] each reported on five generation families with OCD. Each author presented a pedigree, and in all cases, the pedigree was consistent with an autosomal dominant mode of inheritance, usually with fairly high penetrance.

More recently, genetic linkage assays have revealed loci associated with the development of OCD. Jackson *et al*[18] identified a mutation in *COL9A2*, located in an exon splice site which was associated with OCD lesions in two unrelated families with autosomal dominant multiple epiphyseal dysplasia. In 2010, Stattin *et al*[19] conducted a genome wide linkage study in the same series of patients they described in their 2008 family study[15] and identified the aggrecan (*ACAN*) gene as a prime candidate locus for OCD.

## Discussion

The wide disparity in the literature regarding the cause of OCD suggests a poor understanding of its pathophysiology. While in 1979 Petrie[17] concluded that OCD was not caused by genetic predisposition, it is important to remember that many cases of OCD are asymptomatic, and that asymptomatic relatives who may have had OCD were not examined in this study.

We reviewed 35 research articles related to the genetics of OCD; however, 34 were of a low level of evidence ($\leq 4$). The genome wide linkage study conducted by Stattin *et al*[19] was the only high quality study that we found in our systematic search of the literature. In this study, the authors identified one candidate gene, *ACAN,* linked to the development of OCD.

## Conclusion

The evidence in the literature for a genetic nature of OCD is predominantly of low quality. One candidate gene has been identified in a single genome wide linkage study, though the majority of published findings are inconclusive. Future studies of higher quality must be conducted to determine the genetic nature of OCD.

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U·P·O·J

# Operative Technique: Pediatric All-Epiphyseal Anterior Cruciate Ligament Reconstruction with Quadrupled Semitendinosus Autograft

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## Introduction

Anterior cruciate ligament (ACL) tears in skeletally immature patients are more prevalent today than ever before.[1-4] The management of ACL injury in this patient population is challenging and controversial. Employing non-operative measures with bracing and activity modification or delaying surgical intervention to skeletal maturity raises concerns from a compliance standpoint and risks further intra-articular damage.[5-8] Although prompt surgical reconstruction provides functional knee stability, risk for disruption of the physis and growth disturbance is present, potentially resulting in limb length inequality or angular deformity.[9-11]

For partial tears of the ACL, non-operative treatment has been shown to be successful in children and adolescents less than fourteen years of skeletal age.[12] A recent systematic review of current evidence found overwhelming support for surgical stabilization as the preferred treatment in skeletally immature patients with complete ACL tears.[13]

## Background

For pediatric ACL reconstruction, several principles guide treatment to reduce the risk of growth disturbance: avoid fixation across the physis, refrain from disrupting the perichondrial ring and surrounding tissues, make drill holes small and centrally located when crossing the physis, and be wary of tensioning a soft tissue graft across the physis if significant growth remains.[9,14-16]

Various physeal-sparing techniques have been previously described.[17-21] However, there are limitations to these techniques, such as tensioning of the graft across the tibial physis[17-19] or nonantomic positioning of the ACL graft.[20,21] We developed and previously described an all-epiphyseal ACL reconstruction technique using a socket in the tibia to place the graft at the native footprint of the ACL.[15] Subsequent to that study, recent refinements to the instrumentation have allowed for the all-epiphyseal ACL reconstruction to be less invasive and less disruptive to the anatomy of prepubescent patients. For more skeletally mature patients, partial transphyseal and traditional transphyseal techniques may be considered.

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## Preoperative Evaluation and Surgical Indications

The anterior drawer, Lachman, and pivot shift tests may reveal pathologic laxity in the ACL-deficient knee. Radiographs of the knee are performed, including AP, lateral, notch and patellar views, to assess for other potential injuries common in pediatric and adolescent patients, such as tibial spine avulsion fractures or osteochondritis dissecans. Knee magnetic resonance imaging (MRI) can confirm the presence of an intra-substance ACL tear as well as meniscal or chondral pathology.

The severity of the ACL tear is important to characterize. Incomplete ACL tears may be treated nonoperatively if the patient and family's are willing to adhere to a strict activity restriction protocol. For complete tears of the ACL, surgical reconstruction is recommended after a thorough discussion with the patient and family about the risks and benefits. Preoperative wrist radiographs are taken to determine bone age using the Greulich and Pyle atlas.[22]

## Procedure

Standard anteromedial working and anterolateral viewing arthroscopy portals are established. Arthroscopic confirmation of a complete intra-substance tear of the ACL is first accomplished. Any residual ACL stump is removed, and the femoral and tibial footprints are identified. Associated meniscal pathology, if present, is also addressed.

For all-epiphyseal reconstruction, pilot tracks are created by guide pins in the tibial and femoral epiphyses centered in the ACL footprint in a trajectory that also avoids the physes. Confirmation of positioning is accomplished with either O-arm 3-D CT scanner (Medtronic, Inc., Minneapolis, MN) or C-arm imaging. A stepped guide pin sleeve is placed over the pins and is malleted into tibial and femoral cortical bone to its depth stop. A FlipCutter (Arthrex, Naples, FL) allows "inside-out" drilling of tibial and femoral sockets without violation of the exterior cortices and periosteum.

Two ACL TightRope RT implants (Arthrex, Naples, FL) are placed on opposite ends of

a quadrupled semitendinosus autograft. Alternatively, a TightRope ABS Implant and Button (Arthrex, Naples, FL) may be used on the tibial side of the graft. A total graft length of at least five millimeters shorter than the combined total measured femoral and tibial bone socket lengths and intra-articular distance allows for proper graft tensioning to be achieved during fixation.

Solid and striped high-strength sutures are utilized to assist in passing the graft into the femoral and tibial sockets. After button flipping is confirmed, cinching suture limbs are pulled to draw the graft into the sockets. Additional tibial fixation may be achieved, if desired, by securing the tensioning suture limbs into epiphyseal bone using a PushLock anchor (Arthrex, Naples, FL).

The partial transphyseal technique combines the all-epiphyseal femoral tunnel with a traditional transphyseal tibial tunnel.

## Postoperative Protocol

Cryotherapy and continuous passive motion are used for the first three weeks postoperatively. For the initial four weeks, weight-bearing is restricted to toe-touching with a brace locked in extension during ambulation. Physical therapy following a standard ACL protocol is initiated five days postoperatively and continued until strength and functional testing are equal to the contralateral, unaffected limb. Routine follow-up visits and radiographs are conducted to monitor progress and signs of growth disturbance. Patients return to sports at nine months postoperatively and are followed on a yearly basis thereafter until skeletal maturity.

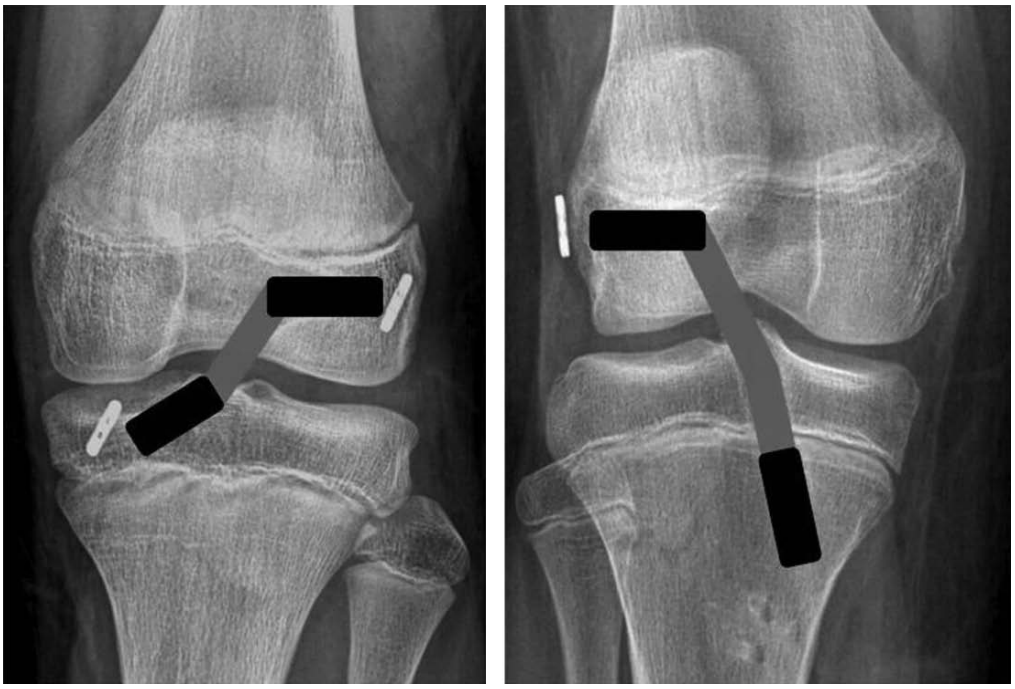
## Discussion

For the skeletally immature patient with a complete ACL tear, the potential sequelae of growth disturbance of the physis are significant. Therefore, the appropriate technique based on bone age and remaining growth should be employed. We advocate stratifying ACL reconstruction techniques based on bone age determined by wrist radiographs, similar to a previously described treatment algorithm.[16]

For patients with bone ages between ten and twelve, the refined all-epiphyseal technique with cortical button fixation is advised (Fig. 1A). The senior author has observed good functional outcomes with this technique without evidence of growth disturbance.

A partial transphyseal technique is recommended for patients with bone ages ranging from twelve to fourteen, where a moderate amount of growth remains (Fig. 1B). Previous clinical studies of a partial transphyseal technique have documented good results. Andrews *et al* followed eight patients with a mean age of 13.5 years status post partial transphyseal reconstruction to skeletal maturity and found excellent stability and no difference in lower limb lengths.[23] Similarly, Lo *et al* reported on five consecutive patients with a mean age of 12.9 years and a minimum follow-up of 4.5 years and found no evidence for leg length discrepancy.[24]

Seven of the nine patients (mean age of thirteen years) in the report by Bisson *et al* had excellent results with no signs of growth disturbance and full return to sports.[25] Two grafts ruptured and were considered failures. Guzzanti *et al* performed their reconstruction with a transphyseal femoral tunnel.[26] Ten adolescents in Tanner stages two and three



A B

**Figure 1A-B.** Postoperative ACL reconstruction radiographs revealing tunnel locations (black) and course of soft tissue graft (gray). A) Patient with a bone age of 10 having undergone the all-epiphyseal technique with cortical button fixation. In summary: 1. Tunnels avoid physes. 2. The senior author prefers hamstring autograft; however, surgeons may elect graft of choice. 3. Fixation avoids the physes. B) Patient with a bone age of 12 having undergone a partial transphyseal procedure. In summary: 1. Femoral tunnel is below physis 2. Tibial soft tissue graft only traverses physis 3. Fixation again avoids physes.

reached skeletal maturity with no evidence for growth disturbance and returned to sports with no restrictions.

A traditional transphyseal reconstruction, as conducted in adults, is preferred for patients with bone ages above fourteen, where the risk for growth disturbance is minimal. Prior reports of the transphyseal technique have also documented satisfactory results. Aronowitz *et al* showed satisfactory patient results and no growth disturbance in nineteen adolescents with a skeletal age of at least fourteen years.[27] Kocher *et al* reported excellent functional results and a low revision rate and minimal growth disturbance on fifty-nine skeletally immature adolescents in Tanner stages three with mean chronological age of 14.7 years.[28] Sankar *et al* conducted a survivorship analysis of girls with bone ages greater than 13 years and boys with bone ages greater than 14 years undergoing transphyseal ACL reconstruction.[29] At one year and five years, 96.4% and 93.1% of patients, respectively, had no reports of knee instability or required revision surgery.

By using bone age as a guide for ACL reconstruction in the skeletally immature patient with a complete ACL tear, the benefits of operative intervention are provided while the risks for growth disturbance across the distal femoral and proximal tibial physes are minimized.

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# Tibial Eminence Fractures: A Review and Algorithm for Treatment

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## Background

Fractures of the tibial eminence, first described by Poncet in 1875,[1] are bony avulsions of the ACL from its insertion on the intercondylar eminence of the tibia (Figure 1). Tibial eminence fractures are relatively rare with an incidence of approximately 3 per 100,000 per year,[2] and account for 2 to 5% of knee injuries in the pediatric pediatric population.[3,4] While most commonly seen in children between 8 and 14 years of age,[5] recent literature suggests that the incidence of tibial eminence fractures in adults is higher than previously thought.[6] Hayes *et al* found that 40% of tibial eminence fractures reported in the literature occurred in adults.[7]

Arthroscopic reduction of tibial eminence fractures has gained popularity due to its successful outcomes, decreased invasiveness, and improved recovery time.[8-11] However, controversy still exists regarding the optimal method of arthroscopic surgical fixation. The risk of arthrofibrosis, which can diminish range of motion (ROM) of the affected knee, particularly extension, is of primary concern when treating tibial eminence fractures both surgically and non-surgically.[12]

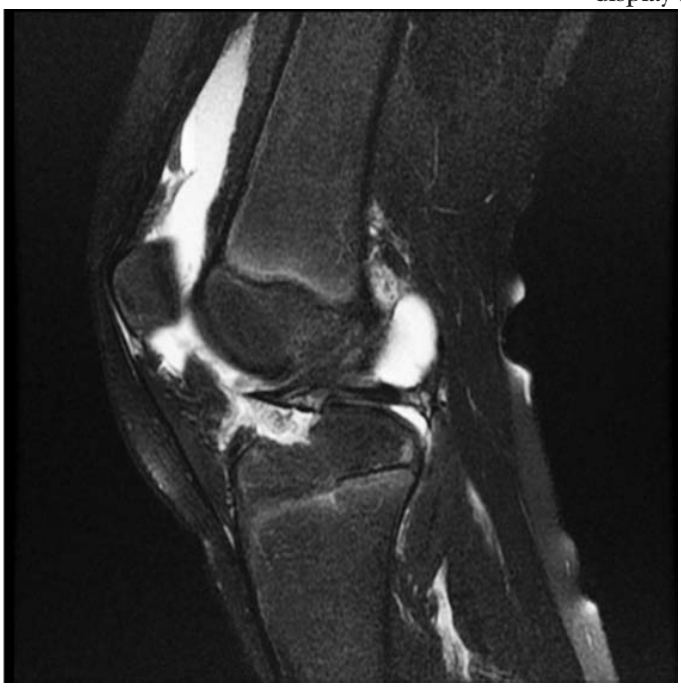

**Figure 1.** T2-weighted sagittal MRI demonstrating a displaced tibial eminence fracture.

## Anatomy

The tibial eminence is anatomically divided into four distinct regions by the medial and lateral intercondylar spines and anterior and posterior recesses. It serves as the insertion point for the anterior and posterior cruciate ligaments and the menisci. The ACL inserts on the tibial eminence at the anterior intercondylar area in a recess anterior to the medial tibial spine. The anterior attachment of the medial meniscus is anterior to the ACL insertion, and the anterior attachment of the lateral meniscus is posterior to the ACL insertion.[8] The intermeniscal ligament traverses between the medial and lateral menisci anterior to the tibial eminence where it is vulnerable to entrapment within these fractures, thereby blocking reduction.

## Classification

In 1959, Meyers and McKeever published a system for classifying tibial eminence fractures.[13] They recognized three main types based on the amount of displacement and the fracture pattern seen on the initial radiographs. Type I fractures display minimal elevation of the anterior margin of the fragment. Type II fractures show anterior lifting of one-third to one-half of the tibial eminence from the epiphyseal bed through a posterior hinge (i.e. a trap-door configuration). Type III fractures have completely displaced from the osseous bed in the intercondylar eminence. These can be broken down into type IIIA fractures, which have no rotational malalignment, and type IIIB fractures, which have rotated such that the cartilaginous surface of the fracture fragment faces the exposed bone at the fracture site.

The classification system was updated by Zaricznyj in 1977 to include Type IV fractures, or comminuted fractures of the tibial eminence.[14] Lateral plain radiographs are the most helpful basic imaging modality to assess which fracture type is present. Thetreatment modality is

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highly dependent on fracture type, so a good quality lateral radiograph is of paramount importance.

## Treatment

Type I fractures are best managed by immobilization in a long-leg cast or fracture brace. The amount of flexion recommended varies by author and can range from 10-40 degrees,[15-17] with some advocating for immobilization in full extension[18,19] or hyperextension.[20] Immobilization in hyperextension is poorly tolerated[15] and puts posterior structures such as the popliteal artery under tension, potentially resulting in the development of compartment syndrome.[21] The decision to evacuate the hematoma is at the discretion of the treating physician. Healing occurs rapidly in skeletally immature patients and most physicians treat type I fractures with 4-6 weeks of immobilization.[18,22-24] In older children, adolescents, and adults, long periods of immobilization may cause development of significant knee stiffness and muscle atrophy.[25] Therefore, the shortest period of immobilization possible to maintain reduction is recommended,[26-28] often 2-3 weeks, followed by protected ROM activity. Isometric quadriceps exercises are prescribed throughout the immobilization period to minimize the effects of disuse. Interval radiographs are obtained to ensure maintenance of fracture reduction.[8]

Many have promoted closed reduction by knee extension under anesthesia followed by knee immobilization for type II fractures of the tibial eminence.[29-31] However, the ability of manipulation under anesthesia to achieve reduction is controversial.[16,29,30,32] Reduction is most likely caused by femoral notch and sulcus pressures during knee extension. Importantly, a minimal amount of fragment elevation (less than 4mm) does not appreciably affect subjective outcomes.[24,33] However, if an acceptable reduction cannot be achieved or maintained by closed manipulation, operative treatment is indicated.The inability to achieve reduction is often secondary to entrapment of the intermeniscal ligament in the fracture.[34,35]

Surgical reduction and fixation is standard of care in type III and IV fractures because soft tissue entrapment, which occurs in 65-100% of these fractures,[34,35] must be resolved for adequate reduction. Several arthroscopic techniques have been reported including metal screw,[36-41] staple,[42] Kirschner wire,[43-46] and suture fixation.[42,46-51] The optimum fixation technique remains controversial;[52] some surgeons favor suture fixation[51] while others prefer screw fixation.[53]

The success of surgical intervention is dependent on prompt treatment,[20,54] secure fixation, and early mobilization.[55] Biomechanical studies have reported that the strength of suture fixation is higher than that of screw fixation.[56,57] However, Mahar*et al* found that both suture and screw fixation had increased fracture separation during cyclic physiologic loads which could cause loss of fracture reduction.[58] Recent reports have indicated that the use of a hybrid technique, using both suture and screw fixation, may achieve a more stable reduction allowing early return to ROM, thereby decreasing risk of arthrofibrosis.[59] The authors' preferred treatment algorithm is presented in Figure 2.

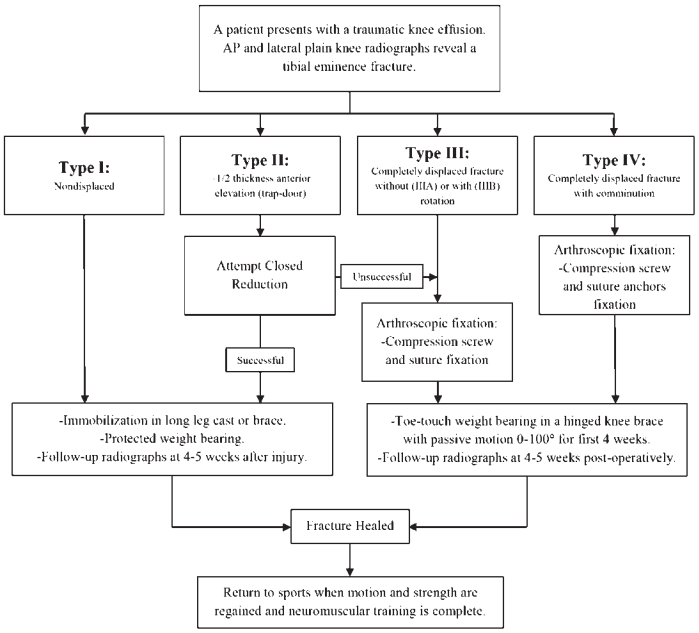


**Figure 2.** The authors' preferred algorithm for the treatment of tibial eminence fractures.

## Keys to Avoid Pitfalls

- To avoid misdiagnosis of fracture classification, a true lateral radiograph is necessary.
- Early treatment, secure fixation, and early mobilization can help avoid complications such as arthrofibrosis with loss of knee extension.
- Mid-patellar portals allow good visualization and easy placement of screws perpendicular to the fracture site
- Provisional fixation of the fracture fragment with Kirschner wires before final fixation can help maintain reduction

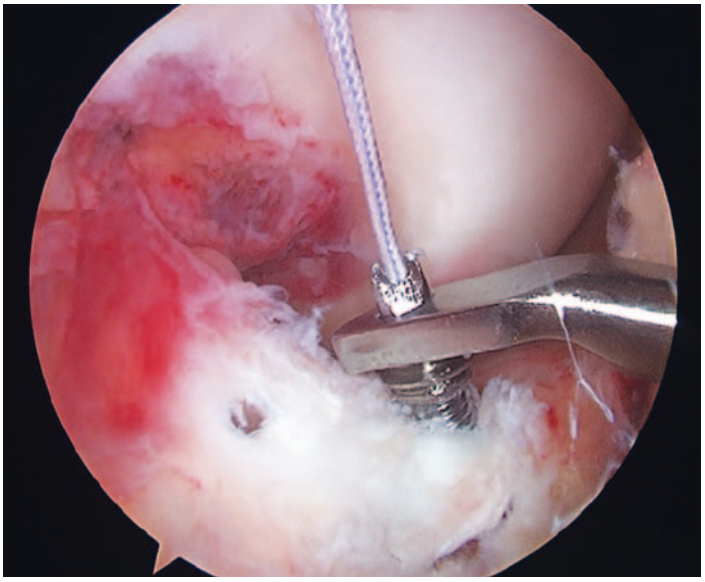

**Figure 3.** When attempting suture fixation of tibial eminence fractures, use of a cannulated ACL guide allows for passage of sutures from distal to proximal through the tibial tunnel into the joint.

- Fixation can be aided by use of a washer when the tibial eminence fracture is thin or has slight comminution
- The use of cannulated ACL guides may assist passage of sutures from distal to proximal into the joint (Figure 3)
- In comminuted (type IV) fractures, use arthroscopic shoulder fixation techniques for the knee: pass the sutures through the base of the ACL (as one would secure the capsule and labrum for a shoulder) and secure with shoulder anchors on the proximal tibia anterior to the fracture site.

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# Four-Rod Constructs for Complex Spinopelvic Reconstruction

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## Introduction

Segmental instrumentation has allowed for increasingly-complex spinal deformity correction, as well as reconstruction and stabilization following tumor resection or trauma. While pedicle screw and rod constructs have improved upon the early limitations of segmental wiring or hook techniques, spinopelvic fixation remains biomechanically-demanding and has been associated with high rates of pseudoarthrosis and instrumentation failure.[1-5]

A variety of methods have been described to optimize screw pull-out strength in high-demand cases;[6-9] however, these techniques do not address the risk of subsequent rod fracture. The use of additional rods has been described to increase spinopelvic construct stability and afford the achievement of bony fusion following extensive reconstructive procedures.[10-12]

## Indications

Due to the increased cost and potential for complications associated with additional instrumentation, the use of four-rod constructs should be considered only in cases that present a high risk of pseudoarthrosis. Procedures resulting in extensive destabilization of the lumbosacral junction, or long thoracolumbar constructs resulting in a long lever arm, may benefit from additional rod placement. In general, fusion constructs extending cranially past L2 may be at risk for pseudoarthrosis with extension to the sacrum, as seen in deformity correction with pedicle subtraction osteotomies or posterior vertebral column resections. Four-rod constructs may also be beneficial in cases of total sacrectomy for tumor, permitting early mobilization despite a lack of initial bony structural support. These reconstructive goals are similar for cases of traumatic spondylopelvic dissociation or comminuted sacral fractures requiring iliolumbar instrumentation. In addition, four-rod constructs may be especially useful in cases of spinal cord injury to facilitate aggressive rehabilitation and potentially decrease the risk of neuropathic spondyloarthropathy (Charcot spinal arthropathy).

## Operative Technique

Preoperative imaging is essential to confirm that the patient's anatomy is amenable to implantation of the planned spinopelvic instrumentation. The patient is positioned prone on a radiolucent table to facilitate the use of intraoperative fluoroscopy with attention paid to the maintenance of appropriate lumbar lordosis. A posterior midline exposure is performed. Depending on the surgeon's preference, instrumentation may or may not be placed prior to decompression or exposure of the spinal canal.

To facilitate dual-rod placement on both sides, the surgeon must be cognizant of the need to place pedicle screws using two different trajectories at corresponding alternating levels: 1) the "convergent" trajectory as described by Magerl,[13] and 2) the "straight-ahead" trajectory as described by Roy-Camille.[14] The heads of the convergent screws are thus connected by the lateral rod, and the straight-ahead screws connected by the medial rod. While the optimal biomechanical configuration of the alternating screws has not been defined, the senior author prefers to use convergent screws at the most cranial level due to their superior pull-out strength and lower risk of impingement on the preserved cranial adjacent facet joint.[15]

In order to serve as a base for the medial and lateral rods, two divergent iliac screws must be inserted on either side of the pelvis. The distal screws are placed using a Galveston-like technique from a starting point at the posterior-superior iliac spine directed toward the anterior-inferior iliac spine.[16] A second set of screws are placed from a more proximal starting point on a divergent trajectory into the iliac wing; the exact trajectories of these screws are dependent the rod trajectory from the corresponding lumbar screws and individual anatomic variations. The starting points of all pelvic screws should be recessed and the screws fully seated to minimize screw head prominence. If at all possible, iliac crest bone graft harvesting is avoided so as not to diminish distal fixation of the pelvic screws. However, the risk-benefit of biologic augmentation with autologous bone grafting

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versus diminished screw purchase must be considered on a case-by-case basis. When necessary, cancellous bone may still be harvested while preserving the tables of the ilium to maximize screw purchase.

Utilization of the four-rod technique with monoaxial side-loading screws as originally described presented significant technical challenges. The use of polyaxial screws has made four-rod constructs easier to achieve, as it is possible to

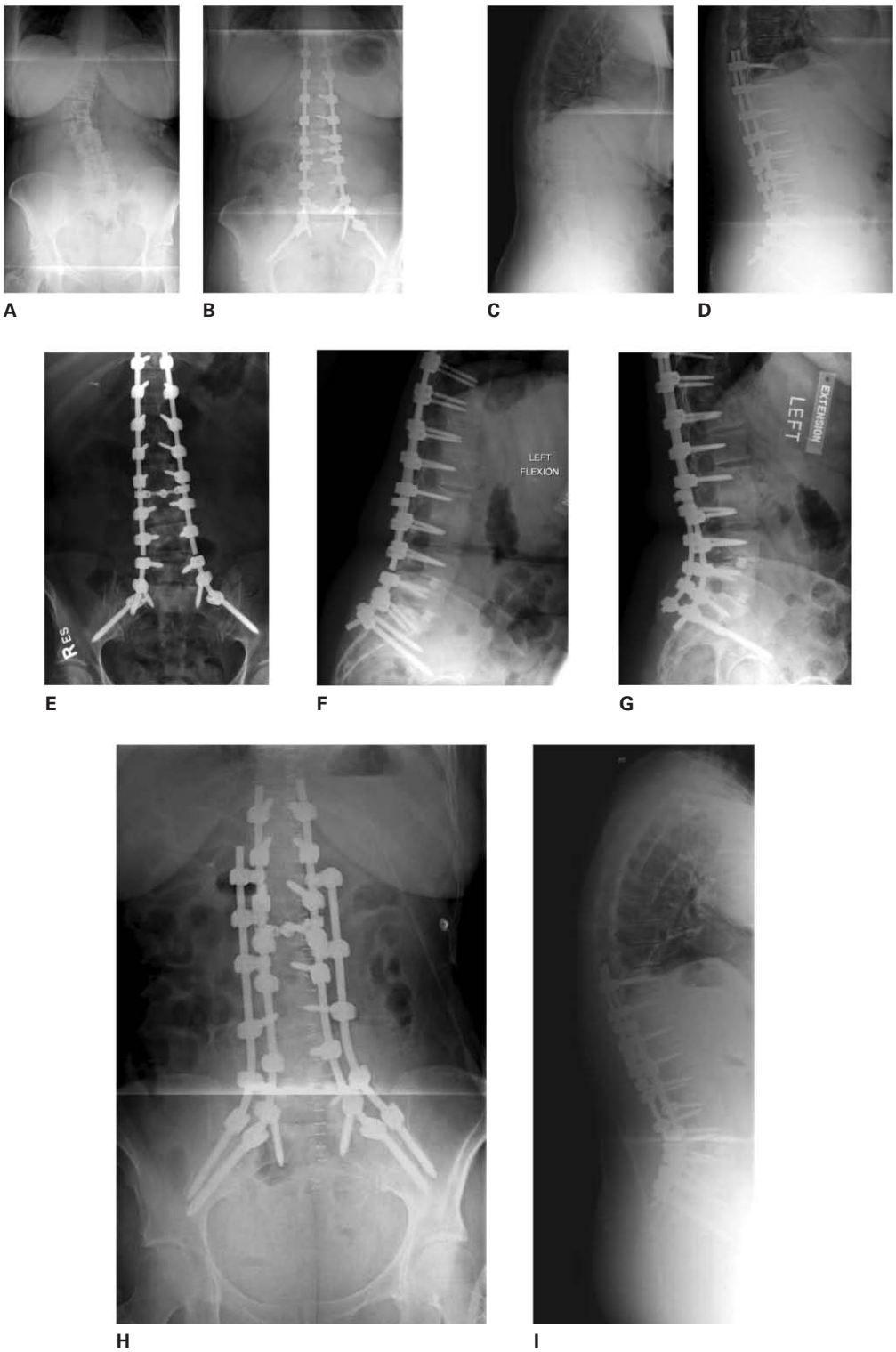


**Figure 1.** Case Example: preoperative (A,C) and immediate postoperative (B,D) standing radiographs of a 56 year-old female who underwent posterior instrumented fusion from T10 to the pelvis with transforaminal lumbar interbody fusion at L4-5 and L5-S1 for correction of thoracolumbar degenerative kyphoscoliosis. At five months postoperatively, the patient complained of recurrent pain and deformity, and fracture of the bilateral 6.3mm titanium rods was noted (E,F,G). The patient subsequently underwent revision instrumentation from T10 to the pelvis with use of a four-rod construct (H,I).

tilt the screw head crown medially for the medial rod and laterally for the lateral rod. This allows for increased latitude in the placement and connection of the rods. In addition, the lateral screws may be left slightly proud in order to facilitate connection to the lateral iliac screws.

While cross-links have been demonstrated to increase the torsional stiffness of four-rod constructs in cadaveric mechanical testing,[10] the optimal configuration of cross-links is uncertain and highly-dependent on anatomic considerations. It is the senior author's practice to place the proximal cross-links in compression and the distal cross-links in distraction; this configuration offers the theoretical advantages of grasping the lumbar vertebrae with the cranial pedicle screws and driving the caudal pelvic screws into the ilium. Preparation of the posterolateral fusion bed and bone grafting are performed in the standard fashion following placement of the instrumentation.

## Discussion

Use of the four-rod technique for spinopelvic reconstruction ideally results in sufficient stability to permit immediate postoperative weight-bearing and activity as tolerated. This postoperative protocol has been employed successfully even in cases of total sacrectomy for tumor.[11]

Jacobs *et al* were among the first to report clinical outcomes with the use of four-rod constructs as part of a series of 23 patients with neuropathic spondyloarthropathy following fusion for traumatic spinal cord injury (SCI).[17] The spinopelvic four-rod technique was used in 9 of these patients treated after 2000 with SCI levels in the lumbar spine; 4 of these were revisions of failed prior instrumentation, and 5 were used at the index procedure. While spondyloarthropathy cranial to the fusion mass prompted inclusion in the cohort, no cases of instrumentation or spinopelvic fixation failure were observed in patients with four-rod constructs.

As demographic trends result in increasing numbers of adults undergoing spinal deformity correction, the four-rod technique is emerging as a powerful means of achieving spinopelvic fixation (Figure 1).[12] However, despite promising biomechanical data and clinical experience, it must be acknowledged that comparative evidence or cost-effectiveness data regarding four-rod constructs is limited at this time. Future studies will help elucidate the ideal indications for and refine the technique of four-rod constructs in spinopelvic reconstruction.

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U·P·O·J

# C3-C4 Unilateral Facet Fracture Dislocation with Vertebral Artery Injury in an Adolescent: A Case Report, Review of the Literature, and Suggested Management Protocol

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## Introduction

Unilateral facet fracture dislocations of the cervical spine with a jump-locked facet are a rare injury in adolescents. The infrequency of the injury can result in delayed diagnosis and treatment. Significantly, these fractures can be associated with a neurologic complications and vascular injuries to the adjacent vertebral artery. A thorough investigation is needed to identify these associated injuries and to achieve a timely diagnosis. This case report describes our experience with an adolescent who presented with a jump-locked facet at C3-C4 and vertebral artery injury. We provide a discussion of problems related to the injuries and the potential for delay in their recognition. We also suggest a rational plan for investigation and treatment.

## Case History

A twelve year-old male presented to his primary care physician with neck pain and headache following an accidental injury two days prior. At that time, the patient had been involved in a pillow fight with a friend that resulted in a fall to the ground with the friend landing on his head. He did not lose consciousness and was able to stand without assistance. At his primary care physician's office, the patient was offered symptomatic treatment. Despite oral analgesics, the patient experienced persistent neck pain, prompting presentation to our institution's emergency department. Careful evaluation revealed that he was alert and oriented, followed commands well, and had normal motor function in all four extremities. There were no signs of concussion or spinal cord injury; however, radiographs revealed a unilateral fracture dislocation with a jump-locked facet at C3-C4 on the left (Figure 1).

Computed tomography (CT) scan confirmed the fracture of the C4 superior facet and rotatory dislocation of the C3 vertebral body on C4. Also, the scan identified a fracture of the posterior arch of C3 on the left that extended through the adjacent intravertebral foramen. Magnetic resonance imaging (MRI) confirmed the malalignment of the cervical spine, the jump-locked facet, anterior–rotatory dislocation, and mild wedging of the C4 vertebra without evidence of disc injury or herniation (Figure 2). MRI also revealed an injury to the left vertebral artery as seen by a high intensity signal on the T2 weighted image.

To further evaluate vascular injury, magnetic resonance angiography (MRA) was ordered and confirmed that the left vertebral artery was smaller than the right (Figure 3). Although this indicated partial obstruction, reduced blood flow and risk for developing thrombosis, MRA of the brain demonstrated no areas of reduced perfusion, indicating less risk for an acute intracranial ischemia.

With confirmation that the intervertebral disc was intact, closed reduction of the locked facet

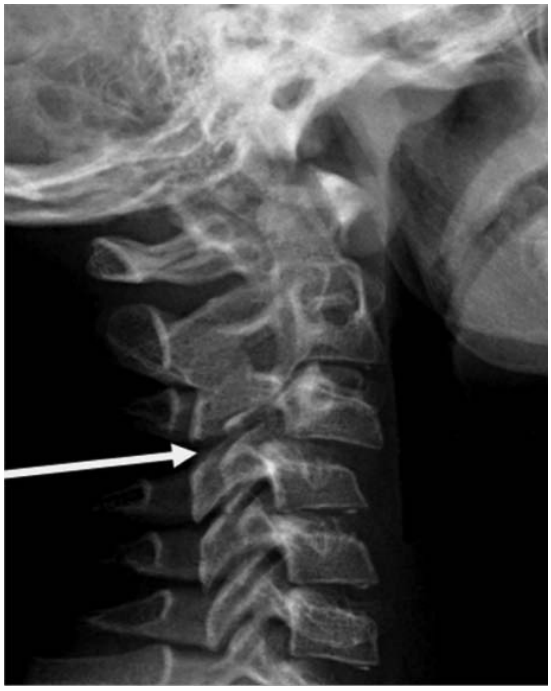

**Figure 1.** Lateral radiograph of the cervical spine showing facet dislocation of C3-4 and anterior translation of C3 on C4.

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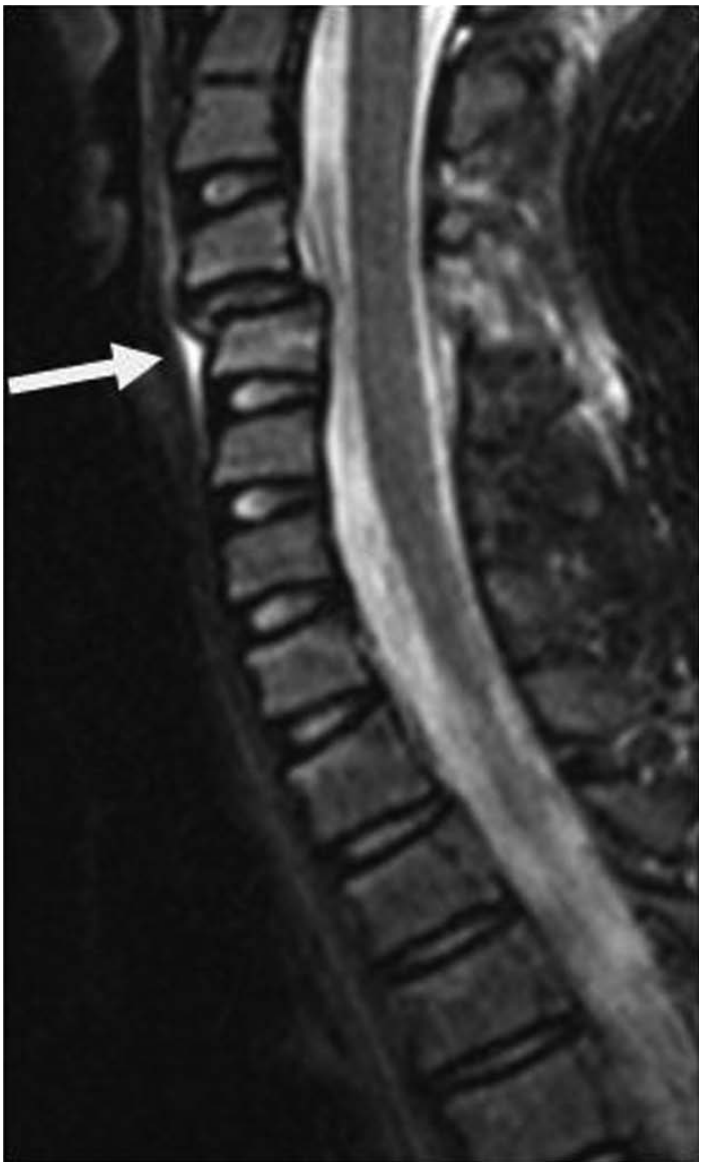

**Figure 2.** Sagittal MRI showing C3-4 ventral subluxation, intact interverterbral disc and mild wedging of C4 vertebra.

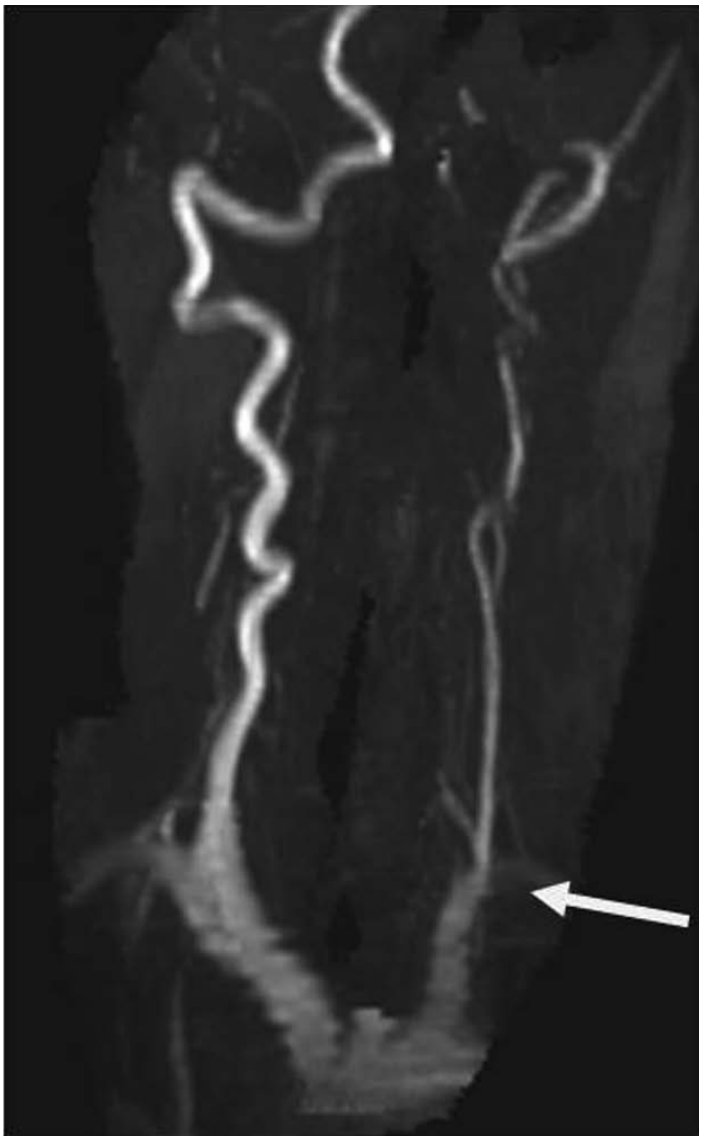

**Figure 3.** MR angiographic image demonstrating partial obstruction of the left vertebral artery.

was attempted using the Gardner-Wells traction technique with application of gradual incremental weights.[1] A 10 lb weight was applied initially and sequential 5 lb weights were added. With each change in traction weight, lateral radiographs were performed. After applying a total of 31 lbs, the lateral radiograph revealed an over distraction of the cervical spine without improvement in alignment. At this time, the traction was stopped and open reduction was deemed necessary.

The open reduction was done through the posterior approach utilizing spinal cord monitoring throughout. With surgical exposure, the ventral and rotational deformity was confirmed, the posterior longitudinal ligament (PLL) was disrupted from the vertebral body of C3, and the ligamentum flavum and the inter spinal ligaments were also both torn.

Gentle reduction under direct visualization was achieved after partial facetectomy of the C4 facet. The reduction and arthrodesis were stabilized with lateral mass screws and titanium rods (Figure 4). Following the procedure, the neck was immobilized in a cervical collar, which was discontinued after four weeks. Postoperative aspirin therapy was used as thrombosis prevention. An angiogram at one month continued to show reduced but unchanged blood flow. There was no clinical or radiologic evidence of neurologic injury at that time.

## Discussion

Cervical injuries in children often present late due to a delay in diagnosis that often results from difficulty of reading the radiographs.[2-4] Incomplete ossification of the cervical vertebrae, presence of multiple growth centers and physiological hypermobility all contribute to these difficulties in radiographic recognition and achieving a diagnosis.[5]

In this case, injury was caused by distraction and a lateral flexion/rotation force and, thus, was classified as an Allen-Ferguson distraction-flexion stage II type.[6] With distraction, the

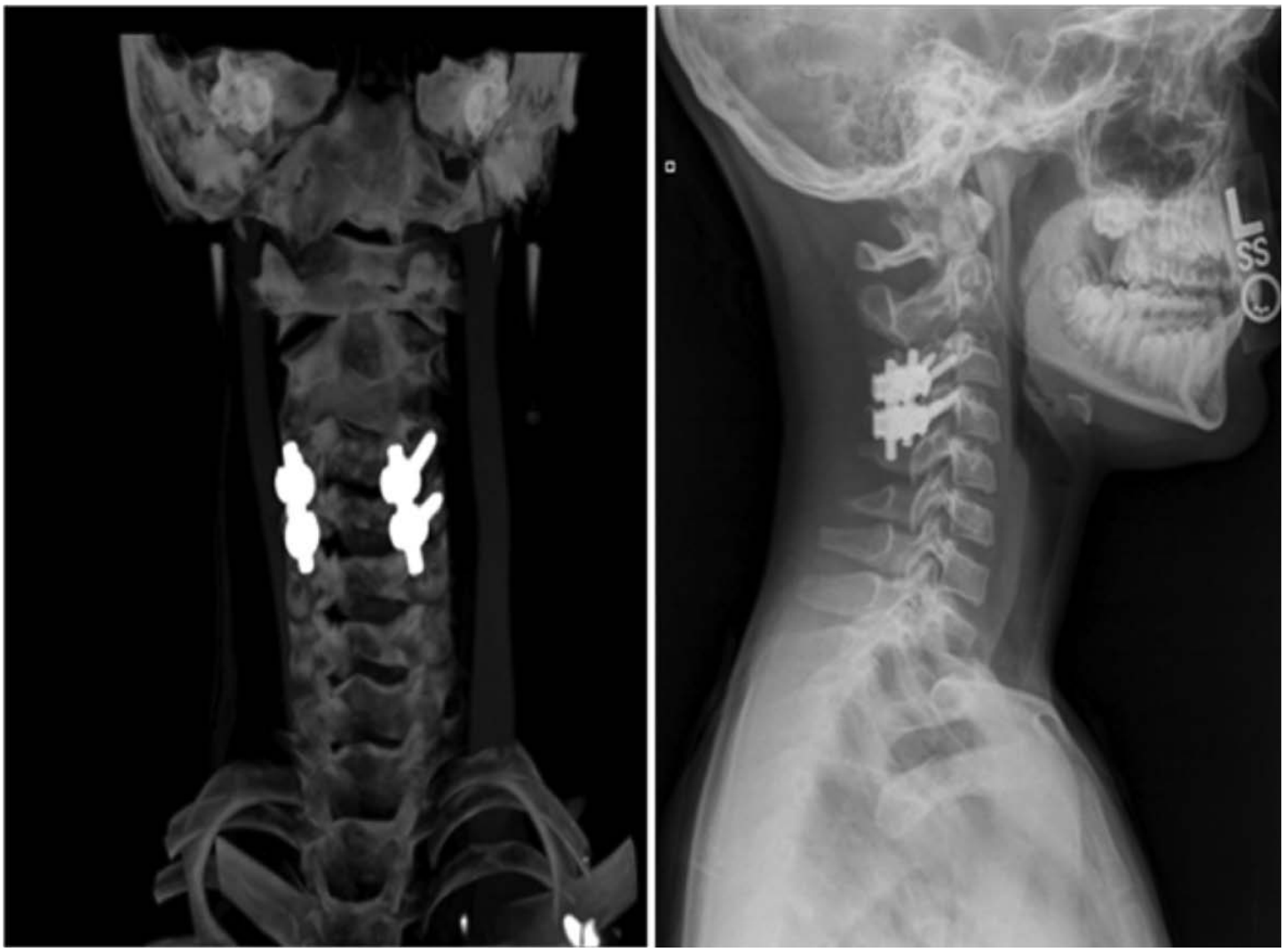

**Figure 4.** AP and lateral views of the cervical spine after reduction and C3-4 posterior fusion with lateral mass fixation.

facet joint was vertically separated, and with flexion, an anterior dislocation of the left C3-C4 facet resulted. The intact right facet joint served as a fulcrum around which the left side of the C3 vertebral body displaced anterior and rotated to the right. When these forces of dislocation ceased, the facet joint settled in the dislocated position and muscle contraction fixed the facet joint in the jump-locked position.[7] These injuries present with pain, restricted motion and with or without neurologic involvement. Also, because of the acute distraction and flexion forces associated with the injury, the ipsilateral vertebral artery may also be at risk. Finally, cervical spine and head injuries often present simultaneously; thus, careful examination for head injury is required when there is a serious neck injury.

On presentation to the emergency department, these patients should be evaluated and closely monitored for evolving neurologic or vascular injuries. The injuries should be investigated utilizing a range of imaging modalities, including radiographs, CT scan and MRI.[8] CT may provide a clearer view of the facets to better understand the jump-locked joint and discover fractures of the ipsilateral transverse process that can extend laterally and injure the vertebral artery.[9] MRI is useful for detection of any intervertebral disc pathology that may increase the potential for associated spinal cord injury.[10-13,15] In the adult literature, reported rates of traumatic disc herniation with this injury range from 15% to 54%.[11,12,14,16] No specific rate has been reported for pediatric cohorts; this is possibly due of the rarity of this injury in children. In addition to disc herniation, other pathology can be detected by MRI, including rupture of the posterior longitudinal ligament and posterior annulus, as well as injury to the posterior vertebral vessel on the ipsilateral side. MRA may be needed to confirm the vertebral artery injury, determine the extent of injury and evaluate the blood perfusion to the brain.[16-18] In patients without a reliable clinical examination, MRI should be performed prior to attempting closed reduction. Patients with subluxation within the cervical spine may suffer neurologic deterioration during closed reduction in the presence of an associated herniated disc.[10,13,19] With this situation, closed reduction is contraindicated and open reduction and spinal stabilization becomes the procedure of choice. Closed reduction with traction is also contraindicated

in the presence of fracture of the cranium. In the absence of these associated injuries, closed reduction may be attempted. Craniocervical traction should be applied incrementally in all patients.[20-23] With the Gardner-Wells Technique, incremental weights are added beginning with 10 pounds. Weights are gradually added while the patient's neurologic status is closely monitored. Serial lateral radiographs are performed after each change in weight to observe alignment, monitor for possible concomitant atlanto-occipital dissociation, and avoid over distraction. With any of these problems, traction should be discontinued and open reduction performed. If closed reduction is achieved, a halo vest or other type of external bracing may be utilized for immobilization.

Open reduction can be performed by anterior, posterior, or combined approaches,[22-24] though the posterior approach is used most commonly.[25-31] One advantage of the posterior approach is that the reduction is performed under direct visualization. The procedure consists of partial or complete facetectomy followed by reduction and instrumentation to maintain the correction and facilitate arthrodesis. Various techniques have been described to achieve fixation and fusion including facet wiring, interspinous wiring, and lateral mass plates or rod-screw constructs.[8,23,25-32] The anterior approach is used less frequently but is useful when there is an associated disc injury or herniation. If an indirect reduction can be safely achieved following anterior discectomy and decompression, then an anterior cervical fusion can subsequently be performed.[33]

Traumatic unilateral vertebral artery injury with cervical fracture is frequently asymptomatic.[34] Therefore, a high index of suspicion must be maintained and imaging carefully reviewed to detect these injuries. The vascular injury frequently heals after reduction and stabilization of the facet joints.[34-37] As a result, in the setting of normal perfusion to the brain, the vascular injury can be treated with reduction, stabilization and observation.[35-37] Postoperative monitoring is controversial, though CT angiography or MRA may be employed. Consideration should also be given to the prevention of thrombosis by supplemental antiplatelet or anticoagulation therapy.[37]

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U·P·O·J

# Review of Patient Reported Outcome Measures used in Pediatric Spinal Deformity Surgery

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## Introduction

Healthcare interventions are under increasing scrutiny regarding cost-effectiveness.[1] Patient reported outcome measures (PROM) have revolutionized clinical research facilitating objective interpretation and comparison across different healthcare systems. The objectives of our study were to identify all available PROM instruments and questionnaires designed for pediatric spinal deformity to evaluate and compare their respective clinimetric domains.

## Materials and Methods

A comprehensive search for all available PROM and published review articles for spinal deformity surgery was undertaken on PubMed up to December 2012. Twenty disease-specific spinal deformity questionnaires were identified (10 for ankylosing spondylitis alone and 10 for adult, adolescent and early-onset spinal deformities). The questionnaires specific to ankylosing spondylitis were excluded from analysis. The remaining 10 questionnaires were evaluated and the following clinimetric domains were each scored on a scale of 0-6 points:

1. Validity (content, construct and criterion validity)
2. Reliability (internal consistency and reproducibility)
3. Responsiveness to change

All published full-text articles reporting evaluation, validation, surgical outcomes of these spinal deformities PROM were retrieved and independently analyzed by two investigators (NSH and JPD).

## Results

Only 3 of 10 PROM had satisfied all six clinimetric domains in methodological evaluation (score 6/6). These included:

- Pediatric Outcomes Data Collection Instrument (PODCI) - designed by the AAOS and POSNA[2]
- SRS-22 questionnaire (Scoliosis Research Society) - designed by Asher *et al*[3]
- Spinal Appearance Questionnaire (SAQ) - designed by Sanders *et al*[4]

Four of 10 PROM were not evaluated (either by designers of PROM or other investigators) for at least 50% of the six clinimetric domains (scores of less than or equal to 3 of 6). The SRS-22 is the most popular PROM used globally and has been translated into at least 9 languages (Chinese, French-Canadian, German, Japanese, Korean, Persian, Spanish, Turkish and Thai) with independent validation studies in each of those languages. Though PODCI is a generic questionnaire designed for pediatric musculoskeletal pathologies, at least one study has used it to report results following scoliosis surgery.

## Discussion

Clinicians should be cautious in the choice of the appropriate validated outcome measures for reporting of their surgical results. Recommendations from governing bodies (NIH, FDA) and specialist societies (AAOS, SRS) should be considered. The SAQ is less popular than SRS-22/SRS-22r despite demonstrating excellent psychometric behavior and better responsiveness to change following surgical intervention. Early-onset scoliosis (EOS) presents unique challenges and the sole questionnaire has only recently been developed in 2011.

## Conclusions

SRS-22/22r is the most widely used PROM amongst scoliosis surgeons. Validated translations of SRS-22 have facilitated cross-cultural adaptation and global comparison of surgical results. Incorporation of SAQ elements into SRS-22/22r to make the existing questionnaire more robust constitutes ground for further research. Validation studies of other clinimetric domains for EOS questionnaire are desired.

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**Table 1. Summary of Patient Reported Outcome Measures used in Pediatric Spinal Deformity Surgery**

| No. | Questionnaire / Outcome measure | Content Validity | Construct Validity | Criterion Validity | Internal Reliability | Reproducibility | Responsive to change | Total Score |
|---|---|---|---|---|---|---|---|---|
| 1 | Quality of Life Instrument for adolescent idiopathic scoliosis[6] | √ | √ | --- | √ | √ | --- | 4/6 |
| 2 | PODCI - AAOS & POSNA[2,3] | √ | √ | √ | √ | √ | √ | 6/6 |
| 3 | SRS – 24[7] | √ | √ | --- | --- | --- | √ | 3/6 |
| 4 | Spina Bifida questionnaire[8] | √ | √ | --- | --- | √ | --- | 3/6 |
| 5 | Modified SRS – 24 & SRS-23[9] | √ | √ | --- | √ | √* | --- | 4/6 |
| 6 | SRS – 22 & SRS-22r[4] | √ | √ | √ | √ | √ | √ | 6/6 |
| 7 | Walter Reed Visual Assessment Scale (WRVAS)[10] | --- | √ | √ | √ | √ | --- | 4/6 |
| 8 | Scoliosis Quality of Life Index Questionnaire (SQLI)[11] | --- | √ | --- | √ | √ | --- | 3/6 |
| 9 | Spinal Appearance Questionnaire (SAQ)[5] | √ | √ | √ | √ | √ | √ | 6/6 |
| 10 | EOS Questionnaire[12] | --- | √ | --- | √* | --- | --- | 2/6 |

*Uncertain if evaluated in the original paper - we have given authors the benefit of the doubt

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# Do Diabetes and Hypertension Precede the Development of Adhesive Capsulitis?

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## Introduction

Previous studies show a convincing association between adhesive capsulitis and diabetes mellitus.[1-6] The prevalence of diabetes or pre-diabetes in adhesive capsulitis patients has been reported to approach 72%.[7] Data suggests that metabolic syndrome accounts for 30-52% of people who later develop type II diabetes.[8] Metabolic syndrome is defined by the World Health Organization as a group of metabolic abnormalities including evidence of insulin resistance as well as at least two of the following: obesity, hypertension, dyslipidemia, and hypertriglyceridemia.[9]

There is limited evidence to date regarding the possible association between the metabolic syndrome and adhesive capsulitis. One study reported no association between hypertension or Body Mass Index (BMI) and adhesive capsulitis,[3] while another reported that hypercholesterolemia and hypertriglyceridemia were associated with the condition.[10] These trends were observed exclusively in diabetic patients, and neither study formally looked at the association of metabolic syndrome and adhesive capsulitis.The goal of the present study was to evaluate possible associations between metabolic syndrome and adhesive capsulitis by comparing the prevalence of metabolic syndrome medications and obesity rates in a series of patients with adhesive capsulitis to previously reported nationwide data.

## Methods

We completed a retrospective review of 150 consecutive patients, age 18-71, who were diagnosed with adhesive capsulitis at our sports medicine clinic. We evaluated the BMI and medication list for each patient to determine which metabolic syndrome indications were present. Based upon the proportion of patients taking medications for each component, a prevalence rate with a 95% confidence interval was calculated using the Wilson procedure.[11]

We compared the prevalence of medication use and obesity in our series of adhesive capsulitis patients with previously reported data from The National Health and Nutrition Examination Surveys (NHANES).[12-15] From this data we calculated the prevalence of anti-hypertensive and lipid-lowering medications nationwide. Direct statistical comparison of the prevalence of metabolic syndrome medications in our adhesive capsulitis population to the prevalence in the general population using chi-square testing was not possible. However, 95% confidence intervals allowed the prevalence values from the two groups to be effectively compared.

## Results

Two-hundred-and-seven patient charts were queried; 54 were incomplete and 3 were excluded due to patient age.The average age was 51.3 (± 10) in the group, and 59.3% of patients were female. Overall, 27.1% [95% CI 17.4-39.6] of male group members aged 20 and above were obese; a prevalence similar to the 32.2% [95% CI 29.5-35.0] rate reported for this group in the NHANES.[12] In the subcategory of females 20 years or older with adhesive capsulitis, the overall prevalence of obesity was 27.2% [95% CI 18.7-37.7]. This value is similar to the overall 35.5% [95% CI 33.2-37.7] prevalence of obesity observed in the NHANES.[12] All age-group specific analyses also showed obesity rates similar to the general population.

The overall rate of hypertensive medication use by patients aged 18 and older in our adhesive capsulitis group was 33.1% [95% CI 25.9-41.2], a number notably higher than the 21.6% [95% CI 19.8-23.4] observed within the NHANES (Table 1).[13] In the 40-64 year old age-group comparison, the prevalence of hypertensive medications was also notably higher than nationwide rates. The overall prevalence of cholesterol-lowering medication use by patients aged 20 and older in the adhesive capsulitis patients was 20.6% [95% CI 14.7-20.8], a number similar to the 16.1% [95% CI 13.7-18.8] observed nationwide (Table 1).[14] Age group-specific comparisons also showed similar rates of cholesterol medication use between the adhesive capsulitis group and the general population.

The observed rate of diabetic medications in adhesive capsulitis patients ages 20 and above

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**Table 1. The prevalence of obesity and medications used to treat diabetes, hypercholesterolemia and hypertension in the NHANES cohort as compared to our cohort of patients with adhesive capsulitis. *Notable differences where 95% confidence intervals do not overlap.**

| Metabolic Syndrome Component | Prevalence of Disease or Calculated Prevalence of Medication Use for Disease | |
|---|---|---|
| | NHANES Overall Cohort | Adhesive Capsulitis Cohort |
| Obesity in Females Age 20 and Above[12] | 35.5% (33.2-37-7) | 27.2% (18.7-37.7) |
| Obesity in Males Age 20 and Above[12] | 32.3% (29.5-35.0) | 17.4% (7.0-37.1) |
| Hypertension Medication in Adults Age 18 and Above[13] | 21.6% (19.8-23.4)* | 33.1% (25.9-41.2)* |
| Hypercholesterolemia Medication in Adults Age 20 and Above[14] | 16.1% (13.7-18.8) | 20.6% (14.7-28.0) |
| Diabetic Medications in Adults Age 20 and Above[15] | 7.6% (6.7-8.5)* | 18.4% (12.9-25.7)* |

was 18.4% [95% CI 12.9-25.7], a number notably above the national rate of diagnosed diabetes in the NHANES[15] of 7.6% [95% CI 6.7-8.5] (Table 1). In the 20-39 year old age group analysis of adhesive capsulitis patients, 26.3% [95% CI 11.8-48.8] were taking diabetic medications while only 2.1% [95% CI 1.5-2.8] were diagnosed nationwide. Higher rates of diabetes were also observed in the 40-59 year old adhesive capsulitis group.

## Discussion

Studies looking for a connection between the degree of hyperglycemia or the duration of diabetes and the risk of developing adhesive capsulitis have produced conflicting results.[3,5,6] Authors have suggested that a period of hyperglycemia before a diabetes diagnosis, estimated at 9-12 years,[16] may be necessary before the occurrence of shoulder damage.[3,17] Metabolic syndrome is a constellation of abnormalities that often precedes a diagnosis of type II diabetes. In this study, we explored the possible associations between metabolic syndrome elements and adhesive capsulitis.

We observed an overall prevalence of diabetic medication use in adhesive capsulitis patients that was more than twice the national prevalence of diagnosed diabetes, as well as a prevalence in the 20-39 year-old age group that was 10 times greater in adhesive capsulitis patients.[15] These increased rates are consistent with past studies showing a clear association between diabetes and adhesive capsulitis,[1-6] and suggest that the diagnosis of diabetes should be considered in all patients presenting with adhesive capsulitis. The overall rate of antihypertensive use in patients with adhesive capsulitis was also approximately 50% greater than the prevalence observed in the general population;[13] an association that has not been reported previously. In our study, 72% of patients diagnosed with hypertension did not carry a concurrent diagnosis of diabetes, indicating that hypertension may be independently associated with adhesive capsulitis. While we were able to compare our patients to the nationwide population, the prevalence of metabolic syndrome in the United States is over 30%,[18] and it is possible that this high rate may have masked relatively higher rates of metabolic syndrome risk factors in the adhesive capsulitis patients.

## Conclusion

Our results continue to highlight the role that diabetes plays in the development of adhesive capsulitis. Interestingly, the rate of antihypertensive medication usage was also notably higher in our cohort, lending support to the idea that hypertension may be an additional factor in the development of adhesive capsulitis. Further studies investigating the role of metabolic syndrome in the development of adhesive capsulitis are warranted.

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# Concurrent Ipsilateral Total Elbow Arthroplasty and Reverse Total Shoulder Arthroplasty: A Case Report and Review of the Literature

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## Introduction

Intra-articular fractures of the humerus at the shoulder or elbow are common yet difficult injuries to address in elderly patients with osteoporotic bone. In this patient population, poor bone quality often precludes rigid fracture fixation. As such, joint replacement options may provide more predictable functional outcomes for many of these injuries. Articular insufficiency fractures that occur concurrently in the same upper extremity present an additional challenge for the treating orthopaedic surgeon.

We report the use of an ipsilateral reverse total shoulder arthroplasty and total elbow arthroplasty in an elderly patient who suffered comminuted distal and proximal humerus fractures in the same arm.

## Case Report

A 74 year-old, right hand-dominant female was referred to our facility one week after sustaining an injury to her left shoulder and elbow after a fall. The patient lived independently and had tripped on an uneven sidewalk resulting in a fall directly onto her left upper extremity. She presented with the chief complaint of left shoulder and elbow pain and limited range of motion. The patient denied any history of prior shoulder or elbow pain, instability, or dislocation. Her past medical history was otherwise unremarkable. On physical examination, the patient had significant ecchymosis and tenderness to palpation about the left proximal and distal humerus with limited range of motion and crepitus at the elbow and shoulder joints. She had no neurological deficits. Radiographs of the left shoulder and elbow revealed a head-splitting fracture of the proximal humerus and a comminuted intercondylar fracture of the distal humerus (Figures 1 and 2).

Due to the significant articular comminution at each fracture, poor bone quality, and the patient's age, the possibilities of both surgical fixation of the fractures and arthroplasty for both the shoulder and/or elbow were discussed. The patient expressed understanding that these factors rendered arthroplasty the most likely option pending intraoperative assessment.

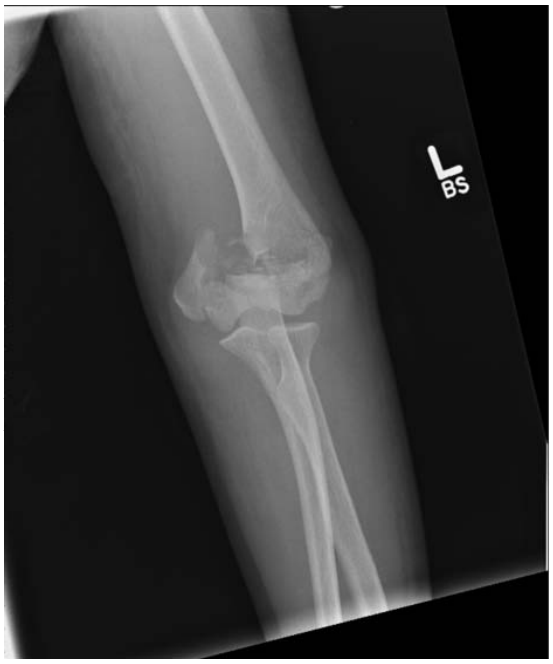


**Figure 1.** Preoperative distal humerus AP radiograph.

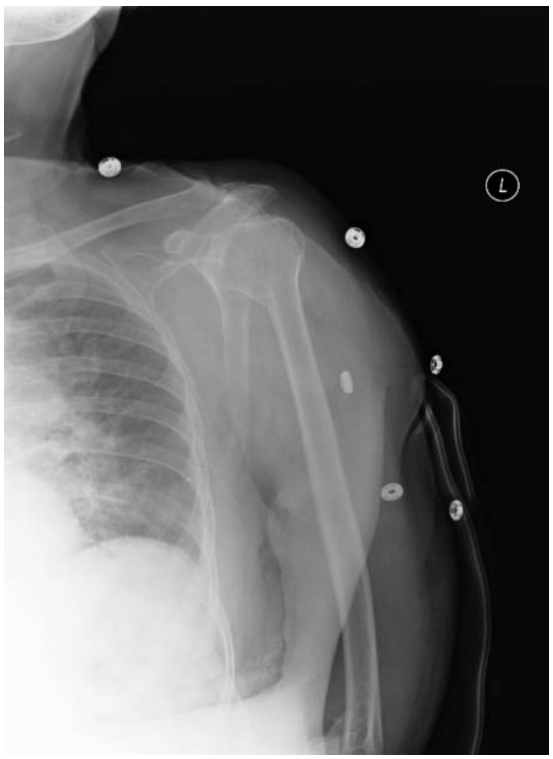


**Figure 2.** Preoperative proximal humerus AP radiograph.

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pronator mass, which was partially torn from the fracture. The ulnar nerve was identified and decompressed at all points of compression from the arcade of Struthers down to Osborne's ligament in the cubital tunnel. The ulnar nerve was protected the rest of the procedure within the flexor pronator mass. The triceps insertion was left intact throughout the procedure to facilitate immediate active elbow motion postoperatively and to ensure soft tissue coverage of the implant.

The intercondylar fracture was assessed and was reconstructable. Attention was first turned to preparation of the ulna by cutting the tip of the olecranon. The humeral and ulnar preparations for a semi-constrained, Coonrad-Morrey (Zimmer) total elbow prosthesis were performed in standard fashion. As there was no capitellum from which to reference the humeral length, the provisional condylar reconstruction, anterior humerus, and epicondylar axis were used to reference humeral implant length, version, and rotation. Components were trialed to ensure full elbow extension and 145 degrees of flexion. Fluoroscopy was used to confirm implant position. A bone wedge was prepared to graft distally with the anterior humeral flange. Finally, the humeral and ulnar components were cemented into place with the arm held in full extension (Figure 3). Once the cement was cured, range of motion of the elbow was tested with full extension and 145 degrees of flexion achieved. Both full pronation and supination were preserved. The epicondyles were debulked, and the shell of epicondylar bone with attached soft tissue was repaired to the implant and humeral shaft using non-absorbable suture. An anterior subcutaneous transposition of the ulnar nerve was performed and the wound closed in a layered fashion over a drain. No tourniquet was used, blood loss was 100mL, and operative time was approximately 70 minutes.

Next, attention was turned to the fracture of the proximal humerus. A standard deltopectoral approach was utilized. After identification of the cephalic vein, the deltopectoral interval was dissected with lateral retraction of the vessel. Both the musculocutaneous and axillary nerves were identified and protected. The subdeltoid, subacromial, and subcoracoid spaces were developed.

The clavipectoral fascia was incised and the fracture hematoma was evacuated. Fracture fragments were identified and sutures were placed in the rotator cuff to control the proximal fragments. There was a humeral head split with the majority of the articular segments of the humeral head having no soft tissue attachment. Given the fracture pattern, risk of avascular necrosis, and patient's age, the decision was made to proceed with reverse total shoulder replacement. The humeral head fragments were removed and the tuberosities were debulked. The long head of the biceps was released from the supraglenoid tubercle and the glenoid was exposed. The glenohumeral capsule was released circumferentially. The glenoid was prepared by drilling a central pin in the inferior half of the glenoid with inferior inclination. The pin was then drilled over and baseplate reaming was performed by hand. Excellent press fit and bicortical screw fixation secured the glenoid baseplate. A 36mm standard glenosphere was seated over the Morse taper.

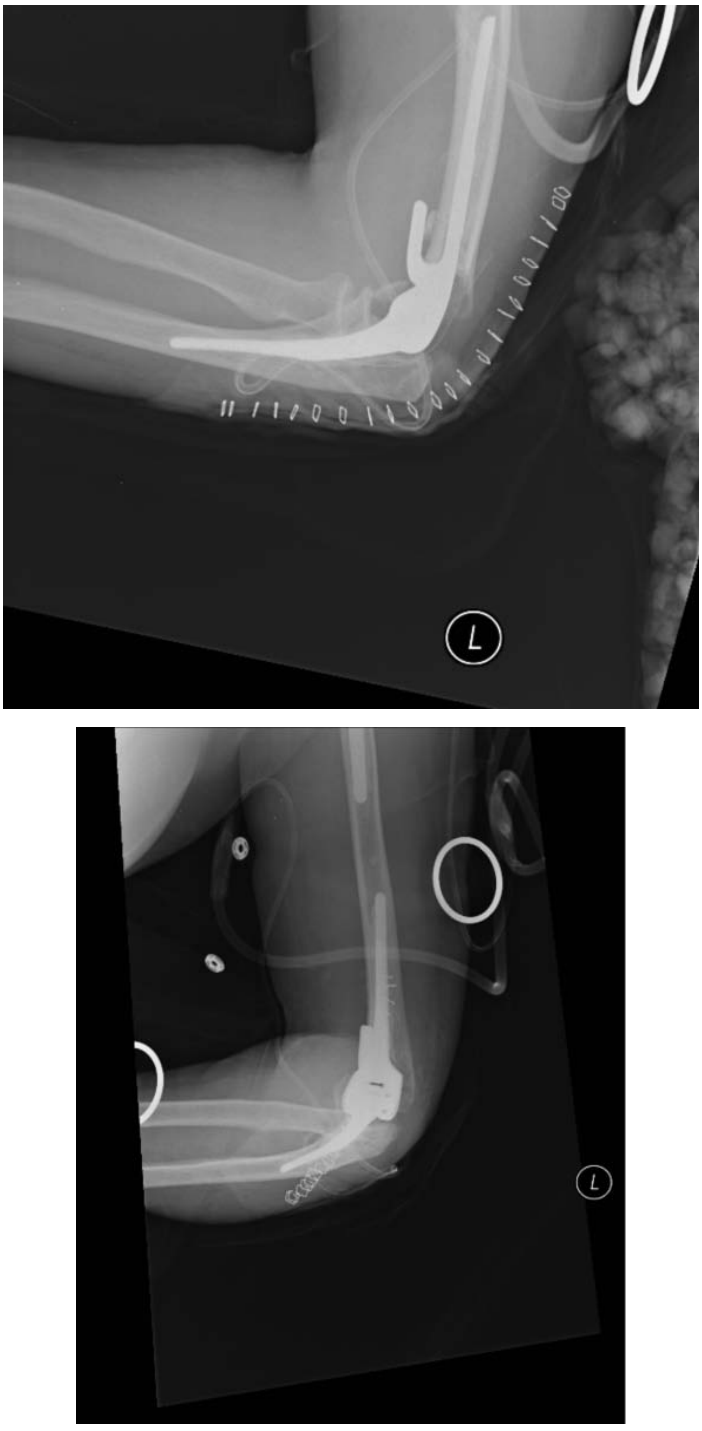


**Figure 3.** Postoperative elbow AP and lateral radiographs.

The humerus was prepared next with sequential reaming up to 10mm. The 10mm reamer was found to have good cortical chatter and a larger size or diaphyseal press fit implant was avoided to minimize creation of a stress riser between the total elbow humeral and total shoulder implants. Therefore, an 8mm trabecular metal stem was cemented in 10 degrees of retroversion. Next, a 36mm, plus-3, standard polyethylene liner was trialed and offered the best soft tissue tension while preserving motion. The plus-3 liner was then impacted in

place. At this point in time, the debulked greater and lesser tuberosities were repaired with non-absorbable sutures passed through the implant to restore the transverse force couple (Figure 4). No superior rotator cuff tissue was repaired. The wound was irrigated and a deep drain was placed. The incision was then closed in a standard layered fashion. A sterile stocking was applied to ensure uniform compression to minimize swelling and the patient was placed in a sling.

Postoperatively, small hemovac drains were placed in the elbow and shoulder. These were removed postoperative day one. A soft dressing and sling were applied. Occupational therapy was utilized for hand motion, edema control, and forearm rotation. Gravity pendulum hangs were initiated at two days postoperatively.The patient was instructed to remain non-weight bearing for three weeks, after which full-time use of the sling was stopped. Active elbow extension and flexion was allowed after the first week. Formal physical therapy for the shoulder and elbow were delayed until three week radiographs were reviewed by the attending surgeon.

## Discussion

Ipsilateral arthroplasty of the shoulder and elbow was first established as treatment for patients suffering from upper extremity rheumatoid arthritis.[1-4] Typically, these procedures were performed in a staged fashion. Gill *et al* retrospectively studied eighteen two-stage ipsilateral total elbow and total shoulder arthroplasties in seventeen patients with rheumatoid arthritis and found fair to excellent clinical outcomes for both joints in seventeen cases (9 excellent, 4 good, 4 fair).[2] The time between surgeries ranged from three months to ten years with neither time between surgeries nor their sequence found to influence outcomes. Friedman and Ewald also found two-stage ipsilateral shoulder and elbow arthroplasties to have no compromise of patient motion, function, or pain.[5] Similarly, one-stage ipsilateral arthroplasty of the shoulder and elbow has also been established in the setting of rheumatoid arthritis with good outcomes. Vrettos *et al* studied twenty one-stage ipsilateral shoulder and elbow arthroplasties with all patients showing significant improvement in pain and function.[4] The authors favored one-stage surgery as a more cost-effective and safer means of addressing ipsilateral joint arthroplasty by allowing the patient to undergo one hospital admission, one exposure to anesthetic agents, and earlier rehabilitation.To our knowledge, only one previous case of a one-stage ipsilateral shoulder and elbow arthroplasty has been documented in the traumatic setting.[1] In that prior published case report, a total elbow arthroplasty was performed immediately followed by a shoulder hemiarthroplasty. In the patient with ipsilateral shoulder and elbow fractures, the benefits of earlier pain control and rehabilitation are potentially even greater as compared to the risk-benefit ratio of one- versus two-stage surgery in an elective setting.

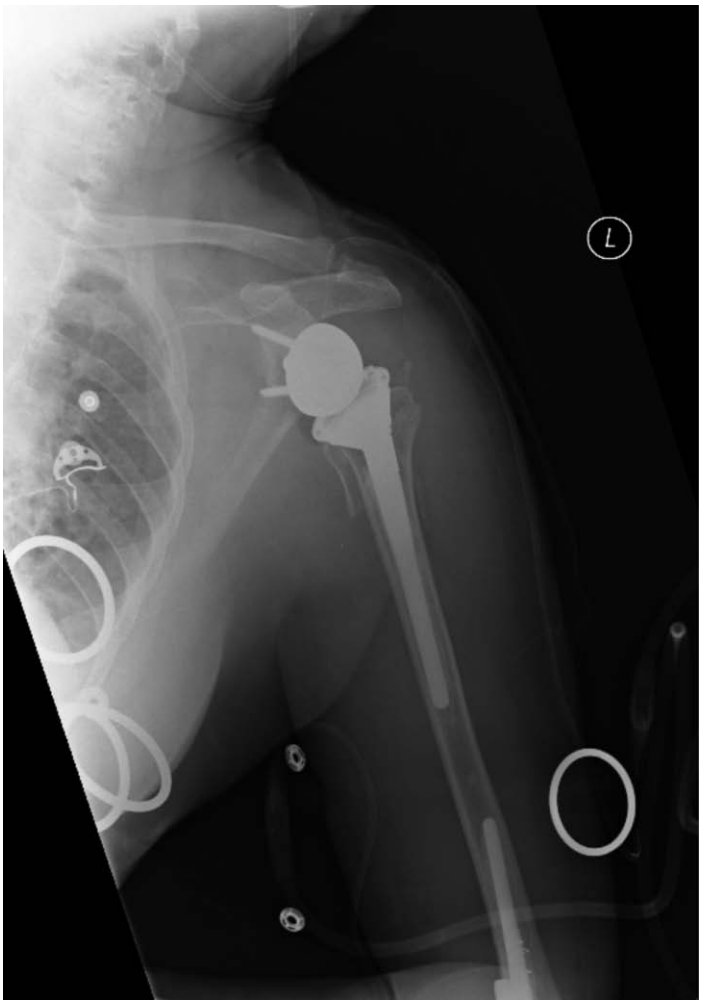


**Figure 4.** Postoperative shoulder AP radiograph.

The proper sequence of single-stage ipsilateral upper extremity joint replacement remains controversial. Advocates of performing the shoulder arthroplasty first declare a decreased risk of rupturing recently repaired ligaments and subluxation of the elbow that can be stressed during the external rotation needed for exposure of the proximal humerus.[6] This risk is lower with the use of a linked elbow implant.[1,2] Moreover, in the traumatic setting of a fragmented proximal humerus, this risk is theoretically decreased by the fracture pattern offering improved exposure of the shoulder joint. Performing the elbow arthroplasty first creates a stable distal segment, which can provide easier manipulation of the upper extremity and allow more accurate placement of the shoulder arthroplasty by using the forearm and epicondyles as a guide for rotation of the proximal humerus.[1,3] As such, we chose to initially address the distal humerus.

Our decision to then proceed with a reverse total shoulder arthroplasty deviates from the previously published case report in which a hemiarthroplasty was used to address the proximal humerus fracture. Hemiarthroplasty remains the treatment of choice for proximal humerus fractures in which fragment fixation is contraindicated in patients under the age of 70.[7-9] However, hemiarthroplasty for proximal humerus fractures is not without its complications, and functional outcomes are less predictable than pain relief. The most common of these complications compromising function is nonunion or malunion of the repaired tuberosities.[10] If such a nonunion occurs, the resultant lack of rotator cuff attachment leaves

the patient without shoulder function above waist height. Tuberosity malunion or malpositioning also leads to altered glenohumeral contact forces and diminished function.[11,12]

Because of the less predictable functional results for hemiarthroplasty in elderly patients with unfixable proximal humerus fractures, reverse shoulder replacement has been advocated as a means of eliminating pain and avoiding reliance on accurate and secure tuberosity fixation. Reverse shoulder arthroplasty indications have expanded from the initial indication of rotator cuff tear arthropathy to include treatment complex proximal humerus fractures in elderly, low-demand patients.[13-15] The advantage of reverse shoulder arthroplasty is that it permits the patient to rely less on rotator cuff function and tuberosity healing.[13-15] In the case of our elderly female patient who suffered a severely comminuted fracture pattern of the proximal humerus, the concern for healing of her tuberosities and of the risk of subsequent humeral head avascular necrosisis eliminated.

Regardless of shoulder arthroplasty design choice, one of the concerns that remain when performing ipsilateral upper extremity joint replacements is the potential increased risk of fracture between the humeral components.[1,2,4,16] With the humeral component of the shoulder proximal and the humeral component of the elbow distal, the remaining portion of bone not violated by reaming, cement, or stem is a small fraction of the humeral length. This small segment of uninterrupted bone is theoretically subjected to increased torsion and bending stress that can lead to a stress riser between the two components.[1,2] In the setting of osteoporotic bone that is often encountered in the elderly population, this fracture risk is further increased.[2] Initially, many authors recommended various techniques such as maximizing component length or filling in a cement mantle to decrease the possibility of a periprosthetic fracture.[2,17] However, a biomechanical study by Plausinis *et al* found no significant reduction in bone stress when longer stemmed prostheses or cement between the two components was used.[16] The authors felt the use of cement in the unviolated canal posed potential difficulties with component revision and prosthetic revision. Similarly, the use of longer stemmed prostheses would leave the patient with less potential bone stock in the event of a revision. The authors concluded that cemented shoulder and elbow components could be considered independent of one another in terms of risk of periprosthetic fracture. In our patient, the shoulder humeral component was sized to obtain a metaphyseal press fit only, leaving the diaphyseal cortices undisturbed. Similarly, smaller diameter total elbow components were cemented into place, again in an effort to minimize the risk of future diaphyseal fracture.

## Conclusion

Patients with ipsilateral proximal and distal humerus fractures pose a serious challenge for the treating orthopaedic surgeon. For patients unwilling or unable to undergo extensive rehabilitation following fracture fixation, concurrent total elbow and shoulder arthroplasty may allow for early functional restoration while minimizing the complications associated with multiple procedures or hospital admissions. We report on one such case of ipsilateral proximal and distal humerus fractures in which a one-stage reverse shoulder arthroplasty and total elbow arthroplasty resulted in minimal hospitalization, early rehabilitation, and excellent patient satisfaction.

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# Arthroscopic Localization of the Coracohumeral Ligament

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## Introduction

The rotator interval (RI) is the triangular region of shoulder capsule between the supraspinatus and subscapularis tendons that contains both the coracohumeral (CHL) and superior glenohumeral ligaments (SGHL). Lesions of these ligaments, particularly the CHL, have been shown to play a major role in the development of glenohumeral joint instability.[1] As a result, RI closures are often incorporated into soft tissue repairs for shoulder instability.[1-6] Several modern arthroscopic techniques for rotator interval closure are performed in the superior-inferior direction.[2-6] However, these techniques have failed to reproduce the positive results of open medial-lateral CHL imbrication.[7] Anatomic studies have shown that the CHL traverses the rotator interval from medial to lateral, suggesting that gainful shortening of this ligament to augment shoulder stability is only attained when tissues are imbricated in this direction.[8-11] The purpose of this cadaveric study is to identify the relationship of the CHL to arthroscopically-visible anatomic reference points in order to facilitate an improved arthroscopic medial-lateral rotator interval closure. This change in technique should result in a true shortening of the CHL that may potentially reproduce the favorable results of open medial-lateral CHL imbrications without the morbidity of an open procedure.

## Materials and Methods

Two fresh-frozen human donor cadavers were obtained for this study. Gross dissection was performed using a supine deltopectoral approach to identify the coracohumeral ligament. Three 18-gauge spinal needles were placed into the glenohumeral joint through the lesser tuberosity limb of the CHL in 2 mm increments. The shoulders were then placed in lateral decubitus position with 45 degrees of abduction and 20 degrees of forward flexion. A routine posterior arthroscopic portal was used to visualize the intra-articular CHL course as marked by the spinal needles. Photographs were taken to identify the course of the CHL as seen arthroscopically and in gross dissection. As shown in Figures 1 and 2, these photographs were then used to determine the angular relationships of the CHL relative to the subscapularis tendon (SSc), the glenoid articular surface, and the tendon of the long head of the biceps (LHB).

## Results

Four shoulder specimens from two donor cadavers were included for analysis. One gross dissection image was obtained from each of the four shoulders, from which the angular relationships between the CHL and subscapularis tendon were calculated. One arthroscopic image was also obtained from each of the four shoulders, from which angular relationships between the CHL and glenoid surface were calculated. Arthroscopic images from two of the four shoulders were used to determine the angular relationship between the CHL and LHB tendon. The CHL was found to subtend a mean angle of 29 degrees (range 16-39 degrees, n=4), 59 degrees (range 38-77 degrees, n=4), and 29 degrees (range 11-47 degrees, n=2) with the subscapularis tendon, glenoid surface, and LHB tendon, respectively. Table 1 displays the angular relationships found between these anatomic structures for each of the cadaveric specimens.

## Discussion

Several studies have discussed the use of arthroscopic rotator interval closures as a means of treating shoulder instability.[2-6] Despite the variety of surgical techniques described in these studies, arthroscopic rotator interval closures have failed to reproduce the results of open CHL imbrication.[1,7] These reports have raised concerns regarding the efficacy of arthroscopic rotator interval closure. However, the recently reported arthroscopic RI closure techniques all share an inherent limitation in that each of the described techniques were performed in the superior-inferior direction in contrast to the open medial-lateral rotator interval closure described by Harryman *et al*.[1] The CHL has been shown to cross the rotator interval from medial to lateral in multiple anatomic studies,[8-11] suggesting that shortening this ligament to augment shoulder stability is only attained when the RI is imbricated in this direction. Since superior-inferior techniques do not effectively shorten the course of the CHL, it is unlikely that any variation of this technique will reproduce the positive results of open medial-lateral RI imbrication.

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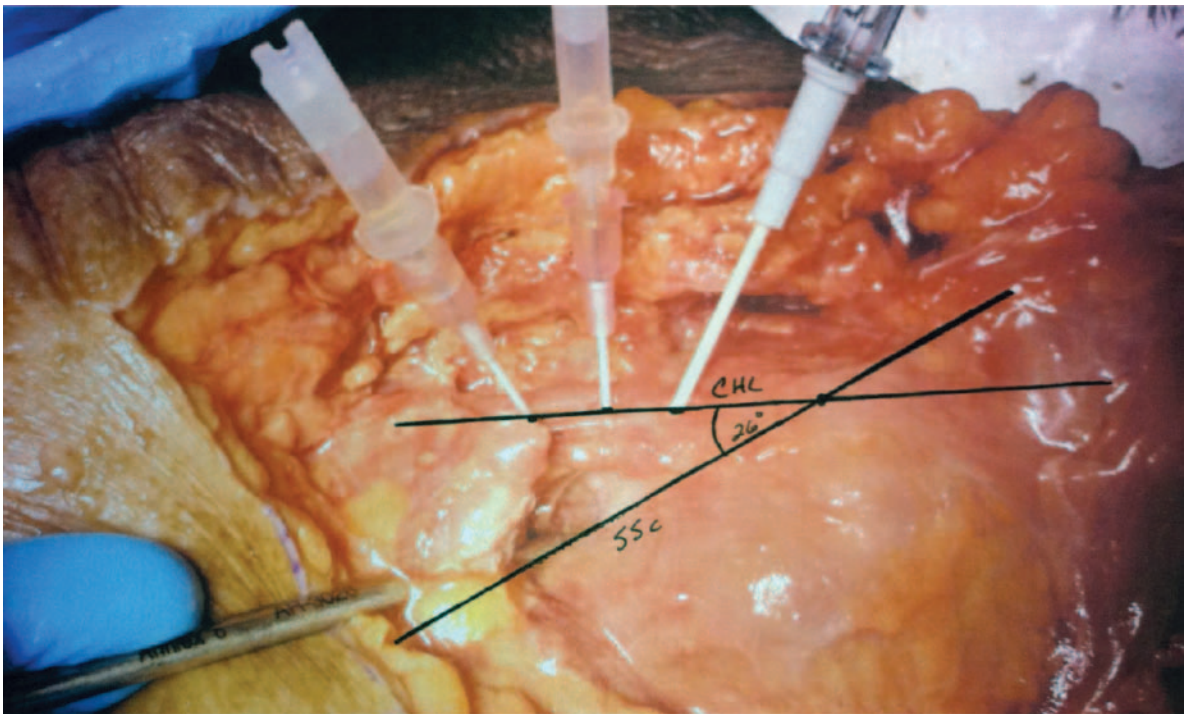


**Figure 1.** Determination of angular relationship between CHL and subscapularis by gross dissection.

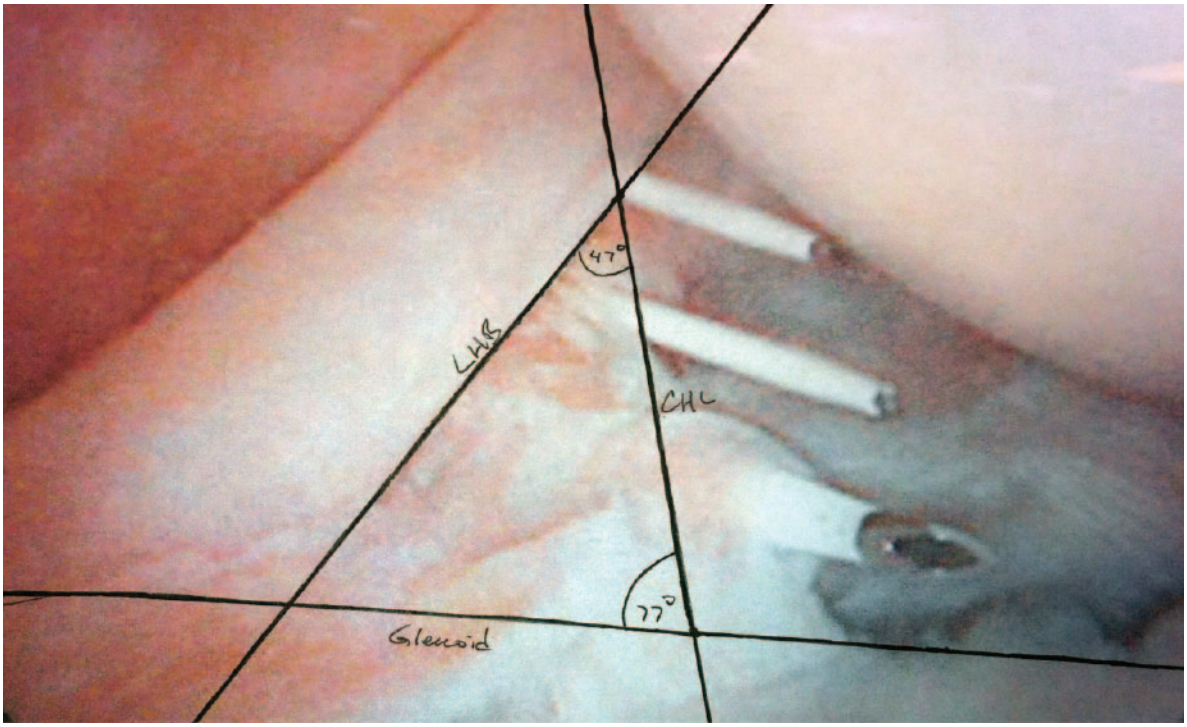


**Figure 2.** Determination of angular relationships between CHL, glenoid surface, and LHB tendon by arthroscopic imaging.

This study aims to provide orthopaedic surgeons with a reliable method for arthroscopic identification of the course of the CHL. Our results indicate that a surgeon can approximate the course of the CHL arthroscopically by using the angular relationships between the CHL and subscapularis (29 degrees), glenoid surface (59 degrees), and LHB tendon (29 degrees). Arthroscopic determination of the true course of the CHL facilitates arthroscopic medial-lateral RI closure as an alternative to more commonly-performed arthroscopic superior-inferior RI closure.This may allow for true shortening of the CHL and reproduction of the favorable results of open medial-lateral CHL imbrication without the morbidity of an open procedure. Future clinical studies will need to be performed to confirm the clinical efficacy of performing arthroscopic medial-lateral RI closure as a component of the surgical management of recurrent shoulder instability.

Before interpreting the results of this study, it is necessary to identify some inherent limitations. Most notably, this

**Table 1. Angular relationships of coracohumeral ligament (CHL) to subscapularis (SSc), glenoid (Glen), and long head of biceps (LHB) tendon**

| Specimen | Image | Angle | Result | Image | Angle | Result | Image | Angle | Result |
|---|---|---|---|---|---|---|---|---|---|
| C1L | Gross | CHL/SSc | 16° | Arthroscopic | CHL/Glen | 38° | Arthroscopic | CHL/LHB | NR |
| C1R | Gross | CHL/SSc | 39° | Arthroscopic | CHL/Glen | 53° | Arthroscopic | CHL/LHB | NR |
| C2L | Gross | CHL/SSc | 26° | Arthroscopic | CHL/Glen | 68° | Arthroscopic | CHL/LHB | 11° |
| C2R | Gross | CHL/SSc | 35° | Arthroscopic | CHL/Glen | 77° | Arthroscopic | CHL/LHB | 47° |
| Mean Angle | | | **29°** | | | **59°** | | | **29°** |

study includes the analysis of only four cadaveric specimens. Anatomic variability noted in this study has identified the need to obtain a greater number of cadaveric specimens to determine a more accurate measurement of the relationships between the CHL and the above anatomic structures. In addition, the utilization of thawed fresh-frozen cadaveric specimens may result in some degree of inaccuracy due to the difference in appearance of soft tissues of cadaveric shoulders when compared to the shoulders of living patients. Measurements obtained in this study could also be subject to human error during the interpretation of the angular relationships between anatomic structures depicted in photographs of the dissection.

## Conclusion

While the relationships of the CHL to the subscapularis tendon, glenoid surface, and LHB tendon show moderate degrees of anatomic variability, these structures provide anatomic reference points to assist in arthroscopic localization of the CHL, and subsequently may facilitate the execution of arthroscopic medial-lateral rotator interval closure.

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U·P·O·J

# Operative Technique: Arthroscopic Remplissage

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## Introduction

Glenohumeral bone deficiency has been correlated with recurrent shoulder instability following arthroscopic capsulolabral repair.[1-3] In response to this problem, a spectrum of interventions have emerged for the management of large Hill-Sachs lesions including humeroplasty, remplissage, allograft reconstruction, allograft mosaicplasty, rotational osteotomy, partial resurfacing, and prosthetic replacement.[4,8,17] Remplissage, which means "filling" in French, involves the fixation of the infraspinatus and posterior capsule into Hill-Sachs lesions to prevent humeral bony defects from engaging with the glenoid rim. Several clinical studies have reported decreased recurrence rates of glenohumeral instability with the use of arthroscopic remplissage as an adjunct to standard Bankart repairs when large engaging Hill-Sachs lesions are present.[9-13] This article reviews the surgical indications for performing arthroscopic remplissage and provides a detailed discussion of its surgical technique and postoperative care.

## Preoperative Evaluation and Indications

Arthroscopic remplissage is a treatment option that should be considered when evaluating patients with recurrent anterior shoulder instability. Recurrent anterior glenohumeral instability can be diagnosed on the basis of a history of multiple shoulder dislocations or subluxations with physical examination findings consistent with anteroinferior instability. Examination maneuvers that can be particularly helpful in reaching this diagnosis include the apprehension test, relocation test, and load-and-shift test. Apprehension in lower degrees of abduction often signifies the presence of a significant engaging Hill-Sachs lesion.

All patients should be evaluated with preoperative radiographic and MRI imaging.When reviewing preoperative imaging, the physician should pay particular attention to the presence of bony defects involving the humeral head and glenoid that may contribute to instability.

Patients with history and physical exam findings consistent with recurrent anteroinferior instability and imaging studies that reveal large humeral head defects with glenoid bone loss less than 25% are excellent candidates for an arthroscopic remplissage procedure performed in conjunction with a routine capsulolabral repair.[9-13] Patients with Hill-Sachs lesions associated with glenoid bone loss greater than 25% are better managed with an open Latarjet procedure.[5] The presence of a humeral head defect that engages the anterior glenoid rim within the position of athletic function should be confirmed at the time of arthroscopy prior to proceeding with remplissage.[11,12]

## Surgical Technique

Examination under anesthesia is performed to assess shoulder stability on passive range of motion, particularly in abduction and external rotation. The patient is placed in the lateral decubitus position with the shoulder held in 45 degrees of abduction and 15 degrees of forward flexion using 10 pounds of traction. A standard posterior portal is established slightly lateral to the convexity of the humeral head to allow for complete visualization of the anterior capsular injury. An anterior-inferior portal is then created within the rotator interval under direct visualization. An anterior-superior portal is also established at the anterior margin of the acromion, superior-posterior to the biceps tendon. This portal is used for visualization of the humeral defect (Figure 1) and to assess the location of the posterior portal, which should be directly superior to the humeral head to facilitate anchor placement.

While viewing from the anterosuperior portal, the Hill-Sachs lesion is gently debrided with a shaver or thermal device to prepare for the remplissage and the size of the defect is measured using an arthroscopic probe. At this time, the anterior labrum and glenoid are also prepared for a routine capsulolabral repair; however, the Bankart repair should not be performed until after completion of the remplissage procedure. After adequate debridement, a double-loaded suture anchor is placed in the Hill-Sachs defect using the posterior portal (Figure 2). The cannula is then withdrawn external to the infraspinatus.A

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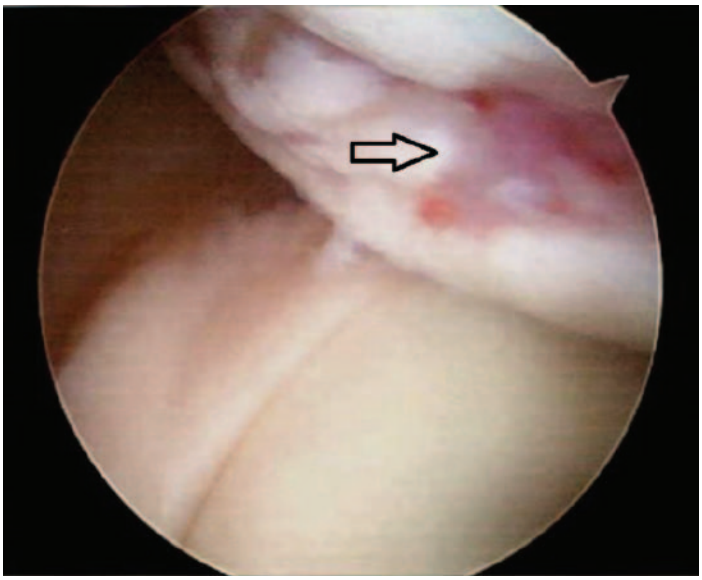

**Figure 1.** Hill-Sachs lesion: An anterior-superior portal established at the anterior margin of the acromion can provide excellent visualization of the humeral head defect. The Hill-Sachs lesion in this image is marked by the arrow.

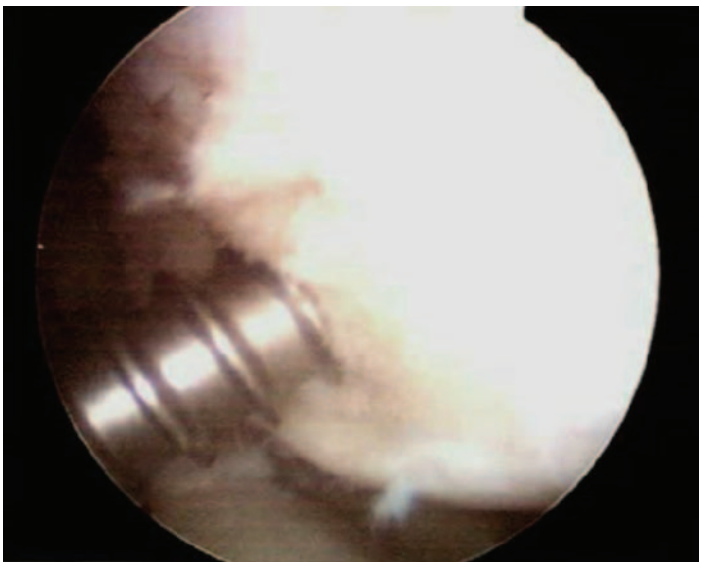

**Figure 2.** Anchor placement: A double-loaded suture anchor is placed in the Hill-Sachs defect using the posterior portal.

penetrating grasper is passed through the infraspinatus tendon and posterior capsule proximal to the initial portal entry site to grasp and pull one suture limb. This step is then repeated to pull the second suture limb through the posterior capsule and infraspinatus tendon distal to the initial portal site.The inferior suture is first tied with the knot remaining extra-articular in the subdeltoid space.The superior set of sutures is tied next.

If multiple anchors are needed to complete the remplissage, the first anchor should be implanted and tied prior to the implantation of an additional anchor. The optimal location of the initial anchor placement should be as far lateral and superior in the defect as possible to minimize the potential loss of external rotation and maximize capsular volume reduction and soft tissue fill of the Hill-Sachs defect.When the decision is made that a second anchor is necessary to achieve adequate fill of the defect, a grasper is used in the same fashion to pass one suture limb proximal and distal to the initial portal entry site.The sutures are again tied in succession beginning with the inferior suture. Additional anchors may then be placed as necessary. The surgeon should plan placement of all anchors prior to implantation of the first anchor since placement of additional anchors can become difficult after previous anchors are implanted and tied. Once all anchors are placed and sutures are tied, the infraspinatus tendon and posterior capsule should be firmly attached to and filling the prepared bony surface of the Hill-Sachs lesion (Figure 3). After completion of the remplissage procedure, the surgeon can proceed with a routine Bankart repair. If remplissage is done after performing a Bankart repair, there is a high likelihood of failure as the posterior shift resulting from remplissage may induce anterior capsular laxity.

## Postoperative Protocol

The senior author prefers a standard Bankart postoperative protocol for all patients following an arthroscopic Bankart repair with or without remplissage. Patients are maintained in a sling for five weeks following surgery. During this time, patients are permitted to perform passive supine forward flexion in the scapular plane. Hand, wrist, and elbow range of motion are not restricted. After five weeks, patients are progressed to active-assisted shoulder range of motion exercises with physical therapy. At 8 to 10 weeks, patients are instructed to gradually advance to resistance exercises using bands guided by their physical therapist.

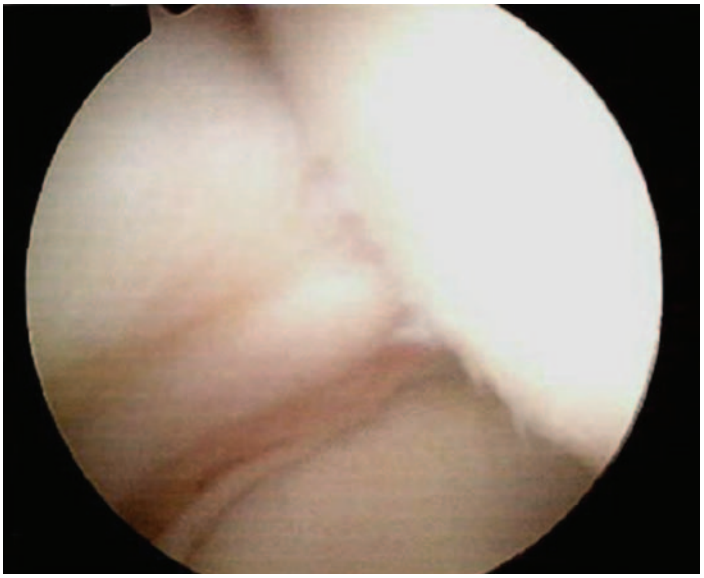

**Figure 3.** Completion of remplissage: After inserting all suture anchors and tying all sutures, the infraspinatus tendon and posterior capsule are fixed to the prepared bony surface of the Hill-Sachs lesion and 'fill' the defect as shown in this image.

## Discussion

The remplissage procedure is an important adjunct to routine Bankart repairs for the surgical management of patients with recurrent shoulder instability primarily due to large Hill-Sachs lesions. This surgical technique offers significant advantages when compared to alternative methods to address humeral bony defects associated with glenohumeral instability. The all-arthroscopic nature of the remplissage avoids the morbidity associated with open surgical interventions. Arthroscopic remplissage can be performed in the acute and chronic setting and can be performed in conjunction with Bankart repair with minimal additional surgical time. In addition, this technique does not require the use of autograft or allograft bone. A case series performed at our institution by Park *et al* reported improved function, diminished pain, and patient satisfaction in 85% of patients treated with an all-arthroscopic remplissage and Bankart repair with episodes of recurrent instability reported by only three of twenty patients at two-year follow-up.[9] Many of these patients had large bone defects and would be otherwise considered candidates for a Latarjet procedure.

A few complications of arthroscopic remplissage have been reported, including persistent posterosuperior shoulder pain in 5 of 15 patients treated with arthroscopic remplissage in one clinical study,[14] and one case report of significant loss of external rotation.[16] However, several studies have not demonstrated a correlation between remplissage and persistent shoulder pain,[9-13] and have shown no significant loss of shoulder range of motion following this procedure.[9-14] We believe that the use of arthroscopic remplissage is an effective means of addressing shoulder instability when used as an adjunct to routine capsulolabral repairs in carefully selected patients with large Hill-Sachs lesions and no significant glenoid bony defect.

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# Pediatric ACL Injury Prevention: Improving Strength and Performance with a Prevention Program

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## Introduction

Pediatric anterior cruciate ligament (ACL) injury prevention programs have become increasingly noteworthy in recent years, due in large part to the ever-increasing incidence of ACL injury in young athletes.[1-4] Increased sports participation, intensity of training and competition, participation on multiple teams, heightened awareness, and improved methods for diagnosis have all been cited as contributing factors to the growing frequency of ACL injuries in children and adolescents.[1,2]

Females are also known to have a greater risk for ACL injury than males.[5-8] The gender-based discrepancy may be caused in part by differing neuromuscular activation patterns in females, resulting in increased genu valgum and tendency towards injury in the landing position.[6] Given the special challenges faced in the treatment of pediatric ACL injuries, prevention programs are of special importance in not only reducing rates of injury but also increasing athletic strength and performance.

## Background

Several studies of high school female athletes have shown comprehensive, off-field injury prevention programs focusing on stretching, plyometric jump training, and weight training to decrease the incidence of ACL injuries[9,10] and increase strength and performance.[11-13] Such programs often impose demanding schedules with sessions lasting up to ninety minutes in duration and occurring three times per week over the course of several weeks, ultimately resulting in poor compliance.[9,10] In contrast, prevention warm-up programs allow for focused training to occur over a ten to twenty minute period as a team activity at a convenient time before practices or games, offering the theoretical benefit of improved compliance.[14,15]

A two-year prospective evaluation of the Santa Monica Prevent Injury and Enhance Performance (PEP) warm-up program led to a reduction in ACL injuries in adolescent female soccer players.[16] However, the few research studies evaluating the effect of warm-up programs on strength and physical performance have reported conflicting findings. In this article, we review pediatric ACL injury prevention warm-up programs and discuss the philosophy behind employing a pre-participation program to improve athletic ability and decrease injury risk.

## Literature Review and Discussion

The available evidence in the current literature regarding the impact of an ACL injury prevention warm-up program on strength and performance is limited and provides mixed results. Two prior studies failed to find a beneficial effect. Vescovi *et al* assessed linear sprinting, counter-movement jump height, and agility performance in adolescent female soccer players completing a twelve-week PEP program.[17] The five components of the twenty minute PEP program are warm-up, stretching, strengthening, plyometrics, and agility.[16] The authors found small and transient improvements and concluded little benefit of the PEP program on overall performance. Similarly, Steffen *et al* reported on a ten-week injury prevention warm-up program called "11."[18] Designed as a structured warm-up program targeting the most common soccer injuries, the "11" is a fifteen minute, ten exercise program focusing on core strength stability, neuromuscular control, eccentric hamstrings strength, and agility.[19] The authors did not observe gains in linear sprinting, jumping, or strength in adolescent female soccer players.

Both Vescovi *et al* and Steffen *et al* pointed to the lack of intensity of the exercise drills and low volume as the likely explanation for their poor outcomes. They posited that the ultimate purpose of the prevention program is to reduce noncontact ACL injuries and not to enhance performance.

Other studies, however, support the notion that prevention warm-up programs have a positive impact on strength and performance. Lim *et al* assessed an eight-week modified-PEP program, called the Sports Injury Prevention Training Program.[15] The six parts of the twenty minute program were warm-up, stretching, strengthening, plyometrics, agilities, and alternative exercises. The authors evaluated high school female basketball players and found significant gains in maximum knee extension

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**Table 1. *Ready. Set. Prevent.* is a lower extremity injury prevention program developed by physicians and physical therapists at the Sports Medicine and Performance Center at The Children's Hospital of Philadelphia. The fifteen to twenty minute warm-up program is conducted prior to each practice or game and consists of dynamic stretching, strengthening, and plyometrics. The strength and plyometrics programs have two phases. Phase one is conducted from weeks one through four and is designed to provide a framework for proper form development. Phase two is conducted from weeks five through the end of the season and is more challenging. A more detailed program guide can be found at www.chop.edu/export/download/pdfs/articles/sports-medicine/ready-set-prevent-field-sheet.pdf.**

**Weeks 1-4:**

Warm-up, dynamic stretching, initial strength & plyometric exercises

**Weeks 5-end of season:**

Warm-up, dynamic stretching, progression strength & plyometric exercises

**Warm-up:**

Shuttle Run – 10-15 yards, 2 laps each

-Forward/Backward Shuttle Run

-Side Shuffles and Carioca

**Dynamic Stretching:** (10s rest between each exercise)

Inchworm Stretch (hamstring, calves) –5 reps

Spider Stretch (hip flexors, hip adductors, quadriceps) – 5 reps each side

Straight Leg March – 10 kicks total

Leg Cradle – 10 cradles total

**Strength Exercises:** (10s rest between each exercise)

| Initial: Weeks 1-4 | | Progression: Weeks 5-end of season | |
|---|---|---|---|
| Double-leg Squat | 20 reps | Single-leg Squat | 10 reps per leg |
| Alternating Lunge | 20 reps | Side Lunge | 10 reps per leg |
| Double-leg Bridge (ball or ground) | 20 reps | Single-leg Bridge (ball or ground) | 10 reps per leg |
| Side-lying Plank | 10s, 3 x each side | Side Plank | 15s, 3 x each side |

**Plyometric Exercises:** (10s rest between each exercise)

| Initial: Weeks 1-4 | | Progression: Weeks 5-end of season | |
|---|---|---|---|
| Wall Jump | 15 reps | Single-leg Squat Jump | 10 reps per leg |
| Squat Jump | 15 reps | | |
| Double-leg Low Cone Hop (side-to-side) | 15 reps | The Single-leg Cone Hop | 10 reps per leg |
| 180° Jump | 10 reps | Lunge Jump | 10 reps per leg |
| Jump, Jump, Vertical Jump | 5 reps | Single-leg Forward Hop | 5 reps per leg |

torque and hamstring-quadriceps ratio as well as in flexibility and biomechanical markers. DiStefano *et al* also found significant improvements in balance and vertical jump height after a nine-week integrated injury prevention warm-up program in youth male and female soccer players.[20] The ten to fifteen minute program consisted of a dynamic warm-up, static flexibility, balance, strengthening, agility, and plyometric exercises on both limbs.

## Our Program

***Ready. Set. Prevent.***

ACL pre-practice programs have the potential to enhance an athlete's strength and performance and, consequently, reinforce the neuromuscular activation patterns necessary to modulate knee and hip biomechanics to diminish risk of injury, particularly in females.[6,21,22] The most advantageous prevention warm-up program, however, remains unclear, although components such as dynamic warm-up, stretching, strengthening, and plyometric exercises are all reasonable to include.

Our sports medicine group at the Children's Hospital of Philadelphia has developed a warm-up program called *Ready. Set. Prevent.* (Table 1). For patients undergoing ACL reconstruction at our institution, we have incorporated these regimens into the postoperative protocol for the affected knee to reduce the chance of re-injury and for the contralateral, unaffected knee to address potential future injury.

Prevention warm-up programs benefit both athletes and parents. Athletes can find motivation from working with teammates and the competition that ensues to increase one's strength and performance. Parents can potentially avoid excessive costs and time commitments on off-field programs since pre-participation programs occur on scheduled days of practices and games. Most importantly, all involved wish to avoid injury and the need for management of an ACL injury as well as the long-term rehabilitation process required for recovery.

## Conclusions

We believe that an injury prevention warm-up program has the capacity to improve strength, flexibility, and biomechanical properties associated with ACL injuries in pediatric and adolescent athletes to lower their risk of future injury. Increasing evidence for augmented strength and performance in athletes may lead to greater desire by coaches to implement ACL injury prevention warm-up programs and to better compliance among participating athletes. Future prospective large-scale studies are still necessary to clarify the most appropriate protocol to maximize strength and performance while reducing noncontact ACL injuries utilizing pediatric ACL injury prevention programs.

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# Functional Recovery following Ceramic-on-Ceramic Total Hip Arthroplasty in Patients Younger than Fifty-Five Years of Age

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## Introduction

Total hip arthroplasty (THA) is widely regarded as one of the most successful surgeries in orthopaedics.[1] In young patients (variably defined, here we will use the cutoff of younger than 55 years of age), there is concern that patients' expected lifetime will exceed the expected lifetime of their implants. Additionally, because of their younger age, they are presumed to be more active and therefore will subject their implants to more cycles per unit time, as well as higher stresses and wear rates.[2]

Hard-on-hard bearing materials have demonstrated decreased wear rates and increased survival compared to traditional bearings.[3,4] Second generation ceramic-on-ceramic bearings, for example, have been reported in Level 1 studies to survive at 100% at 51 months and 96% at 8 years.[3,4] For these reasons, alternative bearing surfaces are promoted for young patients with the assumption that they will be more active, subjecting their joints to high loads and cycles. The magnitude of increase in activity following ceramic-on-ceramic THA in young patients has not been quantified.

We asked: 1) what magnitude does activity level increase in young patients following ceramic-on-ceramic THA, 2) what are their midterm (minimum 2-year) clinical outcomes, and 3) what is their complication profile?

## Methods

We reviewed 100 consecutive uncemented ceramic-on-ceramic THAs in 79 patients younger than 55 years of age at the time of surgery (Table 1). Procedures occurred between February 1999 and April 2006, and all were performed by two high volume hip arthroplasty surgeons (JPG and CLN). In all patients, the choice of the ceramic-on-ceramic was based on age and reported activity levels. Fourteen patients were not included in the final analysis: three patients died due to causes unrelated to their arthroplasty (two from gun-shot wounds and one from an unknown cause), four patients refused consent to participate in the study, and seven patients were lost to follow

**Table 1. Patient characteristics**

| | Original cohort | Included in final analysis |
|---|---|---|
| Number of Hips | 100 | 80 |
| Male | 37 | 30 |
| Female | 42 | 35 |
| Average Age (years) | 38 (18-55) | 39 (18-55) |
| BMI (kg/m$^2$) | 30.1 (18.8-60.2) | 29.4 (18.8-60.2) |
| Follow-up (months) | | 54 (24-110) |
| Diagnosis | | |
| AVN | 36 | 31 |
| Osteoarthritis | 34 | 29 |
| Dysplasia | 4 | 2 |
| Rheumatoid arthritis | 2 | 2 |
| Post traumatic | 3 | 1 |
| Implant | | |
| Reflection cup:Synergy stem | 58 | 49 |
| Reflection cup:Spectron stem | 12 | 7 |
| Reflection cup:Anthology stem | 7 | 5 |
| Trident Cup:Secur-Fit stem | 22 | 19 |
| Lineage cup:Profemur stem | 1 | 0 |

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up at the time of study. The remaining 65 patients comprised 30 men and 35 women with a mean age of 39 at the time of surgery. Preoperative diagnoses included avascular necrosis (31), osteoarthritis (29), dysplasia (2), rheumatoid arthritis (2), and posttraumatic arthritis (1). Six prostheses failed and were excluded from the activity level analysis. The minimum follow-up period was two years with a mean of 54 months (range 24 – 110 months). The study was approved by our institutional review board and was carried out according to its guidelines.

All patients underwent THA through a standard posterior approach with implantation of modern ceramic-on-ceramic THA designs. Fifty-eight were Reflection cups coupled with Synergy stems, 12 were Reflection cups with Spectron stems, seven were Reflection cups with Anthology stems (all Smith & Nephew, Memphis, TN), 22 were Trident cups with Secur-Fit stems (Stryker, Kalamazoo, MI), and one was a Lineage cup with Profemur stem (Wright Medical, Arlington, TN). Postoperatively, patients were allowed full weight-bearing and underwent uniform post-operative care, which followed a standard protocol of physical therapy beginning on the first post-operative day.

All patients were followed routinely after surgery; this included, at a minimum, visits at two weeks, six weeks, three months, one year, and two years postoperatively. Primary outcome measures included preoperative and two years post-operative UCLA Activity Scores and Harris Hip Scores (HHS) recorded by the attending surgeons (JPG and CLN).[5,6] Secondary outcome measures included radiographic evaluation by two investigators (RC and GCL) for signs of radiolucency around the implants, malposition, and subsidence. Their independent assessments had a correlation of 1.0. All patients were contacted by telephone at the time of study (between two and nine years post-operatively) to confirm implant survival and current UCLA score. Any discrepancy was investigated with an additional clinic visit and radiographic examination (two patients). Patients were asked whether they were satisfied with their current activity level, and this was recorded as a binary answer. Patients were asked to identify their activity limiting factors; answers were categorized as: 1) no limitations, 2) other (non-operative hip) musculoskeletal limitation, 3) psychological impediments and lack of motivation, and 4) pain or disability of the operative hip. Finally, patients were asked whether they experienced a change in occupation activity level following THA; answers were categorized as: 1) same or similar occupation activity level, 2) more active occupation, 3) less active occupation or disability.

The UCLA and HHS results were analyzed for statistical significance using a two-tailed, paired student t-test using Excel (Microsoft, Redmond, WA).

## Results

Patients under the age of 55 years demonstrated an increase in activity level following ceramic-on-ceramic THA (Table 2). The mean UCLA activity score increased from 4.0 to 7.7. Only 9 patients (13.9%) reported that their activity was limited by symptoms from their operative hip (residual pain in eight patients and embarrassment of squeaking in one patient, Table 3). Twenty-eight patients (43.1%) felt unlimited in their activity level, while 15 patients (23.1%) were limited by other musculoskeletal complaints and 13 patients (20.0%) were limited by psychological constraints (disinterest in greater activity or fear of accelerating bearing wear). The majority of patients (52,80%) were satisfied with their overall activity level. Fifty-seven patients (87.7%) reported keeping the same or similar occupation, while two patients (3.1%) reported having a more active occupation following surgery: one transitioned from disability to waitressing and the other became a bus driver following a more sedentary position (Table 4). Six patients (9.2%) reported having an occupation preoperatively but were collecting disability benefits by the time of survey. Interestingly, five of these patients demonstrated an increase in activity levels, from a mean of 3.9 (range 3-6) to a mean of 6.4 (range 5-7), while one patient demonstrated an unchanged UCLA score of 3.

Midterm clinical outcomes following ceramic-on-ceramic THA in patients under 55 years old showed an improvement in HHS and reassuring radiographic measures. The mean HHS increased from 52.8 (range 30-65) to 91.0 (range 38-100). Radiographic evaluation of all hips included serial AP pelvis, AP hip, and frog-lateral hip radiographs. The radiographs were evaluated for radiolucent lines, osteolytic lesions, and component failure (e.g., fractures). At a mean radiographic follow up of 49 months (24-98 months), no hips had evidence of subsidence, loosening, or osteolysis. The seven patients lost to follow-up at two years demonstrated satisfactory radiographic evaluation and HHS greater than 90 at the one year follow-up visit.

At this midterm follow-up period, ceramic-on-ceramic THA in young patients demonstrated a failure rate of 7.5% and a subjective squeaking complaint of 21.6%. Of the 80 hips included in this study, 74 (92.5%) survived at time of study and 6 required revision by two years following index surgery. Two patients underwent revision for ceramic liner fracture (2.5%), and one patient (1.3%) each for acetabular component loosening, intolerable squeak, periprosthetic fracture, and instability. The two ceramic fractures occurred early in the life of the implant (average 12 months). One fractured upon the patient falling forcefully from standing onto a stone surface; the other was due to a fall from a horse onto the patient's operative side. Of the surviving hips, 16 patients (21.6%) complained of subjective squeaking; however, only five patients (6.8%) demonstrated objective squeaking on clinical examination. Including the hip that was revised for squeaking, this yields a demonstrable squeaking rate of 8.1%.

## Discussion

When discussing the use of ceramic-on-ceramic and other alternative bearings in young patients, authors distinguish the young based on longer life expectancy and presumed increased activity level, leading to increased demand.[4,7] One prior report suggested that patients under 75 years were

**Table 2. Activity score results**

| | Preoperative | At time of follow-up | P value |
|---|---|---|---|
| UCLA Activity Score | 4.0 (1-10) | 7.7 (2-10) | <0.001 |
| Harris Hip Score | 52.8 (25-69) | 91.0 (38-100) | <0.001 |

**Table 3. Self-reported reasons for activity limitations**

| | No. (%) |
|---|---|
| Symptoms from the operative hip (pain, squeaking) | 9 (13.9%) |
| Symptoms from other musculoskeletal area(s) | 15 (23.1%) |
| Psychological/motivational causes | 13 (20.0%) |
| No reported limitation | 28 (43.1%) |

**Table 4. Occupational changes**

| | No. (%) |
|---|---|
| Maintaining the same or similar occupation | 57 (87.7%) |
| Now in a greater physically demanding occupation | 2 (3.1%) |
| Now collecting disability | 6 (9.2%) |

physically more active than those older than 75 years at one year following conventional THA;[8] however, the magnitude of activity increase following ceramic-on-ceramic THA in young patients has not been reported. We asked: 1) what magnitude does activity level increase in young patients following ceramic-on-ceramic THA, 2) what are their midterm (minimum 2 year) clinical outcomes, and 3) what is their complication profile?

The improvements in activity scores observed in our series are similar to those reported by Yoo *et al* using a modified UCLA score following ceramic-on-ceramic THA.[9] They reported that 59 patients (97%) were able to participate regularly in moderate activities such as housework, shopping, and light occupational work (loosely correlating to a UCLA of 6). Fifty-five (90%) patients could regularly play sports (UCLA of approximately 7-8), and 34 (56%) could participate in impact sports (UCLA of approximately 9-10). Another study of activity level after ceramic-on-polyethylene hips reported a postoperative UCLA score of 6.3.[10] Using a pedometer, the authors found that the average gait cycles per year was comparable to that of older patients reported in the literature, and concluded that young patients following THA may not be more active than older patients. Our results show that in cohort of patients under 55 years old who are selected to undergo ceramic-on-ceramic THA, both activity level and function significantly increase at a mean of 54 months. To take our findings to the next logical step of concluding that younger patients return to a higher activity level following THA than traditional patients, we can compare our UCLA score of 7.7 (average age 39, average duration 54 months) to that reported in the literature of 6.3 (average age 58.4, duration greater than six months).[11] These findings are also consistent with several series demonstrating comparable improvements HHS following ceramic-on-ceramic THA with low rates of ceramic fracture, instability, and loosening.[12,13,9]

Yoo *et al* also reported no change in occupation due to a hip joint problem following ceramic-on-ceramic THA.[9] Our study found that most young patients maintained their occupation or entered a more active occupation. However, 9.2% of our patients were previously employed but now collecting disability benefits at the time of final follow-up. It is unclear whether hip symptoms contributed to their disabilities, but notably activity level increased in all but one patient. Possibly, social and cultural factors distinguish our cohort from that of the mentioned study.

A meta-analysis of observational studies comparing bearing surfaces in patients under 55 years found the 10 year survival for ceramic-on-ceramic bearings to be 88.9% in an overall sample size of 294 patients.[7] Our 54 month survival rate of 92.5% is consistent with these results.

Rates of ceramic fracture in the literature rates are 0.02 to 0.1%.[3] Our results showed two ceramic fractures at a rate of 2.5%, which is consistent with the mentioned cohort of patients with a mean age of 30 years. Our ceramic liner fractures occurred early at 9 months and 15 months and both were due to traumatic impact. It is possible that younger patients experience a higher rate of ceramic fracture than traditional patients due to their higher exposure to traumatic events.

The incidence of squeaking in ceramic-on-ceramic THA has been variably reported between 2 and 23%.[14-17] Our results are within the lower half this reported range, and our discrepancy between subjective and objective squeaking confirms one study reporting that 10.7% of patients complained of squeaking, but only 3.1% demonstrated objective squeaking

on clinical exam.[18] The higher rate of subjective complaints of squeaking may be related in part to the awareness of this complication from popular media and legal advertisements. It has been suggested that fourth generation ceramics do not suffer from the squeaking phenomenon, but definitive studies have not yet been reported.

This study makes several important assumptions to tests the hypothesis that activity level increases dramatically in young patients receiving THA. One assumption is that the static UCLA Activity Score at time of final follow-up reflects the dynamic activity level following THA in these young patients.This can be problematic in patients with polyarthritic disease that lead to the index THA; increased activity in the early years might lead to debilitation due to aggravation of other musculoskeletal disease, leading to a lower UCLA score that evades the question of interest. Other limitations of this retrospective study include: selection bias, loss to follow-up, and measurement bias. Three patients died and four refused participation, the inclusion of whom might have skewed these results. Seven patients were lost to follow-up but their 1-year results suggest that their inclusion would not have skewed the results. Finally, the measures of HHS and UCLA Score were collected by the operative surgeons and could have been influenced by an inherent desire for successful outcomes.

## Conclusion

Our cohort of patients demonstrated an increase in activity level, an improvement in clinical outcomes, and a low incidence of failures and complications. The value of this present study comes from its quantification of activity level increase and its confirmation of prior literature of favorable outcomes following ceramic-on-ceramic THA in young patients. Interesting findings include the frequency of patients collecting disability following surgery and the self-assessments of the reasons for their limitations to do more activity.

## Disclosures

No funding was received for this study. The following relationships with industry are disclosed: Zimmer (CLN-paid consultant; GCL-research support), Salient Surgical (GCL-speaker bureau), Smith & Nephew (JPG-royalties, paid consultant), Ceramtec (JPG-speaker bureau), Depuy (JPG-research support).

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U·P·O·J

# Long Tapered Hydroxyapatite-Coated Stems in Revision Total Hip Arthroplasty

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## Introduction

Component stability is critical in the reconstruction of the failed total hip arthroplasty (THA). Femoral component options used during revision THA include diaphyseal engaging long fully porous-coated stems and modular tapered stems designed for distal fixation.[1] While these femoral components have been shown to be reliable at achieving stable fixation in the setting of revision THA, one disadvantage of these distally fixed rigid implants is proximal stress shielding and the potential for femoral bone loss.[2]

In Europe, long tapered revision femoral components coated with hydroxyapatite (HA) have been shown to provide stable fixation and ingrowth in cases with adequate proximal femoral bone stock and favorable canal geometry.[3-6] Osteoconductive properties of the HA coating may fill microdefects and provide additional bony contact to augment bone restoration.[7] In the United States, however, the experience with these implants has been limited. Therefore, the purpose of this study is to: 1) evaluate the clinical outcome of THA revisions using long tapered HA-coated femoral components; 2) evaluate radiographs for evidence of bone ingrowth, loosening, or stress shielding, and 3) to report complications associated with the use of these implants.

## Methods

Fifty-five patients underwent revision THA using the Kar (Depuy, Warsaw, IN) long tapered HA-coated femoral revision stem. Preoperatively femoral bone loss was classified using the Paprosky classification.[7] Postoperatively patients were followed at two weeks, three months, one year, two years and five years. The Harris Hip Score (HHS) was used to assess clinical outcomes.[8] Serial radiographs were reviewed for evidence of loosening, osteointegration, stress shielding, or femoral bone loss.

## Results

Twenty-three men and eighteen women were available for follow up with average age of 62 years (range 28-92). Patients were followed for average of 59 months (range 26-117). One patient died and 13 were lost to follow up. Reasons for revision were aseptic loosening in 31, infection in 10. Preoperative femoral Paprosky classifications were as follows: 24 type I, 14 type II, and 3 type IIIA. There were no type IIIB or IV femurs.

The average HHS at final follow up was 71 (range 22-100). Three patients required subsequent revision: one for infection, one for aseptic loosening at 15 months, and one due to symptomatic limb length discrepancy. There were no cases of instability or fracture.

Radiographically, 40 stems were well fixed; one stem had subsided compared to postoperative images and was subsequently revised. No hips showed evidence of proximal femoral resorption or stress shielding. Evidence of osteointegration (spot welding) was present in all femurs postoperatively.

## Discussion

Long, tapered, HA-coated revision femoral components have been shown to provide stable fixation and ingrowth in cases where there is good proximal femoral bone stock and favorable canal geometry.[9-13] The Kar™ stem, in addition to being fully HA-coated, possesses distal slots which improve stem elasticity as well as a trapezoidal design with vertical and horizontal grooves to increase metaphyseal and proximal diaphyseal fit and improve rotational stability.[14,15] However, the experience with these implants has been limited in the United States.

We report on a series of 55 patients undergoing revision THA using a long tapered HA-coated prosthesis. At a mean 59 months of follow up, 41 patients were available for analysis with a femoral component survivorship of 93 percent. Radiographic analysis revealed osteointegration in all but one case with no evidence of loosening. One patient underwent revision for aseptic loosening of the femoral component. Preoperatively, the femoral bone loss was classified type IIIA according to the Paprosky classification system. These results are comparable to other series of proximally HA-coated cylindrical components. Gosens and van Langelaan reported on a series of 48 revision

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THA procedures using a Mallory-Head proximally HA coated femoral component.[16] All femoral defects were Paprosky class I and II and at a mean of 6.1 year follow up, there were no aseptic failures of the femoral component. Furthermore, Trikha *et al* reported on a series of 107 patients revised with a JRI Furlong hydroxyapatite-ceramic femoral component.[17] At an average follow up of 8 years, there were no femoral component failures, radiolucent lines, or evidence of failure of osteointegration. Consequently, a long tapered fully HA-coated femoral component can achieve reliable fixation in patients with Paprosky I and II femoral defects.

Most cases of femoral bone loss in this series were Paprosky types I and II. The only femoral component failure in this series was a case in which the patient had Paprosky type IIIA femoral bone loss. The patient had subsidence and loosening of the femoral component and underwent revision to a fully porous coated femoral component. Femoral components with conical distal tapers have been shown to be able to achieve stability in cases of significant bone loss.[18] Wedge-shaped tapered stem designs rely on interference fit against the medial and lateral cortices proximally that provides initial rotational stability that facilitates osteointegration. However, when the bone loss is substantial and involves a large portion of the metaphysis and extends to the isthmus, it can compromise the prosthesis ability to achieve initial axial and rotational stability that is crucial for eventual bone ingrowth. As a result, we have limited the use of these stems to cases with only mild proximal femoral bone loss.

We acknowledgeseveral limitations of this study. First, this is a retrospective study and therefore limited by recall bias. Secondly, because there was no control group of patients treated with traditional revision femoral components, no direct comparison between the femoral components can be performed. Finally, this is a relatively short-term follow up of a group of patients treated with this type of prosthesis. Longer follow up will be necessary to evaluate the true effects of this particular stem design and geometry on the bone quality and quantity of the proximal femur.

In conclusion, a wedge shaped long tapered HA-coated prosthesis can provide reliable fixation and osteointegration in patients with Paprosky I and II defects of the proximal femur. The advantages of these stems include preservation of the distal disphyseal bone, reduction of stress shielding of the proximal femur, and no end of stem thigh pain. In patients with adequate bone stock and favorable canal geometry, these stems can be considered viable reconstructive options.

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# The Cost of After-Hours Operative Debridement of Open Tibia Fractures

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## Introduction

Open long-bone fractures occur at a rate of 11.5 per 100,000 persons per year.[1,2] These severe injuries are associated with a high rates of complications, such as infections, with reported rates ranging from 4% to 63% of patients.[3] These injuries are associated with significant health care expenditures, with the lifetime per-patient cost of the most severe injuries reported to be as high as $509,275.[4] The cost of infection following open fractures has not been specifically calculated; however, the overall individual and socioeconomic burden of musculoskeletal infection is significant.[5] Historically, timing to operative debridement has been regarded as an important factor in reducing infection rates following open fractures. However, a recent meta-analysis revealed no difference in infection rates between early and delayed initial surgical debridement of open long bone fractures, even in the most severe injuries.[3] The aim of this study was to evaluate the additional cost associated with performing after-hours operative debridement of open fractures within six hours of injury.

## Materials and Methods

Economic modeling was performed based on population estimates obtained from the National Trauma Database and the National Inpatient Sample. The number of open tibia fractures that occur annually in the United States, including the number that presented after-hours (defined as between the hours of 6:00pm and 2:00am) that underwent operative debridement within six hours were calculated. This model estimates incremental cost for after-hours surgery based on overtime wages for on-call surgical personnel (nurses and surgical technicians) required to staff after-hours cases, as published by the United States Department of Labor and obtained from our own institution. As many Level 1 hospitals are capable of performing after-hours cases without additional cost, a sensitivity analysis was performed to determine the effect of designated level of care of the trauma hospital.

## Results

A total of 17,414 open tibia fractures were recorded in the National Inpatient Sample for

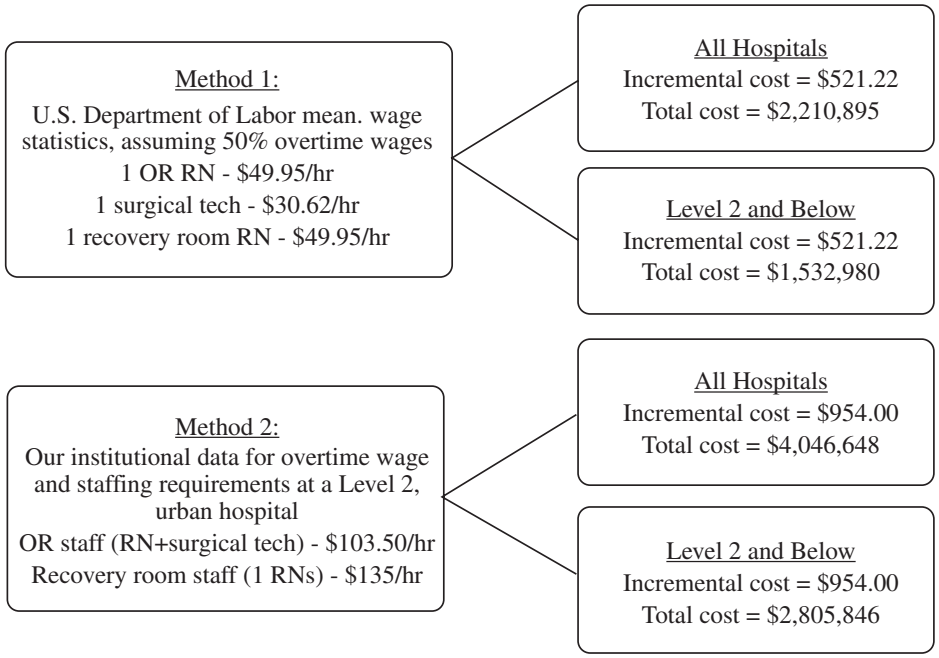


**Figure 1.** Methods for determination of incremental and total costs associated with after-hours debridement of open tibia fractures.

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2009. An estimated 7,485 open tibia fractures presented after-hours, of which 4,242 underwent operative debridement within six hours of presentation. Overtime wage data yielded an estimated total additional cost for after-hours operative debridement of open tibia fractures within six hours of $2,210,895 to $4,046,648 annually, respectively. For hospitals without Level 1 designation, the cost of performing after-hours operative debridement of open tibia fractures was calculated at $1,532,980 to $2,805,846 annually (Figure 1).

## Discussion

Our data indicated that the overall cost of performing after-hours operative debridement of open tibia fractures is as high as $4,046,648 annually. Given that there is little to no documented benefit of this practice, and with increased pressures from federal and state governments and insurers to practice cost containment, elective delay of operative debridement of open fractures may be one means of decreasing the economic burden associated with such injuries. This conclusion remains contingent upon prospective confirmation that delayed operative debridement of open fractures is associated with outcomes equivalent to those of emergent after-hours debridement.

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# Fractures of the Scapula: Diagnosis, Indications, and Operative Technique

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## Introduction

Scapular fractures account for 3% to 5% of all fractures of the shoulder girdle and compose 0.4% to 1% of all fractures.[1]The annual incidence of these injuries is estimated at 10 per 100,000 persons.[2]The scapula plays an integral role in the association between the upper extremity and the axial skeleton. Scapular fractures have the potential to cause significant pain and to alter normal function of the shoulder girdle as a result of malunion, nonunion, rotator cuff dysfunction, scapulothoracic dyskinesis, or impingement.

## Presentation and Diagnosis

Fractures of the scapula typically result from a high-energy, blunt-force mechanism.[3-7]Direct force may cause fractures in all regions of the scapula, while indirect force via impaction of the humeral head into the glenoid fossa can cause both glenoid and scapular neck fractures. Motor vehicle collisions account for the majority of scapular fractures with 50% occurring in occupants of motor vehicles and 20% in pedestrians struck by motor vehicles.[5,8]

Because of the high-energy nature of scapular fractures, 80% to 95% are associated with additional traumatic injuries.[2-5,9,10] On average, patients with fractures of the scapula have four additional injuries.[6] Potentially life-threatening injuries may include pneumothorax, pulmonary contusion, arterial injury, closed head injury, and splenic or liver lacerations,[5,6] with the associated mortality rate reaching nearly 15%.[3,6] Brachial plexus injury occurs in 5% to 13% of cases and serves as an important prognostic indicator of ultimate clinical outcome.[3-5]

Patients with scapular fractures present with the ipsilateral upper extremity adducted against the body and protected from movement.Typical physical examination findings include swelling, ecchymosis, crepitus, and tenderness about the shoulder. Range of motion of the shoulder is limited, particularly with abduction.A meticulous neurovascular examination is necessary in order to evaluate for injury to the ipsilateral brachial plexus and/or vascular structures.

The earliest opportunity to diagnose a scapular fracture may be on the initial supine anteroposterior chest radiograph taken in most trauma patients; however, one study found that 43% of trauma patients with scapular fractures did not have this injury recognized

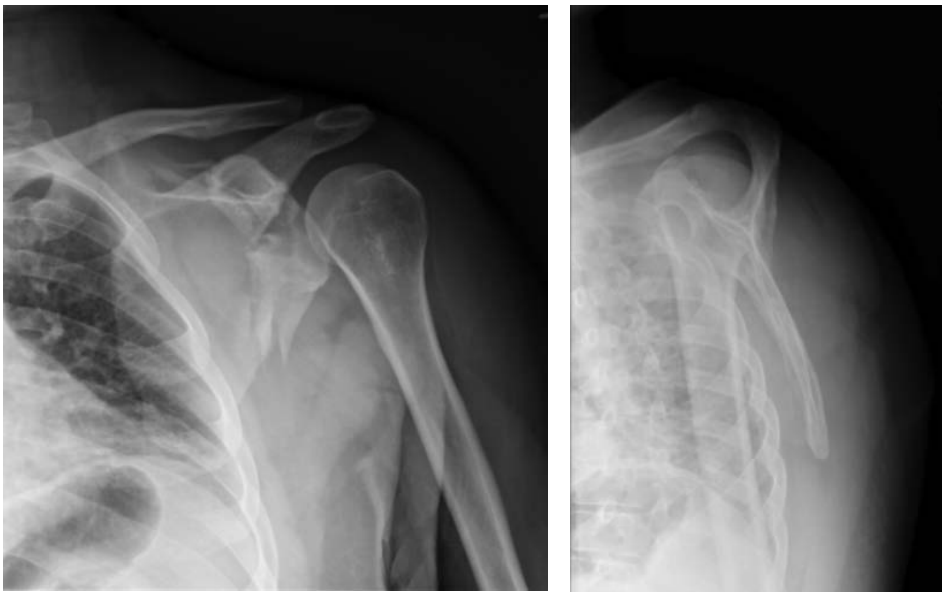

**Figure 1.** Anteroposterior and lateral radiographs of the left shoulder demonstrating a comminuted fracture of the lateral aspect of the left scapula with glenoid involvement.

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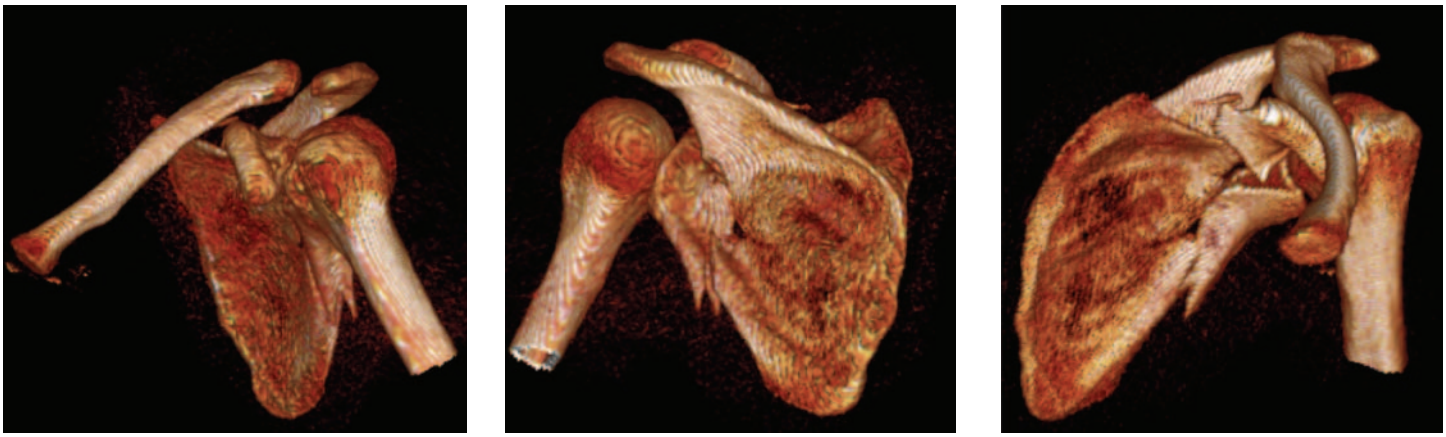

**Figure 2.** Three-dimensional reconstructions of the left shoulder CT scandemonstrating a displaced, comminuted scapular fracture that originates at the base of the coronoid process and extends into the posterior glenoid and into the midbody of the scapula.

on their initial chest radiograph.[11] Therefore, all patients at risk for scapular fractures should have a dedicated series of shoulder radiographs (Figure 1), including anteroposterior, lateral, and axillary views. A computed tomography (CT) scan is recommended for complex or displaced fractures, as it allows for assessment of the size, location, and degree of displacement of fracture fragments, as well as confirmation of the position of the humeral head in relation to the glenoid fossa.[12] Furthermore, three-dimensional CT reconstructions may be helpful in visualizing complex fracture patterns and planning for operative treatment (Figure 2).

## Indications

Historically, scapular fractures have been treated non-operatively. In 1805, Desault provided an early description of closed treatment of scapular fractures in his treatise on fractures. More recent research has shown that over 90% of scapular fractures are non-displaced or minimally displaced and can be effectively managed with conservative treatment.[4,5,7] However, advanced imaging techniques have allowed for the identification of certain subtypes of scapula fractures that may portend a poor prognosis without surgical intervention.

For glenoid fossa fractures, some surgeons advocate open reduction and internal fixation for patterns that result in articular displacement greater than 5 mm,[13] as this is the approximate maximum thickness of the glenoid articular cartilage.[14] Surgical treatment is also indicated if the glenoid fracture is associated with persistent or recurrent instability of the glenohumeral joint. Surgical intervention may also be beneficial in severe cases of shoulder suspensory complex disruption or scapulothoracic dissociation.[15]

While most extra-articular scapular fractures can be treated non-operatively, surgical intervention should be considered for significantly displaced fractures.[8,13,16] Nordqvist and Peterson evaluated 37 displaced glenoid neck fractures that were treated nonoperatively and found that functional results were only fair or poor in 32% of cases at 10- to 20-year follow-up.[17] Similarly, Ada and Millar reported that, of

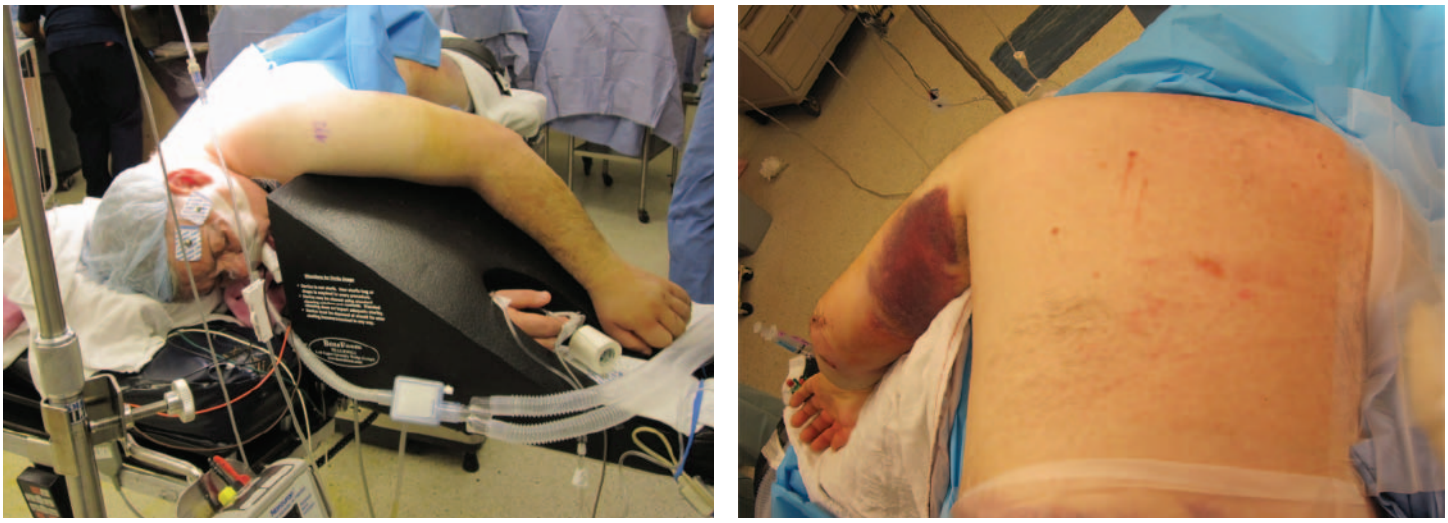

**Figure 3.** The patient is positioned in lateral decubitus on a beanbag with the operative arm in the prone position.

the 16 patients treated conservatively for displaced scapular neck fractures in their series, 50% complained of pain at night, 40% had weakness with abduction, and 20% had decreased range of motion.[8] Hardegger noted that displaced glenoid neck fractures altered the relationship of the glenohumeral joint with the acromion and nearby muscle origins, thereby resulting in functional imbalance.[16] As a result, some surgeons recommend operative treatment for all glenoid neck fractures with at least 1 cm of translation or 40 degrees of angulation in the AP plane of the scapula.[8,17,18]

Approximately 50% of scapular fractures involve the scapular body and spine.[15] These fractures generally heal with conservative treatment and do not require operative intervention.[3-5,7,9,19] In their systematic review, Zlowodzki *et al* found that 99% of scapula body fractures were being treated non-operatively with excellent or good results in 86% of cases.[20] These favorable results are likely due to the fact that the scapular body is associated with an extensive muscular envelope, which assists with fracture healing and minimizes displacement.

## Operative Technique

For the patient with scapular fractures that do not involve the anterior glenoid, the following procedure can be performed in the lateral decubitus position (Figure 3). We prefer to use a radiolucent table that is reversed to allow additional room for fluoroscopic imaging intraoperatively. It is critical to offload all bony prominences and areas of possible nerve compression, including the use of an axillary roll. The operative arm is draped free as it is often necessary to manipulate the limb in order to facilitate reduction, and the arm supported on a padded, freely movable stand. The non-operative arm is positioned on a padded, radiolucent arm board. The primary surgeon stands posterior to the patient and fluoroscopy should be positioned to enter the operative field anteriorly. Appropriate pharmacologic relaxation is necessary to manipulate the fracture fragments. In addition, suspending the arm in gentle traction will facilitate visualization of the articular surface of the glenoid. Positioning of the patient should account for the potential need to manipulate the arm.

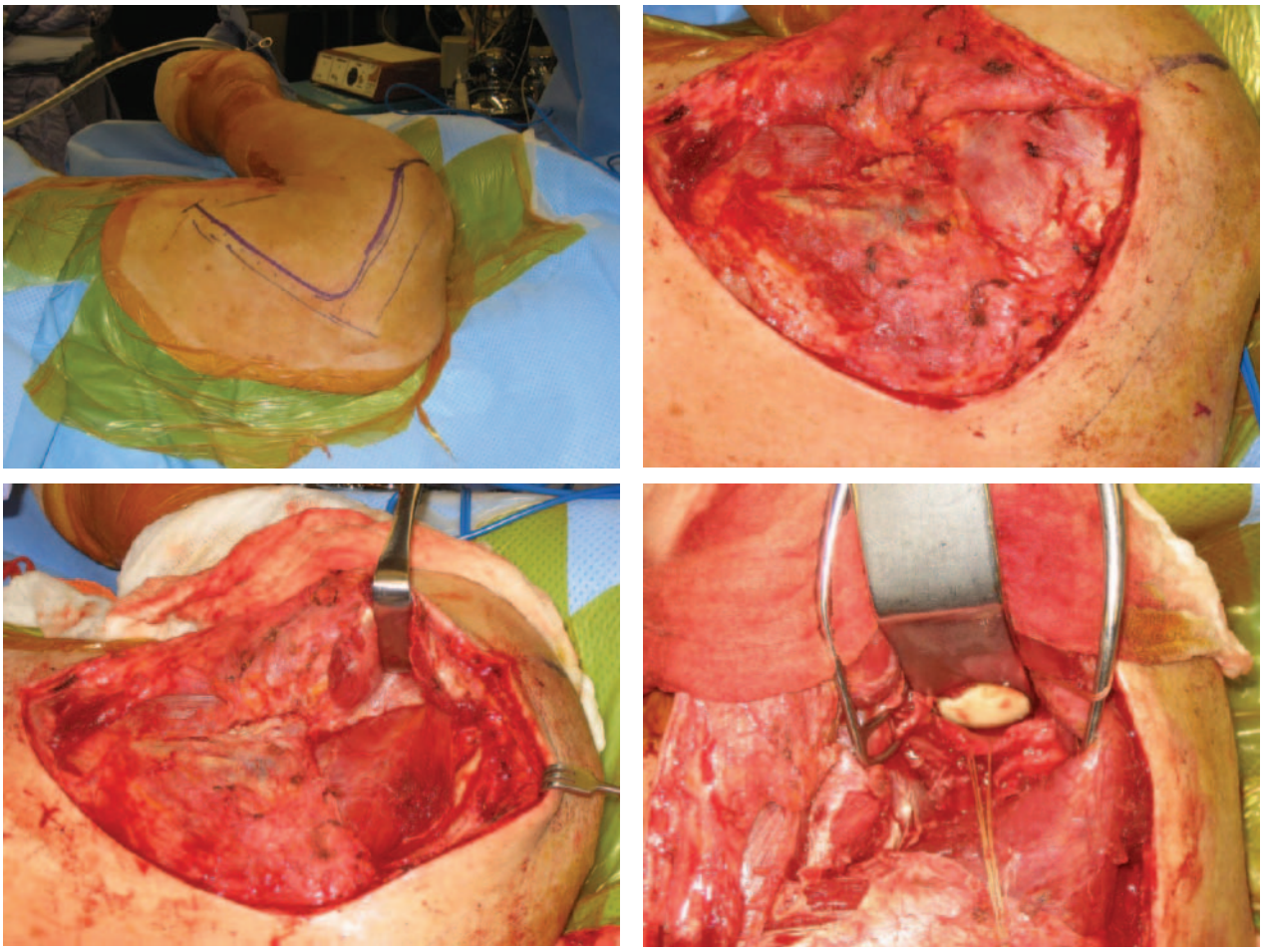

**Figure 4.** Intraoperative photographs demonstrating a curvilinear incision along the medial border of the scapula and the scapular spine. Subsequently, a full-thickness flap overlying the deltoid fascia is created, exposing the posterior deltoid. The deltoid origin is sharply released from the scapular spine, and the deltoid is retracted laterally. The interval between the infraspinatus and teres minor is developed with meticulous care taken to avoid the axillary nerve and the innervation to the infraspinatus. The scapular fracture is exposed within this interval.

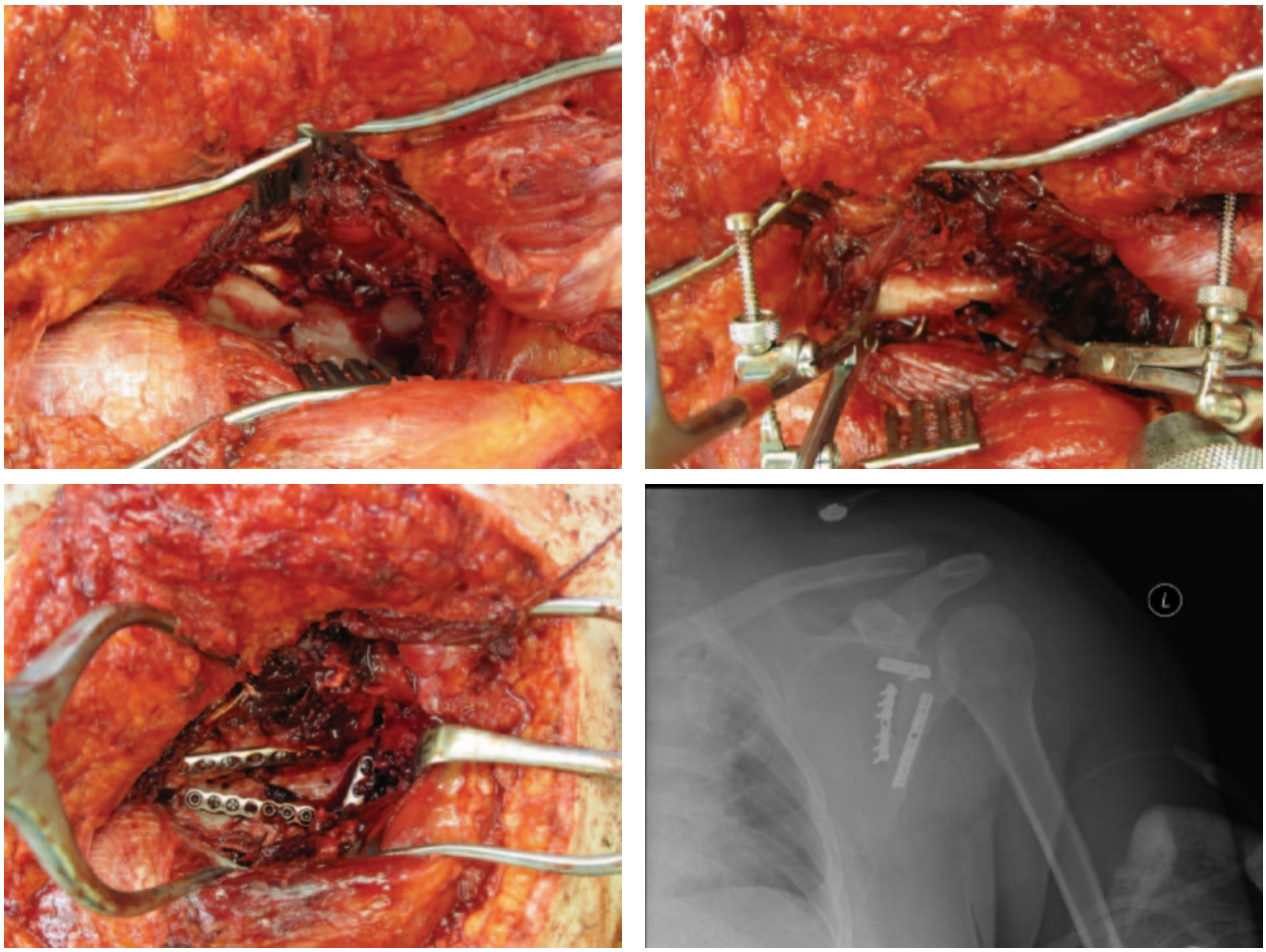

**Figure 5.** Intraoperative photographs demonstrating the scapular fracture before andafter reduction using a 4-mm Shantz pin and two point-to-point clamps. Three small fragment plates were then placed to maintain reduction of the scapular fracture. The postoperative anteroposterior radiograph of the left shoulder demonstrates an anatomic reduction of the scapular fracture with good positioning of the implants.

Exposure is obtained via a modified Judet approach. A curvilinear incision is positioned along the medial border of the scapula and the scapular spine (Figure 4). Sharp dissection is carried down to the level of the deltoid fascia with maintenance of a full-thickness skin flap. Hemostasis is achieved, and a full-thickness flap overlying the deltoid fascia is created, thereby exposing the posterior deltoid. It is vital not to violate the fascia of the deltoid. The inferior deltoid is then gently dissected off of the infraspinatus, and the deltoid origin is sharply released from the scapular spine. A stitch is placed in the superomedial corner of the deltoid origin in order to allow for anatomic repair back to the scapular spine at the conclusion of the procedure. Using the tagging stitch to pull gentle traction, the deltoid is reflected from medial to lateral. In general, bony exposure is obtained through two separate windows: 1) the interval between infraspinatus and teres minor (exposes the lateral border of the scapula and the inferior glenoid neck), and 2) via elevation of the medial origin of the infraspinatus (exposes the superomedial scapula). The interval between infraspinatus and teres minor is developed with meticulous care taken to avoid the axillary nerve and the innervation to the infraspinatus. It is important to note that a formal Judet exposure would involve reflecting the infraspinatus on its neurovascular pedicle for more complete visualization and may be necessary for more complex or chronic injuries.

Once the fracture site is identified, it is gently debrided. Fracture reduction and fixation is dependent on the fracture pattern and the bone quality. The fracture is reduced using a 4 mm Shantz pin placed proximally in the more lateral fragment for mobilization and reduction and using point-to-point clamps for provisional fixation (Figure 5). Reduction and fixation is conducted from medial to lateral as reduction of the medial scapular body can provide a framework to which one can accurately reduce the lateral border and glenoid neck. It is important to note that draping the arm free is helpful at this stage as manipulation of the limb can further assist in achieving an anatomic reduction. Our preference is to utilize small fragment or mini fragment plates across the fracture using compression technique if the fracture pattern allows. Once reduction and implant position are confirmed with fluoroscopy, the deltoid is repaired either with heavy non-absorbable suture if a cuff of tissue is left attached to the scapular spine or through 2 mm bone tunnels. Our preference

is to use bone tunnels, as deltoid detachment is a potentially-devastating complication. The wound is thoroughly irrigated and a deep drain is placed prior to closure of the posterior myocutaneous flap. Patients are placed in a sling, and radiographs are obtained prior to extubation. The deltoid repair is protected for six weeks by limiting the patient to gentle passive motion exercises. After six weeks, active and active-assisted range of motion is initiated, and strengthening generally commences at approximately 3 to 4 months postoperatively.

## Disclosure

The contents of this article were previously published in the open-access journal *Advances in Orthopedics*.[21] The authors retain the copyright for this work.

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# Blowing Smoke: A Meta-Analysis of the Effects of Smoking on Fracture Healing and Postoperative Infection

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## Introduction

Worldwide, over 1.3 billion individuals smoke tobacco. An estimated six million deaths are caused annually due to the multiple unwanted effects of cigarette smoke.[1,2] While cigarette use may be decreasing in some areas of the industrialized world, nearly one-in-five Americans still uses tobacco. In the developing world, the use of tobacco continues to rise at a rate of nearly 3.4 percent annually.[3,4] While the deleterious effects of smoking on many organ systems have garnered significant attention, its effects on the musculoskeletal system, including on fracture healing and postoperative infection after long-bone fracture surgery, have not been well characterized. The aim of this study was to systematically review the association between smoking, fracture healing, and postoperative infection.

## Materials and Methods

Medline, EMBASE, and Cochrane literature databases were queried and a manual search of bibliographies was performed. Randomized controlled trials and cohort studies, both retrospective and prospective, evaluating the associations between smoking and long bone fracture healing, as well as smoking and infection were included. Descriptive and quantitative data were extracted. A meta-analysis was performed using a random effects model for nonunion, superficial infections, and deep infections in smoking and non-smoking cohorts. Time to healing was evaluated using frequency-weighted means and group-weighted standard deviations. Three sensitivity analyses were performed to evaluate the effects of tibia fractures, open fractures, and level of evidence. Study heterogeneity, criteria of methodological quality, and publication bias were also evaluated; these factors were adjusted for using trim and fill analysis.

## Results

Our initial search identified 7,110 references. Of the 237 articles further inspected by title, 20

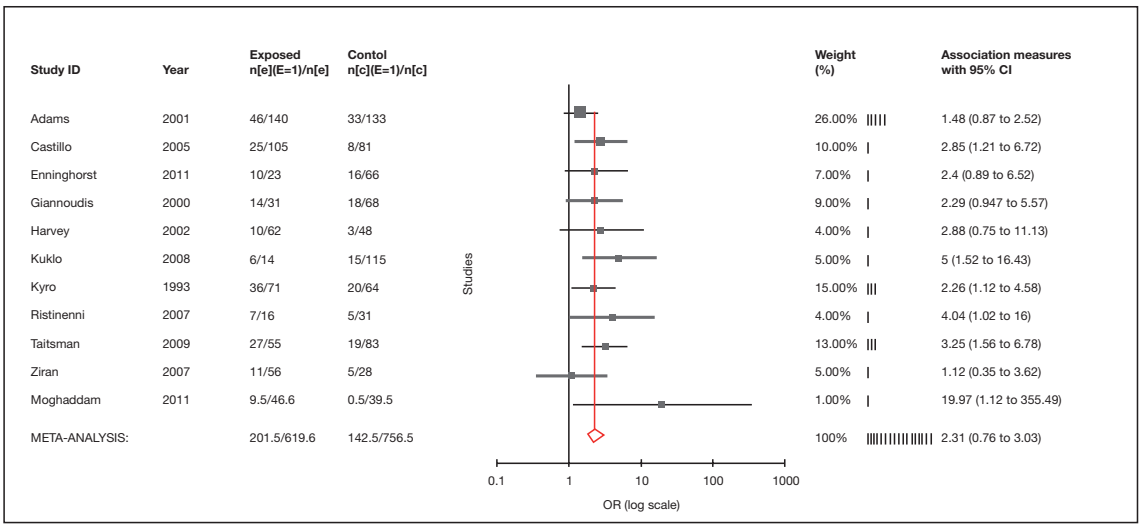


**Figure 1.** Forest plot demonstrating meta-analytic adjusted odds of nonunion among smokers with tibia fractures.

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were included (7 prospective and 13 retrospective cohort studies), and 18 offered sufficient data for meta-analysis. The adjusted odds of nonunion was 2.3 times in the smoking group compared to the non-smoking group (95% confidence interval: 1.8-3.0; $p<0.01$; Figure 1). Risk difference calculation revealed a 15 percent higher risk of overall long bone nonunion in smokers (95% CI: 10-19%). There were increased rates of nonunion in smokers with tibia fractures (OR 2.42, 95% CI: 1.7-3.4; $p<0.01$), and with open fractures (2.42, 95% CI: 1.7-3.4; $p<0.01$). For all fracture types, the mean healing time was longer for smokers (30.2 weeks, 95% CI: 22.7-37.7 weeks) than non-smokers (24.1 weeks, 95% CI: 17.3-30.9 weeks). For tibia fractures, the mean healing time was longer for smokers (32.0 weeks, 95% CI: 23.2-41.0 weeks) than non-smokers (25.1 weeks, 95% CI: 16.4-33.9 weeks). There was no difference in post-operative superficial and deep infections between smokers and non-smokers undergoing long bone fracture surgery ($p=0.13$). Publication bias was noted in the small studies showing a larger effect size than larger studies. Trim and fill analysis was performed which resulted in similar results to the original meta-analysis.

## Discussion

This study provides a systematic review of the evidence in the literature regarding the effects of smoking on fracture healing and postoperative infection. Smoking was associated with increased nonunion for all fractures, tibia fractures, and open fractures. Additionally, smokers trended towards longer mean healing times. These potential risks should be discussed with all fracture patients. Further studies are warranted to determine the potential benefits of smoking cessation programs on outcomes following fracture fixation.

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# How to Write a Systematic Review: A Step-by-Step Guide

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## Introduction

A systematic review attempts to comprehensively and reproducibly collect, appraise, and synthesize all available empirical evidence that meets pre-defined criteria in order to answer a research question. The quantitative combination and statistical synthesis of the systematically-collected data is what defines a meta-analysis. Here, we first attempt to delineate the basic steps for conducting a systematic review: initial planning, conducting the search, data extraction, and quality analysis. We then outline the fundamental steps for assessing the appropriateness of meta-analytic technique for your review and an explanation of statistical tools available for data analysis and presentation. An academic discussion regarding the strengths and weaknesses of systematic review methodology is beyond the scope of this guide, as are detailed instructions regarding statistical analysis.

## Initial Planning

When initiating a systematic review, it is important to plan ahead and anticipate problems. By maintaining a clear study focus from the beginning, identifying a well-defined research question, outlining strict inclusion and exclusion criteria, and understanding the eventual contribution of your work to the existing literature, you can effectively minimize reviewer bias and streamline the review process.

### *Defining a Research Question*

An appropriate, focused research question is based on an extensive *a priori* literature review to understand the scope of evidence available on your topic. It is often helpful to write down your question first, then to conduct a literature review to determine whether your question has already been answered, can be answered, or is irrelevant and would pose an insignificant contribution. The PICO mnemonic (Population, Intervention, Comparison, Outcome) is a commonly used tool to help delineate a clearly defined, clinically-based question for your systematic review. In detail, the mnemonic refers to the following:

1. Population: Define your subject group. Think about the age, sex, race and other patient characteristics, as well as relevant co-morbidities, pathology, and outcomes.
2. Intervention: Consider the prognostic factor or exposure (includes intervention) of interest.
3. Comparison: Repeat steps 1 and 2 for the group to whom you will compare your initially defined population and intervention (note: this step does not apply to all questions).
4. Outcome: The item you hope to accomplish, measure, or define.

For example:

1. P: Are adults with open fractures
2. I: who undergo operative irrigation and debridement
3. C: after a delay of greater than six hours from the time of injury at an
4. O: increased risk of developing osteomyelitis, soft tissue infection, and fracture non-union?

In the process of outlining a study question, it is clear that many critical terms within the question stem will need to be defined and characterized further. It is important that these terms are evaluated and discussed amongst your collaborators at the initial stages of the project, so as to eliminate potential confusion moving forward. For instance, in the above question, terms that require strict definitions are age (include pediatric patients?), open fractures (gunshot injuries excluded? only long bones?), osteomyelitis (culture-positive patients only?), soft tissue infection (those treated with antibiotics? or those who required an additional surgery?), and non-union (how long from initial injury?). With your question and these terms in mind, the future identification of relevant and appropriate literature will be easier.

### *Study Justification*

An initial literature review is required so that you can justify the significance of your work. Your study may intend to do one or more of the following: 1) clarify strengths or weaknesses of existing literature; 2) summarize large amounts of literature; 3) resolve conflicts; 4) evaluate the need for a large clinical trial; 5) increase the statistical power of smaller studies;

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or 6) improve study generalizability. Bear in mind that the purpose of a systematic review is to not only collect all the relevant literature in an unbiased fashion, but to extract data presented in these articles in order to provide readers with a succinct *synthesis* of available evidence. As a general guide, you should easily find—on a broad non-systematic search—numerous papers that are relevant but may be excluded. Look carefully to see if your work has been previously published. If the most recent review is more than a few years old and the topic remains relevant, your contribution may still be of value. Finally, check the PROSPERO site (http://www.crd.york.ac.uk/NIHR_PROSPERO/) to see if others are working to answer the same questions. If not, consider registering your study.

***Literature Search***

To execute a well-designed study there are two requirements: 1) an organized team including a statistician, an expert in the field, and at least two individuals to oversee each section of the review process; and 2) a detailed study protocol. For the latter, consideration will need to be given to specific search terms, inclusion and exclusion criteria, databases to be searched, and eventual data which will need to be collected and reported. Finally, persons experienced in conducting a search, a medical librarian, or both may offer guidance as you proceed.

***Selecting Search Terms***

Selecting the appropriate terminology is what guides the entire search, and thus is of crucial importance. Consider alternate terms, historical terminology, and even common misspellings. List these terms in the protocol before starting the search. Each search term (or terms) will need to be queried in each database that is used. A detailed search may be produced with the assistance of an experienced librarian who can "customize" a search in order to limit the number of extraneous hits. In cases with extremely specific questions this may be appropriate. Additionally, the librarian may be able to assist you in obtaining rare journal articles or texts which may constitute part of your review. It is important to obtain the services of someone with expertise in systematic reviews to minimize the prospect of bias infused by terms which are too restrictive.

***Inclusion and Exclusion Criteria***

Strict criteria are necessary to determine the appropriate articles for inclusion. Some of these criteria will depend on your specific question (i.e. exclude gunshot injuries as a mechanism of open fracture). General criteria applicable to any systematic review are: level of evidence, language, and animal or human subjects. First, choose the level of evidence included for your particular study. This will depend on the existing literature and the overarching aim of your research. For topics that are well-represented in the literature with the aim to synthesize available evidence, it is common to include articles with high levels of evidence only (Levels I and II). For topics that are less well-characterized with the aim to justify a larger clinical trial, inclusion of all levels of evidence may be warranted. It is important to remember that the quality of a systematic review is defined by the lowest quality of the included studies. Next, decide whether the resources are available to include articles published in other languages. The inclusion of English-language articles only will certainly introduce bias, but is often necessary when resources are not available for translation.

***Databases***

Multiple information sources will need to be searched to perform a comprehensive systematic review. Medline includes articles published since 1966 and is freely available via PubMed. EMBASE includes articles published since 1974 and requires a personal or university subscription to access. Surprisingly, *there is only a 34% overlap* of journals included in these two databases.[1] Therefore, using a single database alone is insufficient, with reports that only 30 to 80% of randomized controlled trials will be identified with Medline database search alone.[2] Additionally, the Cochrane Controlled Trials Register does not overlap with the previous two databases and will need to be individually searched. If you are conducting a review that is related to medical education, quality control, bioengineering, etc., there are a number of additional databases for alternate fields including education-focused, nursing, or engineering literature that may require the use of additional resources. A further search of the "grey" literature may produce additional references. For example, sites like opengrey.eu may prove fruitful, especially if the topic is unusual or if a large publication bias is found. Keep in mind that Medline and EMBASE articles are more likely to be well vetted, but also more vulnerable to publication bias.

***Data Organization***

A key aspect to conducting and writing a systematic review is reporting your exact methods for data collection. The most recent guidelines on conducting and reporting systematic reviews are the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta Analyses).[3] These guidelines facilitate the reporting of appropriate information (Figure 1).

***Conducting and Reviewing the Search***

Once a justified study question and detailed study protocol are in place, the systematic review process can proceed. First, accounts must be created with each database (Medline, EMBASE, Cochrane) in order to save searches that may need to be retrieved at a later time. Terms must be entered into the search field only once, and the date the search is conducted must be recorded. If a search is conducted, and subsequently re-typed into the database *de novo* one week later, there may have been additional articles published or uploaded within that week. It is better to record the date and report this than to constantly re-do the search. Type search terms into the database (remember to use filters as defined by your study protocol). Export references to a reference-managing program that allows for efficient identification and exclusion of duplicate entries.

Once the references have been recorded, collected, and duplicates excluded (record this number too), the first-pass review may begin. In this stage, the reviewers (minimum of two), should read through each study title and exclude clearly irrelevant studies. If either reviewer feels that the study may be of value, it is included for further analysis. A second-pass review is then conducted where the abstracts of included titles are analyzed further. Eventually, articles still included must undergo full-text review. Once this is complete, the bibliographies of each article also need to be systematically reviewed for further relevant articles. This process again necessitates a first-pass review (exclusion by title), a second-pass review (exclusion by abstract), and a third-pass review (exclusion by full-text), as was conducted for the primary search. Any additional articles found to meet all inclusion criteria will again need a systematic bibliography review until no further articles are identified. Once this last step is complete, it is useful to provide a measure of inter-rater agreement in order to determine how robust the initial search words were. Be sure to record the number of studies searched and excluded at each stage of the process. Review the flowchart in Figure 1 frequently as a reminder of data which needs to be recorded and reported.

### *Data Extraction*

The data extraction component of a systematic review is driven by a well-organized spreadsheet. The spreadsheet should be carefully piloted on a few select studies before incorporating it into the entire review. The structure of the data collection form will vary between different systematic

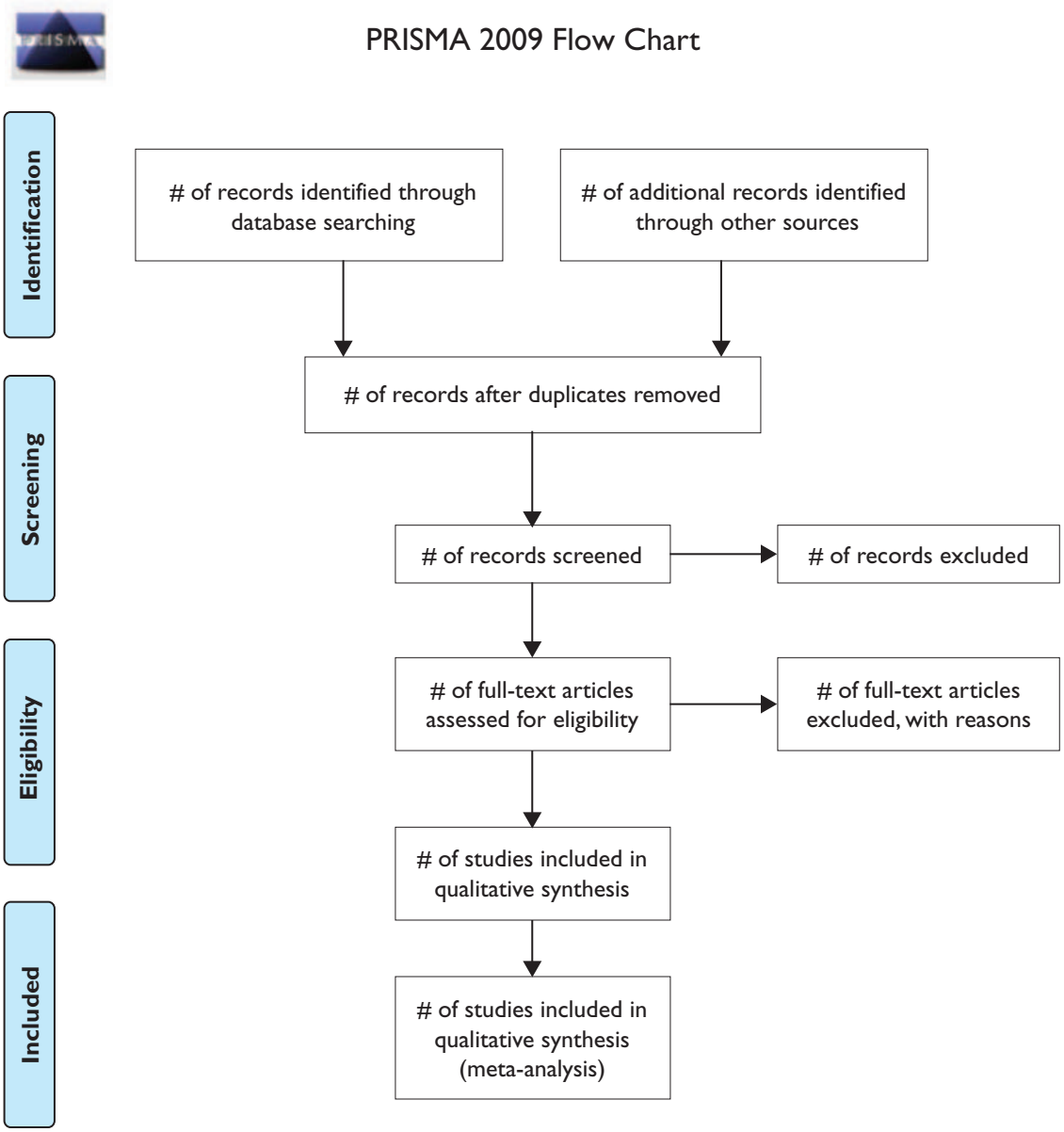


**Figure 1.** PRISMA 2009 Flow Diagram. A flowchart outlining the information required for reporting in systematic reviews according to the PRISMA guidelines.[3]

reviews, thus depending on the systematic review, more specific data collection items may need to be extracted for full appropriate review. We recommend beginning with a more detailed spreadsheet to avoid having to return to the primary articles after the initial data extraction. It is important to remember that the data extraction should be performed by two independent reviewers and any differences need to be reconciled by mutual agreement.

## Quality Analysis

A key step in a systematic review is the critical appraisal of the included studies. An assessment of "study quality" is a bit nebulous, but at a minimum, an assessment of the internal (i.e. minimization of study methodological error and bias) and external (i.e. generalizability to other populations) validity of all the studies included in the systematic review is necessary. Several potential threats to the validity of the studies need to be assessed in a reproducible manner, and include description bias, selection bias, measurement bias, analytic bias, and interpretation bias.

- Description bias: is the intervention well described?
  - *Did the authors report antibiotic timing and dosing, in addition to the operative debridement times?*
  - *Is the fracture population adequately described?*
- Selection bias: did the authors describe the screening criteria for study eligibility?
  - *Did the authors describe why some open fractures were excluded from the study or transferred to another facility?*
- Measurement bias: was the exposure (i.e. open fracture classification) and outcome measures (i.e. infection diagnosis) valid and reliable?
  - *Did the authors report reliability for the classification of the open fractures?*
  - *Did they use quantitative cultures or subjective clinical examination findings for the definition of "infection"?*
- Analytic bias: did the authors conduct an appropriate analysis by conducting statistical testing, controlling for repeated measures, etc.?
  - *Did the authors account for severity of injury in their statistical analysis?*
  - *Did they report any statistics or just observations?*
- Interpretation bias: did the authors correct for controllable confounders?
  - *Was there adequate follow-up of the patients with open fractures?*

Several quality scales and checklists have been reported,[1] including many that are available for randomized trials. Quality measures for non-randomized studies are variable, and none have been developed specifically for use in orthopaedic trials. Many of the available scales are able to generate overall quality scores. However, overall scores may not provide adequate information regarding the strengths and weaknesses of the individual studies, and may be misleading, by providing a high overall summary score in spite of a single critical methodological flaw. Therefore, many researchers prefer to use checklist of necessary elements to quality appraisal. The items on the checklist can be presented in a qualitative manner in the systematic review.[4] A minimum of two independent reviewers should assess the quality of the studies. Differences can be reconciled by mutual agreement or by a third reviewer.

## Meta-Analysis

Prior to embarking on a meta-analysis, it is important to determine whether or not the data are appropriate for meta-analytic methods. The term "meta-analysis" is most commonly associated with the summation of randomized controlled trials. Every meta-analysis implies that a systematic review has been done, but not every systematic review is amenable to meta-analysis. True meta-analyses are somewhat uncommon in orthopaedic surgery relative to the number of systematic reviews. Recently, many authors have begun applying meta-analytic techniques to observational comparative studies. Care must be taken to consider selection bias when the groups are not similar, as well as reporting bias if it is unclear whether the entire sample was used in some of the parent studies. For these reasons, sensitivity analyses have shown that meta-analysis of different levels of evidence may produce disparate results.

### *Publication Bias*

Every meta-analysis should include an assessment of publication bias. Publication bias, or "the file drawer effect," is the tendency for articles to get published based on the magnitude and direction of the results. As such, small studies that demonstrate a difference are more likely to get published than large studies. This type of publication bias may be assessed in several ways. Two of the most common means of assessing publication bias are funnel plots and the Egger's intercept.

A funnel plot should be symmetric (Figure 2). This indicates that the size of the studies did not correlate with the effect size of the outcome measure of interest. If the scatter plot here shows dots which fall outside the confidence ranges, then publication bias can be considered a possibility (i.e. small studies showing a greater effect size).[5] This implies that small studies with a smaller or negative effect size may exist but were never published.

Egger's intercept is a quantitative method to identify asymmetry in a funnel plot. Mathematically it is equal to the Y intercept of a line produced by a regression of the normalized effect size (estimate divided by standard error) by precision of that estimate (1/SE).[6] This produces a recognized p-value that can be interpreted as the chance that this funnel plot would have been produced by a random set of studies by chance.

### *Study Heterogeneity*

Differences in study populations, methods, and in the case of surgery, surgical techniques and follow-up, can all have a profound influence on effect size. Unless techniques are relatively standardized, it is often useful to assume that heterogeneity is present between studies in surgical trials and

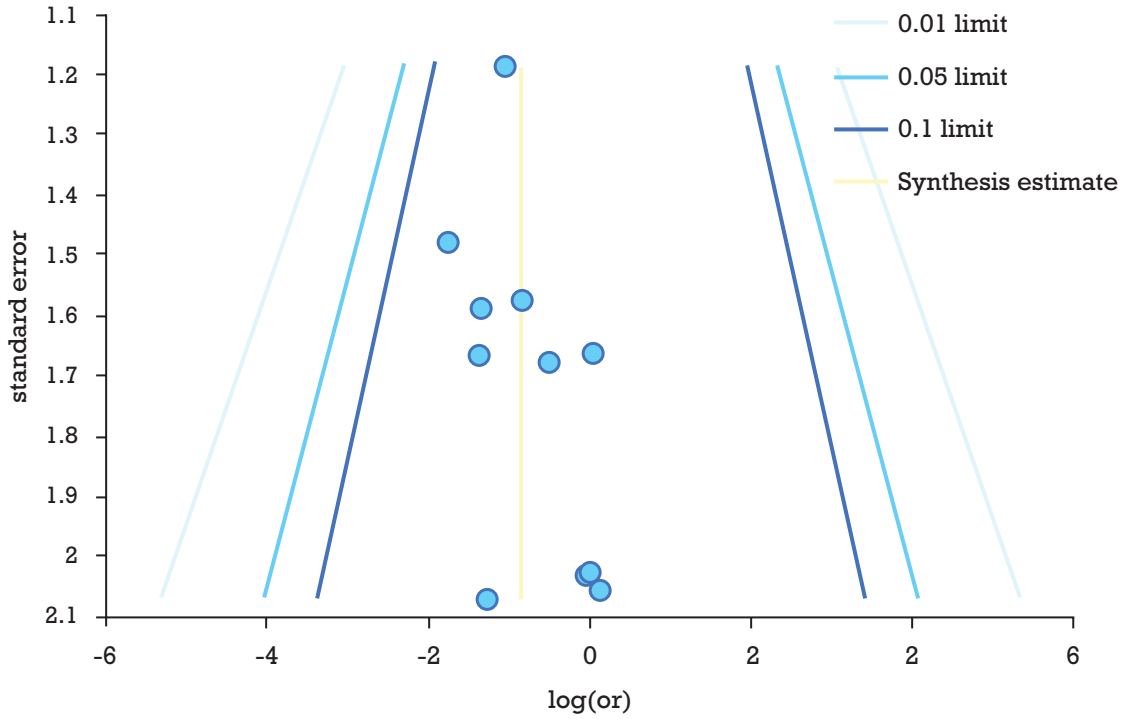


**Figure 2.** Funnel Plot. A symmetric representation or a funnel plotwith all studies (blue dots) remaining within the demonstrated confidence intervals (blue lines).This indicates that smaller studies do not demonstrate a greater effect (i.e. less likelihood of publication bias).

observational studies, simply by virtue of practice variation between surgeons.This does not mean that studies cannot be summed to produce a meaningful result. Common practice methodology is variable, and therefore a meta-analysis can be the means for increasing external validity.

In order to assess statistical heterogeneity, two methods are generally employed: The Cochran's Q statistic, and the $I^2$ range. Cochran's Q attempts to detect if greater heterogeneity exists in the effect sizes than can be accounted for by sampling error. This statistic has been criticized because it has poor power to detect heterogeneity when a small number of trials are present, and too much power when a large number of trials are present.The $I^2$ range is somewhat more descriptive in the sense that it describes the range of possible heterogeneity by the confidence interval. This confidence interval can be interpreted as the range of potential heterogeneity. It is acceptable to assume homogeneity if the $I^2$ range includes 0%. It is our practice, however, to assume heterogeneity to be conservative for the aforementioned rationale regarding surgical trials if the range is large (i.e. 0 to 50%).This increases the risk of a type II error, but decreases the rate of a type I error.

### *Fixed or Random Effects*

Selection of an appropriate model is very important in meta-analysis. Fixed effects models assume that all the variance in the data comes from variance within studies. As such, an underlying assumption of such models are that variance between studies is negligible. Selection of a fixed effects model implies that heterogeneity statistics have been performed and show minimal inter-study statistical heterogeneity. It also demonstrates that populations and methods between studies are of sufficient similarity that the assumption of negligible inter-study variability can be safely made.This model assumes that there is one true effect, and the studies all estimate this effect. All differences from this effect are then assumed to be the result of sampling error. In surgical trials, this may not be believable, because surgical techniques are difficult to standardize.

A random effects model on the other hand, assumes that the studies performed represent a random sampling of the effect size which varies and has a mean and a 95% confidence interval. The underlying assumption is that the effect sizes follow a normal distribution. A random effects model is more conservative in the setting of study heterogeneity. This is because a random effects model allows for inter-study variability. The nature of many orthopaedic studies is that there are differences in populations and methods because the vast majority of studies are observational. An argument can be made that the fixed effects assumption is always faulty in this setting. Additionally, in the setting of minimal inter-study variance, a random effects model will approach the results of a fixed effects model. In random effects models, standard errors are larger and confidence intervals wider than in fixed effects models, hence researchers are less likely to reject the null hypothesis.

Although using a random effects model helps to account for inter-study variability, the statistical test itself does not

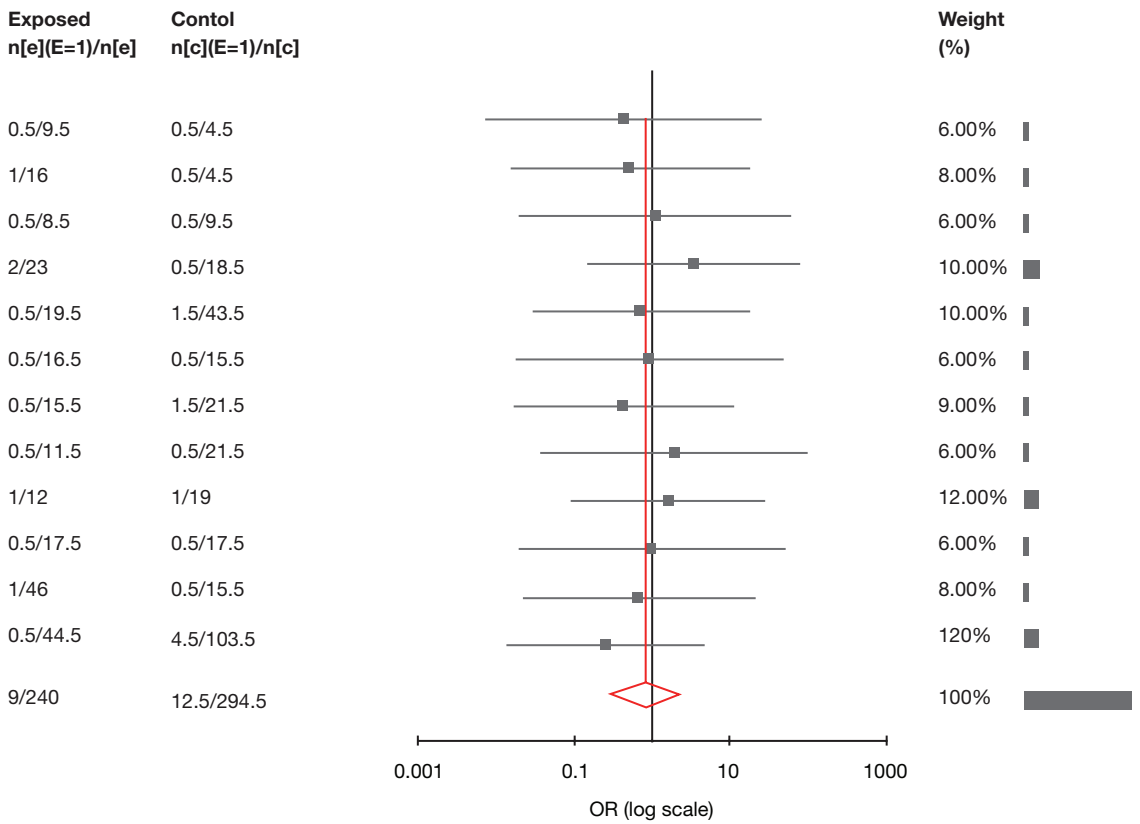


**Figure 3.** Forest Plot. A graphical representation of the distribution of effect sizes of the parent studies. The summary effect size is provided with confidence intervals is represented by the red diamond.

eliminate this heterogeneity. Rather, it adds variance to the summary effect proportional to variability. In other words, simply using a random effects model does not indicate that the statistical methods can in some way overcome the problem of heterogeneity. If the studies identified are clearly heterogeneous, a summary estimate should not be calculated.[7]

### *Summary Effect Sizes*

After a model has been chosen, summary effect sizes can be generated. The most common graphical representation for summary effect sizes is the forest plot, illustrating the distribution of effect sizes of the parent studies (individual squares with horizontal bars to correspond to each study).A summary effect size is provided (vertical line) with confidence intervals (diamond at the bottom of the vertical line). The midline represents an odds ratio of 1 or "no difference" (Figure 3). Consideration for "zero-event" studies is given by adding 0.5 to each cell. This provides for an addition of 0.5/0.5 to each ratio or 1 (so nothing is added, but an odds ratio can be calculated), thus allowing for usage of zero-event studies and making the model more robust by increasing the n of available studies.[8]

## Conclusion

Conducting a systematic review and incorporating meta-analytic statistical techniques takes a great deal of planning, cooperation among team members, time, and sincere effort to conduct a thorough analysis of all available empirical evidence. Adherence to guidelines and strict reporting of search methodology are essential. Most importantly, it is essential to remember that the quality of a systematic review and/or meta-analysis cannot exceed the quality of the individual studies included in the analysis.

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# Practitioner Bias in the Interpretation of the Effects of Resident Work Hour Restrictions

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## Background

In 2003, the Accreditation Council for Graduate Medical Education (ACGME) placed restrictions on the number and frequency of resident work hours.[1] The regulations were rooted in the 2001 New York State mandate that resulted from of the death of Libby Zion.[2,3,4] There is currently a large and growing body of literature which underscores the benefits and shortfalls of reduced resident work-hours on patient safety, resident morale, quality of life, education and operative experience.[2,5-18]

Previously, we have performed a systematic review of the literature, and a cost analysis to assess the early effects of this mandate on patient safety as measured by mortality, provider errors and patient complications.[19,20] The assessment of the effectiveness of work hour rules (WHR) is impaired by the occurrence of the effects of WHR subsequent to enactment of the rule.[19] We hypothesized that when presented with the data from a meta-analysis[19] without the benefit of a discussion or conclusion regarding the results, the interpretation of the study information would be different between practitioners from different specialties. We additionally hypothesized that attending physicians trained in internal medicine would interpret the data more in favor of WHR, compared to surgeons (orthopaedic and general).We also hypothesized that physicians trained before WHR would interpret the data less favorably in regards to WHR. Lastly, we hypothesized that physicians with a favorable or unfavorable view of WHR would interpret the data in line with their bias.

## Methods

Institutional review board exemption was obtained, and power analysis determined that 168 responses would be needed to detect a medium sized difference. Assuming a response rate of 25%, we needed to sample 672 academic physicians to achieve our desired power.[21] The survey included 10 questions and was delivered via email weblink to 700 academic physicians (526 medical, 123 surgical, 51 orthopaedic) within our tertiary level academic medical center. Data was collected over a two month period, with a response rate of 30.5%. 66.5% of respondents (133/188) graduated residency prior to inception of the 80 hour work week, while the remaining 33.5% (55/188) had at least one year of exposure to the WHR as a resident. Overall, our survey had 188 total respondents, 95.7% filled out a full survey.

The major results our systematic review and meta-analysis of the available literature regarding WHR were paraphrased and presented to the survey takers.[19] Questions were constructed around each major result of the study and survey takers were asked to draw from a list of conclusions regarding each data point. Descriptive statistics were generated, and statistical analysis consisted of Kruskal Wallis, Mann-Whitney U, Pearson's chi square, Fisher's exact tests where appropriate. Binary logistic regression was used to adjust odds of answering dichotomous questions for multiple variables. All statistics were calculated using SPSS version 16.0 (SPSS Inc. Chicago, IL).

## Results

### *Personal Views of Study Group*

Overall, 101 total respondents were "somewhat strongly" or "strongly" in favor of the WHR as set by the ACGME (53.7%). 58.6% of internal medicine trained physicians agreed with the ACGME rules as written, compared to 41.8% of surgeons (p value 0.002). 87.2% of all physicians surveyed felt that some level of restriction of work hours was warranted. This included 91.7% of internal medicine physicians and 76.4% of surgeons (p value 0.008).

### *Interpretation of systematic review data by personal bias regarding WHR as defined by ACGME*

Only 30.4% of respondents who disagreed with the ACGME rules as written felt they improved patient mortality based on the data from the systematic review, compared to 58.2% of respondents who agreed with the ACGME rules (p value 0.012). In terms of medical errors/ surgical complications, 16.5% of those who did not agree with the ACGME definition of WHR

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felt the results of the systematic review showed a decrease in errors/complications compared to 35.7% of those who agreed (p value 0.004). Only 10.1% of respondents who did not agree with the ACGME felt the data in the review warranted continuation of WHR compared to 35.7% who agreed (p value <0.001). Only 7.6% of respondents who did not agree with the ACGME rules felt that WHR were at least somewhat responsible for the decrease in observed mortality, compared to 22.4% of those who agreed (p value 0.007).

### *Multiple Regression Analysis*

Binary logistic regression was used to determine if the answers to questions related to interpretation of data on the 80 hour work rule was conditional on discipline (medicine or surgery), date of graduation (before or after WHR inception) or pre-test attitude toward the ACGME work rule (support or disagree). We found that after adjustment, individuals with a positive attitude toward the WHR as defined by the ACGME were 3.1 times more likely (1.5, 6.4) to agree that the WHR were responsible for decreasing mortality based on the data presented compared to those who disagreed (p value 0.002). Similarly, physicians with a positive attitude towards the ACGME WHR were 3.4 times (1.2, 10.0) more likely to feel that the effects were symmetric across disciplines, 5.0 times more likely (2.1, 12.1) to feel that the data showed a decrease in medical errors/surgical complications, and 7.0 times more likely (2.8, 17.3) to feel that the data supported continuation of the WHR compared to those who did not hold a favorable view. Neither specialty nor personal exposure to WHR was a significant predictive factor after adjustment for multiple variables.

## Discussion

Though prior studies have analyzed the influence of ACGME imposed WHR on patient outcomes, resident performance, education, and quality of life, this is the first investigation to determine variables that influence a physician's interpretation of this data. We demonstrate that a respondent's interpretation of data from a systematic review of mortality and medical errors pre- and post-WHR is most influenced by his/her pre-test attitude regarding WHR. Contrary to our hypotheses, personal exposure to WHR and medical or surgical specialty were not significantly related to attitudes toward the 80-hour work week.

We confirm that bias regarding WHR influences a respondent's interpretation of the data presented. As a result, when committees are created to investigate and discuss additions or revisions to the current WHR, we suggest a group that is equally represented in terms of medical specialty and baseline perceptions. Perhaps prior to creating a taskforce or committee on WHR, leaders should survey possible members regarding their perceptions of WHR in order to create a group that is diverse in both demographics and opinions. Our survey can be validated on a subsequent population then potentially used for this purpose.

Few studies have specifically investigated perceptions of WHR amongst practitioners of specific specialties. Nuthalapaty *et al* evaluated the perceived impact of duty hour restrictions on the residency environment in a series of obstetrics and gynecology program directors and found that opposition to duty hour regulations and a preference for higher limits was associated with a higher prevalence of negative impressions regarding duty hour regulations.[22] Dozois *et al* evaluated the perceived impact of WHR at a single-institution among nine surgical subspecialties and found that 15% of attending surgeons, 30% of residents who trained before WHR, and 67% of residents who trained after WHR believed patients were safer since the implementation of WHR.[23] Schlueter *et al* attempted to identify discrepancies of WHR interpretation within and between specialties, and determined that there was disagreement among program directors of different specialties on the interpretation of WHR.[24] It is likely that the baseline perceptions of physicians regarding WHR result from a conglomeration of variables of which baseline perception may be most significant.

Although only a little over half of physicians agreed with WHR as written, close to 90% agreed that some level of WHR is warranted. Despite this, only a very small minority believed that the effects of WHR were symmetric across disciplines. In fact, many more (almost 43%) respondents felt WHR should be changed to reflect the various needs of differing disciplines than felt that they should not (13%). For example, Yaghoubian *et al* sought to compare the outcomes of trauma surgery performed by surgical residents during daytime and evening hours versus those performed by residents working beyond 16 hours.[25] The authors determined that trauma surgery performed at night by residents who have worked longer than 16 hours have similar favorable outcomes compared with those performed during the day, and that instituting a 5-hour rest period at night is unlikely to improve outcomes of these commonly performed operations. In contrast, Gohar *et al* investigated internal medicine residents and concluded that a month of call rotations reduced overall sleep per night and working memory capacity was adversely affected.[26] As indicated by many of the respondents of our survey and by the variability in the literature, perhaps medical disciplines require different levels and types of WHR.

Our sample contained a nearly 3:1 medicine to surgery ratio, improving the external validity of our findings in keeping with the recommendations of the ACGME data resource book for primary medicine specialties, and primary surgery specialties.[27] Second, our response rate of 33% is comparable to recent studies which used an email or web-based strategy that showed an average response rate of 31%.[21] However, since this is the first study of its type attempting to assess physician bias in the interpretation of data related to the ACGME WHR, our instrument could not be validated prior to its administration. As such, this study could be considered a pilot of this instrument.

We believe that this study raises interesting dilemmas when interpreting the medical literature as it is presented in our journals. The chosen journal of publication, audience of the journal, reviewer and editor bias, and author bias all dictate the way in which objective medical data is received, interpreted,

and disseminated. Perhaps understanding this interplay is as critical in obtaining and deciphering data from a study as the implementation and design of the study itself. As such, we urge restraint and consultation with this or any other contentious issue, as the best education of our future physicians and the best care of our patients cannot be left to chance.

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# Mentorship in Orthopaedics

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## Introduction

In Greek mythology, Mentor was a trusted friend and servant of King Odysseus of Ithaca, who was entrusted with the care of his son Telemachus when the king departed for the Trojan War. In the king's absence over twenty years, Mentor nurtured and protected Telemachus, imparting upon him a varied range of leadership skills. This name continues to be passed down over time and generations. Dictionaries define a mentor as a friend, confidante, trusted guide, wise counselor and advisor. It's a unique relationship between a protégé (mentee) and a more experienced, accomplished, and wiser senior colleague. A mentor is more than just a teacher, for he or she upholds many challenging roles as a philosopher, guardian, role-model, protector, and/or disciplinarian as the need arises.

## Background

McLain observed orthopaedic mentors to be on an 'endangered species list' and that we are at risk of losing them in our professional environment.[1] Successful models of mentor-protégé relationships are abundant in the business world but are sparse in the orthopaedic community. Both the American Academy of Orthopaedic Surgery (AAOS) and American Orthopaedic Association (AOA) have identified mentorship to be an obligation, heritage, legacy, and a commitment with a continued need for nurturing.[2,3] More than 50% of newly appointed orthopaedic attendings (consultant orthopaedic surgeons) in Scotland felt mentorship to be very useful in boosting their clinical and managerial skills,[4] yet relatively little has been published in the literature to date regarding this important topic.

## Questions

- What are the stages involved in a mentor-protégé relationship?
- What makes one a successful mentor (i.e. skills needed to succeed as a mentor)?
- What are the barriers to successful mentorship?
- Are there advantages or benefits of mentoring?
- What does the published evidence say?
- What needs to be done to maintain this lineage or legacy of mentorship?

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## Discussion

Mendler outlined ten stages of evolution of effective mentoring processes (Table 1). A mentor possesses a diverse repertoire of skills and methods of communication offering feedback, encouragement, and guidance. He or she takes their junior colleague from the known to the unknown, showing the protégé unchartered seas while imparting wisdom and strategic thinking along the way. The AOA, AAOS, and at least eleven of the AAOS subspecialty societies offer ample opportunities for young residents and fellows to acquire these mentorship skills. The AAOS and Orthopaedic Trauma Association (OTA) have resident and fellow members on its board, and the Pediatric Orthopaedic Society of North America (POSNA) and Scoliosis Research Society (SRS) also have opportunities for fellows to serve on its committees.

## Conclusion

Mentorship is an active two-way process that promotes professional excellence. Residents who chose their own mentors reported higher personal satisfaction as compared to others who were assigned mentors and those who had none.[6] Strong mentorship ties and mentors as role models have been shown to influence the subspecialty training that residents opt to pursue.[7] However, mentorship is not for everyone, as it is an enormous responsibility presenting unique challenges. True mentors

**Table 1. Mendler's stages of mentoring**

| | |
|---|---|
| 1 | Attraction |
| 2 | Cliché exchange |
| 3 | Recounting |
| 4 | Personal disclosure |
| 5 | Bonding |
| 6 | Fear of infringement |
| 7 | Revisiting framework |
| 8 | Peak mentoring |
| 9 | Reciprocity |
| 10 | Closure |

have always been in short supply. Little time exists outside the operating rooms and patient wards for the formal teaching of management skills (business planning, negotiations, medico-legal work, and practice management) and academic skills (leadership of multi-disciplinary groups, acquisition of extra-mural funding sources). It is in these areas where a productive mentor-protégé relationship may maximize personal and professional achievement.

## Acknowledgements

The authors are grateful for their own mentoring and would like to dedicate this article to their mentors.

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U·P·O·J

# Nanotechnology: Translational Applications in Orthopaedic Surgery

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## Introduction

The infinite molecular interactions that take place in the human body occur on the scale of nanometers (nm), or one billionth of a meter.[1,2] Particles of less than 100nm have drastically different behavior versus larger particles with regard to melting point, conductivity, and reactivity.[3] Materials with nanoscopic grain size have altered chemical properties that may produce unique and advantageous surface characteristics.[4] Nanotechnology has developed into a multibillion dollar industry that has applications in dozens of fields, including science, electronics, cosmetics, and medicine. Basic science and translational research has revealed many important potential applications for nanotechnology in orthopaedic surgery. In this brief overview, we will discuss current concepts and future directions of nanotechnology in total joint arthroplasty, trauma surgery, orthopaedic oncology, musculoskeletal infection, and the treatment of peripheral nerve injuries.

## Nanotechnology and Bone

Bone synthesis takes place at the nanoscopic level through interactions between macromolecules that promote osteoblast function. When orthopaedic implants are introduced into the natural cell environment, interactions between the implant and extracellular proteins are critical for osteointegration. Extracellular adhesion proteins, such as fibronectin and vitronectin, mediate osteoblast activation and adhesion to biomaterials, resulting in osteointegration.[5,6] Unlike conventional implants, nanoscale surface topography mimics the topography of the natural cell environment allowing them to interact more effectively than conventional materials with extracellular adhesion proteins.[3] Adsorption of these molecules is significantly increased on nanosurfaces as compared to conventional surfaces.[4] Furthermore, nanostructured materials have been shown to inhibit the activity of cells that impede ingrowth and ongrowth, including smooth muscle cells, fibroblasts, and chondrocytes, resulting in improved osteointegration of implants.[7]

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## Orthopaedic Device Applications

The application of nanotextured materials may reduce the risk of implant failure through improved osteointegration.[4,8] As previously discussed, nanotextured surfaces enhance osteoblast function and decrease fibroblast function. This preferential cell activity results in increased bone formation on nanotextured hydroxyapatite coated surfaces when compared to similar materials with conventional roughness.[3,9,10] When nano-sized hydroxyapatite is added to morselized cancellous bone graft, *in vitro* acetabular cup integration and stability following impaction grafting is significantly enhanced.[11] Improved mechanical properties are also seen in bone cement reinforced with nanoclay filler material.[8] Some additional materials that display nanophase characteristics include nanoceramics, alumina, titania, carbon, selenium, nanometals Ti6AlV, cobalt chrome alloys, and nanocrystalline diamond.[4,7,9,10,12-18]

Nano-composite scaffold implants composed of Type I collagen and nanostructured hydroxyapatite are being used clinically in the treatment of osteochondral defects of the knee. This type of implant may provide an 'off the shelf' cell-free solution to chondral defect treatment that is easier and less morbid than autograft or stem cell procedures [10,19,20].

*In vitro* studies have shown promise for nanotechnologic applications in orthopaedic oncology. Selenium has been found to be a powerful potentiator of chemotherapeutic agents.[21] When manufactured on the nanometer scale and coated on titanium orthopaedic implants, nanophase selenium appears to inhibit malignant osteoblastic growth at the implant-tissue interface.[22] Similarly, nanophase hydroxyapatite causes *in vitro* inhibition and apoptosis of osteosarcoma cells.[23]

Advancements in nanotechnology have also shown potential for use in the prevention of infection. Nanophase silver dressings have proved to be more effective at preventing wound infections and stimulating wound healing than traditional silver-based dressings.[24,25] Nanophase silver incorporated onto the surface of titanium orthopaedic implants has demonstrated strong, immediate bactericidal and anti-adhesive effects lasting for up to 30 days.[26]

Nanophase materials have also had encouraging results when utilized for the treatment of peripheral nerve injury. Nanophase silver-impregnated Type I collagen scaffolds increase the amount of adsorbed proteins critical to nerve healing and lead to significant decreases in the time to nerve regeneration. In one study, the use of these scaffolds for the treatment of sciatic nerve defects in rabbits showed thicker myelin sheaths, improved nerve conduction, and higher rates of laminin adsorption when compared to control Type I collagen scaffolds.[27]

## Safety and Areas of Future Research

Critical unanswered questions remain regarding the safety of nanomaterials. The toxicity profiles of many nanomaterials are currently not known. Nanoparticles may be released over time through the degradation of implanted nanomaterial or may potentially enter the body through the dermal pores of individuals involved in their manufacture.[28] The metabolism of nanoparticles has been shown to involve various organ systems, including blood, liver, and kidneys, and may result in inflammation and oxidative stress.[29,30] Nanoparticle wear debris has uncertain local tissue effects,[9] and has been correlated with brain and lung toxicity in the in some studies.[9,31] In contrast, nanosize wear debris has been associated with increased cell viability in bone and lung when compared to conventional wear particles in other studies.[9] Due to the uncertainty regarding the safety of nanomaterials, studies evaluating the toxicity of nanophase materials must be conducted prior to the clinical application of these materials on a large scale.[32,33]

## Conclusion

The extensive basic research on nano-scale materials may yield beneficial orthopaedic surgical applications; however, relatively few clinical studies have been performed to confirm utility and safety of these agents. Though still in its infancy, nanotechnology has promising applications in arthroplasty, trauma, sports medicine, orthopaedic oncology, orthoplastic surgery, and many other facets of musculoskeletal medicine. The vast opportunities for advancement of nanotechnology and its applications within orthopaedic surgery present an exciting frontier in orthopaedic research.

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# Location-Specific Changes in Flexor Carpi Ulnaris Tendon Mechanical Properties in the Absence of Biglycan or Decorin

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## Introduction

The small leucine-rich proteogylcans (SLRPs) decorin and biglycan are known to impact tendon growth and healing, but their role in fully-developed tendon is still unclear. Previous studies in the Achilles tendon demonstrated that mechanical changes induced by the digestion of glycosaminoglycans (GAGs) found in SLRPs and other proteoglycans are localized at the insertion site.[1] Furthermore, levels of biglycan (but not decorin) are concentrated near the insertion of the supraspinatus tendon.[2] However, the spatial dependence of mechanical changes in SLRP-null tendons has not been investigated. Therefore, the objective of this study was to measure changes in the viscoelastic mechanical properties and location-dependent quasi-static mechanical properties of the flexor carpi ulnaris (FCU) tendon of the wrist in the absence of biglycan or decorin. We hypothesized that 1) mechanical properties would be unaltered by the absence of decorin; and 2) mechanical properties would be impaired by the absence of biglycan, but only near the insertion.

## Methods

C57BL/6 wild-type (WT, n=31), decorin transgenic null (*Dcn*−/−, n=11) and biglycan transgenic null (*Bgn*−/−, n=23) mice were sacrificed at 150 days post-natal with IACUC approval. FCU tendon-pisiform complexes were then dissected from a randomly chosen forelimb (right or left) of each mouse and tendon cross-sectional areas were measured using a laser-based device. After speckle-coating each tendon with Verhoeff's stain to facilitate optical strain measurement, specimens were tensile tested according to the following protocol: 1) preload, 2) preconditioning, 3) stress relaxation to 4% strain, 4) sinusoidal frequency sweep, 5) return to gauge length, and 6) ramp to failure at 0.1% strain/second. The frequency sweep consisted of 10 cycles of 0.125% amplitude sinusoidal strain at frequencies of 0.01, 0.1, 1, 5, and 10 Hz. The dynamic modulus |E*| (defined as the stress amplitude divided by the strain amplitude) and the tangent of the phase angle δ between the stress and strain (tanδ a measure of viscoelasticity) were computed for each frequency. Step 6 was tracked optically, and the toe modulus $E_{toe}$, linear modulus $E_{lin}$, and transition strain $\gamma_{trans}$ were determined at the insertion (0-1 mm from the bone), midsubstance (1-4 mm from the bone), and proximal (4-5 mm from the bone) regions. A one-way ANOVA with Bonferroni post-hoc analysis was used to assess the effects of genotype on |E*| and tanδ at each frequency and the effect of genotype on $E_{toe}$, $E_{lin}$, and $\gamma_{trans}$ at each location. Significance was set at $p \pm 0.05$ with corrections for multiple comparisons.

## Results

*Bgn*−/− tendons had a decreased |E*| compared to WT at all frequencies (Fig. 1a). The maximum stress $\sigma_{max}$ was decreased in *Bgn*−/− compared to both WT and *Dcn*−/− (Fig. 1b). *Bgn*−/− tendons also had a decreased $E_{toe}$ compared to WT in the proximal region and a decreased $E_{toe}$ and $E_{lin}$ compared to WT in the midsubstance (Fig. 1c-d). No differences were found between WT and *Dcn*−/− tendons, and no differences among genotypes were found in insertion site properties, tanδ, or $\gamma_{trans}$ (data not shown).

## Discussion

This is the first study to investigate local changes in the mechanical properties of tendons from decorin- and biglycan-null mice. As hypothesized, the absence of decorin did not impact tendon mechanics in the FCU tendon. However, the absence of biglycan unexpectedly led to mechanical changes in the midsubstance and proximal regions, but not in the insertion. While biglycan is known to play a role in regulating fibril growth in tendon and in interacting with collagen I, our results suggest that its role in establishing and maintaining a functional tendon may be region-specific.

The absence of mechanical changes in decorin-null tendons and the reduction of modulus and failure load in bigylcan-null tendons were consistent with results in the flexor digitorum longus (FDL) tendon.[3] Interestingly, SLRP-null FCU tendons did not exhibit changes in tanδ while SLRP-null FDL tendons did not exhibit changes in percent relaxation, an

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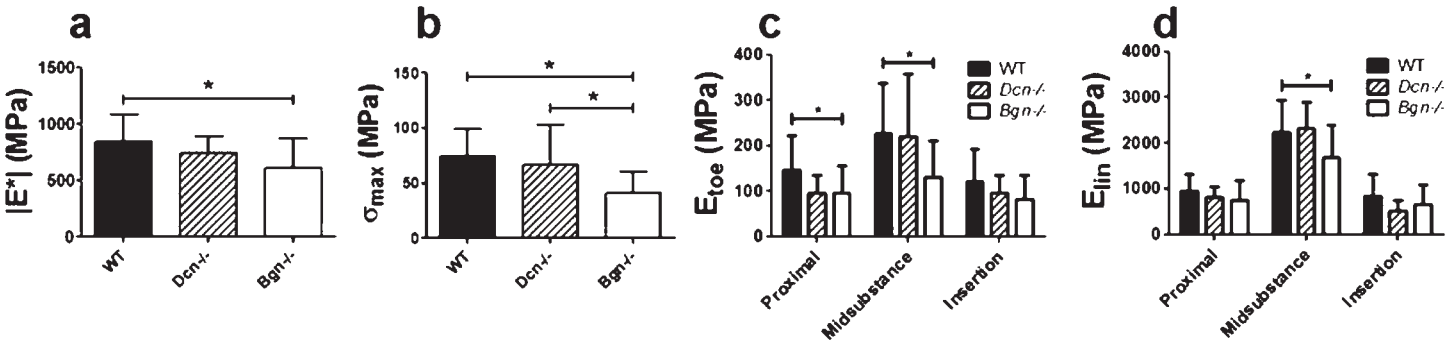


**Figure 1**. a) Dynamic modulus |E*|, b) maximum stress $\sigma_{max}$, c) region-dependent toe modulus $E_{toe}$, and d) region-dependent linear modulus $E_{lin}$ for WT, *Dcn−/−* and *Bgn−/−* FCU tendons. In general, mechanical properties were reduced in *Bgn−/−* tendons compared to WT, and changes were restricted to the proximal and midsubstance regions. In a), data is shown for 1 Hz, but results for other frequencies are similar. Mean±SD, (*) p≤0.05/3.

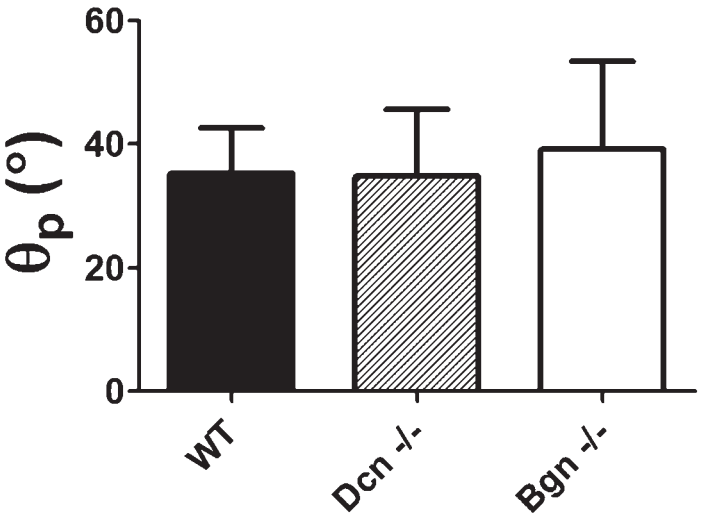


**Figure 2**. Principal angle $\theta_p$ measured from the direction of loading in FCU tendons. $\theta_p$ ranged from 35-39° across genotype groups, indicating a large degree of induced shear strain. Mean±SD.

alternative measure of viscoelasticity. Conversely, modulus and percent relaxation were both increased in decorin-null patellar tendons.[3] Although the FCU and FDL tendons come from distinct locations (i.e., the wrist and hindlimb), our data suggest that, in general, flexor tendons may respond similarly to the absence of both biglycan and decorin.

Given that tendon biglycan levels are typically higher close to the bone,[2] it is surprising that the mechanical properties of *Bgn−/−* FCU tendons were decreased only away from the insertion. These findings could be explained by the high aggrecan content present in the FCU-pisiform enthesis.[4] Since aggrecan is more than 50 times larger than biglycan, its well-established effects on tissue mechanics may dominate the potential impact of biglycan deficiency at the insertion. The presence of aggrecan at the FCU-pisiform insertion is thought to result from the uniquely high levels of shear and compression in this region.[4] Supporting this concept, in the current study, we determined that the principal axis angle $\theta_p$ (measured from the direction of loading) is 35-39° in the FCU tendon (Fig. 2), suggesting that this tendon is well-adapted to withstand shear strain. In contrast, a vertical (0°) principal angle is expected from a tendon undergoing purely tensile strain. Future studies will examine the spatially-varying levels of biglycan, decorin and aggrecan in FCU tendons in order to better understand the mechanisms responsible for the observed location-dependent mechanical alterations in the absence of biglycan.

## Significance

According to this study, SLRPs have a tendon- and location-specific effect on tendon function. Therapies designed to treat tendon damage and disease, which are often localized, must consider and account for these variations.

## Acknowledgements

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# Effects of Decorin and Biglycan on Re-Alignment and Mechanical Properties of Aging Supraspinatus Tendons

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## Introduction

Tendons exhibit complex mechanical behavior modulated by the tissue's structure and composition, such as the collagen fibers and surrounding matrix. Numerous studies have investigated the mechanical properties of tendons as they age, but results have been inconclusive. One mechanism by which tendon responds to load is by re-alignment of collagen fibers. The ability of tendon to respond in this manner varies throughout development,[1] but has not been studied during aging. In addition, it is unknown how proteoglycans (PGs) affect re-alignment in aged tendons. Therefore, the objective of this study is to measure the tensile mechanical properties and collagen fiber re-alignment of the mouse supraspinatus tendon throughout age and to investigate how this process is affected by the absence of key PGs. We hypothesize that: 1) tendons will get stiffer but will re-align later during the mechanical test as aging progresses and 2) both mechanical and re-alignment changes will be altered in PG-deficient mice.

## Methods

Sample Preparation: Supraspinatus (SST) tendons from 106 mice at three ages (90 day, 300 day, 570 day) and three genotypes (biglycan knockout (*Bgn*−/−), decorin knockout (*Dcn*−/−) and wild type (WT)) were isolated. Cross-sectional area was measured and stain lines were placed to denote the tendon insertion and midsubstance. The humerus was fixed in a pot and the tendon was secured in grips.

Mechanical Testing: Samples were loaded in a testing system integrated with a polarized light setup.[2] Tendons were tested in tension as follows: preload, 10 cycles of preconditioning, return to zero displacement, stress relaxation, followed by a 60 second hold and ramp to failure. Images were obtained for strain analysis and image sets were acquired as the polarizers rotated for measurement of fiber alignment during loading.[2]

Data Analysis: Local strain was measured optically. Circular variance (VAR), a measure of the distribution of collagen fiber alignment, was calculated for fiber distributions before preconditioning, after preconditioning, at transition strain (intersection of the toe- and linear-regions, determined using a structural fiber recruitment model at 50% fiber recruitment[3]), and at linear-region strain (at 75% fiber recruitment). Fiber re-alignment during preconditioning was evaluated by comparing VAR values before and after preconditioning. Similarly, fiber re-alignment in the toe- and linear-regions of the stress-strain curve was determined.

Statistical Analysis: Comparisons were made across age and genotype using ANOVA. If significant, post-hoc t-tests with Bonferroni corrections were used. Wilcoxon signed-rank tests were used for the non-normally distributed VAR data. Alignment data is presented as representative samples and mechanics data is presented as mean+SD (*Sig = $p<0.025$).

## Result

In WT tendons, stress relaxation was decreased at 300d and 570d compared to the 90d tendons and maximum load was increased from 90d to 300d (not shown). No other mechanical property changes were found in the WT tendons. However, significant changes in re-alignment were found (Fig. 1). At the insertion site, the 90d tendons re-aligned during the preconditioning and linear regions, while the 300d and 570d only re-aligned during the linear region. At the midsubstance, the 90d tendons re-aligned during the preconditioning and linear regions, while the 300d tendons re-aligned only during the linear region and the 570d tendons showed no significant re-alignment throughout the test.

In contrast, mechanical changes were found in the *Dcn*−/− and *Bgn*−/− tendons. Specifically, the *Bgn*−/− tendons at 90d and 570d had a lower modulus and stiffness at the insertion site than the 300d tendons (Fig. 2), while the *Dcn*−/− tendons had an increased insertion site modulus at 300d and 570d compared to 90d. In addition, the *Dcn*−/− tendons had a decreased stress relaxation at 300d and 570d compared to

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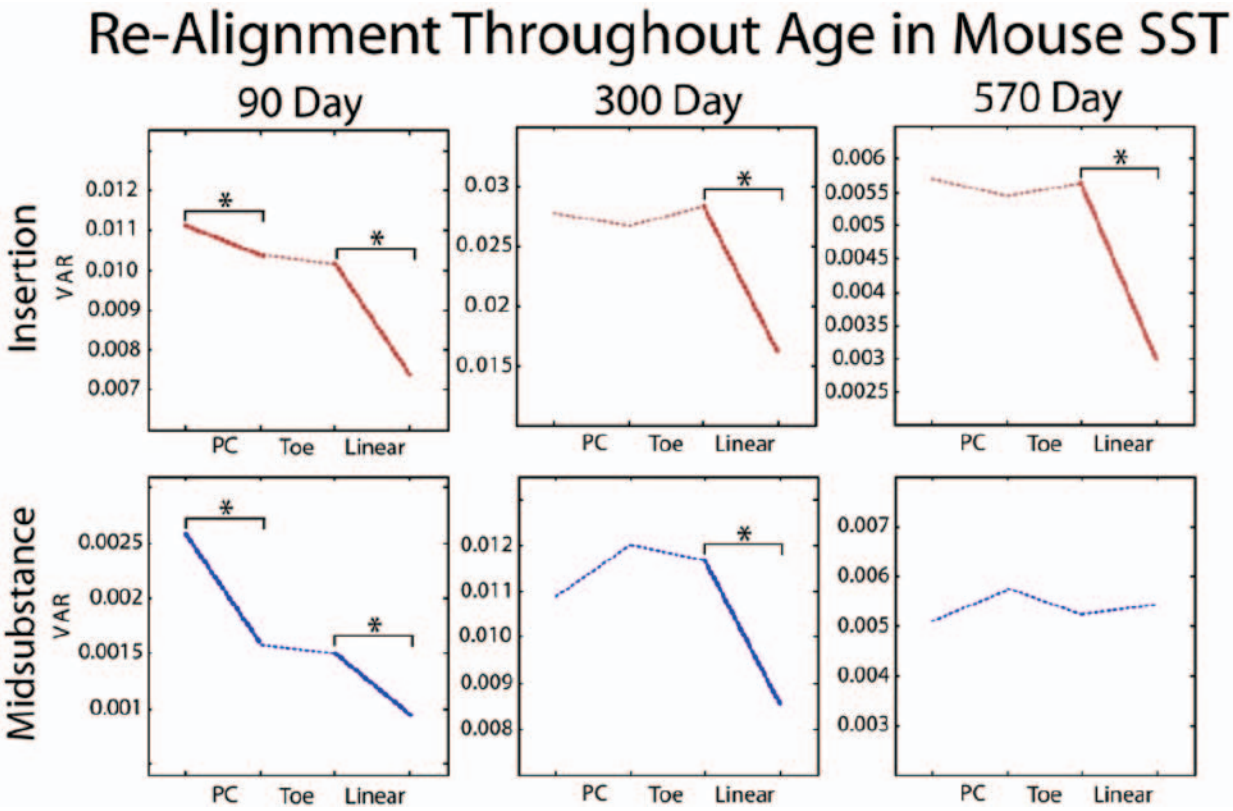


**Figure 1**. Re-alignment occurred during the preconditioning (PC) and linear regions in both locations of the wild type tendons at 90d (left). At 300d (middle), re-alignment occurred during the linear region in both locations. At 570d (right), the insertion re-aligned in the linear region but no significant re-alignment occurred in the midsubstance.

the 90d tendons (not shown). At the insertion of the *Bgn−/−* tendons, re-alignment occurred during the preconditioning and linear regions at 90d, while re-alignment only occurred during the linear regions at 300d and 570d (similar to the WT insertion). However, at the midsubstance of the *Bgn−/−* tendons, re-alignment occurred only during the linear region at all ages. In the *Dcn−/−* tendons, the midsubstance re-aligned in the same fashion as the WT insertion and the *Bgn−/−* insertion, but the insertion site re-aligned only during the linear region at all ages.

## Discussion

While previous studies have reported broad changes in mechanical properties of WT tendons with age, this study did not support those findings. However, changes in re-alignment in the WT tendons did show a decreased response to load with age. Tendons at 300d and 570d do not re-align their collagen fibers until the linear region, a later response than 90d tendons. This result, seen well in the WT tendon midsubstance (Fig. 1), is indicative of a breakdown of the structural organization of tendon over time and mirrors the response of tendon during development.[1]

The PG-deficient tendons showed altered mechanical properties with age, predominantly at the insertion site (Fig. 2). However, changes in re-alignment throughout age were not found in the midsubstance of the *Bgn−/−* tendons or at the insertion of the *Dcn−/−* tendons. While a diminished capacity at those locations is present when comparing the knockout tendons to the WT 90d tendons, this capacity does not degrade further after 90d. This suggests that decorin and biglycan may play a role in the aging process in this tendon and that the lack of these PGs may shield the tendon from deteriorating effects. Although changes in mechanical properties with removal of

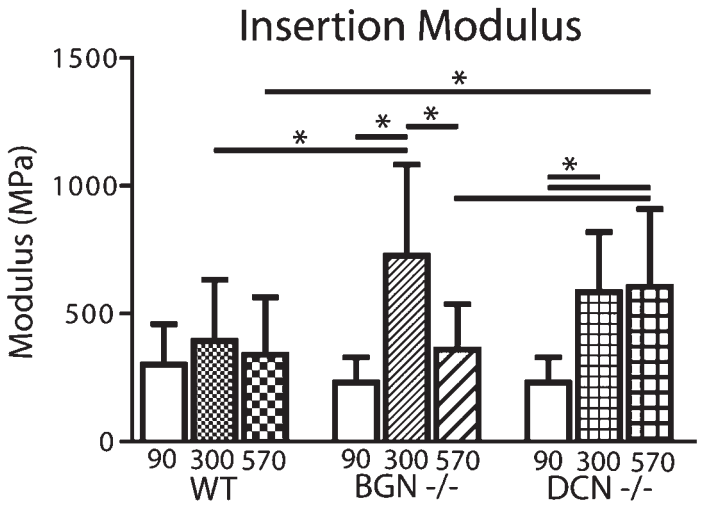


**Figure 2.** Changes were found in the insertion modulus of the PG-knockout tendons, but not in WT, with age.

PG and glycosaminoglycans have been debated,[4] this study shows that decorin and biglycan contribute to tendon's response to load, in particular with re-alignment of collagen fibers. Finally, changes in mechanical properties did not occur in concert with changes in collagen fiber re-alignment, suggesting that typical mechanical property measurements alone are insufficient to describe how structural alterations affect tendon's response to load.

## Significance

Collagen fiber re-alignment and mechanical properties are altered with aging in the mouse supraspinatus tendon, and proteoglycans play an important role in regulating this process.

## Acknowledgements

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# Dynamic Mechanical Properties of Tendon Repair Tissue are Unaffected by Aging

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## Introduction

Tendon injuries are common, especially in the aging population,[1] and incomplete tendon healing is a well-established problem. Furthermore, aging tendons are at increased risk for injury due to changes in their mechanical properties and structural integrity.[2] Age has also been correlated with poorer clinical outcomes for repaired tendons,[3] which may be attributed to an inferior repair response. While a previous study investigating aging and healing in rabbit patellar tendons found no age-related mechanical alterations in uninjured or injured specimens,[4] this study evaluated only quasi-static mechanical parameters. We have recently demonstrated that dynamic properties are more sensitive to changes due to damage from both aging and injury.[5,6] Therefore, the objective of this study was to determine the effect of aging on dynamic properties in the healing patellar tendon in a murine model. We hypothesized that 1) tendons of aged mice will exhibit declining mechanical properties compared to mature mice, and 2) with more advanced age, the healing response will be inferior, leading to decreased mechanical properties in injured tendons.

## Methods

Healthy C57BL/6 wild-type mice were sacrificed at 150 (mature), 300 (aged), or 570 (extremely aged) days old (n=14-17 per group). Patellar tendons of additional animals were injured bilaterally (n=11-19 per group) as described.[7] Animal use was IACUC approved. Briefly, a skin incision was followed by longitudinal cuts adjacent to the tendon, under which a rubber-coated backing was passed. This provided support against a 0.75 mm diameter biopsy punch, used to create a full thickness, partial width (~60%) tendon transection. Skin incisions were sutured and mice were allowed cage activity. Injured animals were sacrificed 6 weeks post-operatively. Patellar tendons were subjected to biomechanical testing or RT-qPCR analysis.

For mechanical testing, a single hind limb from each animal was dissected to isolate the tibia-patellar tendon-patella complex. The tendon was stamped into a "dogbone" shape to isolate the repair portion of the tendon. Tendon cross-sectional area was measured with a laser device and the tibia was potted and loaded in an Instron, submerged in a 37°C PBS bath, and tested as follows: 1) preload, 2) preconditioning, 3) stress-relaxation and sinusoidal frequency sweeps at 4%, 6%, and 8% strains, 4) return to gauge length and 5) ramp to failure (0.1%/s). Each frequency sweep was comprised of ten sinusoidal cycles with amplitude of 0.125% at 0.01, 0.1, 1, 5 and 10 Hz. The dynamic modulus $|E^*|$ (the ratio of stress amplitude to strain amplitude) and the tangent of the phase angle $\tan\delta$ (a measure of viscoelasticity equal to the ratio of dissipated to stored energy) were computed at each strain level and frequency. Two way ANOVAs with Bonferroni analyses were performed across frequency and age at each strain level to compare the uninjured and injured states. Significance was set at $p \leq 0.05$ with corrections for multiple comparisons.

For RT-qPCR, total RNA was extracted from patellar tendons of contralateral limbs (n=6-12/group) to assess expression of small leucine-rich proteoglycans (SLRPs) decorin (Dcn), biglycan (Bgn), fibromodulin (Fmod), and lumican (Lum) relative to β-actin. Two way ANOVAs with Bonferroni analyses were performed across age and injury state. Significance was set at $p \leq 0.05$ and a trend was defined as $p \leq 0.1$ with corrections for multiple comparisons.

## Results

At 4% strain level, $|E^*|$ of the patellar tendon decreased significantly between P150 to P300 and again between P300 to P570 (Fig. 1a) at all frequencies. $\tan\delta$ increased significantly between P150 to P300 and again between P300 to P570 (Fig. 1b). Results were similar for 6% and 8% strains (data not shown). These alterations were consistent with our hypotheses and suggest a decline in tendon functionality and ability to transfer force throughout aging. Contrary to our hypothesis, healing tendons exhibited no differences in either $|E^*|$ (Fig. 2a)

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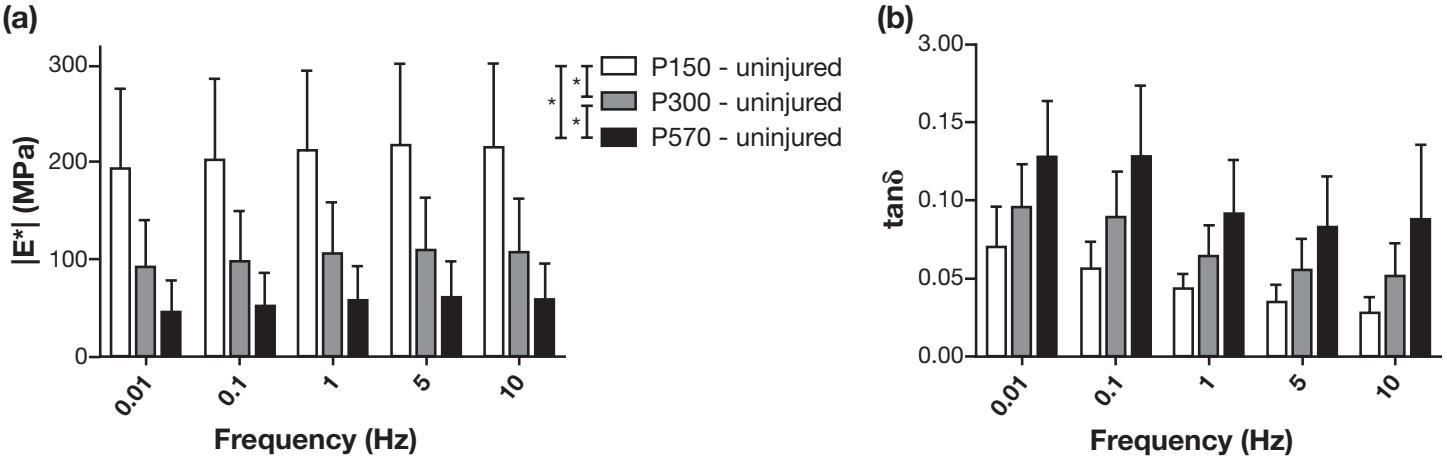


**Figure 1.** a) |E*| was significantly decreased in uninjured tendons with age while b) tanδ was significantly increased. * shown in legend denotes p≤.05/2 at each frequency for both |E*| and tanδ.

or tanδ (Fig. 2b) with age. Expression of Dcn had a decreasing trend at all ages post-injury, and Bgn expression significantly decreased after injury at 120 and 540 days. Expression of Fmod and Lum was maintained.

## Discussion

Contrary to our hypothesis, this study demonstrates that despite age-related differences in uninjured tendons, there are no significant differences in injured tendon tissue after 6 weeks of healing across age groups. Interestingly, the values of the tested parameters in the injured tendons are roughly equal to those in the aged (P570) uninjured group, suggesting that the post-operative repair tissue at any age is approximately as damaged as a normal tendon of advanced age.

Post-injury levels of SLRPs decorin and biglycan had a decreasing trend compared to uninjured; expression of these SLRPs is essential to tendon development. Reduced levels of these SLRPs could impact repair and affect biomechanical outcomes.

Our results are consistent with literature examining the repair response in tendon as a function of age,[4,8,9] and further supports the notion that tendon healing is not fundamentally age-dependent. In this study, the injured central portion of the tendon was isolated from the lateral and medial struts by stamping. In vivo, this injured region is flanked by these uninjured struts. The properties of the uninjured struts likely influence the loading environment of the injured portion. Thus, in an aged tendon, the injured portion is flanked by inferior tissue, bears a greater portion of the load, and is therefore at an increased risk of reinjury.

This study provides significant insight into the effect of aging as well as into the repair response to injury at any age, and is instructive to both basic science efforts and to clinical care. Future work will investigate an earlier time point after the injury as well as the roles of molecular constituents in an attempt to understand the mechanisms governing the findings presented here.

## Significance

This study demonstrates that tendon's repair response to injury does not deteriorate with age. Rather, inferior tendon healing in the aging population may be due to the quality of the tendon as a whole rather than due to its repair potential.

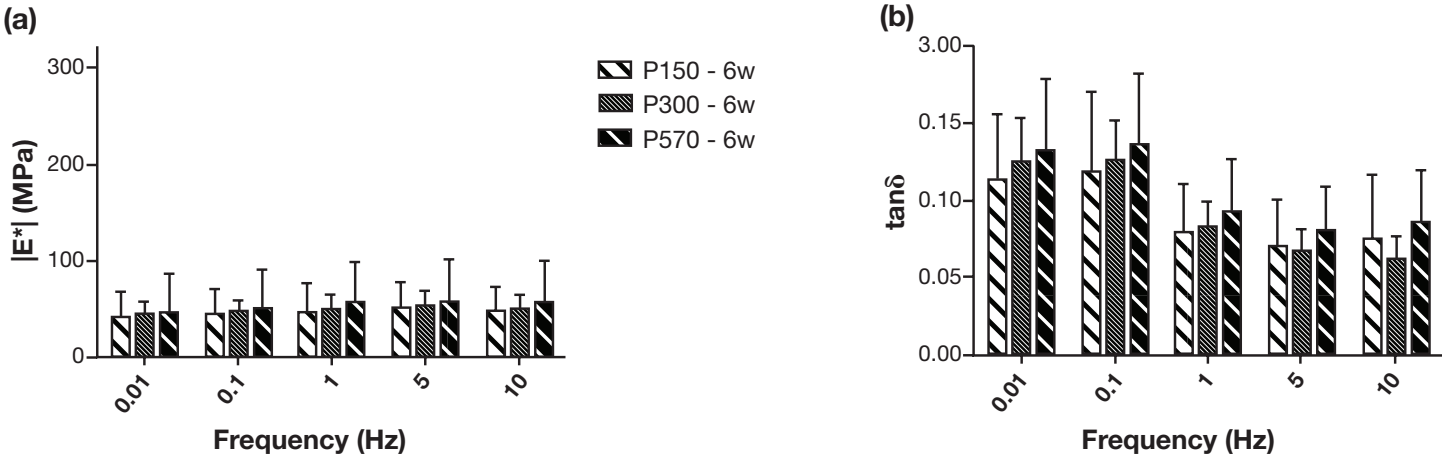


**Figure 2.** Neither a) |E*| nor b) tanδ of injured tendons differed with age.

## Acknowledgements

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# Injured Achilles Tendon Exhibits Inferior Mechanical and Structural Response During Fatigue Loading

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## Introduction

Achilles tendon ruptures occur frequently and result in significant pain and disability with extensive recovery time.[1] Since the Achilles tendon experiences repetitive loads at or near failure during normal activity,[2] knowledge of tendon fatigue properties is critical for determining when patients may resume normal activity. Several studies have suggested the benefits of fatigue testing over traditional failure tests, such as the ability to detect subfailure damage accumulation and changes in structure with repetitive loading.[3] Specifically, during fatigue loading, tissue stiffness initially increases and then gradually decreases as sub-rupture damage accumulates, followed by a dramatic increase in peak deformation prior to failure.[4] While it is generally believed that injury affects the mechanical and structural response of tendon during fatigue loading, this relation has not yet been fully established. Therefore, the objective of this study was to examine the mechanical and structural properties of mouse Achilles tendon during fatigue loading following an acute injury. We hypothesized that an acute injury would dramatically decrease tendon mechanical and structural fatigue properties.

## Methods

Twenty four tendons from twelve C57BL/6 mice at 120 days of age were used (IACUC approved). Six P120 mice were immediately euthanized and received bilateral excisional injuries in the mid-substance of the Achilles tendon using a 0.5 mm diameter biopsy punch (~50% of the width).The remaining six P120 mice were used as controls. Following tissue harvest, surrounding musculature was removed and the bone-tendon unit was prepared for mechanical testing. Cross-sectional area was measured using a laser device.[5] Tendons were fatigue tested and imaged with an integrated polarized light system which consisted of a backlight, 90° offset rotating polarizer sheets on both sides of the test sample, and a digital camera.[6] Specimens were fatigue loaded between 1 and 3.8N at 1Hz using a sinusoidal waveform, with the maximum load corresponding to 75% of the monotonic failure strength.[7] During loading, force and displacement data were acquired at 100 Hz. Sets of alignment images were captured at 0.5 and 1.0 N after preconditioning, 10 cycles of fatigue loading, and on intervals of 100 fatigue loading cycles until failure.

Peak cyclic strain, tangent stiffness, hysteresis, and cycles to failure were computed from mechanical data.To quantify collagen alignment, the birefringent signal phase and magnitude were determined from alignment image series and used to determine the circular standard deviation[6] (CSD) and the signal's peak-to-mean and peak-to-peak intensity. All parameters were analyzed at time points proportional to the fatigue life of the specimen (5%, 50%, 95% of fatigue life) as well as for comparisons in the first 200 cycles of loading (1, 10, 100, and 200 cycles). T-tests compared parameters between injured and control tendons.

## Results

In all tests, peak cyclic strain followed the three phase pattern typically reported in fatigue testing literature.[3,4] As hypothesized, injury caused a dramatic change in both mechanical and structural fatigue properties. Specifically, following injury, the number of cycles to failure decreased dramatically (CTRL: 3759±2578 cycles; INJ: 301±360 cycles (12.5-fold), $p<0.001$), stiffness decreased (at 5%, 50% and 95% of fatigue life, Figure 1A, Table1), and hysteresis increased (at 5%, and 50% of fatigue life). Peak strain was not different at 5%, 50% or 95% of fatigue life. In terms of tissue birefringence, injured tendon had increased CSD at both loads (initially and at 5% ($p=0.05$), with trends at 50% ($p=0.06$) and 95% ($p=0.07$) of fatigue life), and decreased peak-to-peak intensity (at 5% ($p=0.03$), 50% ($p=0.04$) and 95% ($p=0.003$) of fatigue life). Results through the first 200 cycles were similar, indicating that differences between groups can be detected early with fatigue loading (Figure 1B).

## Discussion

This study provides evidence for inferior mechanical and structural fatigue properties following injury in the Achilles tendon. Although injured tissues were ~70% of the normal tendon stiffness, specimen failure occurred at ~8% of the

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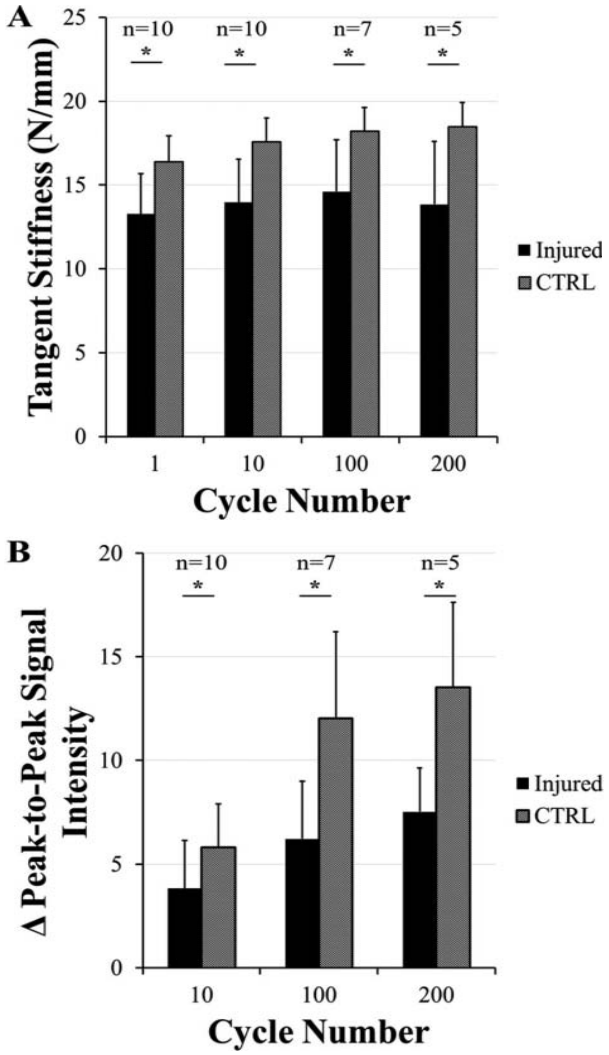


**Figure 1. (A)** Tangent stiffness was significantly lower in injured tissues compared to control ($p<0.01$). **(B)** Peak-to-peak intensity signal for collagen alignment was not different between groups prior to fatigue loading, but increased relative to the first map at 0.5N, by cycles 10 ($p=0.05$) 100 ($p=0.006$) and 200 ($p=0.008$) of fatigue loading. Similar results existed for alignment maps at 1.0N (not shown). These results, together with CSD, indicate that an injured tissue has inferior fatigue properties and alignment initially, and that these changes progress rapidly with induction of fatigue loading. *Indicates $p<0.05$. "n" in figure indicates the number of Achilles tendons in each injured group at each cycle number and n=6 for the control group (8 tendons total lost during preparation).

normal fatigue life, suggesting the importance of measuring fatigue properties to assess the mechanical integrity of tissues that experience cyclical loading near their failure strength. Altered structural changes were consistent with studies using other imaging methods,[8,9] but the tissue response near failure had not previously been reported. Current work is investigating the role of healing at 1, 3, and 6 weeks post injury and the effect of different genotypes on the mechanical and structural response of tendon to fatigue loading. Future work to investigate peak-to-peak intensity and CSD regionally may provide evidence of local changes in tissue structure due to injury and in response to loading.

## Significance

Injury to the Achilles tendon resulted in a dramatic decrease in the number of cycles to failure. Significant changes in mechanical and structural properties of the Achilles tendon became larger in response to fatigue loading. Knowledge of these changes in response to loading is critical to best determine when it may be safe for patients recovering from an Achilles tendon rupture to return to normal activity.

## Acknowledgements

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**Table 1. Mechanical parameters throughout fatigue life. Although the mechanical properties for control and injured specimens vary throughout fatigue life, their respective values differ significantly for tangent stiffness and hysteresis.**

| | | % Fatigue Life | | |
|---|---|---|---|---|
| **Parameter** | **Group** | **5%** | **50%** | **95%** |
| Peak Strain | INJ CTRL | 0.20±0.06 | 0.22±0.07 | 0.24±0.08 |
| (mm/mm) | p-value | 0.11±0.04 | 0.21±0.05 | 0.23±0.04 |
| | | 0.4 | 0.5 | 0.4 |
| Tangent Stiffness | INJ CTRL | 13.1±3.2 | 13.7±2.9 | 12.3±2.7 |
| (N/mm) | p-value | 18.3±1.4 | 18.3±1.4 | 16.7±1.6 |
| | | *0.001 | *0.001 | *0.002 |
| Hysgteresis | INJ CTRL | 1.01±0.65 | 0.80±0.37 | 1.65±1.81 |
| (N*mm/mm) × 100% | p-value | 0.44±0.06 | 0.41±0.05 | 0.74±0.64 |
| | | *0.03 | *0.007 | 0.1 |

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# Achilles Tendon Repair Response to Injury is Enhanced by the Absence of Decorin

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## Introduction

Achilles tendon ruptures are a common problem preventing athletic participation and daily life activities, often requiring surgical repair and extensive rehabilitation. In rabbit Achilles tenocytes *in vitro*, down-regulation of the proteoglycan decorin suppressed the expression of TGF-β1, a growth factor associated with fibrotic scar.[1] Similarly, in the medial collateral ligament *in vivo*, down-regulation of decorin improved healing.[2] Conversely, in mouse patellar tendon, the absence of decorin reduced uninjured tendon mechanical properties and had no effect on healing tendons 6 weeks after injury.[3] The effects of reduced decorin appear dependent on the site investigated[4] and its effect on Achilles tendon in particular is unknown. Since decorin plays a key role in collagen fibrillogenesis, inhibition of decorin would be expected to alter Achilles tendon properties. Therefore, the objective of this study was to investigate the effect of the absence of decorin *in vivo* on native and healing mouse Achilles tendons. We hypothesized that the absence of decorin would 1) impair the native mechanical properties of the Achilles tendon and 2) improve the healing mechanical properties of the Achilles tendon.

## Methods

C57BL/6 wild type (WT) and decorin transgenic null (*Dcn−/−*) mice were used in this IACUC-approved study. Control, uninjured (UNJ) animals were sacrificed at 150 days of age (n=7-9 per genotype). Animals in the injured group (INJ) underwent a bilateral, centralized, full-thickness, partial-width injury to their Achilles tendon at 120 days of age (n=4-8 per genotype). For the injuries, animals were anesthetized, and skin incisions were made to visualize the Achilles tendons. Rubber-coated backings placed underneath the tendons provided support against a 0.5 mm biopsy punch used to create the defects. Incisions were sutured closed. Animals returned to cage activity and were sacrificed 3 weeks later.

At sacrifice, one Achilles tendon-calcaneus unit from each mouse was dissected. Tendon cross-sectional area was measured using a laser device. Stain dots were placed on the tendon for optical strain analysis. Tendons were stamped into a dog-bone shape to isolate the defect region. Cross-sectional area was also measured after stamping for use in calculation of material properties. The calcaneus and Achilles tendon were gripped in fixtures to create a gauge length of 5 mm from the bony insertion. The tendon was submerged in a 37°C heated PBS bath and tensile tested as follows: 1) preload, 2) preconditioning, 3-5) stress relaxation and sinusoidal frequency sweeps at 4%, 6%, and 8% strains, 6) return to gauge length, 7) ramp to failure at 0.1%/sec. The sinusoidal frequency sweeps were performed at 0.01, 1, and 10 Hz for 10 cycles at 0.125% strain for each frequency. The tensile modulus was determined from the ramp to failure. The dynamic modulus (|E*|, ratio of stress-to-strain amplitude) and tangent of the phase angle between the stress and strain (tan(δ), a measure of viscoelasticity) were calculated at each strain level and frequency.

Comparisons between genotypes for cross-sectional area and tensile modulus were made using separate t-tests for the UNJ and INJ groups. At each strain level, the effects of genotype and frequency on tan(δ) and |E*| were evaluated using a 2-way ANOVA, separately for the UNJ and INJ groups. When significant, p-values were calculated from t-tests comparing genotypes. Additionally, a bootstrapping technique, which creates random pairs of data to compare genotypes, was used to calculate the ratios of injured to uninjured data for tan(δ) and |E*| for each genotype.

## Results

*Dcn-/-* uninjured tendons had increased area (Fig 1a), decreased linear modulus (Fig 1b), increased tan(δ) (Fig 2a), and decreased |E*| (Fig 2c) compared to WT. Frequency significantly affected tan(δ), but there were no interactions. Interestingly, results were opposite for injured tendons. *Dcn-/-* injured tendons had decreased area (Fig 1a), increased linear modulus (Fig 1b), decreased tan(δ) (Fig 2b), and increased |E*| (Fig 2d) compared to WT. For simplicity, results for tan(δ) and |E*| are shown for 8% strain; similar trends existed at the other strain levels. The bootstrapped data (not shown) confirmed that the ratio of INJ/UNJ resulted in cross-sectional area, linear modulus, tan(δ), and |E*| that were closer to native properties for the *Dcn-/-* group compared to WT.

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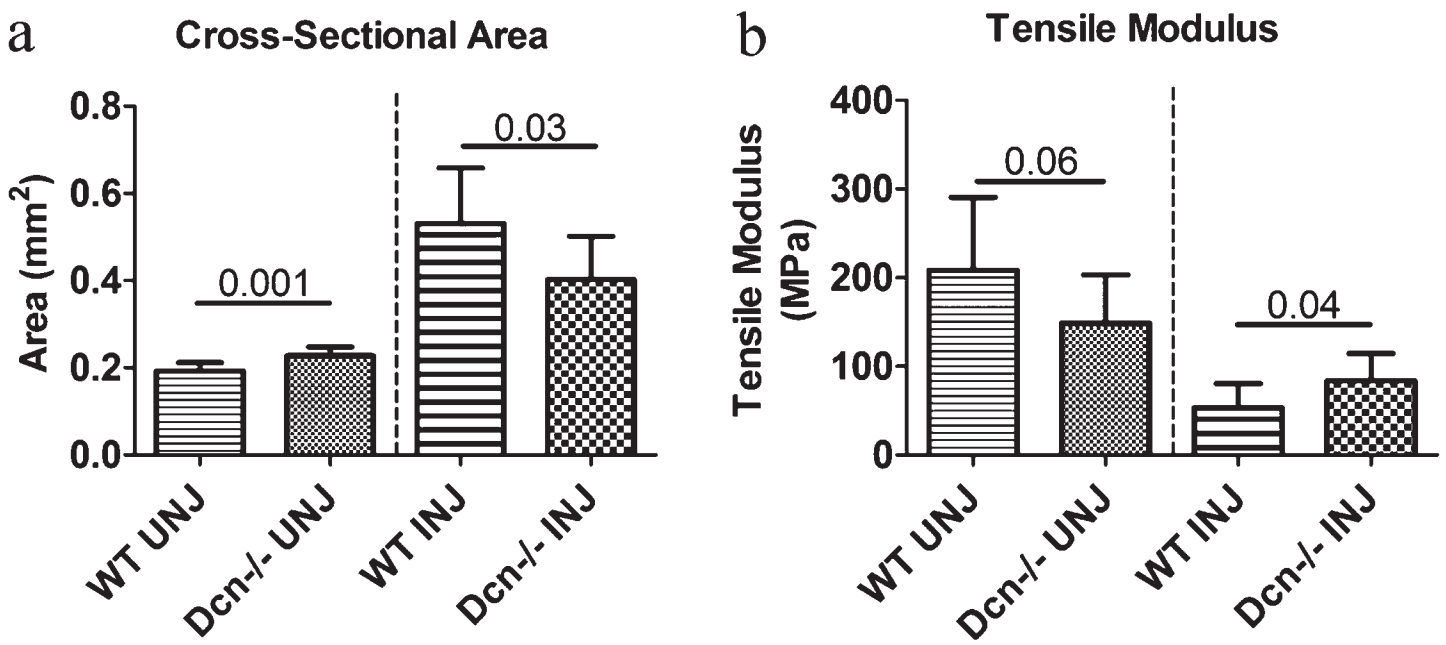


**Figure 1.** Uninjured *Dcn−/−* tendons (vs. WT) had increased cross-sectional area **(a)** and decreased tensile modulus **(b)**; injured *Dcn−/−* tendons (vs. WT) had decreased cross-sectional area **(a)** and increased tensile modulus **(b)**. Injured *Dcn−/−* tendons healed better than injured WT. mean = stdev.

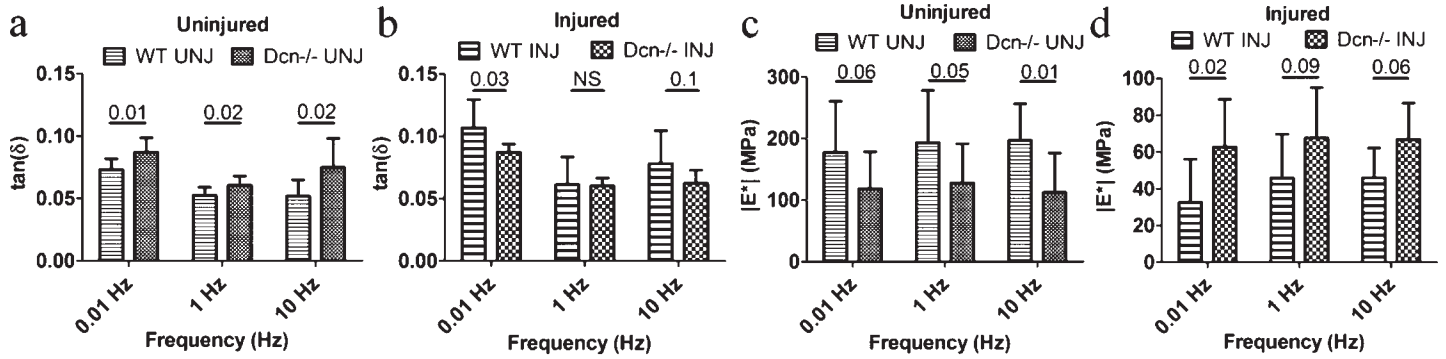


**Figure 2.** Uninjured *Dcn−/−* tendons (vs. WT) had increased tan(δ) **(a)** and decreased |E*| **(c)**; injured *Dcn−/−* tendons (vs. WT) had decreased tan(δ) **(b)** and increased |E*| **(d)**. Injured *Dcn−/−* tendons healed better than injured WT. Not shown are the differences between frequency for tan(δ): 0.01 Hz differed from both 1 Hz and 10 Hz ($p < 0.005$, Tukey's). mean = stdev, NS= not significant.

## Discussion

Results support our hypotheses. Uninjured data suggests that decorin-deficient mouse Achilles tendons are mechanically weaker than wild type tendons. These results are in agreement with previous findings in the flexor digitorum longus tendon.[5] Injured *Dcn-/-* Achilles tendons healed better than WT tendons, as evidenced by the decreased area, increased tensile modulus, increased |E*|, and decreased tan(δ). The bootstrapped data further support that the decorin-deficient mice better recovered their native properties than the wild type mice 3 weeks after injury to their Achilles.

Decorin regulates the formation of larger collagen fibrils.[6] Inhibition of decorin during tendon healing may reduce scarring and improve collagen fibrillogenesis by allowing the formation of more mechanically stable collagen fibrils. Future work includes testing biglycan transgenic null tendons, examining a later time point, and performing additional assays to elucidate the mechanisms responsible for the differences between genotypes and the function of decorin in these processes.

## Significance

The absence of decorin impairs native mouse Achilles tendon mechanical properties but enhances healing mechanical properties at a 3 week time point. This study provides support for reducing decorin expression as a treatment to improve Achilles tendon healing.

## Acknowledgements

The authors thank A. Dunkman for useful discussion. This study was supported by the NIH-NIAMS.

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# Biceps Mechanical Properties Are Not Altered in the Presence of Asymptomatic Rotator Cuff Tendon Tears

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## Introduction

The long head of the biceps (LHB) tendon has different loading patterns in its intra- and extra-articular regions. The intra-articular region is exposed to complex loads including tension, compression, shear, and frictional forces, while the extra-articular portion is subjected primarily to tensional loads.[1] Previous studies have also shown that the intra-articular region has a more disorganized collagen organization and higher proteoglycan content than the extra-articular region,[1,2] and may be more prone to increased pathology with decreased healing potential. However, the mechanical properties in each of these regions have not been evaluated. In addition, degenerative changes in the LHB often occur secondary to rotator cuff tendon pathology[3,4] and the incidence of LHB pathology is correlated with the size and severity of rotator cuff tendon tears.[5,6] However, the effect of rotator cuff tear size on the mechanical properties of the human biceps tendon is not known. Therefore, the objectives of this study were to: 1) characterize the mechanical properties along the length of the human LHB tendon and 2) investigate the changes on the LHB tendon in the presence of an isolated supraspinatus (supra only) and combined supraspinatus-infraspinatus (supra-infra) rotator cuff tears. We hypothesized that: H1) in normal shoulders, the properties of the LHB tendon will vary along the length due to different environments and H2) in the presence of rotator cuff tears, the LHB tendon will have inferior mechanical properties, with greater damage seen with increasing rotator cuff tear severity.

## Methods

Experimental Design and Sample Preparation: Fifty-one fresh-frozen human cadaver shoulders without documented history of shoulder pathology were dissected and 24 (48%) of these were found to have a rotator cuff tear. Of all shoulders dissected, 30 were sub-divided to create three age and gender-matched groups for the present study: control (N=11 (6M (male), 5F (female)), age 70.0±5.8), isolated supraspinatus tear (N=11 (6M, 5F), age 67.0±3.9), and combined supraspinatus-infraspinatus tears (N=8 (4M, 4F), age 69.5±5.9). Shoulders were dissected and the scapula and glenoid were resected, leaving the biceps tendon and its glenoid origin intact. At the time of testing, specimens were thawed and stain lines, for local optical strain, were placed along the bursal side, dividing the origin, intra-articular, and extra-articular regions of the tendon (Fig 1). Cross-sectional area was measured using a custom laser device. The remaining glenoid bone was then potted in PMMA and anchored with a screw. Tendon Mechanical Testing: To determine LHB tendon biomechanical properties, tensile testing was performed as follows: ten preconditioning cycles, stress relaxation to 5% strain at a rate of 4.5 mm/sec (5 %/sec) for 600 sec, and ramp to failure at 0.3%/sec.

Statistics: For normal controls (H1), mechanical properties were compared along the tendon length using a one-way ANOVA with Bonferroni post-hoc tests. To determine the effect of rotator cuff tears on tendon mechanics (H2), properties were assessed using a one-way ANOVA with Bonferroni post-hoc tests (significance at $p<0.05$).

## Results

For normal controls, the cross-sectional area was significantly larger at the insertion site compared to both the intra- and extra-articular space regions. Additionally, biceps area was significantly larger in the intra-articular space compared to the extra-articular space (Fig 2). Linear modulus (Fig 3) and structural stiffness (data not shown) were significantly larger in the extra-articular space compared to both the intra-articular space and origin.

In the presence of an isolated supraspinatus tear, increased biceps cross-sectional area (hypertrophy) was measured in the intra-articular region of the tendon compared to control (Fig 2). Regardless of experimental group (control, supraspinatus only tear, supraspinatus-infraspinatus tear), no differences were observed for linear modulus (Fig 3) or stiffness (data not shown) in any region.

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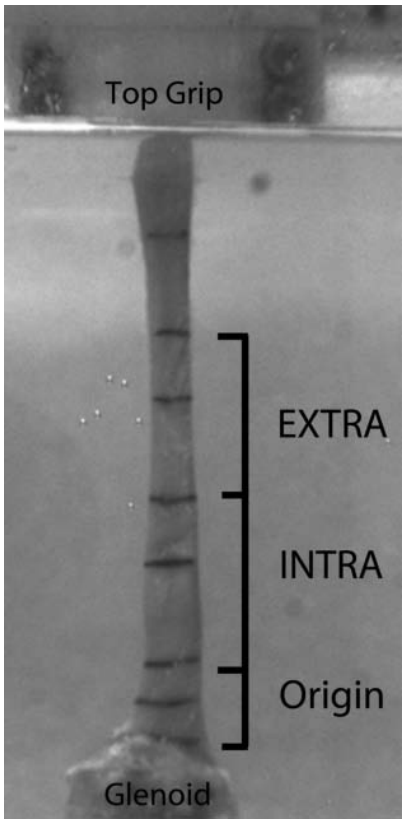


**Figure 1.** Stain lines were placed along the length of the tendon to measure local mechanical properties within each region (Origin, Intra-articular= INTRA, Extra-articular=EXTRA).

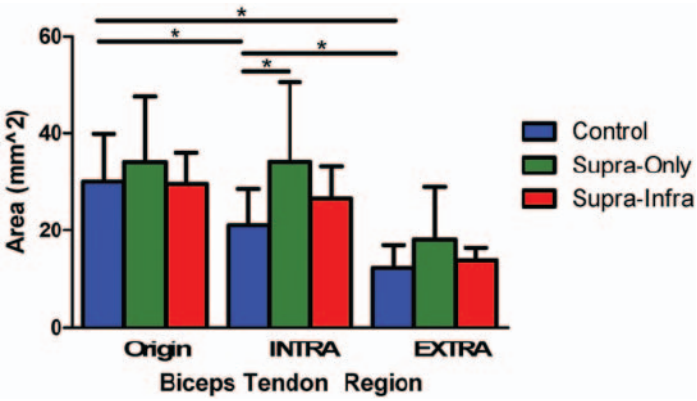


**Figure 2.** In control shoulders, biceps area was significantly decreased along the length of the tendon. In the presence of an isolated supraspinatus (Supra Only) tear, biceps area was significantly increased in the intra-articular space (mean±SD) (*p<0.05).

## Discussion

This is the first study to measure the mechanical properties along the length of the human LHB tendon. Consistent with our first hypothesis, mechanical properties vary along the length of the tendon, with the extra-articular portion having a higher modulus than the rest of the tendon. These mechanical properties are consistent with the structural finding of more organized collagen fibers in the extra-articular region of the tendon as compared to the intra-articular region.[1] Additionally,

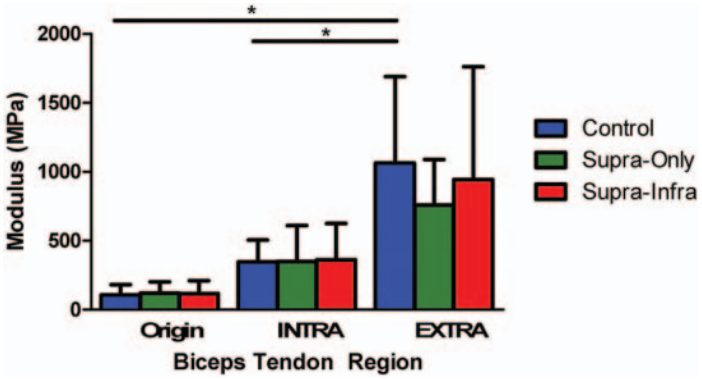


**Figure 3.** In control shoulders, biceps modulus was significantly larger in the extra-articular space. In the presence of rotator cuff tears, no regional differences were identified (mean±SD) (*p<0.05).

the lower modulus values at the origin and intra-articular region may place these regions at a higher risk for injury and are consistent with regions commonly associated with biceps pathology.[7]

Results also demonstrated that the mechanical properties of the LHB tendon were not altered in the presence of rotator cuff tears, consistent with previous studies.[8] However, hypertrophy of the tendon did occur in the intra-articular space (also consistent with previous findings in cadavers[9]) in the isolated supraspinatus tear group. At the shoulder joint, the LHB tendon is believed, by some, to function as a humeral head depressor and has been shown to play an important role as a joint stabilizer, particularly in rotator cuff deficient shoulders.[10] Our results suggest that the mechanical strength of the LHB is maintained and therefore may still function effectively in the presence of a rotator cuff tear.

Management of LHB pain in the presence of cuff tears is controversial and physicians often augment cuff repairs with tenotomy or tenodesis to reduce pain. The cadaver shoulders used in this study were classified as having no history of shoulder pathology and despite this classification, cuff tears were present in 48% of cadavers. Therefore, we speculate that these individuals either did not have sufficient pain to report to their physician or were asymptomatic, as a large percentage of rotator cuff tears are, indeed, asymptomatic. Previous studies have shown that greater humeral head migration occurs in shoulders with symptomatic tears than those with asymptomatic tears.[11] Successful compensation by adjacent muscles including the deltoid and subscapularis (which functions as a humeral head depressor and has shown increased activity in asymptomatic compared to symptomatic cuff tear patients[12]) may be achieved, preserving the loading environment of the LHB tendon and preventing tendon damage.

## Significance

Results of this study suggest that a relationship may exist between asymptomatic cuff tears and the preservation and maintenance of LHB mechanical properties which warrants further investigation.

## Acknowledgements

We acknowledge Jennica Tucker for dissection assistance. This study was funded by NIH/NIAMS.

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# Supraspinatus and Infraspinatus Rotator Cuff Repair Prevents Mechanical Damage to the Intact Subscapularis Tendon in a Rat Model

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## Introduction

Rotator cuff tendon tears are a common cause of pain and disability. An intact rotator cuff stabilizes the glenohumeral joint, allowing for concentric rotation of the humeral head on the glenoid. However, large tears involving the supraspinatus and infraspinatus tendons may disrupt the normal balance of forces, resulting in abnormal joint loading which can cause secondary damage to surrounding joint tissues such as cartilage and other tendons. As a result, surgical repair is often recommended to reduce pain and restore function. Our lab has previously shown that the properties of adjacent intact tendons (subscapularis and long head of the biceps) are significantly diminished following combined tears of both the supraspinatus and infraspinatus tendons.[1,2] However, it is unclear whether early rotator cuff repair can prevent the progression of these secondary degenerative changes. Therefore, the objective of this study was to determine if rotator cuff repair prevents mechanical damage to adjacent tissues (subscapularis and biceps). We hypothesized that rotator cuff repair will provide for superior adjacent tissue mechanical properties compared to no repair.

## Methods

Experimental Design and Sample Preparation: Twenty adult Sprague-Dawley rats (400-450 g) underwent unilateral detachment of the supraspinatus and infraspinatus tendons (IACUC approved). Rats were then randomly assigned to two different treatment groups: no repair (n=10) or supraspinatus and infraspinatus (SI) repair (n=10). For both groups, the same approach to the rotator cuff musculature was used, followed by sharp transection of the supraspinatus and infraspinatus tendons from their insertions. Next, two parallel crossing 0.5 mm tunnels were drilled through the greater tuberosity of the humerus (with entrance and exit holes corresponding to the edges of the anatomic footprint of each tendon). For the repair group, the tendons were then reapposed to their insertion with a Modified Mason Allen technique. For the no repair group, the tendons were allowed to freely retract. All rats were sacrificed 4 weeks after surgery and frozen at -20C. At the time of testing, the animals were thawed and the scapula and humerus were dissected out with the biceps and rotator cuff tendons intact.

Tendon Mechanical Testing: Stain lines, for local optical strain measurement, were placed on the long head of the biceps and upper and lower bands of the subscapularis tendons (each tested separately).[2,3] Cross-sectional area was measured using a custom laser device. To determine biomechanical properties, tensile testing of each tendon was performed as follows: preconditioning, stress relaxation for 600 sec, and ramp to failure at 0.3%/sec.

Statistics: Significance between the two groups was assessed using a t-test (significance at $p<0.05$).

## Results

For the lower band of the subscapularis tendon, the modulus was significantly greater in the SI repair group compared to no repair at both the insertion and mid-substance regions (Figure 1, TOP LEFT). Additionally, upper subscapularis modulus was significantly greater in the SI repair group compared to the no repair group in the mid-substance region (Figure 1,TOP RIGHT). No significant differences in area were determined in either tendon band (data not shown).

For the long head of the biceps tendon, modulus and area were not significantly different between groups (Figure 1, BOTTOM). No significant difference in tendon area was observed (data not shown).

## Discussion

This is the first study to examine the role of rotator cuff tendon repair in the prevention of secondary degenerative changes in an animal model. Rotator cuff repair resulted in superior mechanical properties of the lower and upper bands of the subscapularis tendons relative to no repair (closer to pre-injury values[3]). Specifically, elastic modulus was significantly greater in the

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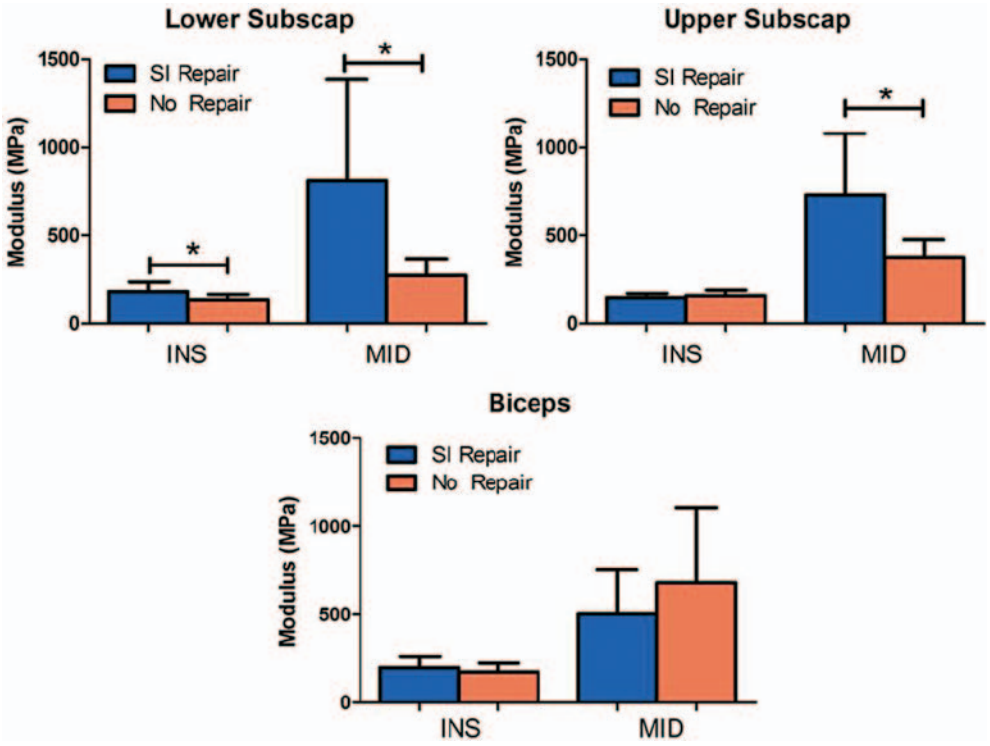


**Figure 1.** Following SI (supraspinatus-infraspinatus) repair, the lower band of the subscapularis tendon modulus is increased at the insertion and mid-substance (TOP, LEFT) and the upper band of the subscapularis tendon modulus is increased at the mid-substance (TOP, RIGHT). No differences were observed in the biceps tendon (BOTTOM). (Insertion=INS, Mid-substance= MID) (Mean±SD,* $p<0.05$).

lower band of the subscapularis tendon at both the insertion and mid-substance regions and in the upper band at the tendon mid-substance compared to no repair. These results suggest that early rotator cuff repair may help maintain subscapularis tendon loading by re-establishing the balance of glenohumeral joint forces and may therefore decrease the risk of anterior cuff tear progression. Interestingly, there was no improvement in biceps tendon mechanical properties observed with cuff repair. Clinically, the long head of the biceps tendon is often damaged in conjunction with rotator cuff tears. Management of biceps pathology is controversial, and surgeons often perform biceps tenotomy or tenodesis when repairing torn rotator cuff tendons to reduce pain and improve clinical outcomes. Results from this study suggest that rotator cuff tendon repair will not recover biceps tendon properties, lending support for augmentation of cuff repairs with biceps tenotomy or tenodesis.

Given the contrasting tendon results, it should be noted that the subscapularis and biceps tendons are functionally and organizationally distinct and therefore may respond in different manners to alterations in mechanical loading secondary to cuff tears. Specifically, the anatomy of the biceps in the rat (and human) is complex, comprising intra- and extra-articular portions, each with distinct nutrient and loading environments.[4] This study suggests that the biceps tendon may have less healing potential than the subscapularis tendon.

Future studies will examine alterations in cartilage properties and glenohumeral joint mechanics in order to elucidate the mechanism by which joint damage may be prevented following cuff repair.

## Significance

This study suggests that rotator cuff tendon repair can prevent subscapularis tendon damage but is insufficient for restoring biceps tendon properties. Clinically, this supports early rotator cuff tendon repair augmented with biceps tenotomy or tenodesis in order to achieve optimal clinical outcomes.

## Acknowledgements

This study was funded by NIH/NIAMS.

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# Biceps Detachment Does Not Worsen Shoulder Function in a Multi-Tendon Rotator Cuff Tear Rat Model

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## Introduction

Rotator cuff tendon tears are common, especially in populations performing repetitive overhead tasks and in individuals over the age of 50.[1,2] Clinically, the most common rotator cuff tears involve either the supraspinatus only (SO) or both the supraspinatus and infraspinatus (SI). Our lab has shown that shoulder function is diminished following SI tears compared to SO tears in an overuse model.[3] In addition, biceps (long head) pathology is often found secondary to SI tears and clinicians often tenotomize or tenodese the biceps to eliminate pain. However, the consequences on shoulder function following detachment of the biceps remains unknown and clinicians currently rely largely on anecdotal evidence to guide treatment. For patients with an intact rotator cuff, releasing the biceps is commonly thought not to have any deleterious effects on shoulder function. As rotator cuff tears become larger, the biceps role on shoulder function may become more important. Therefore, the objective of this study was to examine shoulder function following SO, SI, and supraspinatus, infraspinatus and biceps (SIB) tendon tears in a rat model. We hypothesized that shoulder function would progressively diminish as the size of the injury increased.

## Methods

Experimental Design: Forty Sprague-Dawley rats (IACUC approved) were subjected to a two week training period followed by 4 weeks of overuse treadmill activity as described[4] to induce a chronic, tendinopathic condition prior to undergoing unilateral detachment of the SO (n=19), SI (n=16), and SIB (n=5) to model an acute on chronic injury. Following detachment surgery, animals were returned to normal cage activity for the remainder of the study.

Quantitative Ambulatory Assessment: In all animals, forelimb gait and ground reaction forces were quantified using an instrumented walkway.[5] Data was collected one day prior to detachment surgery to obtain baseline ambulatory values and then collected at day 3, 7, 14, 28, 42, and 56 days after detachment surgery prior to sacrifice. Ground reaction force data, including medial/lateral (ML), propulsion, braking, and vertical forces were collected for each walk. At each timepoint, at least two walks were recorded per animal, as well as animal body weight. Parameters were averaged across walks on a given day for each animal and normalized to the animal's body weight for that day.

Statistics: To evaluate the ground reaction force data, separate 3 (group; SO, SI, SIB) X 7 (time; -1, 3, 7, 14, 28, 42, 56) ANOVA's with repeated measures on time were performed. To compare the main effect for group and time, Tukey post hoc tests were used. To examine the interaction between group and time, post-hoc, paired t-tests were used (significance at $p<0.05$). Prior to statistical analysis, multiple imputations were used for a small number (~1%) of missing data points due to the inability to record a successful walk for a specific rat during a specific timepoint.

## Results

For ML force, there was a significant main effect for time (Fig 1). The pre-injury ML force was greater than all other timepoints. In addition, there was a significant main effect for group. The ML force of the SO group was greater than both the SI and SIB groups.

For the propulsion force, there was a significant main effect for time (Fig 2). The pre-injury propulsion force was greater than later timepoints (3, 7, and 14 days). In addition, propulsion force was significantly greater for the SO group than for both the SI (3, 7, 14, and 28 days) and SIB groups (7 days). The braking force of the SO group (data not shown) was significantly less than the SI groups at 7 and 14 days.

Finally, the vertical force had a significant main effect for time (data not shown). The pre-injury vertical force was greater than later timepoints (3, 7, 14, and 28 days). In addition, the vertical force of the SO group was significantly greater than the SI group (3, 7, 14, and 28 days) as well as the SIB group (7 and 14 days).

## Discussion

This is the first study to examine the functional role of the biceps at the shoulder joint in a multi-tendon rotator cuff tear rat model. Results demonstrate that shoulder function is significantly altered with a combined supraspinatus and infraspinatus tear while an additional detachment of the long head of the

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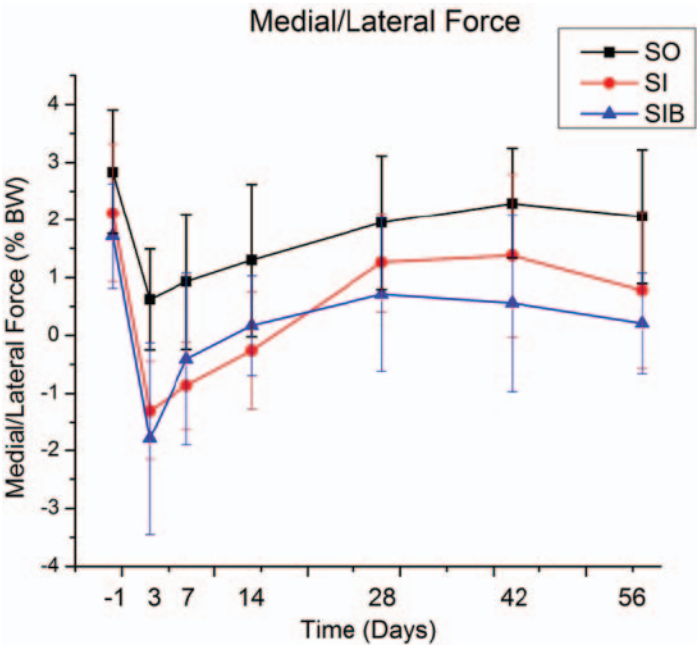


**Figure 1.** ML force (mean±stdev) at pre-injury through 56 days post-injury. Results demonstrate a significant difference between pre-injury and all post-injury timepoints. The SO group was significantly greater compared to both the SI and SIB groups.

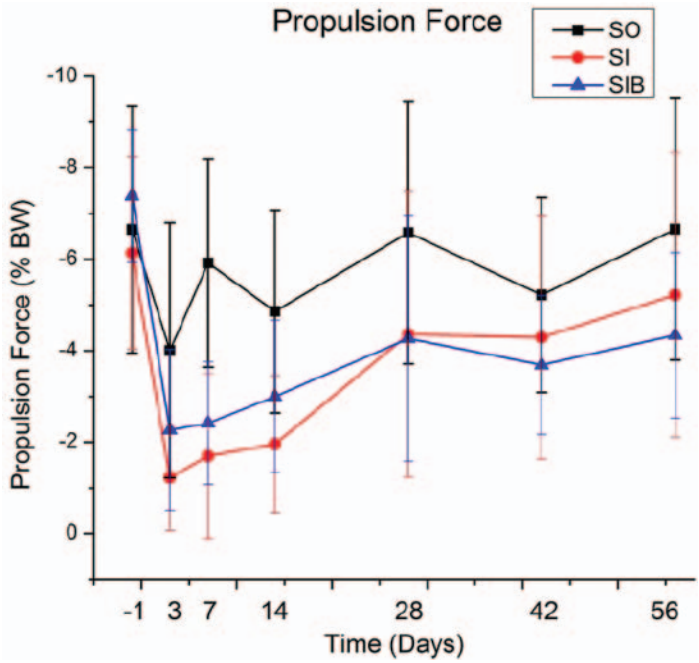


**Figure 2.** Propulsion force (mean±stdev) at pre-injury through 56 days post-injury. The SO group was significantly greater than the SI group at 3, 7, 14, and 28 days and also greater than the SIB groups at 7 days.

biceps tendon did not further diminish shoulder function. Specifically, injury caused a reduction in ground reaction forces and these decreases were larger for the SI and SIB groups compared to SO, but not different between SI and SIB. Furthermore, the directionality of the losses in ground reaction forces is consistent with the diminished dynamic function of the supraspinatus and infraspinatus at the glenohumeral joint. Consistent with our hypothesis, tears involving both the supraspinatus and infraspinatus decreased shoulder function compared to an isolated supraspinatus tear. Results suggest that the infraspinatus plays a significant role in shoulder function which is consistent with the anterior/posterior glenohumeral joint force balance concept.[6] However, contrary to our hypothesis, results demonstrate that a detachment of the biceps tendon does not further diminish shoulder function. Surgical management of biceps pain is controversial because it has been suggested that the biceps tendon plays an important role in shoulder function, particularly in the presence of a multi-tendon rotator cuff tear. However, in the case of a massive irreparable rotator cuff tear, our results suggest that tenotomy or tenodesis of the biceps may be recommended to manage pain because shoulder function was not further compromised in this model. Further investigation is required to determine the mechanical integrity of the remaining joint structures following a SIB injury.

## Significance

Clinically, results suggest that the severity of diminished shoulder function following rotator cuff tears is dictated by disruption of the anterior/posterior force balance. Specifically, tears involving both the supraspinatus and infraspinatus decreases shoulder function while the additional detachment of the long head of the biceps tendon does not. This provides clinicians with valuable information to help guide treatment options for patients with massive rotator cuff tears that also have significant long head of the biceps pain.

## Acknowledgements

This study was funded by NIH/NIAMS.

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# Hyaluronic Acid Hydrogels for Articular Cartilage Defect Repair in a Large Animal Model

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## Introduction

Intrinsic repair of articular cartilage damage is unsatisfactory. Due to limitations of current surgical treatments,[1] tissue engineering (TE) approaches have been pursued as promising alternatives. Our laboratory investigates hyaluronic acid (HA) hydrogels as a scaffold for cartilage TE.[2-6] When seeded with mesenchymal stem cells (MSCs) and cultured in defined media containing the chondrogenic factor transforming growth factor-β3 (TGF-β3) for several months, these constructs can reach near native biomechanical and biochemical properties.[4,5] As opposed to pre-maturing these constructs prior to implantation, an alternative approach could be to encapsulate cells in HA hydrogels along with TGF-β3 laden microspheres[5] (all polymerized in-situ) within a defect to induce differentiation and direct new matrix production in-vivo. Delivering such a high dose of TGF-β3 can induce cartilaginous matrix production in both in-vitro and subcutaneous in-vivo models.[5,6] Our long-term goal is to compare these approaches directly within a clinically relevant in-vivo cartilage injury model. As a first step, the goal of this study was to assess the natural healing response to an HA hydrogels alone or delivering TGF-β3 in a large animal model of cartilage injury and repair.

## Methods

In four Yucatan minipigs, full thickness chondral defects (4 mm diameter) were created in the trochlear groove of the stifle joint. In each animal, four experimental groups were compared: 1) an untreated defect (n=8), 2) a methacrylated HA hydrogel (1% w/v), polymerized in situ using UV light (n=4), 3) a HA hydrogel, laden with alginate microspheres containing TGF-β3 (50 ng) (n=4), as previously described,[5] and 4) a cartilage autograft transfer (CAT) (n=4). Normal cartilage served as a positive control. At 6 weeks, animals were euthanized. Bone morphometry under the defect site was determined using microcomputed tomography (μCT). Bone volume per total volume (BV/TV) was calculated for the first 2 mm underneath the defect. Histological evaluation included cell morphology (hematoxylin & eosin) and matrix composition (proteoglycan and collagen staining via Alcian blue/picrosirius red and Safranin O/fast green). Samples were scored using a modified ICRS-II system.[7] BV/TV between groups was compared via ANOVA with Bonferroni post-hoc tests ($p<0.005$). For histological scoring, individual comparisons were made using the Mann-Whitney test ($p<0.005$).

## Results

Six weeks after surgery, bone morphology of the treated groups featured evidence of bone remodeling and resorption beneath the defects (Fig. 1A). The largest changes in BV/TV were observed in the HA/MS group, which was 72% lower than normal controls (Fig. 1B, $p<0.005$). In terms of histologic appearance (Fig. 2), the untreated group filled incompletely with a mostly fibrous tissue with diffuse staining for type I collagen, but little for type II collagen. HA treatment led to considerable variability, with some samples featuring robust staining for proteoglycans and type II collagen, while others contained more fibrous tissue. The HA/MS group displayed a mostly fibrous appearance and substantial bone remodeling. Nevertheless, marked type II collagen was found within these defects. The CAT group filled the vast majority of the defect space, stained well for proteoglycans, and contained type II collagen; however, these constructs integrated poorly with the surrounding tissue. In terms of ICRS-II scoring, the median overall values for the untreated group were 62% lower than normal (Fig. 3A, $p<0.005$). In terms of defect fill, the untreated, HA, and HA/MS groups were all significantly lower than normal (Fig. 3B, $p<0.005$). No statistically significant differences were detected between the CAT and normal groups ($p>0.005$). Similar results were found in terms of matrix staining (Fig. 3C). The HA group had the highest variability, with two scores above 70%. All experimental groups were significantly different from normal controls in terms of integration to the surrounding cartilage (Fig. 3D, $p<0.005$). Interestingly, the CAT group had the lowest median scores, which were under 50% of normal ($p<0.005$).

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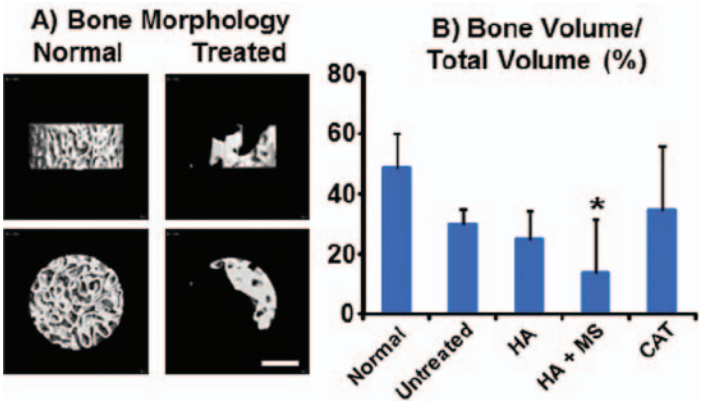


**Figure 1A-B.** Morphometric analysis of subchondral bone. 3-D μCT reconstructions of bone from normal and experimental specimens (A) (centered under defect, scale bar = 0.5mm). Bone Volume/Total Volume (B) (*p<0.005 vs. normal).

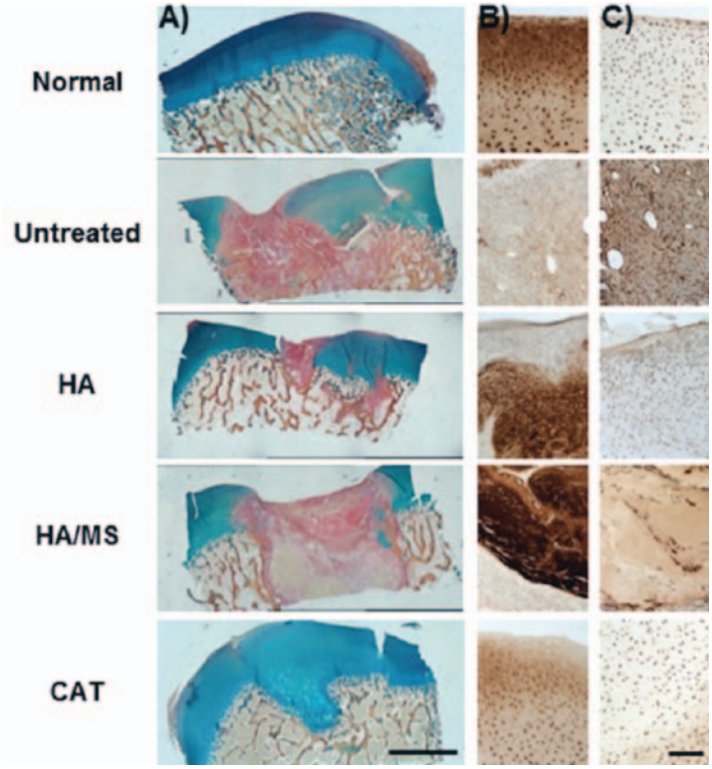


**Figure 2.** Histological staining for proteoglycans (blue) and collagen (red) following 6 weeks in-vivo (A) (scale=2mm). Immunohistochemical staining for type II (B) and type I (C) collagen.

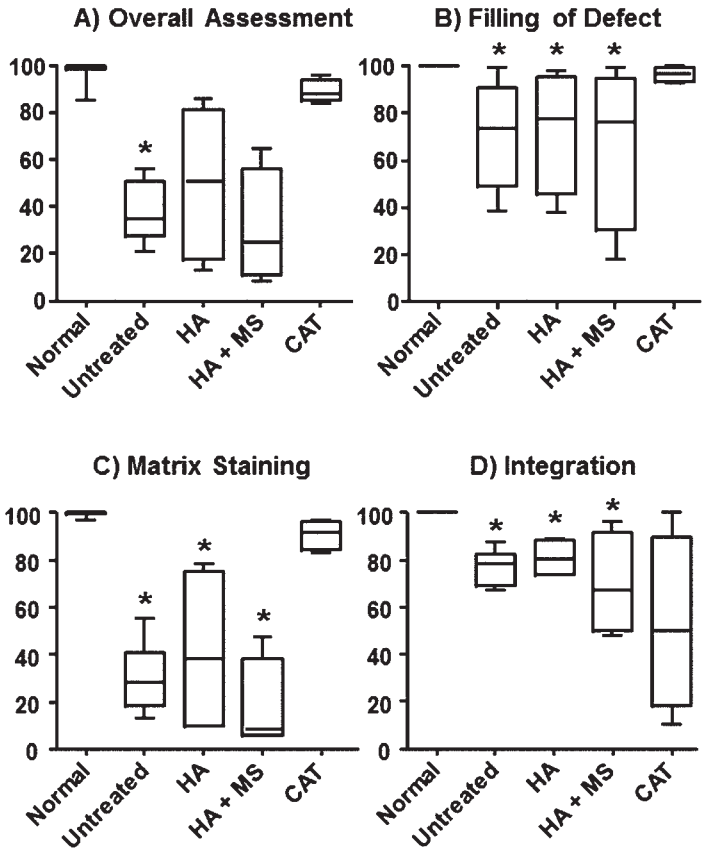


**Figure 3A-D.** ICRS-II scoring: Overall assessment (A), filling of defect (B), matrix staining (C), and integration to surrounding cartilage (D) (*p<0.005 vs. normal).

## Discussion

In this preliminary study, we compared the healing response to HA and TGF-β3 to an untreated defect and a chondral autograft within a porcine model of cartilage injury and repair. Untreated defects were unable to heal spontaneously with cartilage-like tissue by 6 weeks. Alternatively, autologous cartilage autografts were able to fill the defect, but had poor integration to the surrounding cartilage. These results match those observed clinically.[1] Interestingly, HA alone had some positive impact on tissue healing, with increased proteoglycan and type II collagen staining relative to untreated defects. However, these results were highly variable. The addition of microspheres containing TGF-β3 increased type II collagen staining within the defect; however, little proteoglycan staining was found, and substantial subchondral bone remodeling occurred. This indicates a complex response to TGF-β3 within this model, and suggests its use must be carefully controlled in future studies. Longer-term studies are also warranted to determine the full time course of healing following these treatments. Since the healing tissue with HA treatment appeared to be well-colonized with cells, this system will allow us to determine whether extrinsically supplied MSCs or those that migrate to the injury site provide a better outcome. If cells need to be provided, we will also test whether pre-maturation of MSC-seeded HA constructs or direct encapsulation and implantation provides superior outcomes for cartilage repair.

## Significance

The positive, but limited, results with HA alone or HA with microspheres delivering TGF-β3 for cartilage repair suggest that additional factors (e.g. cells) are needed to fully restore the articular cartilage following injury in this model. These data will guide future work in developing cell-laden tissue engineered constructs for cartilage repair.

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# Trajectory-based Tissue Engineering for Cartilage Repair: A Methodology to Better Predict In-Vivo Success

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## Introduction

Given the limitations of current surgical approaches to treat articular cartilage injuries, tissue engineering (TE) approaches have been aggressively pursued over the past two decades, and recently, biochemical and biomechanical properties on the order of the native tissue have been achieved.[1-5] However, in-vitro and in-vivo data suggest that increased tissue maturity may limit the ability of engineered constructs to remodel and integrate with surrounding cartilage, although results are variable.[2,6-8] Thus, "static" measures of construct maturity (e.g. compressive modulus) upon implantation may not be the best indicators of in-vivo success, which likely requires implanted TE constructs to mature, remodel, and integrate with the host over time to achieve optimal results. In order to better predict in-vivo outcomes, it is hypothesized that time-dependent increases in construct maturation in-vitro prior to implantation (i.e. positive rates) may provide a better predictor of in-vivo success. The goal of this "trajectory-based" tissue engineering (TB-TE) approach is to maximize maturation rates before implantation. To explore this hypothesis, the current objective is to quantify and model the time course of maturation of TE constructs during in-vitro culture.

## Methods

Bovine mesenchymal stem cells were isolated and cultured, as previously described.[1-2] Cells were encapsulated within methacrylated hyaluronic acid (HA) (1% w/v) at a seeding density of 20 or 60 million cells/ml (20M and 60M groups, respectively). Following polymerization via UV light, cylindrical constructs (4 mm diameter) were formed and cultured in chemically-defined media containing TGF-β3 on an orbital shaker for up to 9 weeks. At weekly intervals, stress relaxation testing (10% compressive strain, 1000s hold) and cyclic testing (1% amplitude, 1 Hz) were performed to determine equilibrium modulus and dynamic modulus, respectively. Glycosaminoglycan (GAG) content was measured by the DMMB assay, and its distribution determined by Alcian blue staining of histological sections.[5-6] Biomechanical and biochemical data were plotted versus time and fit individually with a sigmoidal curve ($y=C1*e^{(C2*e^{(C3*x)})}$). Using the determined parameters (C1, C2, and C3), the 1st derivative of the function was calculated. For statistical analysis, mechanical and biochemical data were compared between 20M and 60M groups at each time point using unpaired t-tests. Significance was set at $p<0.007$ following a Bonferroni correction. Experimental significance for the 1st derivative was defined as a difference greater than 20% of the peak value for the 60M group. Data were also normalized by their respective peak value to compare relative changes in mechanical and biochemical properties using unpaired t-tests ($p<0.002$).

## Results

The equilibrium modulus data for both groups followed a sigmoidal shape as a function of time, with an initial lag phase for the first 3 weeks, followed by a linear region with increased slope, before plateauing at 7 weeks (Fig. 1A). Following a curve-fit of the modulus data, the plot of the 1st derivative had a parabolic appearance peaking around 5 weeks (Fig. 1B). Similar shapes were obtained for the dynamic modulus and GAG content. Comparing the values for the 20M and 60M groups (Fig. 2), at early time points (3 & 5 weeks), the equilibrium and dynamic modulus were similar between groups ($p>0.007$); yet, the 1st derivative of these parameters at 5 weeks were 233% and 87% higher for the 60M group, respectively (experimentally significant). By 9 weeks, the equilibrium and dynamic modulus of the 60M group was 193% and 60% higher, respectively ($p<0.007$); however, the rates of these parameters were similar between groups and near zero. To examine the relative changes in mechanics and biochemistry, values were normalized to their respective peak values (Fig. 3A). For the 60M group, GAG content was approximately 50% of the peak value at 3 weeks. In comparison, the relative values for moduli were only ~10% of their peak values at 3 weeks ($p<0.002$ vs. GAG). These values remained significantly lower than the GAG content up

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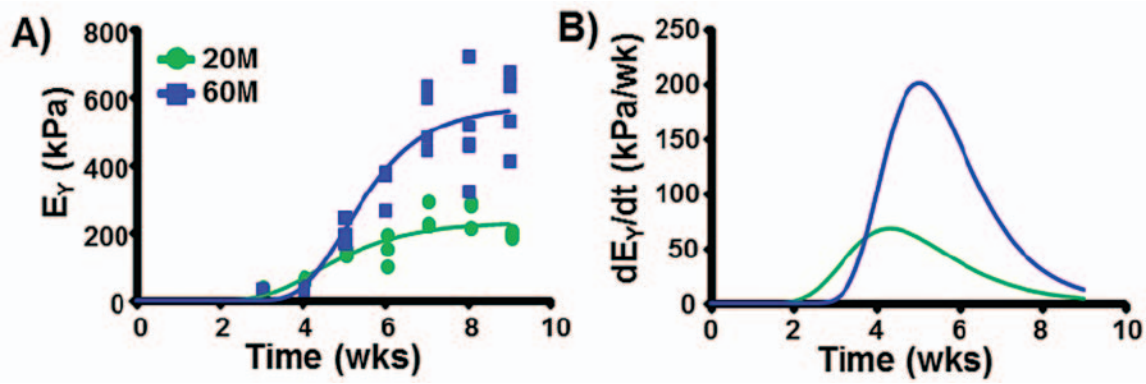


**Figure 1.** Maturation of MSC-laden HA constructs. **(A)** Equilibrium modulus as a function of time for 20M and 60M groups and respective model fits (solid lines). **(B)** First derivative of equilibrium modulus with respect to time.

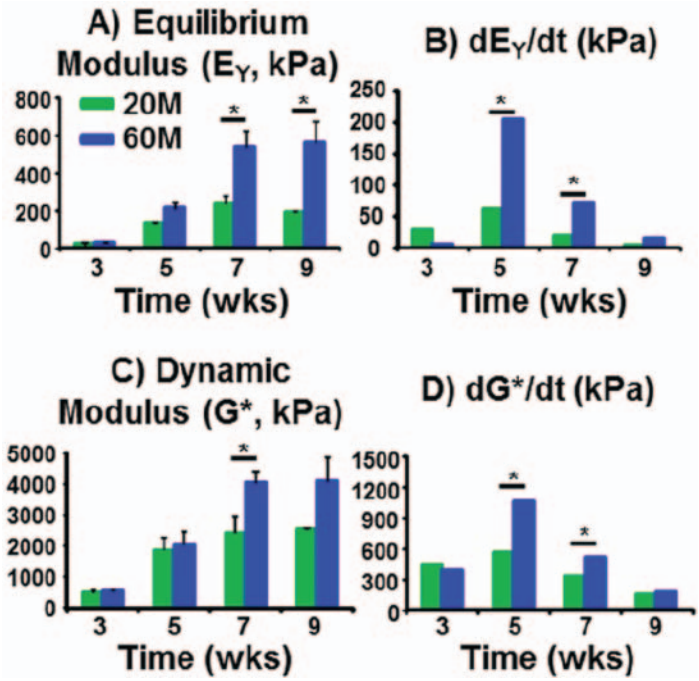


**Figure 2.** Comparison of 20M and 60M groups in terms of equilibrium modulus **(A)** and dynamic modulus **(C)** as well as their respective first derivatives **(B,D)**. (*p<0.0125 between groups, +difference greater than 20% of peak value for 60M group).

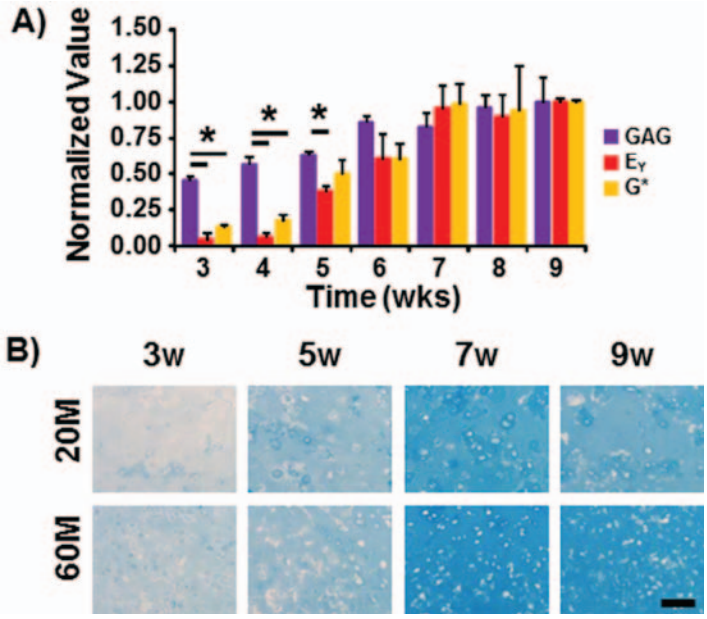


**Figure 3.** Relative increases in biochemical and biomechanical properties during maturation. **(A)** GAG, equilibrium modulus, and dynamic modulus normalized to their respective peak values (*p<0.002). **(B)** Histological staining for proteoglycans throughout maturation.

to the 5 week time point (p<0.002), before reaching similar relative values (p>0.002). Similar results were obtained for the 20M group. Histological staining for GAGs reflected the quantitative data, with notable changes in staining from 3 to 7 weeks and less drastic changes thereafter. Additionally, the 20M and 60M groups stained similarly at 5 weeks, but the 60M group had substantially more intense staining by 9 weeks.

## Discussion

In this study, we performed an investigation into a TB-TE approach by quantifying and modeling the maturation of MSC-laden HA hydrogels during in-vitro culture. The constructs featured non-linear maturation profiles, with the peak rates occurring at 5 weeks. Furthermore, substantial differences in the rate of maturation could be determined for constructs of different cellular composition (changing seeding density). Thus, this system will allow us to test the overarching hypothesis of TB-TE within an in-vivo setting, which is that maximizing maturation rates, not states, prior to implantation will provide a better predictor of in-vivo success. Future work will seek to further increase maturation rates in-vitro through the use of chemical and mechanical stimuli.Additional analyses such as gene expression and more specific analysis of the matrix will be performed and correlated to mechanical data to identify other indicators of construct maturation. In summary, the current work provides a quantitative framework that will allow for the assessment of how constructs of differing maturation states and rates are able to appropriately remodel and integrate in-vivo, in order to optimize TE constructs to effectively restore function of injured cartilage.

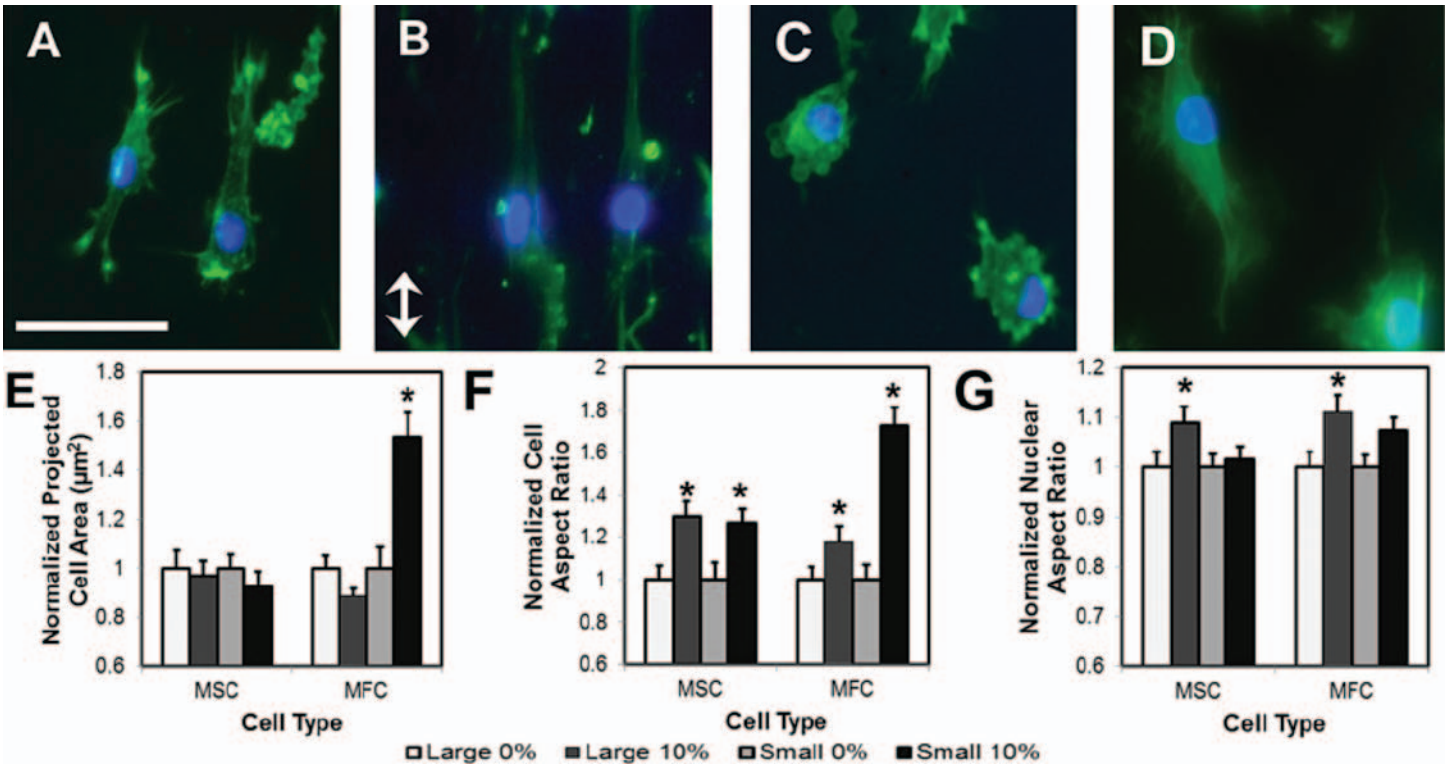


**Figure 3.** MFCs on large **(A,B)** or small **(C,D)** fiber scaffolds after 0% and 10% strain. Projected cell area **(E)**, CAR **(F)** and NAR **(G)** as a function of cell type and normalized to 0% strain. Data represents mean ± SEM. Scale bar = 50 μm. Arrow indicates fiber direction/direction of stretch.

## Significance

This study provides an objective methodology to allow appropriate selection of TE constructs to maximize their in-vivo potential. Successful validation of this approach will allow better prediction of outcomes following implantation, thus enhancing their therapeutic potential.

## Acknowledgements

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# Mesenchymal Stem Cell-Based Cartilage is Unstable in Very Long Term In-Vitro Culture

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## Introduction

Adult derived progenitor cells, including mesenchymal stem cells (MSCs), are a promising cell source for the treatment of non-healing musculoskeletal disorders. Soluble factors combined with appropriate 3D culture materials support the chondrogenic differentiation of these cells,[1,2] and in some instances, a mechanically viable cartilage-like tissue can be produced.[3,4] However, recent studies have also demonstrated that this chondrogenic phenotype is unstable, producing mineralized matrix akin to bone when implanted subcutaneously[5] or challenged with hypertrophic differentiation media *in vitro*.[6] While the focus of the cartilage tissue engineering community has largely been skewed towards the anabolic functionality of these cells, stability must be achieved if constructs are to function *in vivo*. Previously, we have shown that MSC viability in agarose hydrogels is markedly lower than chondrocytes (CH) cultured identically.[7] Because agarose is an unsupportive 3D material (does not provide biologic cues or attachment), alternative hydrogels may yield different outcomes. We have recently shown that hyaluronic acid (HA)-based materials can support the development of tissues that match some native properties.[3] The objective of this study was to evaluate MSC instability in long term agarose and HA culture by delineating the time course of decline in MSC viability in comparison to chondrocytes and by assessing the peaks and declines in matrix accumulation and mechanical properties across gel types.

## Methods

Juvenile bovine bone marrow MSCs (jbMSCs, P2) and primary CH were encapsulated in 2% agarose (Ag) cylinders (4 mm ø x 2.5 mm) at a density of 20M cells/mL. Constructs were fed twice weekly with 1 mL of chemically defined media (CM) with (+) or without (−) 10 ng/mL TGF-β3 as in[7] through 168 days. In a separate study, jbMSCs (P2) were encapsulated at a density of 60M cells/mL in 1% (w/v) methacrylated HA crosslinked via a UV initiated addition reaction.[3] Constructs were fed thrice weekly with CM+ through 126 days. Compressive equilibrium (eq.) modulus was evaluated via unconfined compression (10% strain) (n=3 Ag, 4 HA) and samples were papain digested for biochemical assessment of glycosaminoglycans (GAG) via the dimethylmethylene blue assay. Percent viability in the center of the constructs (n=3, Ag) was assessed in the center of the constructs as in[7] with the Live/Dead Cell Viability Kit. Constructs were paraffin processed and stained for proteoglycans (PGs, Alcian Blue) and calcium deposits (Alizarin Red). Significance ($p<0.05$) was established with 2-way ANOVA (Ag; day and media type as independent variables) and 1-way ANOVA (HA; day as independent variable) and Tukey's post-hoc.

## Results

In the center of Ag constructs, CHs retained stable viability in CM(−); however, the population was only stable through day 56 in CM+ (Fig 1). MSCs in CM(−) and CM(+) showed marked declines in viability as early as day 7, retaining only 50% in CM(−) and 62% in CM(+) (compared to ~90% at day 1). Although MSC CM(−) continued to decline from day 28 to day 56, viability stabilized for CM(+) between days 28 and 112 before declining once again. In terms of eq. modulus, values for CH CM(+) constructs increased from day 56 to day 168, whereas those for MSC CM(+) constructs did not (Fig 1). Interestingly, there was a spike in eq. modulus of MSC CM(−) at the last time point due to mineralization as this tissue stained heavily for calcium deposits (not shown). In MSC-seeded HA constructs, similar instability was observed at later time points. GAG content peaked at ~1.6 mg/construct at day 63, before declining to ~1.2 mg by day 84 and ~0.27 mg by day 126 (Fig 2). Similarly, compressive properties peaked at 218kPa at day 49, declining to 110kPa by day 84 before plummeting to almost zero at day 126 ($p<0.001$). Staining of proteoglycans in day 168 (Ag) and day 126 (HA) MSC CM+ constructs showed a marked decrease in intensity compared to day 56 constructs (Fig. 3). These data confirm the degradation of the previously established matrix.

## Discussion

Recent advances in stem cell based tissue engineered cartilage (particularly with regard to

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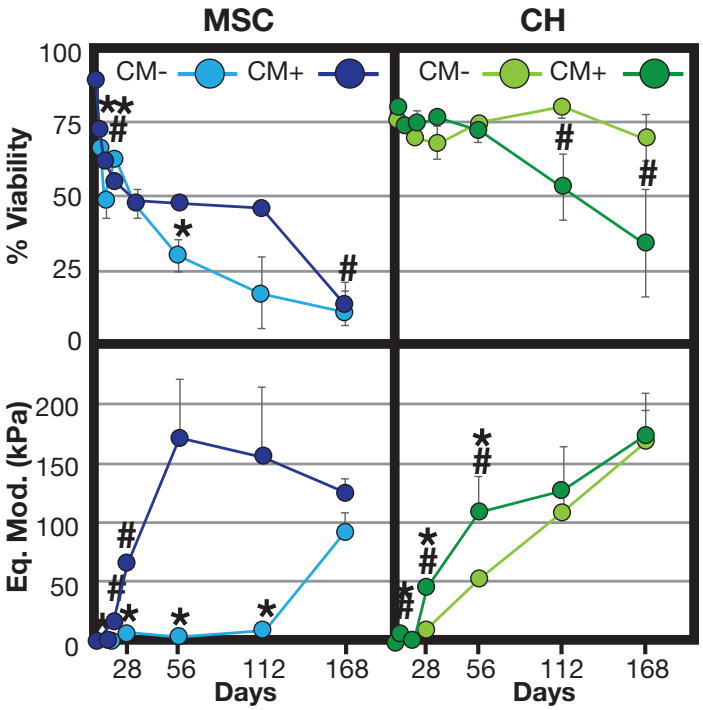


**Figure 1.** (Top) Viability in the center of constructs is less stable for MSCs, particularly at early time points ($p<0.05$, * vs. previous time point CM−, # vs. previous time point CM+). (Bottom) Eq. modulus of CH and MSC-laden constructs. ($p<0.05$, * vs. peak CM−, # vs. peak CM+).

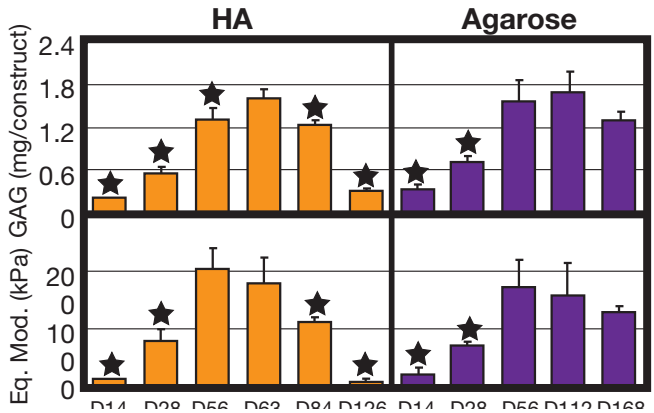


**Figure 2.** GAG content (top) and eq. modulus (bottom) decline significantly from peak values at later time points in HA hydrogels. ($p<0.05$, star vs. peak).

functional properties) support the promise of MSCs for use in cartilage repair; however, the lack of long term stability of these constructs both *in vitro* and *in vivo* raises important new considerations. In this study, we identified a rapid, followed by a progressive, decline in MSC viability in 3D Ag constructs. Furthermore, we showed that with extended time in culture, the instability in MSC phenotype and/or viability resulted in the destruction of previously established matrix and mechanical properties. Perhaps most interestingly, we observed spontaneous calcification of matrix in conditions where TGF-beta was not present after very long culture durations. This instability is not simply a function of Ag culture, as a very similar (and perhaps even advanced) time course of

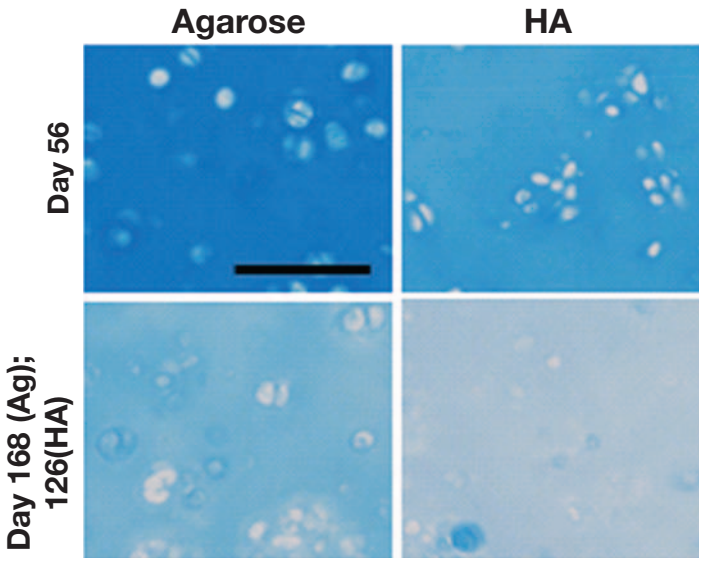


**Figure 3.** Decreased proteoglycan staining intensity at later time points suggests breakdown and/or loss of matrix. Scale = 100 μm.

self-destruction was observed in HA gels. These data suggest that even in a controlled culture environment, removed from any perturbations arising from *in vivo* soluble factors, chondrogenic instability may be inherent to MSCs and will need to be addressed to further the clinical applicability of this cell type.

## Significance

This work demonstrates a pronounced instability in MSC-based cartilage cultured for extended durations, independent of biomaterial scaffold, and despite achievement of near native mechanical properties. If MSC-based cartilage constructs are to be used clinically, concerns related to whether this instability would be progressive and unpreventable after implantation will need to be addressed.

## Acknowledgements

This work was supported by the NIH (R01 EB008722).

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# An Inverse Agonist for Retinoic Acid Receptors Boosts Mesenchymal Stem Cell Chondrogenesis and Functional Properties of Tissue Engineered Cartilage

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## Introduction

Members of the transforming growth factor family are widely used for chondrogenic induction of musculoskeletal progenitor cells. However, given the incompleteness of differentiation mediated by this morphogen on its own, interest has focused on the use of pharmacological agents that can induce chondrogenesis through alternative pathways.[1] Retinoids play a key role in skeletogenesis, with retinoic acid directly interacting with nuclear receptors to modulate transcription. Inhibition of retinoic acid receptors (RARs) positively regulates chondrogenesis through increases in SOX9 expression.[2] Few studies exist examining the potential of RAR antagonists or inverse agonists for cartilage tissue engineering,[3,4] and none have assessed the functional properties that arise from the addition of these molecules. The objective of this study was to assess the molecular and functional effects of supplementation with the pan-RAR inverse agonist BMS 493 on mesenchymal stem cells (MSCs) cultured in three-dimensional pellet and agarose culture systems. In additional to examining target pathways through the use of 96-well gene arrays, we assessed the functional effects this molecule has on matrix content and construct mechanical properties.

## Methods

Juvenile bovine MSCs were expanded through passage 1 or 2. For pellet culture (P), 250,000 cells were pelleted and cultured in a non-adherent conical 96-well plate and cultured for 21 days. For hydrogel culture (H), cells (20 M/mL) were encapsulated in 2% agarose constructs (4 mm Ø, 2.25 mm thick). A 7 day hydrogel study (D7) was conducted independently from a 21 day study (D21). Constructs and pellets were fed twice weekly with chemically defined media (CM) with (+) or without (−) 10 ng/mL TGF-β3. The pan-retinoic acid receptor inverse agonist, BMS 493 (Tocris Bioscience), was added at concentrations of 0.5 μM - 2μM (P / H 7D) or 0.1 μM - 1 μM (H 21D). Cell viability was assessed with the Live/Dead Cell Viability Kit as in[5] (H D7, n=3). Constructs were paraffin processed, sectioned, and stained for proteoglycans (Alcian Blue; H D7, n=3). RNA of D7 constructs was extracted using TRIZOL-chloroform and real-time PCR of 96 genes run using a Signal Transduction PathwayFinder™ PCR Array plate (human; SABiosciences). Samples included CM−, CM+, and CM+ 2uM BMS (n=3 combined). ΔΔCt analysis was performed to assess relative expression across all samples with values normalized to GAPDH and monolayer cells taken as the control group. Additional assays (n=3), including assessment of glycosaminoglycan (GAG) content (DMMB assay as in[5] (P [2 pellets combined per n]/H 21D)) and compressive equilibrium modulus (10% stress relaxation as in,[5] H 21D), were carried out to determine the contribution of BMS to functional properties of engineered constructs. Significance ($p<0.05$) was established with 1-way ANOVA and Tukey's post-hoc correction with media as the independent variable for GAG content, eq. modulus, and viability (comparisons made within time point for pellet culture).

## Results

Addition of 2 μM BMS 493 to chondrogenic media resulted in an increase in GAG in pellet cultures after 21 days in both CM− (~5.4 fold) and CM+ (~1.4 fold) conditions, with CM+2μM BMS resulting in the highest GAG content of 104 μg/pellet (Fig 1). Similarly, Alcian blue staining of hydrogels on day 7 showed an increase in the number of cells with intense pericellular staining of proteoglycans in both 2μM BMS conditions compared to controls (Fig 2). Incorporation of BMS had no effect on cell viability at day 7. Viability ranged from 78.2-82.5% in CM- conditions and 85.1-87.3 in CM+ conditions. In hydrogel cultures (21 days), incorporation of BMS at the highest concentration assessed (1 μM) in CM+ media had a striking effect on both GAG and eq. modulus (Fig 3). Interestingly, the increase in these functional outcomes was not proportional (a 59% increase in GAG with an 87% increase in eq. modulus). PCR arrays revealed the down regulation of several genes as a result of CM+2μM BMS treatment compared to CM+, including those related to metabolism

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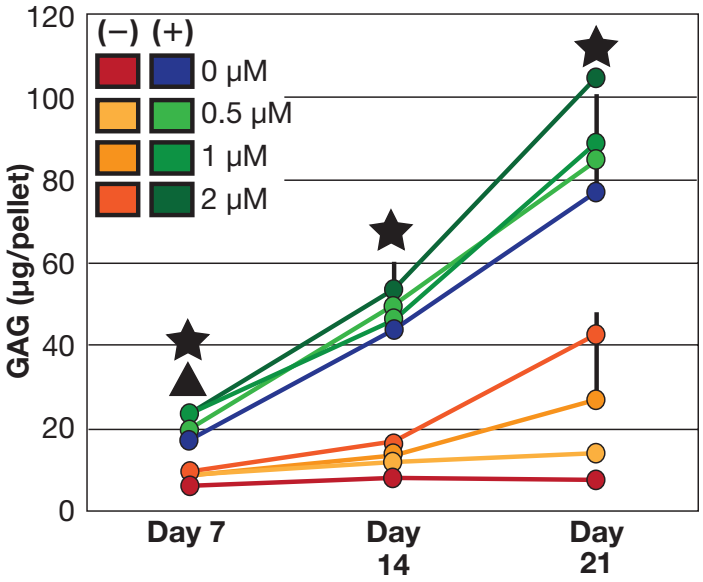


**Figure 1.** Increase in GAG in pellet culture with the incorporation of BMS. ($p<0.05$, star = −/+ 2μM vs. respective control; triangle = −/+ 1μM vs. respective control).

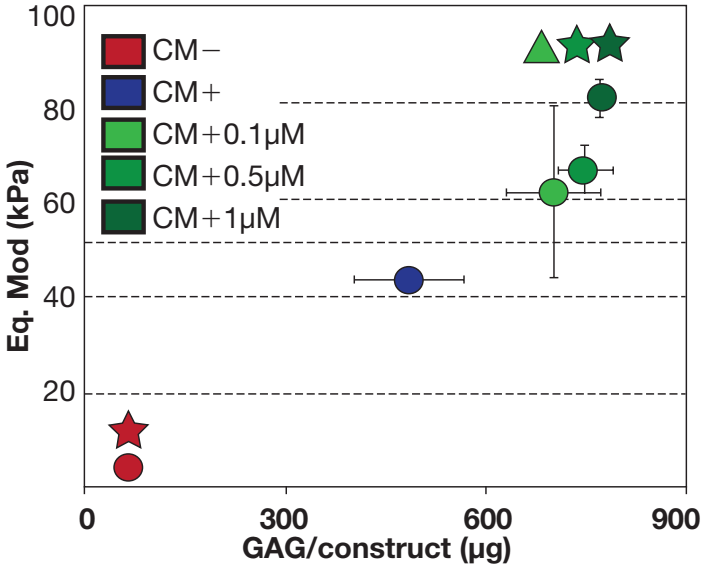


**Figure 2.** Increase in GAG is disproportionate to increase in eq. modulus in hydrogels after 21 days. ($p<0.05$, star = GAG and eq. mod vs. CM+; triangle = GAG only vs. CM+).

(NQO1, LDHA), lipid biosynthesis (ASCL4), anti-apoptotic function (BCL2, BIRC3), and a retinol binding protein (RBP1) (Fig 2). Upregulation of a gene whose product binds fatty acids (PPARD), and a gene involved in chondrogenesis (WNT5A) also occurred in CM+BMS treated versus CM+ cells.

## Discussion

Here we show that antagonism of RARs elicited via an inverse agonist is highly beneficial for early maturation of stem cell based cartilage constructs. Incorporation of the inverse agonist BMS not only resulted in an increase in GAG in pellet and hydrogel cultures, but also an ~2 fold increase in eq. modulus by 21 days. We also found positive regulation of

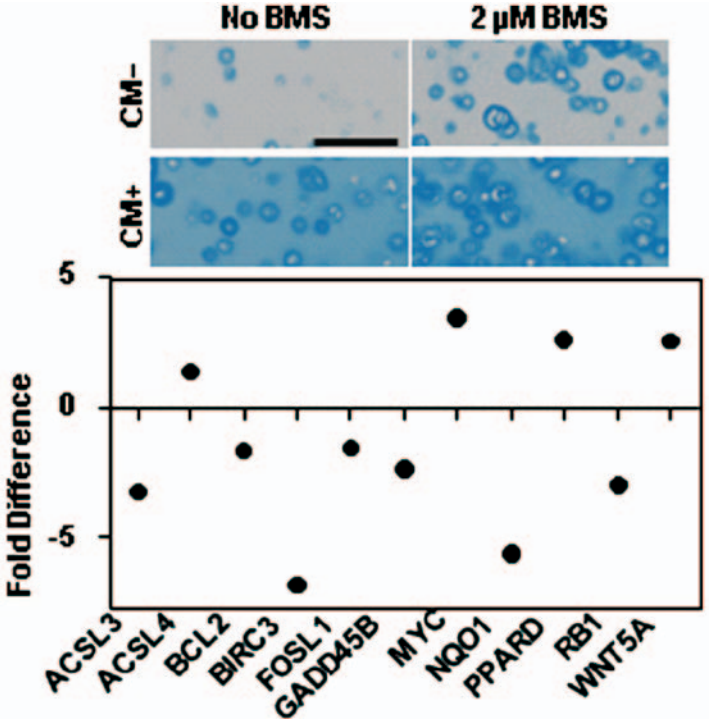


**Figure 3.** Top) Increase in cells with intense pericellular GAG in both CM− and CM+conditions with addition of BMS. (Scale = 100 μm) Bottom) Highest fold changes of CM+2μM BMS to CM+ after 7 days of hydrogel culture.

genes that could prove to be useful in an *in vivo* setting of an osteoarthritic joint, such as WNT5A, which inhibits canonical WNT signaling and thereby promotes chondrogenesis. In addition, we observed down-regulation of metabolic (NQ01, LDHA) and anti-apoptotic genes occurred (BLC2 and BIRC3). Down-regulation of these latter two genes indicates that the cells exposed to BMS were under less stress than those in CM+, and so less in need of activation of anti-apoptotic pathways. While we observed no significant differences in viability of these constructs at the early time point at which gene expression was assessed, longer term evaluation in the context of BMS may reveal differential viability relative to CM+ cultures. Alternatively, if CM+ cells are under stress, while BMS cells are less so, more efficient utilization of cellular resources (and production of extracellular matrix) may occur, leading to the improved functional outcomes we observed.

## Significance

In this study, the use of an RAR inverse agonist significantly enhanced the functional properties of stem cell based cartilage constructs, potentially reducing the *in vitro* culture time necessary prior to implantation. Our findings also suggest that additional activated pathways, including those involved in cell stress and apoptosis, may warrant further investigation as markers of efficient chondrogenic activity in 3D culture.

## Acknowledgements

This work was supported by the NIH (R01 EB008722).

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# A High Throughput Mechanical Model to Study Injurious Compression of Engineered Cartilage

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## Introduction

Post Traumatic Osteoarthritis (PTOA) is caused by a traumatic injury to the joint, where cartilage damage initiates events that progress to OA later on in life.[1] In vitro explant models have been developed to evaluate the mechanisms that govern cartilage degeneration following injury. Several variables (peak stress, final strain level, strain rate) have been correlated with the degree of tissue damage.[2-3] These models have also been used to evaluate the effect of various small molecules on cell viability and matrix degradation caused by injury.[4-5] Although these studies provide insight into the mechanisms of injury, rapid screening of libraries of small molecules, with reproducible samples, is not possible. Alternatively, engineered cartilage tissues analogs (CTA) can be produced in reproducible formats and impacted using a high throughput mechanical screening (HTMS) device.[6] This system may provide a valuable platform to study the timeline of events following traumatic injury, and to discover new molecules that block injury progression into PTOA. Here we show that the degree of impact induced injury to CTAs is dependent on loading parameters, and that high throughput impact initiates a degenerative response.

## Methods

Chondrocytes isolated from juvenile bovine cartilage were seeded into a self-aggregating suspension culture model to create CTAs using poly-HEMA coated 96 well plates ($1X10^6$ cells/well).[7] Constructs were pre-cultured for 4-6 months in DMEM with 10% FBS and vitamin C. Single Impact: Four protocols were evaluated using an Instron (5848): 75% and 50% strain at strain rates of 50%/s and 10%/s for a total compression time of 10s. CTAs were harvested at 12, 24 and 120 hrs post-injury and analyzed for live/dead (N=1) and histology (N=2), biochemical content (GAG, DNA, HYP) (N=3), or frozen in $LN_2$ for gene expression (N=3). Media was collected to measure soluble GAG, nitric oxide (NO), and MMP (N=3). HTMS: Based on induced injury with single impact, CTAs were impacted to 60% strain at 50%/s in a 48 well format. CTAs were harvested at 24 and 120 hrs post-injury for biochemical (N=3) and gene expression (N=3-4) analysis. Media was collected at 24 hrs (N=12-14) and 120 hrs (N=5-7) for assays above. The real-time load response was monitored during impact, and peak stress calculated based on measured CTA geometry.

Statistics: Significance was calculated using one way ANOVA with Tukey's post hoc test, with $p<0.05$.

## Results

The load response of CTAs during single impact testing and the apparatus used are shown in Figure 1A. CTAs in these tests had an equilibrium modulus of 90.1+/−29.0 kPa. Peak stresses at 75% strain were significantly higher than the 50% strain group for both strain rates. Histological sections showed that 50% strain caused internal fissure formation with reduced GAG staining at the fissure edges (Fig 1B). In contrast, 75% strain resulted in significant edge matrix disruption and less diffuse GAG staining throughout. Aggrecan expression decreased compared to control (24 hrs; $p<0.05$) at 75% strain, but by 120 hrs expression had recovered ($p<0.05$). With impact to 75% strain, MMP-13 expression increased compared to previous time points, control, and 50% strain at 120 hrs. Analysis of NO showed a strain dependent increase from 12 to 24 hrs; from this peak level at 75% strain, NO decreased back to 12 hr levels over the remaining time course. Following single tests, CTAs were impacted using the HTMS device (Fig 3A, B) to 60% strain at 50%/s. CTAs had an equilibrium modulus of 97.5+/−65.1 kPa. To ensure accurate displacement of the platen at the appropriate strain rate, and to test analysis methods for determining peak stresses and sensor-to-sensor variation, 10% agarose constructs were first impacted using the device. Peak stresses calculated for engineered cartilage were similar to that of the single tests to 50 and 75% strain. NO released from impacted CTAs was 7-fold higher than controls at 24 hrs, but fell 2-fold by 120 hrs, similar to single impact tests ($p<0.05$) (Fig 3C). Histological analysis and live/dead staining showed cell death in regions

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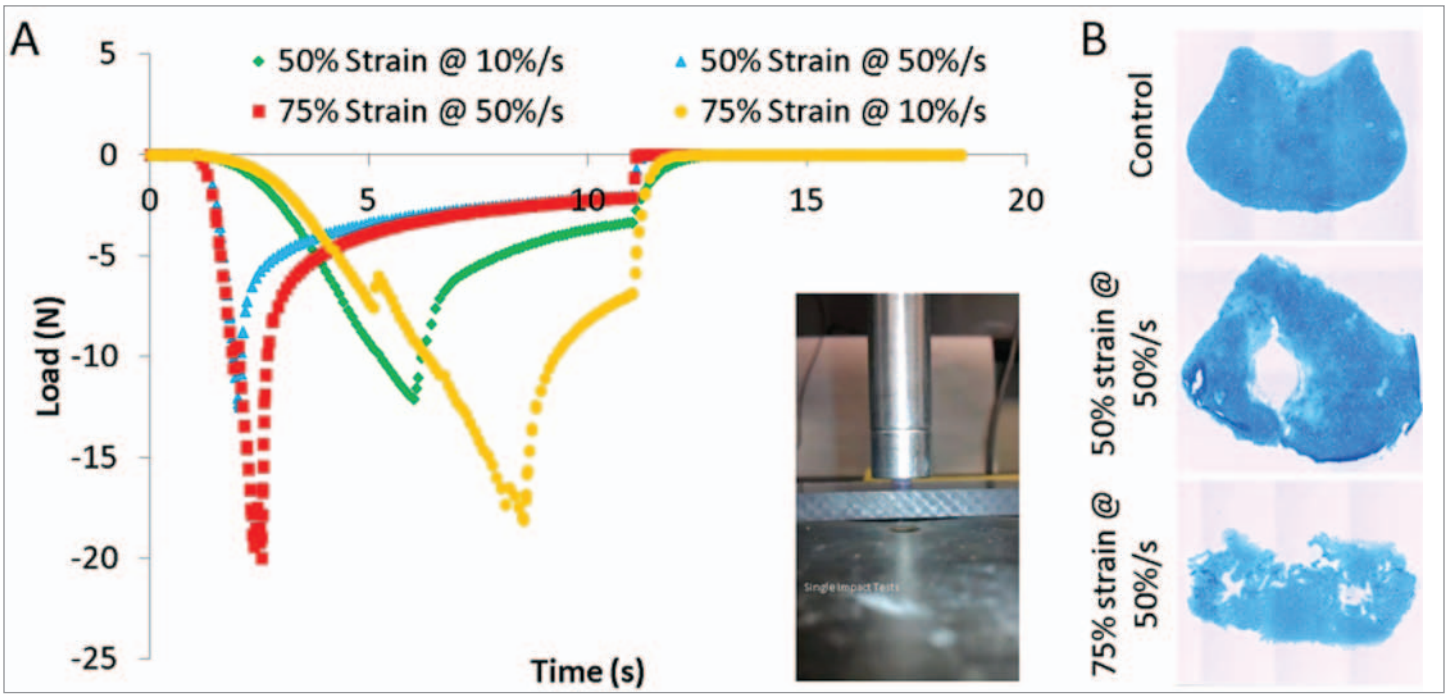


**Figure 1A-B.** (A) Representative load profile and peak stresses of CTAs for single impact tests. (B) Histological sections of impacted CTAs 120 hrs post-injury show structural disruption and loss of GAG due to impact.

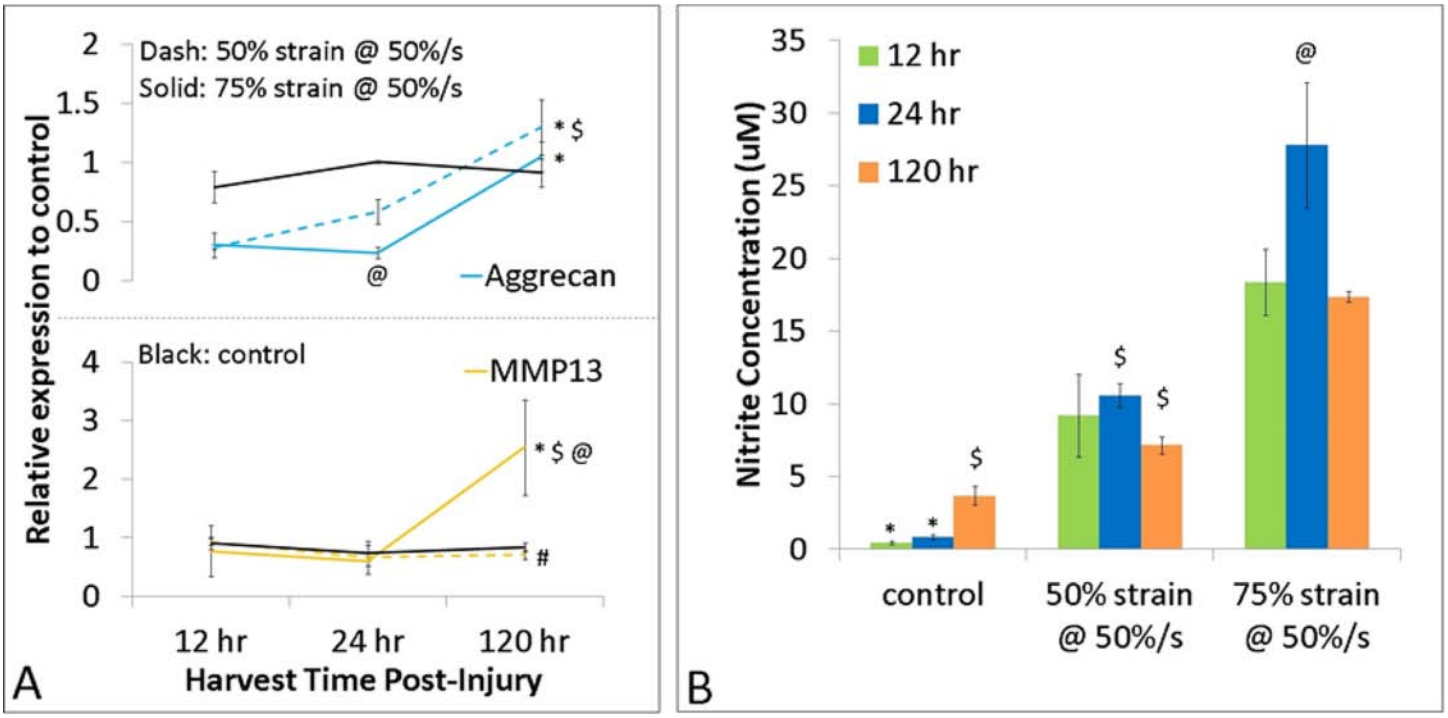


**Figure 2A-B.** (A) AGG expression is initially decreased (24 hrs), but recovers by 120 hrs; MMP-13 is only increased at 120 hrs for the highest strain. $p<0.05$: * vs 12hr; $: vs 24hr; # vs 75% strain; @ vs control( same time point). (B) NO levels show a strain dependent increase up to 24 hrs after impact. $p<0.05$ * vs 50 and 75% strain and $ vs 75% strain at the same time point; @ vs other time points.

adjacent to fissures and internal fissure formation, similar to single tests at 50% strain (Fig 3D).

## Discussion

Impact of engineered cartilage analogs resulted in catabolic events that caused chondrocyte cell death and altered biosynthesis. Previous studies have shown similar changes following impact of osteochondral explants with significant cell death and loss of matrix associated with surface fractures due to high strain rates and peak stresses.[2-3] In this study, injury to engineered cartilage was dependent on the final strain, and the injury response was modulated through gene expression

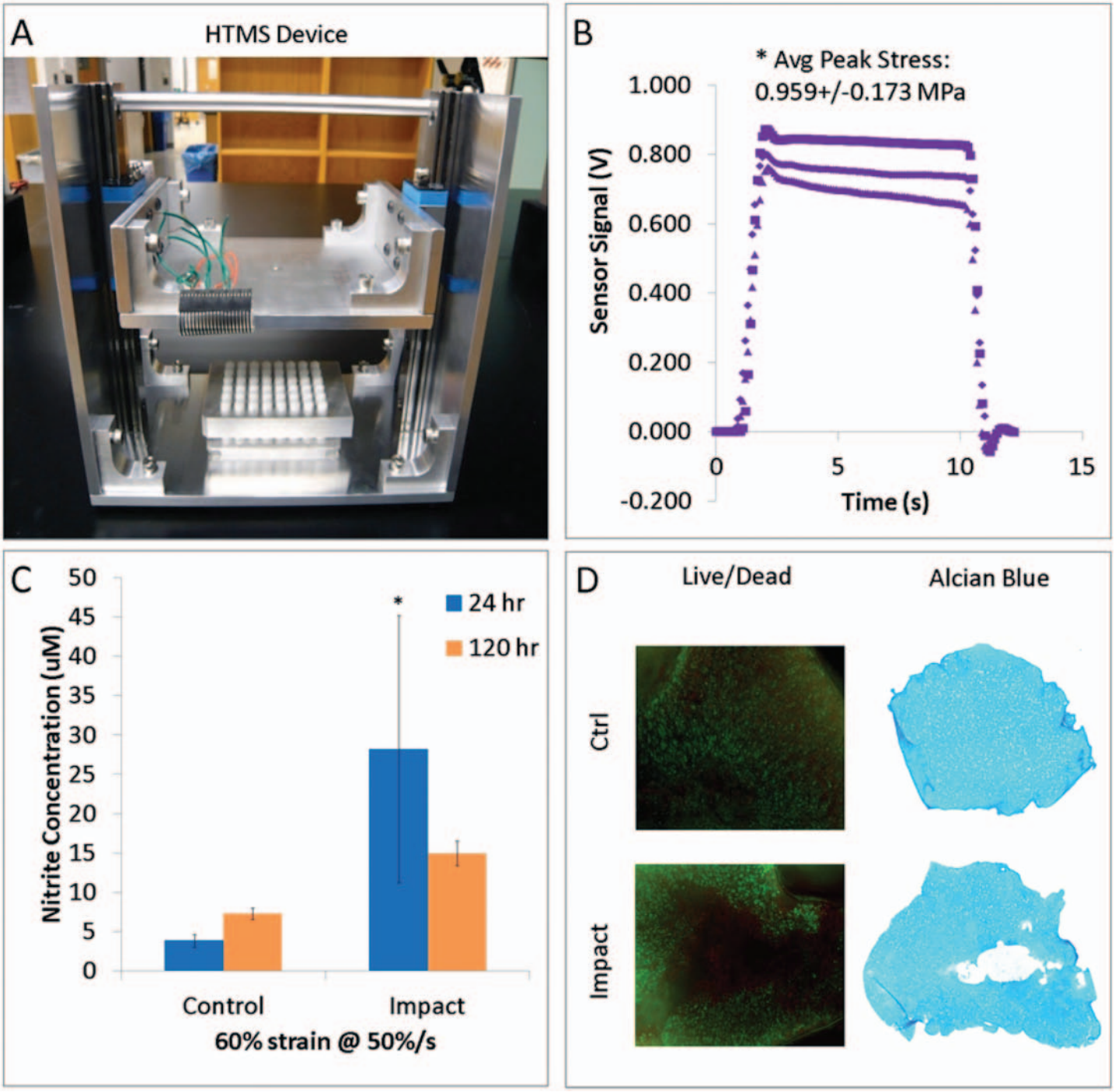


**Figure 3A-D.** (A) HTMS device for impact of 48 samples. (B) Sensor output at 60% strain at 50%/s (N=3). (C) NO levels increase at 24 hrs, but return towards baseline at 120 hrs. $p<0.05$ * vs control at 24 hrs. (D) Histological analysis (4X) shows fissures and localized cell death after impact.

and production of inflammatory molecules. Both single and HTMS impact tests showed similar trends of increased NO during the first 24 hrs after injury, followed by recovery towards baseline by 120 hrs. As nitric oxide is an acute response to injury and inflammation, increased NO may activate cell stress signaling pathways and result in the up-regulation of catabolic molecules and induce matrix degradation.[8] Attenuation of this signal and the return of aggrecan expression to that of control, may indicate a late reparative response after injury. This data describes an impact protocol that causes reproducible, acute injury in engineered cartilage. Following further validation of the impact HTMS device using additional injury-related, cellular responses, it will be possible to begin screening chemical libraries for drugs that might limit progression to PTOA.

## Significance

This HTMS device allows for the study of PTOA-related cellular responses using an engineered cartilage impact platform and allows for screening of chemical libraries for modulators of cell injury and repair towards the discovery of new drugs for the treatment of OA.

## Acknowledgements

Supported by the AO Foundation.

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# Depth-Dependent Properties of a Tri-layered Hyaluronic Acid Hydrogel Construct with Zonal Co-culture of Chondrocytes and MSCs

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## Introduction

Biomimetic design in cartilage tissue engineering is a challenge given the complexity of the native tissue. While chondrocytes (CHs) can be a source for tissue engineering, mesenchymal stem cells (MSCs) are considered a promising alternative as they can undergo chondrogenesis in a variety of 3D contexts.[1] However, MSCs are multipotent and tend towards hypertrophy when removed from a pro-chondrogenic environment (e.g., in vivo implantation). To address this issue, recent studies have investigated co-culture of articular CHs with MSCs. CHs appear to enhance the initial efficiency of MSC chondrogenesis, as well as limit hypertrophic changes in some instances.[2] While these findings are intriguing, articular cartilage also has a unique mechanical and biochemical depth-dependence. A number of studies have shown that zonal CHs seeded in layered hydrogels can produce depth-dependent heterogeneity, suggesting they maintain their identity in 3D culture.[3] Recently, we have shown that the zonal CH populations retained their native production levels and influenced MSC fate decisions in hyaluronic acid (HA) hydrogel co-cultures.[4] In this study, we bring these various ideas together with the creation of a tri-layered HA construct containing zonal CHs in each layer co-cultured with MSCs, and evaluate the depth-dependent properties of these constructs.

## Methods

MSCs (P3) and zonal articular CHs were isolated from juvenile bovine knees (Fig. 1). Full-thickness cartilage plugs were excised from the femoral condyle and divided to three layers to obtain CHs from the superficial (SCH; top 100 μm), middle (MCH; top half of remaining cartilage), and deep (DCH) zone (bottom half of remaining cartilage). CHs were isolated by collagenase digestion and expanded through passage 4. MSCs only or mixed cell populations (MSC:CH ratio = 4:1) were encapsulated at 60×10^6 cells/mL in 1% w/v HA hydrogel (Lifecore Biomedical).[5] Tri-layered constructs were created by exposing the first layer (DCH-MSC) of cell-laden HA solution to UV light for 2 minutes, followed by polymerization of the second layer (MCH-MSC) for 2 minutes, and finally adding the third layer (SCH-MMSC) with completion of polymerization for another 7 minutes. Constructs (Ø4.75 × 3.5 mm) were cultured in a defined medium containing 10ng/mL TGF-β3, with media changed thrice weekly, and constructs turned regularly to improve growth through the depth. Cell viability, distribution, and proliferation of mixed populations of MSCs (blue), superficial (red), middle (purple), and deep (green) zone chondrocytes were followed using CellTracker (Molecular Probes). Bulk compressive properties were assessed via unconfined compression,[6] and local compressive properties[7] were determined using a custom microscope compression device and texture correlation.[8] Glycosaminoglycan (GAG) and hydroxyproline

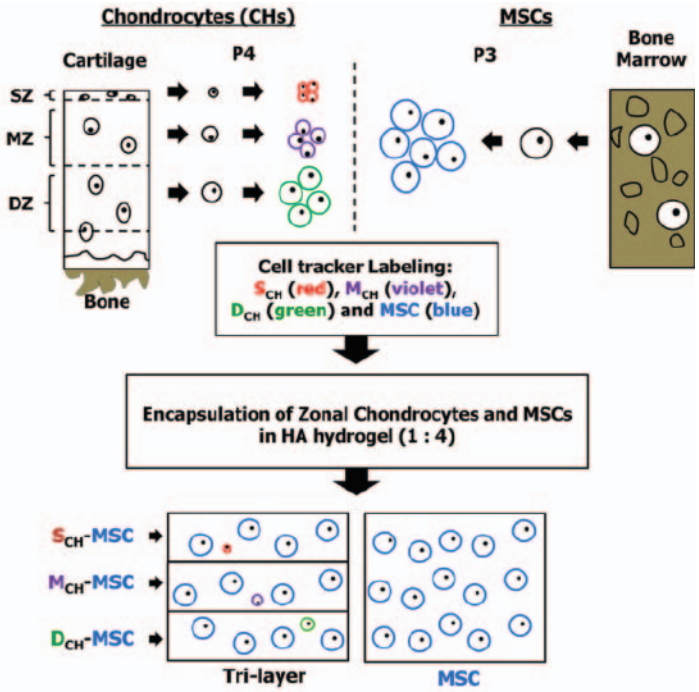


**Figure 1.** Stratified Construct with Co-culture of Zonal Chondrocytes and MSCs.

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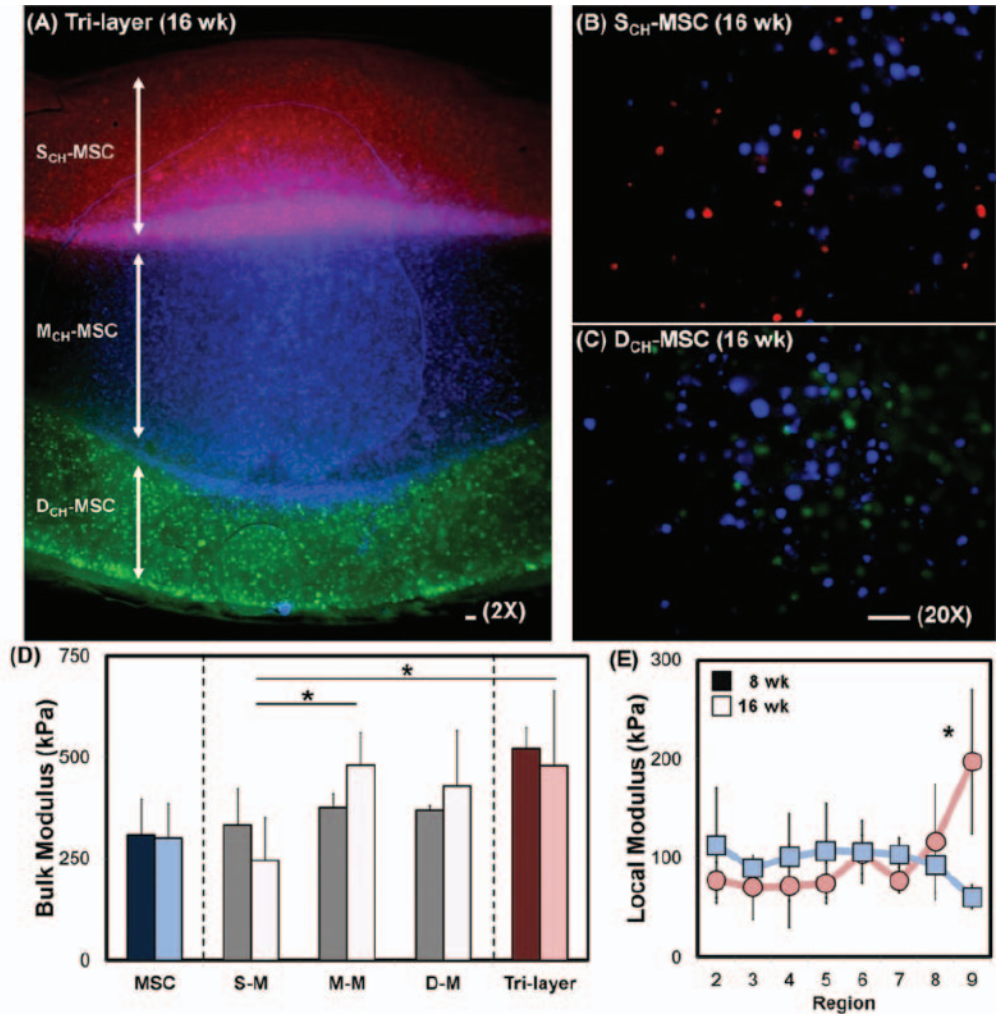


**Figure 2A-E.** Distinct zonal morphology of tri-layered construct and mechanical and biochemical properties at 8 and 16 weeks. (A) Visualization of zonal CHs co-cultured with MSCs in a tri-layered HA hydrogel construct; SCH (red), DCH (green) and MSCs (blue) (scale bar: 100 μm). Zoomed in images of (B) SCH-MSC (20x) and (C) DCH-MSC (20x). (D) Bulk modulus (kPa), where darker bars indicate 8 weeks and lighter bars indicate 16 weeks. (E) Local modulus (kPa) in MSC-only (pink) and tri-layer (blue) constructs, where region 9 is the deep zone ($n=4$; $p<0.05$).

contents were determined. Paraffin embedded sections (8μm) were stained with Alcian Blue for proteoglycans (PG) and by immunohistochemistry for collagen (COL) type I, II, X and chondroitin sulfate (CS). Significance was determined by two-way ANOVA with Tukey's post hoc tests ($p<0.05$).

## Results

MSC and CH subpopulations were viable over the 16 week culture period, with each cell population well mixed within its appropriate layer (Fig. 2A-C). Bulk modulus and GAG content of mixed cell population constructs depended on the zonal origin of CHs; the lowest production was in constructs from the SCH-MSC group, and the highest production in MCH-MSC and DCH-MSC groups (Fig. 2D). The bulk modulus and GAG content of the tri-layered construct was 69% and 32% higher, respectively, than MSC-only constructs at 8 weeks, and 59% and 9% higher at 16 weeks. Further, the local modulus of the tri-layered constructs showed depth-dependent properties (72.6 kPa in region 2 and 197 kPa in region 9), while the MSC-only modulus was homogenous through the depth (Fig. 2E). The local modulus of tri-layered constructs in region 9 (DCH-MSC) was three times higher (197 kPa; $p=0.01$) than that of MSC-only (60 kPa). Both tri-layered and MSC-only constructs showed dense COL II and CS deposition at 8 weeks, with the tri-layered construct showing a clear interface between the layers, and intense COL II staining (Fig. 3).

## Discussion

Here, we investigated the influence of co-culture of zonal articular CHs with bovine MSCs in 3D HA hydrogels, and created a tri-layered construct with mixed cell subpopulations in each layer to mimic the depth-dependent properties of articular cartilage. SCH-MSC produced constructs with the lowest compressive properties and GAG content (240 kPa; 3.2% WW), while MCH- and DCH-MSCs produced constructs with the highest bulk properties (>400 kPa; >4 %). Importantly, these differences were apparent with CH comprising only 20% of the starting cell population. When the single-layered constructs with mixed cell subpopulations were combined into one stratified construct, overall construct properties increased. The tri-layered construct retained a distinct cellular organization and produced constructs with depth-dependent properties, while MSC-only constructs showed no depth-dependence. The local modulus of the DCH-MSC layer in the tri-layered construct was ~2.5 times greater ($p=0.01$) than that of SCH-MSC constructs. Taken together, these results demonstrate that a layer-by-layer fabrication scheme, including co-cultures of zone-specific articular CHs, can reproduce the depth dependent characteristics of native cartilage. Future work will investigate how the individual cells within each layer communicate with one another and with adjacent layers, and scale this technology to produce constructs of anatomic relevance for cartilage repair applications.

## Significance

Biomimetic design in cartilage tissue engineering is challenging. Formation of tri-layered engineered cartilage using zonal CHs co-cultured with MSCs holds promise for the repair of focal defects. This study is the first to demonstrate co-cultures of zonal articular CHs with MSCs to produce

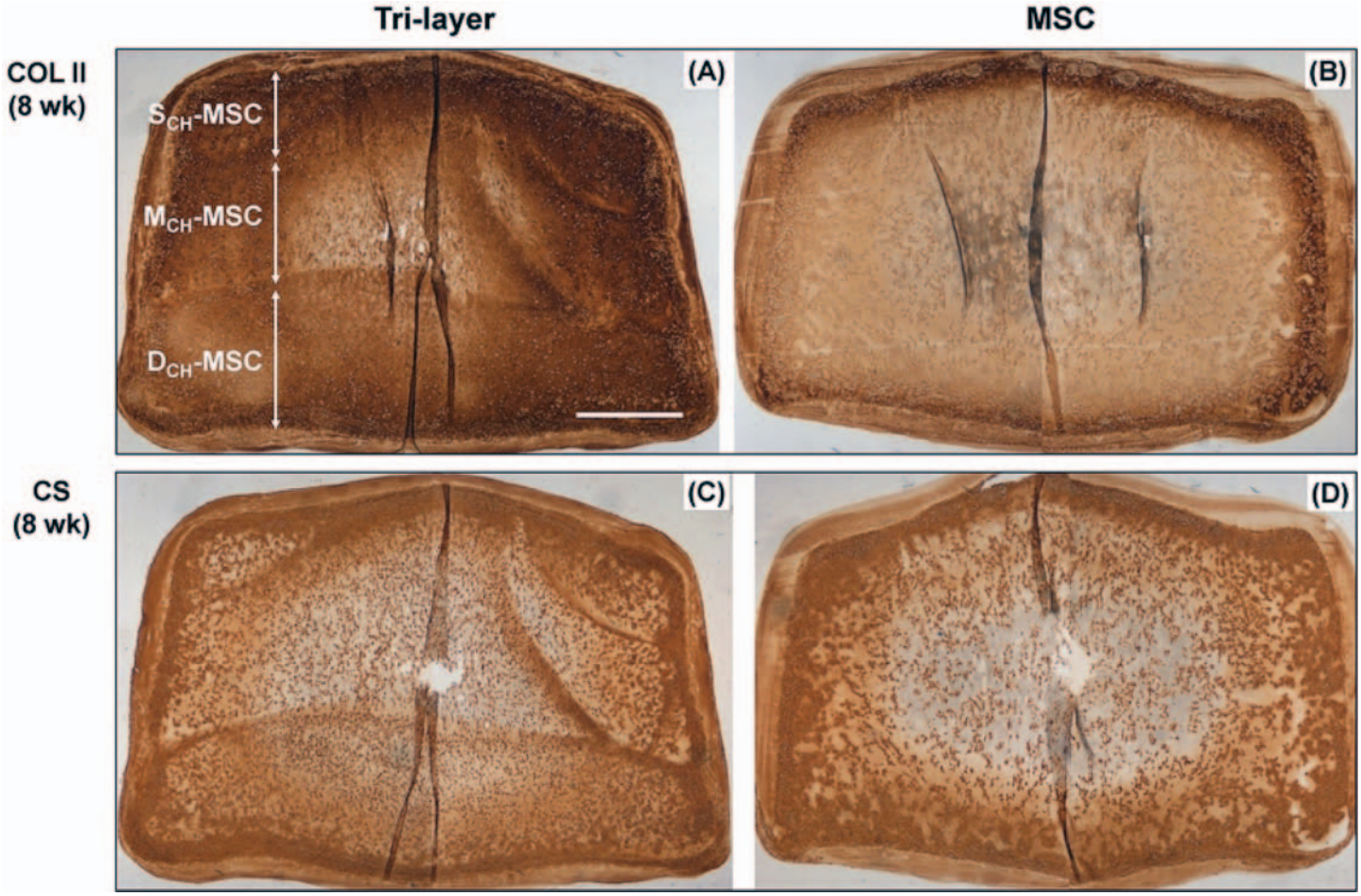


**Figure 3A-D.** Immunohistochemical analysis of tri-layered (A and C) and single layer (MSC only; B and D) constructs. Type II collagen (A-B) and chondroitin sulfate (C-D) staining on day 56 (scale bar: 1mm).

a tri-layered construct with depth dependent cellular and mechanical heterogeneity.

## Acknowledgements

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# Mesenchymal Stem Cells in Chondrogenic 3D Culture Are More Sensitive to Pro-Inflammatory Cytokines than Chondrocytes

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## Introduction

Articular cartilage is a specialized tissue that functions to transmit loads during daily activities. However, with increasing age or following injury, damaged cartilage can progressively deteriorate, leading to osteoarthritis.[1,2] Combining various cell types and biomaterials in cartilage tissue engineering can generate constructs that mimic the architecture and function of native tissue.[3] However, the response of these engineered constructs to the inflammatory environment present in the joint during OA is not well understood. Moreover, given the persistent deficits in constructs formed from mesenchymal stem cells (MSCs) compared to chondrocytes,[4] it is important to evaluate their potential in an inflammatory milieu. Multiple pro-inflammatory cytokines mediate tissue degradation in OA; two key factors involved in these catabolic processes are IL-1β and TNF-α.[5] The current study sought to determine the sensitivity of engineered cartilage based on MSCs and articular chondrocytes to inflammatory cytokines, and to elucidate the pathways that mediate alterations in cellular response and construct properties.

## Methods

Chondrocytes (CH) and MSCs were harvested from matched juvenile bovine knees and seeded in 2% agarose constructs at 20 million cells/mL (MSCs were passage 3; CH were embedded immediately). Constructs (Ø = 4mm; H = 2.25mm) were cultured in chemically defined media with TGF-β3 (CM+) for 21 days.[6] Constructs were then cultured with CM− (no TGF-β3) for 6 days while being treated with 0, 1, 5, or 10 ng/mL of either IL-1β or TNF-α. Media was collected at day 3 (D3), and IL-1β or TNF-α were refreshed during the media change. On day 6 (D6), media was collected and constructs tested in unconfined compression to determine changes in mechanical properties with treatment.[6] Alterations in biochemical content (GAG, DNA) and gene expression were evaluated post-treatment (N=4).[6] Catabolic mediators in the media were measured, including nitric oxide (NO) (Griess assay) and total matrix metalloproteinases (MMP) (Generic MMP kit, Anaspec) (N=2 for media from 5 constructs cultured together). Samples were processed for histology and stained for proteoglycans with Alcian Blue (N=2). Significance was determined using one-way ANOVA and Tukey's post hoc test with $p<0.05$.

## Results

Treatment of chondrocyte (CH) and MSC seeded constructs with either IL-1β or TNF-α, resulted in decreases in mechanical properties and biochemical content over six days ($p<0.05$). For IL-1β treated constructs at 1 ng/mL, the modulus dropped to ~50% for CH constructs, while MSC constructs plummeted by ~80% (Fig 1A) compared to controls. At higher concentrations of IL-1β, the modulus of CH constructs was further reduced, while MSC constructs had little mechanical integrity. In comparison, the modulus of 1 ng/mL TNF-α treated CH constructs was slightly reduced (~15%) compared to controls, but at higher concentrations was reduced by ~70% (Fig 1B). TNF-α treated MSC constructs decreased markedly at 1 ng/mL (~95% decrease in modulus). GAG content of these constructs showed similar declines. Analysis of NO levels showed a concentration dependent increase on D3 and D6. NO levels were highest on D3 of IL-1β treatment and reached similar levels for both cell types. For TNF-α treated constructs, NO levels were higher at all concentrations for MSC compared to CH constructs (Fig 2A,B). In addition, more GAG was released to the media for MSC compared to CH constructs in a concentration dependent manner for both IL-1β and TNF-α on D3. By D6, GAG in the media in MSC was comparable to CH constructs (Fig 2C,D). MMP levels also showed distinct differences between CH and MSC constructs, with IL-1β and TNF-α treated MSC constructs having little MMP on D3, but a 25X increase in MMP on D6. In contrast, CH constructs showed a dose dependent increase in MMP with IL-1β on D3, which was maintained at D6 for the 5 and 10ng/mL treatment groups (Fig 3A). Histological staining for proteoglycans showed a loss of matrix following exposure to TNF-α and IL-1β. Decreased staining of proteoglycan in MSC constructs was observed with increasing concentrations of IL-1β and TNF-α (Fig 3B).

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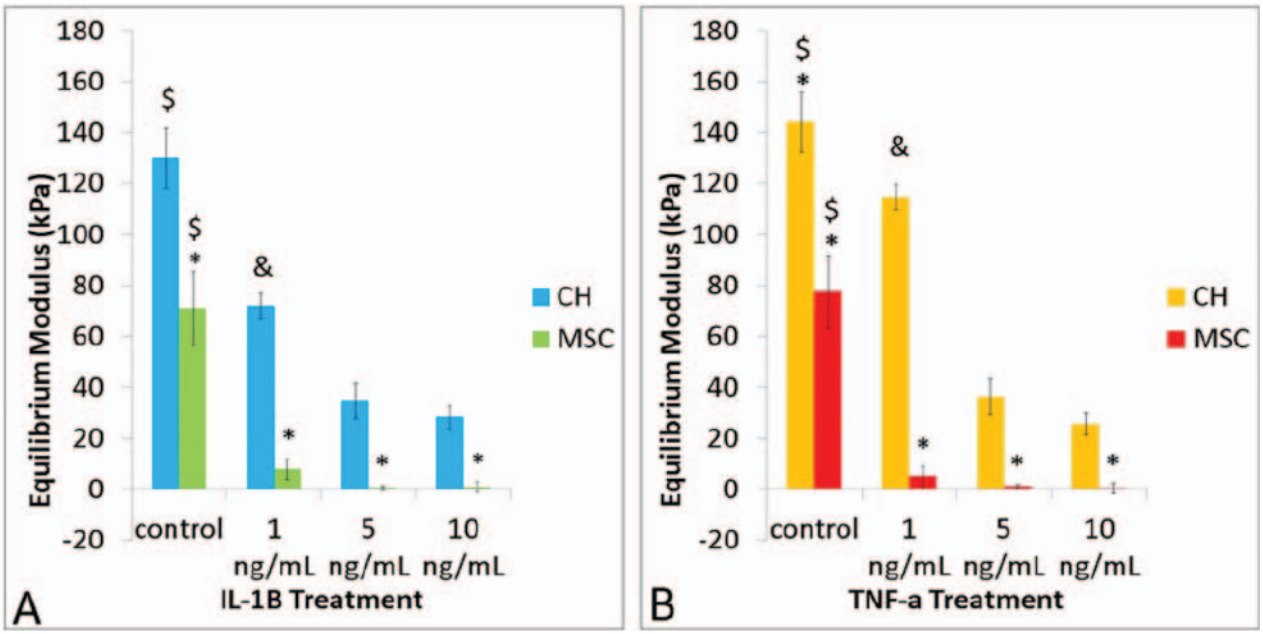


**Figure 1.** Equilibrium modulus of constructs treated with **(A)** IL-1β or **(B)** TNF-α on D6 shows a severe loss of mechanical properties for MSCs. $p<0.05$: * vs. CH; $ vs. 1, 5, and 10ng/mL.

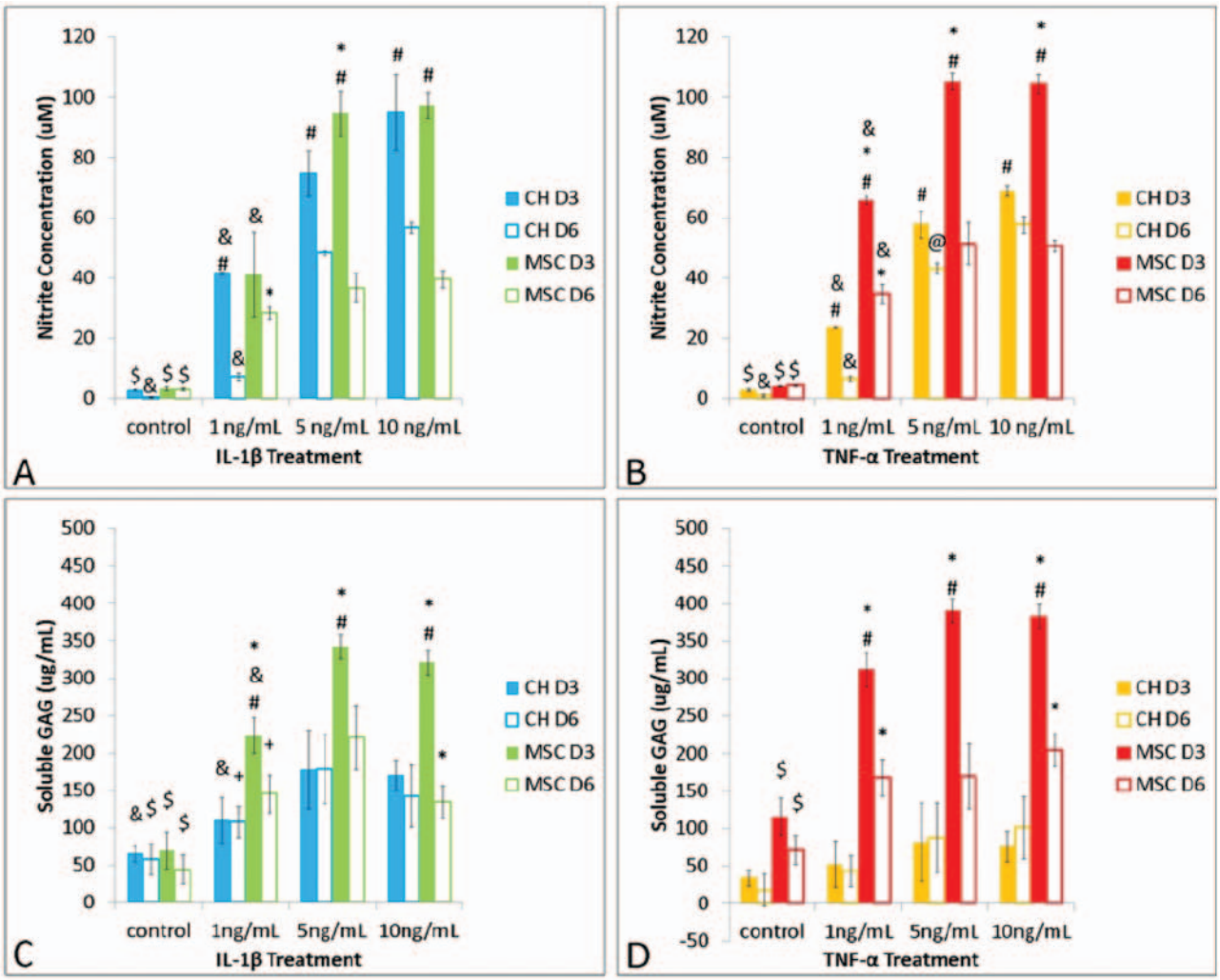


**Figure 2.** NO levels for constructs treated with **(A)** IL-1β are similar between CH and MSCs, but for **(B)** TNF-α, NO levels are 2X higher in MSCs compared to CH on D3. Soluble GAG for **(C)** IL-1β treatment is 1.5X higher and in **(D)** TNF-α treatment is 4X higher in MSCs than CH on D3. $p<0.05$: * vs. CH; $ vs. 1, 5, 10ng/mL, & vs. 5, 10ng/mL, + vs 5ng/mL, @ vs 10ng/mL (same time point); # vs D6 (same cell type).

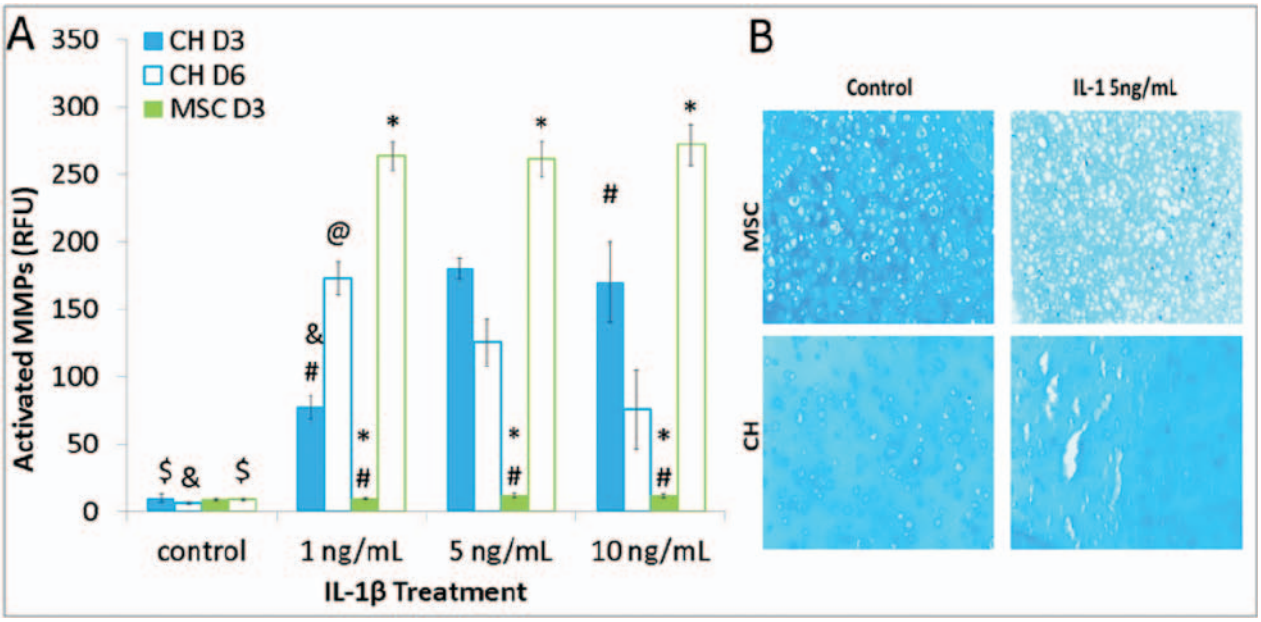


**Figure 3. (A)** For IL-1B treated constructs MMP production occurs in both cell types, but is highest on D6 for MSCs. $p<0.05$: * vs. CH; $ vs. 1, 5, 10ng/mL, & vs. 5, 10ng/mL, @ vs 10ng/mL ( same time point); # vs D6 (same cell type). **(B)** Histology shows that 6 days of treatment with IL-1β 5ng/mL causes severe GAG loss from MSC constructs.

## Discussion

This study demonstrated that the action of inflammatory cytokines on engineered cartilage constructs is dependent upon the cell type employed. MSCs were more sensitive to TNF-α and IL-1β compared to CH constructs. This sensitivity resulted in a significant loss of mechanical properties at a lower dose and correlated to increased early NO production and GAG loss to the medium. Interestingly, both CH and MSCs showed increases in MMP activity, though for MSC it occurred later (day 6). This might suggest that the mechanism underlying the differing responses of CH and MSC to these inflammatory cues is related to their differential capacity to manage stress agents and activity of degradative enzymes. It should be noted that the assay employed here measures both active and pro-enzyme forms of MMP and so direct correlations with matrix loss cannot be made. The rapid loss of GAG does suggest heightened aggrecanse activity, and specific analysis of this enzyme is warranted to further explicate the mechanism underlying these findings. One possible rationale for the attenuated mechanical response of CH constructs may be that native cartilage cells are able to, in part, maintain tissue homeostasis even in the presence of mild inflammation or normal joint stress. Future experiments will investigate differences between CH and MSC function under load within an inflammatory environment to better understand the capabilities of MSCs as a cell source for cartilage repair.

## Significance

Although MSCs can take on a chondrocyte-like phenotype and produce functional engineered cartilage, these cells are more sensitive than native CH to pro-inflammatory cytokines. These findings are critical as it suggests that the use of MSCs for cartilage repair therapies may be compromised when constructs are exposed to the inflammatory environment characteristic of OA joints.

## Acknowledgements

Supported by the NIH (ROI EB008722) and the AO Foundation.

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# Improved Meniscus Integration via Controlled Degradation of the Wound Interface

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## Introduction

Meniscal tears are prevalent and poor intrinsic healing (especially in avascular zones) directs clinical treatment towards partial removal rather than repair. However, removal alters joint biomechanics and can lead to early osteoarthritis.[1] As there are limited restorative strategies (e.g. replacement using allografts), methods to foster repair by promoting cell growth, extracellular matrix (ECM) production, and integration would represent a marked clinical advance. Previously, we showed that fetal and juvenile menisci have greater intrinsic healing capacity compared to adult meniscus,[2] and hypothesized that the high ECM density and low local cell density in adult meniscus may present physical and biologic barriers to endogenous healing. Such considerations have also arisen in cartilage-to-cartilage integration, where decreasing the local ECM density improves tissue repair.[3] To test this hypothesis in the context of the meniscus, we explored how controlled degradation of the local ECM at the wound interface might expedite healing by facilitating cell migration and division at the wound site and subsequent tissue remodeling. Furthermore, we used enzyme-releasing scaffolds to demonstrate how this technology might be applied clinically to promote meniscal repair.

## Methods

Modulation of adult meniscus ECM density: Tissue cylinders were excised with a biopsy punch from fetal and adult bovine menisci (8 mm diameter) and cored with a 4 mm punch. Samples were incubated in basal media (BM) containing 0.05 mg/ml collagenase (type IV) for 6 hours, after which the cores were replaced within the annuli (Fig. 1). Controls were incubated in BM only. Repair constructs were cultured in a chemically-defined medium[2] with transforming growth factor β3 for 4 weeks. Paraffin sections were stained with hematoxylin and eosin (H&E) to visualize cell nuclei and ECM density (n=1-2). To investigate the long-term effect of collagenase treatment on mature menisci, adult samples were incubated with 0 (BM), 0.01 (low collagenase, LC), or 0.05 mg/ml (high collagenase, HC) collagenase, reassembled into repair constructs, and cultured for 1, 4, or 8 weeks. Samples (n=4) were saturated in Lugol's solution and imaged via microcomputed tomography (μCT, ScanCo, VivaCT 70). Afterwards, sections were stained with either H&E, picrosirius red (PSR) for collagen, or 4', 6-diamidino-2-phenylindole (DAPI) for cell nuclei. Integration was defined as the cumulative distance of annulus-to-core contact normalized by the core perimeter (n=3-4 samples/group). Cell density at the interface was determined by counting the number of nuclei present within 100 μm of the interface (n=4 samples/group). Significance was assessed by two-way ANOVA with Tukey's HSD post hoc tests to compare groups ($p \leq 0.05$).

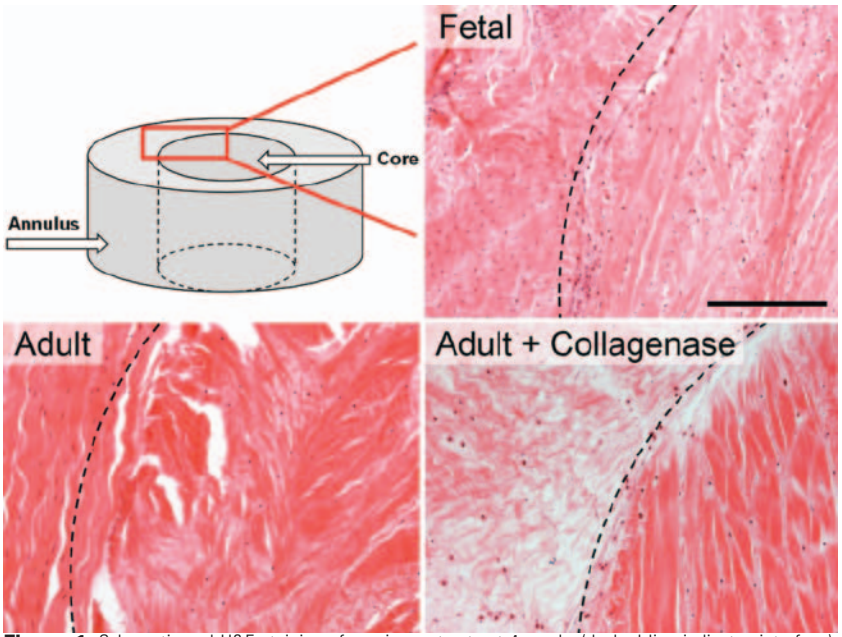


**Figure 1.** Schematic and H&E staining of repair constructs at 4 weeks (dashed line indicates interface). Scale = 0.25 mm.

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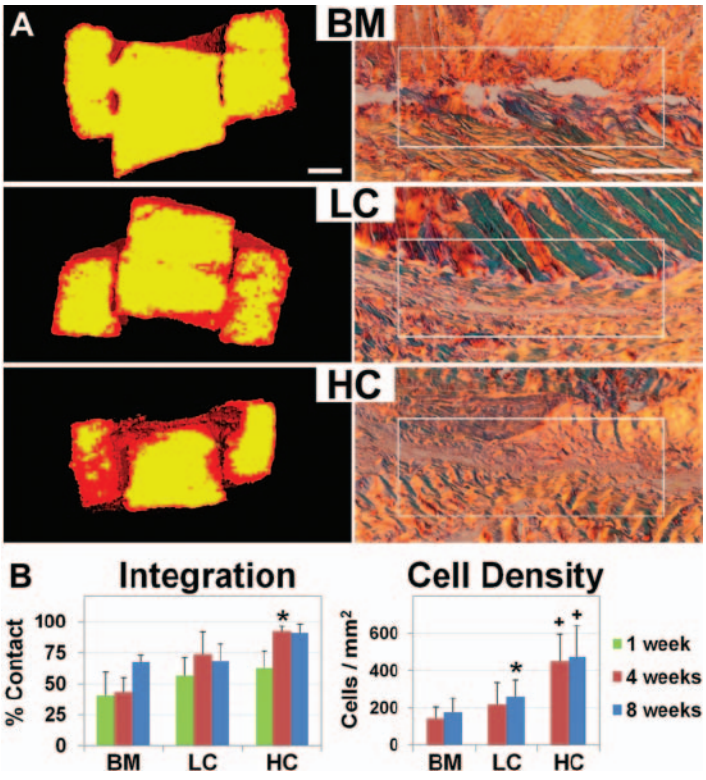


**Figure 2A-B.** Changes with exposure to no (BM), low (HC), and high-dose (HC) collagenase. (A) Left: 1 week μCT scans with low (red) and high (yellow) signal intensity. Scale = 1 mm. Right: 8 week PSR sections of the interface under polarized light. Scale = 0.25 mm. (B) Left: integration normalized to core perimeter. Right: cell density at the interface. *=p≤0.05 compared to BM. +=p≤0.05 compared to BM and LC.

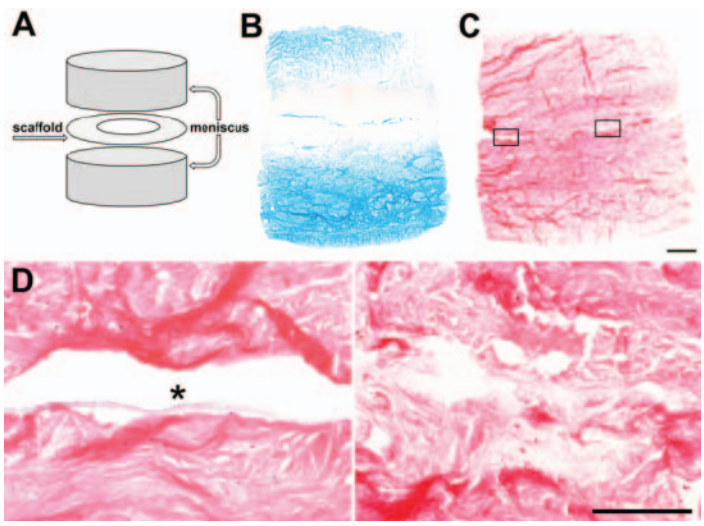


**Figure 3A-D.** Adult meniscus interface treated with collagenase-releasing scaffold at 7 days. (A) Schematic. (B) AB and (C) H&E staining. Scale = 1 mm. (D) Magnified areas from C. Left: lack of integration at the edge by the scaffold (asterisk). Right: bridging tissue in the interior. Scale = 0.25 mm.

Scaffold-mediated degradation of the wound interface: Electrospun nanofibrous scaffolds containing collagenase were placed inside a horizontal defect in cylindrical adult bovine meniscal explants (Fig. 3A). The scaffolds were comprised of poly(ε-caprolactone) (PCL) structural fibers and water-soluble poly(ethylene oxide) (PEO) fibers that released collagenase upon hydration.[4] Scaffolds were constructed in annular form (8 mm diameter with 5 mm core) to permit tissue-to-tissue contact within the construct. The defect was pinned closed and the repair construct cultured for 7 days. Paraffin sections were stained with either H&E or alcian blue (AB) for proteoglycans (PG).

## Results

Collagenase digestion of adult meniscus resulted in a porous microenvironment that closely resembled fetal tissue (Fig. 1). Matrix degradation increased with enzyme dosage, reflected by the lower μCT signal at the construct edges (Fig. 2A). Long-term culture of adult constructs showed improved cellularity and integration with increasing collagenase digestion. By 4 weeks, cells and new collagen fibrils closed approximately 92% of the wound gap in adult HC samples, which exhibited superior integration compared to LC samples and BM controls (Fig. 2A and 2B, p≤0.05). Cell density at the annulus-core boundary was significantly higher for HC samples compared to all other groups, with a 213% and 170% increase over BM controls at 4 and 8 weeks, respectively (Fig. 2B, p≤0.05). Integration was also observed in adult explants exposed to enzyme-releasing scaffolds after 7 days, although the scaffold physically inhibited repair at the construct edges (Fig. 3D). AB staining confirmed localized digestion and loss of PG at the wound site (Fig. 3B).

## Discussion

Our *in vitro* results suggest that partial digestion of the wound interface may benefit meniscal repair. As hypothesized, a dense ECM inhibited cell migration, proliferation, and matrix remodeling, whereas an ECM made penetrable and fetal-like was more conducive to these cell activities. High-dose collagenase treatment significantly improved cellularity at the wound margins while fostering the production of new contiguous tissue spanning the wound site. To ensure targeted degradation of the defect, we developed a delivery system in which collagenase was stored inside electrospun PEO nanofibers and released upon hydration.[4] Preliminary data demonstrated that collagenase-releasing scaffolds acted locally and resulted in a cellular response similar to that of global treatment with soluble collagenase. In the future, these scaffolds can be made more porous to facilitate cellular infiltration and further functionalized by incorporating growth factors that promote cell migration and matrix deposition, released either directly from nanofibers[5] or from drug-delivering microspheres.[6] Given the long time course and high failure rate of fibrous tissue healing, methods to enhance integration and instruct tissue formation will improve treatment of meniscal injuries.

## Significance

Endogenous meniscal repair was improved via the targeted delivery of a matrix-degrading enzyme to the wound interface. This innovative approach may aid the many patients that exhibit meniscus tears, thereby circumventing the pathologic consequences of partial meniscus removal.

## Acknowledgements

This work was supported by the NIH (R01 AR056624), the VA (I01 RX000174), and the Musculoskeletal Transplant Foundation.

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# Effects of Low Oxygen Tension on the Biomechanical Properties, Composition and mRNA Expression of Engineered Nucleus Pulposus

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## Introduction

The central nucleus pulposus (NP) is implicated in the initiation of disc degeneration: decreasing NP proteoglycan content impairs the ability of the NP to transfer and distribute compressive loads leading to progressive structural degradation. NP tissue engineering is currently being explored as a potential therapy for disc degeneration.[1] Previous studies aimed at functional NP tissue engineering have largely been undertaken in normoxic (21% oxygen) conditions; however, due to the avascular nature of the native NP tissue, NP cells reside in a hypoxic tissue niche.[2] The objective of this study, therefore, was to investigate the effects of a physiologically appropriate low oxygen tension on the functional and biosynthetic response of NP cells using an established 3D agarose culture model.[3]

## Methods

*Cell Isolation and Culture:* NP cells were isolated from adult bovine caudal discs and expanded in monolayer. Passage 2 cells were suspended in 2% agarose at 20x106/ml. Constructs 4 mm diam. x 2.25 mm thick were cultured for 2 weeks in chemically defined media with (CM+) or without (CM−) 10 ng/ml TGF-β3, in either 21% oxygen or 2% oxygen in an environmental workstation (HypOxygen, Frederick, MD).

*Histology:* Samples (n=3) were processed into paraffin and sections were stained with alcian blue or picosirius red to evaluate GAG and collagen deposition.

*Mechanical Testing:* Constructs (n=5) were tested in confined compression as described previously [3]. Constructs were subjected to a 0.02 N preload for 500 sec, followed by a stress relaxation test of 10% strain applied at 0.05%/sec followed by relaxation to equilibrium for 10 min.Aggregate modulus was calculated from the equilibrium stress/applied strain.

*Biochemical Composition:* After mechanical testing, constructs (n=5) were digested in papain, and GAG content determined using the DMMB assay and normalized to wet weight. DNA content was determined using the PicoGreen assay.

*mRNA Levels:* RNA was isolated from the constructs (n=3), and quantitative PCR performed to determine mRNA levels of matrix proteins: aggrecan, collagen I and collagen II; the transcription factor SOX9; TGF signaling genes TGF-β1, TGF-βR1 and TGF-βR2; and cell stress markers inducible nitrix oxide sythase (INOS), p53 and Bcl-2-associated X protein (BAX), with expression normalized to GAPDH and presented as a ratio to initial (day 0 of culture).

*Cell Viability:* Viability and cell number was assessed using the Live/Dead® staining kit (n=3). Cells from 10X fluorescent images from three regions on each sample were analyzed using a custom MATLAB program.[4]

*Statistics:* Effects of oxygen tension (21% or 2%) and media (CM+ or CM−) for each outcome measure were established using 2-way ANOVAs with Bonferroni post hoc tests ($p<0.05$).

## Results

After 2 weeks of culture NP cells deposited both GAG and collagen in a uniform manner throughout the construct (Fig.1). Matrix deposition was more robust for the CM+ groups. As expected, modulus and GAG content were both significantly higher for CM+ than CM− for both oxemic states (Fig 2). Constructs cultured in CM− had greater modulus (not significant) in 2% O2 than in 21% O2; however, for constructs cultured in CM+, the 21% O2 group had a significantly higher modulus (Fig. 2A). These same trends were reflected in the GAG content (Fig.2B). Neither the media formulation nor oxemic state had a significant effect on cell proliferation or cell viability. mRNA levels (Fig. 3) of BAX, p53, INOS,TGF-β1,TGF-βR1,TGF-βR2, collagen I, and SOX9 for constructs cultured in 2% O2 were lower than those cultured in 21% O2 for both media conditions. In CM−, mRNA levels for aggrecan and collagen II were significantly lower and higher, respectively, in 2% O2 than 21% O2, and not significantly different between 2% and 21% O2 in CM+ (Fig 3).

## Discussion

In this study we examined the effects of low oxygen tension on the biomechanical

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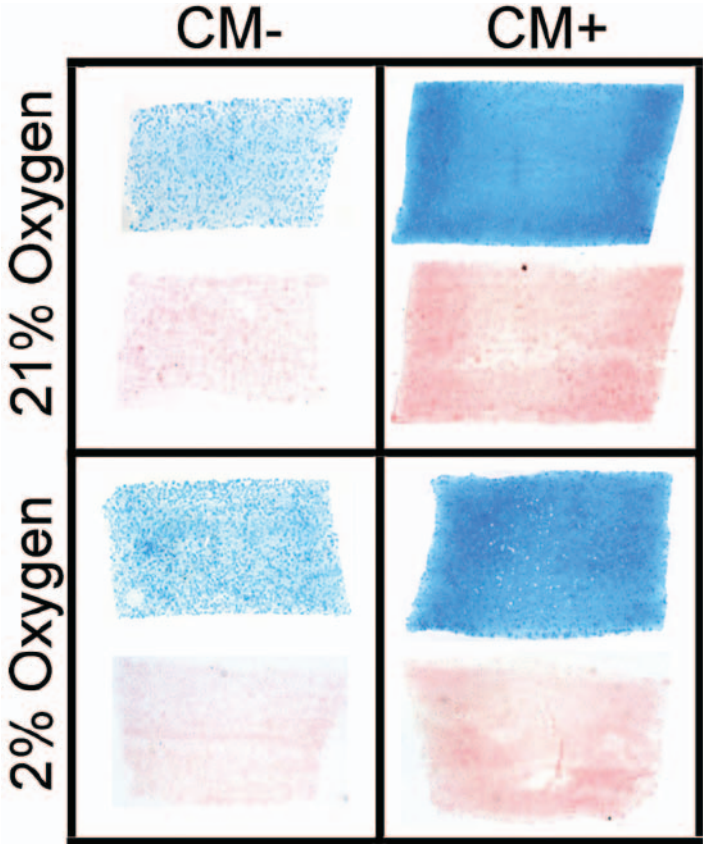


**Figure 1.** GAG (blue) and collagen (red) deposition was similar for both 2% and 21% O2, and in both instances more robust for CM+ than CM−.

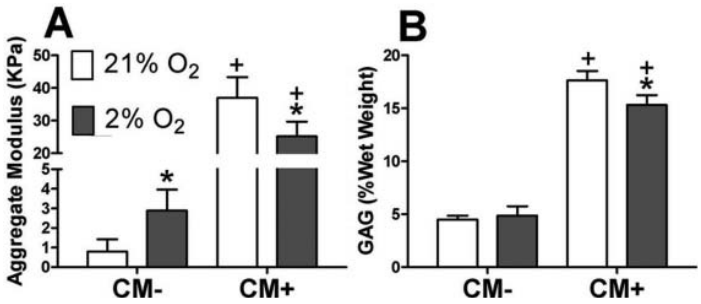


**Figure 2A-B.** A. Aggregate modulus. B. GAG content. *p<0.05 vs 21% O2; +p<0.05 vs CM−.

properties, biochemical composition, and mRNA expression of engineered nucleus pulposus constructs. Our results suggest that low oxygen tension attenuates the biosynthetic response of NP cells in the presence of TGF-β3 (CM+), potentially due to reduced expression of TGF receptors. This has important implications for NP tissue engineering and growth factor-based therapies, as it suggests that under physiologically appropriate oxemic conditions, NP cells are less responsive to anabolic stimulation. Importantly our results demonstrate

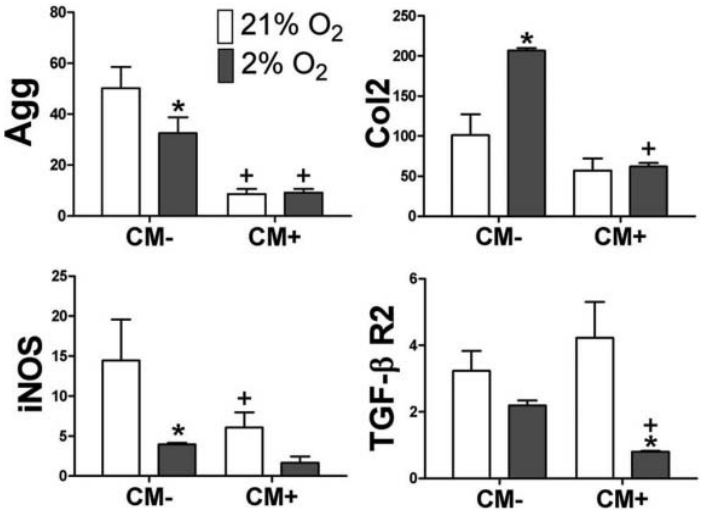


**Figure 3.** mRNA expression levels for aggrecan, collagen II, INOS and TGF-βR2, normalized to GAPDH and presented as ratio to day 0. *p<0.05 vs 21% O2; +p<0.05 vs CM−.

that low oxygen tension does not have a negative effect on NP cell viability, nor increase cell stress as indicated by markers of apoptosis and autophagy. Ongoing work will further examine the associated molecular pathways and examine the effect of low oxygen tension on other important anabolic and catabolic mediators of disc development and function.

## Significance

NP tissue engineering shows promise as a potential therapy for disc degeneration. The work presented in this study furthers our understanding of how low oxygen tension affects the functional biosynthetic properties of NP cells to aid the development of more effective NP therapeutics.

## Acknowledgements

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# Dynamic Stretch Rapidly Alters Nuclear Structure and Increases Chromatin Condensation in Mesenchymal Stem Cells

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## Introduction

Mesenchymal stem cells (MSCs) are an attractive cell type for regenerative therapies in orthopedics given their multipotent nature.[1] Exogenous mechanical stimuli modulate the lineage specification of these cells.[2,3] Our group and others have shown that dynamic tensile strain enhances functional growth by MSCs seeded on aligned nanofibrous scaffolds.[2,4] Within the nucleus of differentiating cells, the distribution of the Lamin A/C (LMAC) network and the condensation state of chromatin are strongly correlated with transcriptional activity.[5] In previous work, we showed that MSC differentiation induced by soluble chondrogenic factors, or dynamic tensile loading (DL) in the absence of these factors, resulted in a marked reorganization of the LMAC, as well as increases in heterochromatin (HTC) content.[6] It has recently been suggested that mechanical perturbation, transmitted through the cytoskeleton, can reach to nucleus more rapidly than soluble signals.[7] In the current study, we investigated the early remodeling of MSC nuclei in response to mechanical stimulation, and compared the rate of these changes to differentiation mediated by soluble factors applied over the same time course.

## Methods

Aligned poly(ε-caprolactone) nanofibrous scaffolds were fabricated via electrospinning.[2] Bovine bone marrow derived MSCs (200,000 cells) were seeded onto scaffolds (5×60 mm2) and pre-cultured in a chemically defined media without TGF-β3 [CM(−)] for 2 days. After pre-culture, 10ng/ml TGF-β3 was added to the CM(−) media [to produce CM(+)] or samples were exposed to dynamic tensile loading (DL, 3%, 6 hrs/day, 1 Hz) using a custom bioreactor[2] in CM(−) media. LMAC organization (Thermo) and HTC levels (Abcam) were visualized by immunofluorescence. HTC staining intensity was measured using MetaMorph® (Molecular Devices Inc.). To assess chromatin condensation, nuclei on scaffolds were stained with DAPI, and scanned across their mid-section using a confocal microscope (Zeiss, LSM 510). To generate a chromatin condensation parameter (CCP) describing internal nuclear structure, a gradient-based Sobel edge detection algorithm was employed using MATLAB to measure the edge density for individual nuclei.[8] Gene expression levels were determined by real time RT-PCR, and normalized to GAPDH. Statistical analysis was performed by ANOVA with Fisher's post-hoc tests.

## Results

Consistent with our previous findings, LMAC was distributed throughout the nucleus in undifferentiated cells. Addition of TGF-β3 did not change LMAC organization over the first 3 days of culture (Fig. 1A). Interestingly, after 2 days of DL in CM(−), LMAC started to become restricted to the nuclear periphery, with full reorganization to the periphery evident after 3 days of DL (Fig. 1A). LMAC gene expression did not change with the addition of TGF-β3, while DL increased expression at each time point (Fig. 1 B). Additionally, HTC formation occurred much more rapidly with DL than with CM(+), with increased HTC staining apparent as early as day 1 for DL compared to day 3 with CM(+) (Fig. 1C). The intensity of HTC staining in DL conditions was higher than both CM(−) or CM(+) conditions at day 1 (Fig. 1D), indicating that mechanical stimulation rapidly increases HTC formation in the absence of exogenous growth factors. To verify induction of true chromatin restructuring, a novel image based technique was applied on day 1. Chromatin condensation was evident in DL nuclei as distinct, chromatin free spaces within the nucleus, with this change leading to an increase in the number of visible edges (Fig. 2C). This was shown through a significant increase in the chromatin condensation parameter for DL nuclei (Fig. 2D). Similarly, gene expression analysis revealed an early and robust response to dynamic loading in comparison to TGF addition. While most markers increased on day 1 for both treatments, SOX9 and BMP2 expression decreased to baseline in CM(+) conditions, but were maintained at high levels in DL conditions through day 3 (Fig. 3). TGF-β3 gene expression

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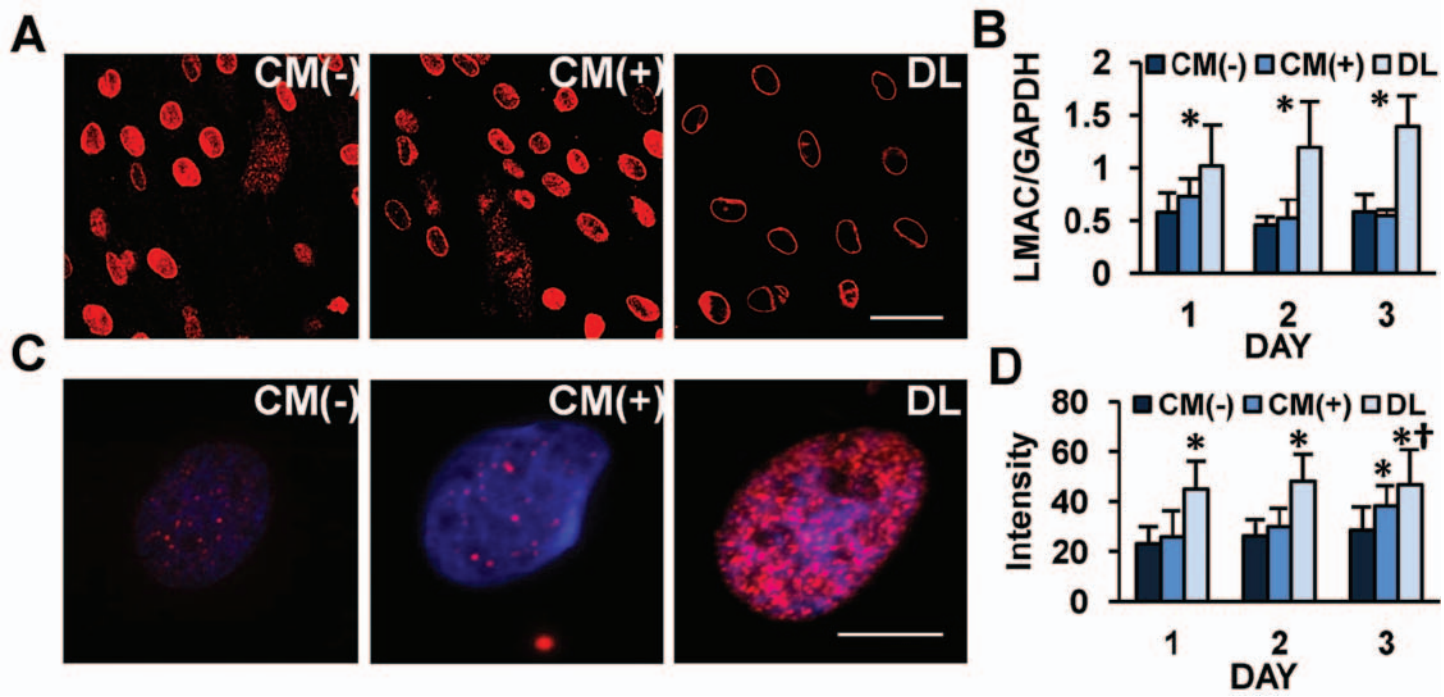


**Figure 1A-D.** (A) LMAC staining on day 3 with treatment (bar = 20 μm, (B) LMAC gene expression over time (n=3, *:p<0.05 vs. CM(−)). (C) HTC staining on day 1 with treatment (red: HTC, blue: DAPI, bar = 10 μm) and (D) quantification of staining intensity (n=20, *:P<0.05 vs. CM(−), †:P<0.05 vs. CM(+)).

did not change in CM(+) conditions, but increased with DL (Fig. 3). AGG expression increased gradually in both CM(+) and DL conditions through day 3, with expression in DL higher than that in CM(+) (Fig. 3).

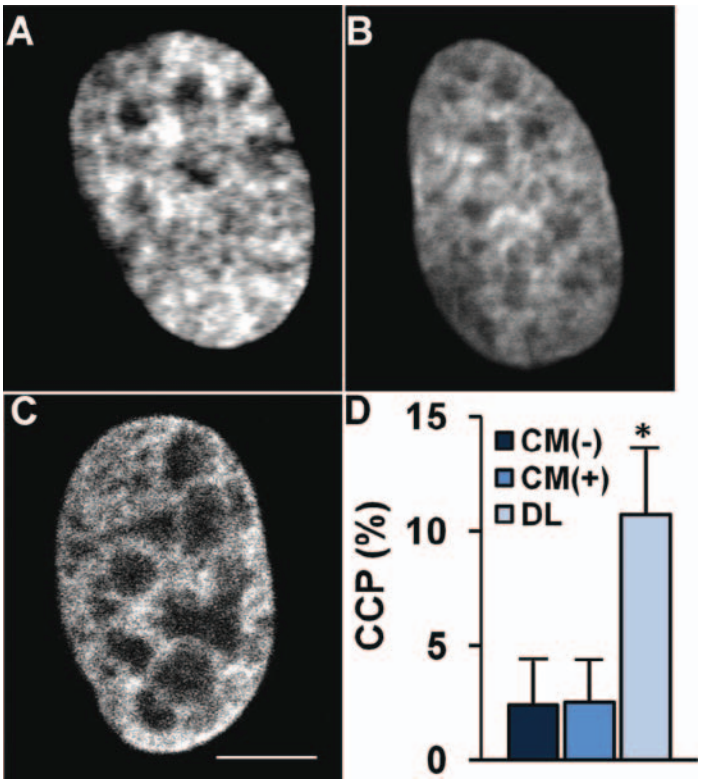


**Figure 2.** Representative DAPI stained nuclei on day 1 with treatment (A: CM(−), B: CM(+) and C: DL, bar = 5 μm), (D) Chromatin condensation parameter (CCP) on day 1 (n=45-50 cells per condition, *: p<0.001 vs. CM(−) and CM(+)).

## Discussion

In this study, we demonstrated that, in the absence of exogenous differentiation factors (TGF-β3), short term DL of MSCs altered their LMAC distribution, and causes rapid chromatin condensation. These responses to DL occurred after only one day of loading, several days in advance of similar changes wrought by the addition of soluble TGF. This suggests that the mechanical input can invoke a rapid change in nuclear structure, and is consistent with the notion that mechanical forces, transmitted to the nucleus through the contractile cytoskeleton via the LINC complex, can more rapidly regulate signaling events in cells.[7] These rapid changes likely have physiologic consequence, as LMAC organization and its interaction with chromatin can influence transcriptional activity.[9] Indeed, along with acute LMAC reorganization and chromatin condensation, DL up-regulated fibro-chondrogenic and TGF-β and BMP2 gene expression in the absence of exogenous growth factors. These expression levels were generally higher than that induced by soluble growth factors, and persisted for a longer period of time. Future work will focus on elucidating the mechanism by which these changes are mediated, as well as the consequence of the mechanically induced changes in nuclear structure on subsequent responses to exogenous mechanical perturbation.

## Significance

Mechanical stimuli are important for driving MSC lineage specification. However, the mechanism by which these stimuli influence fate decisions is still poorly understood, and the consequence of changing cell and nuclear structure and mechanics in this process is not fully defined. Here, we show that

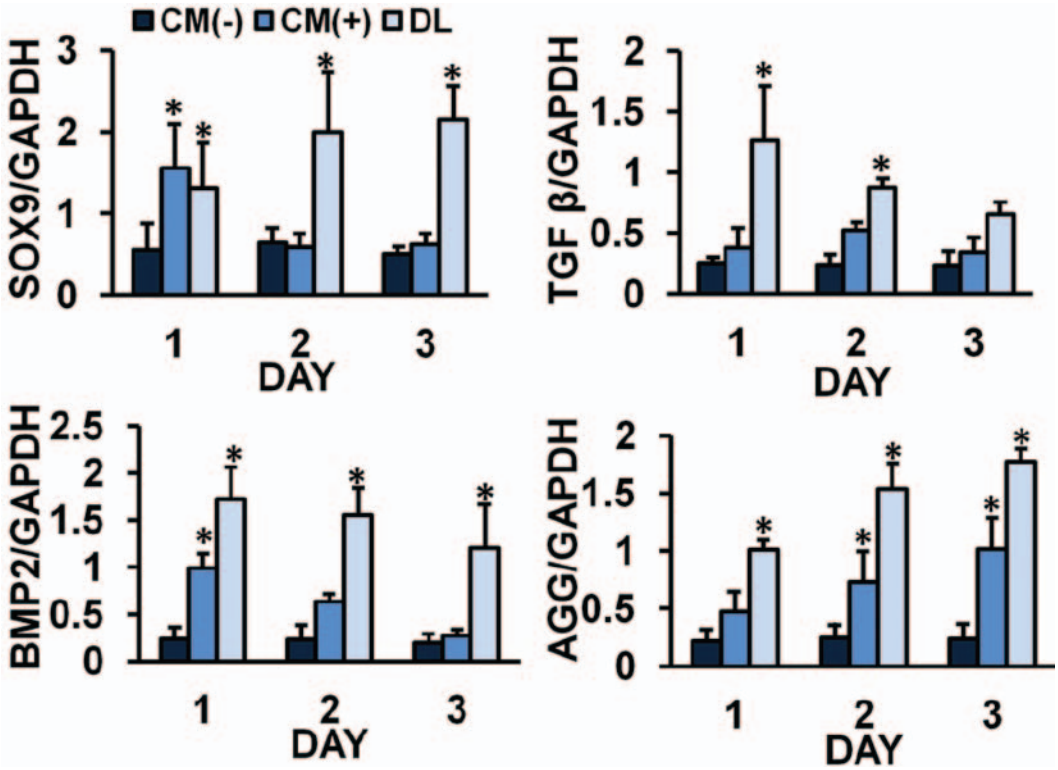


**Figure 3.** SOX9, TGF β, BMP2, and aggrecan (AGG) gene expression (normalized to GAPDH) with treatment (n=3, *: $p<0.05$ vs. CM(-)).

mechanical stimulation rapidly alters LMAC organization and promotes chromatin condensation, along with transcriptional activity indicative of an advanced differentiated state.

## Acknowledgements

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U·P·O·J

# Cytoskeletal Tension is Required for Dynamic Tensile Loading Induced Alterations in Mesenchymal Stem Cell Shape and Nuclear Connectivity

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## Introduction

Marrow derived mesenchymal stem cells (MSCs) show promise for orthopaedic tissue engineering applications. MSC differentiation is influenced by micro-environmental factors, some of which regulate cell and nuclear shape.[1] Aligned electrospun scaffolds provide a fibrous template, which mimics fibrocartilagenous tissue structure and allows for application of physiologic mechanical cues.[2] Cytoskeletal tension, regulated by rho kinase (ROCK), plays an important role in MSC interpretation of these environmental cues,[1] and is significantly increased with TGF-β3 induced differentiation.[3] These cues can be transmitted through the contractile actin cytoskeleton, and the LINC complex (linker of the nucleus and cytoskeleton), to the nucleus. Nesprin 1 giant is a large (~MDa) LINC complex protein that plays a role in differentiation and mechanotransduction for a variety of cell types.[4,5] Nesprin connections to the tensed actin cytoskeleton may provide a direct nuclear mechanotransduction mechanism in MSCs. However, the extent to which cytoskeletal tension and connectivity to the nucleus, contributes to MSC differentiation and mechanotransduction is currently unknown. This study aims to determine the role of MSC cytoskeletal tension in the transmission of mechanical signals to the nucleus, and how these mechanical signals impact nuclear connectivity and differentiation.

## Methods

Static Stretch: Aligned nanofibrous scaffolds were formed by electrospinning poly(ε-caprolactone) onto a rotating mandrel.[2] Fibronectin coated scaffolds (65 x 5 mm$^2$) were seeded on each side with 2x10$^5$ bovine MSCs. Seeded constructs were cultured in a chemically defined media (CM) with or without (+/-) TGFβ3 (10ng/ml) for 7 days. Nuclei were stained with Hoechst (5μg/ml) in DMEM for 20 min and statically stretched (3% increments to 15% strain) using a microscope-mounted device with or without 1 hour treatment with the ROCK inhibitor Y27632 (10μM, Calbiochem). The ratio of the nuclear principal lengths (nuclear aspect ratio, NAR) was calculated at each strain level to quantify nuclear deformation.

Dynamic Stretch: Seeded constructs were pre-cultured for 2 days and then dynamically loaded (DL; 1Hz; 3% strain, 6 hours) in CM(-) for 2 days with or without Y27632 (10μM), which was added 1 hour before the start of loading each day. On day 4, samples were fixed in 4% PFA and stained for F-actin (phalloidin) for quantification of the cellular aspect ratio (CAR) using image J. Additionally, mRNA and whole cell protein was isolated (n=3/grp). qPCR was performed to determine expression of aggrecan, scleraxis, and nesprin 1 giant. Cell lysates (n=3/grp) were separated by column filtration into >1MDa and <1MDa fractions for dot blot analysis of the large splice variant of nesprin 1 (giant, ~1MDa). Western blots were performed for β-actin normalization. One-way and two-way ANOVA with Tukey's post hoc was used to determine significance between groups ($p<0.05$).

## Results

Static stretch experiments showed that undifferentiated MSCs displayed significantly more nuclear deformation at 12 and 15% strain compared to MSCs exposed to TGF-β3 (Fig1A, n=40/grp). This nuclear deformation was abrogated by the addition of the ROCK inhibitor Y27632 (Fig1A), indicating that cytoskeletal tension is necessary for this strain transfer to occur. With dynamic stretch over 2 days, there was a significant increase in cellular elongation, as indicated by an increase in the cellular aspect ratio (n=103/grp) (Fig1B,C). ROCK inhibition resulted in rounder cells for all groups and prevented cellular elongation with dynamic loading (Fig1B,C). qPCR showed that CM(+) and dynamic loading (DL) increased expression of the chondrogenic marker aggrecan (not shown), the tenogenic marker scleraxis (Fig2A), and nesprin 1 giant (Fig2B). ROCK inhibition completely prevented the increase in scleraxis expression with dynamic loading (Fig1D), and partially (but not significantly) blocked the increase in nesprin 1 giant expression (Fig2A,B). Analysis of nesprin 1 giant protein levels (by dot blot) showed a significant increase in nesprin 1

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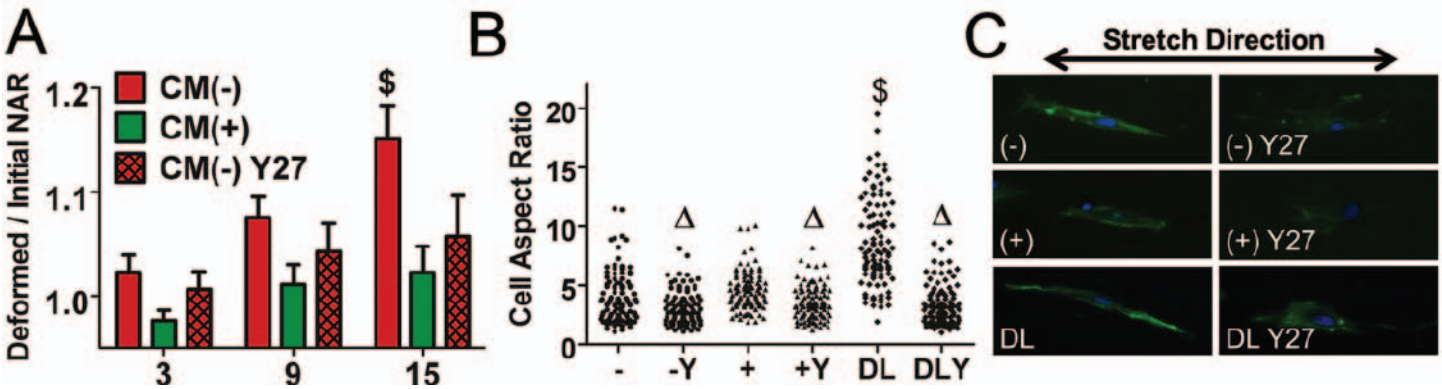


**Figure 1A-B.** Nuclear deformation (A) with static stretch in 3% increments to 15% strain (mean +/− SEM). $ = p<0.05 compared to both other groups (+/− indicates with or without TGF-β3). Quantification of changes in cell aspect ratio (B) after dynamic loading (DL) with or with out Y27632 (Y), and representative images of cells stained for actin/nuclei (green/blue). Δ = p<0.05 compared to non-Y control.

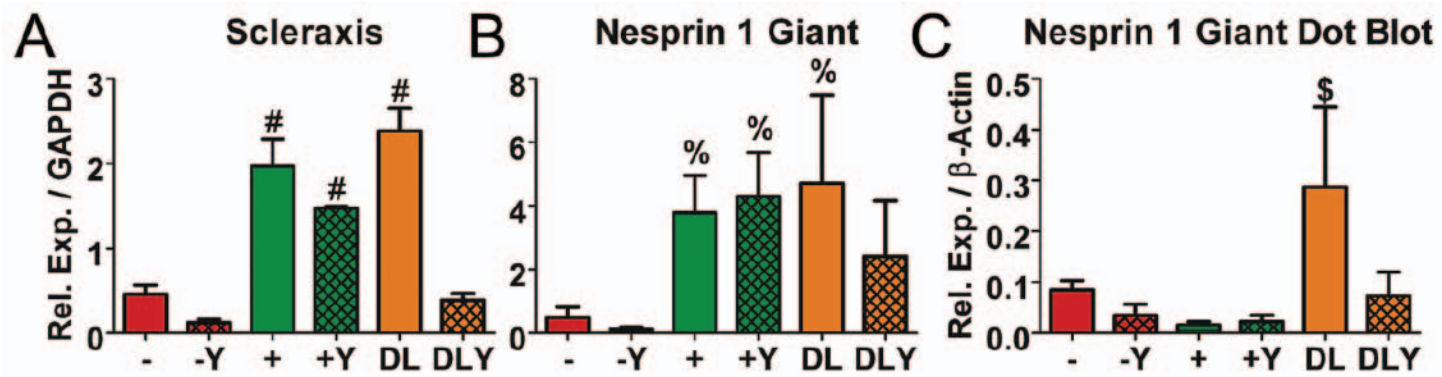


**Figure 2A-B.** Scleraxis expression (A) and nesprin 1 giant expression (B) following 2 days of DL (mean +/− SD). qPCR data is normalized to GAPDH expression. Quantification of dot blot for nesprin 1 giant normalized to β-actin (C). $ = p<0.05 compared to all groups; #=p<0.05 compared to −, −Y and DLY; %=p<0.05 compared to − and −Y.

giant with dynamic loading, which was prevented by ROCK inhibition (Fig2C).

## Discussion

The cellular microenvironment regulates cell shape and MSC fate decisions in a manner that is dependent on the contractility of the actin cytoskeleton.[1] Additionally, this microenvironment can alter the cellular response to mechanical stimulation.[6] Transmission of these mechanical signals from the microenvironment to the nucleus, through the LINC complex and the actin cytoskeleton, provides one mechanism by which cells might respond to mechanical cues. In this study, loss of cytoskeletal tension (by ROCK inhibition) prevented nuclear deformation and dynamic tensile load induced changes in cellular morphology and gene expression. This included prevention of the changes in nesprin 1 giant, a component of the LINC complex that directly connects F-actin to the nuclear envelope, indicating a potential role for cytoskeletal tension and nuclear deformation in regulating the LINC complex. Interestingly, the changes in nesprin 1 giant protein expression in response to load were distinct from TGF-β3 induced differentiation. These differences in nuclear connectivity (through nesprin 1 giant) may result in an altered cellular interpretation of mechanical stimuli. For example, increased nesprin 1 giant may lead to an altered stress distribution at the nuclear envelope, thus influencing activation of nuclear mechanosensative proteins, and providing a potential feedback mechanism by which cells tune there sensitivity to mechanical stimulation. Further, this may be important for understanding the distinction between load-induced and biochemically induced differentiation of MSCs.

## Significance

An understanding of how MSCs sense and respond to mechanical forces will be important for their effective use in tissue engineering. In this study, the influence of altered cellular contractility on MSC nuclear deformation, mechanotransduction and differentiation was investigated.

## Acknowledgements

This work was supported by the NIH (T32 AR007132) and the Human Frontiers in Science Program.

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# Nanofiber Length Scale Differentially Impacts Meniscus and Mesenchymal Stem Cell Morphology and Nuclear Deformation

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## Introduction

Aligned electrospun nanofibrous scaffolds can direct cell alignment and extracellular matrix (ECM) deposition for the engineering of fibrous tissues.[1,2] The morphological properties, proliferation, and gene expression of cells on these scaffolds are influenced by factors such as scaffold architecture and tensile deformation. Changes in fiber size at the nanoscale alter cell morphology and actin organization.[3] Similarly, mesenchymal stem cell (MSC) nuclear morphology on electrospun scaffolds is sensitive to changes in scaffold organization.[4] The degree of nuclear deformation appears to correlate with changes in gene expression.[5] While quite small, the size of fibers within standard electrospun scaffolds (500-1000 nm) is considerably larger than the length scale of the collagen fibers in the meniscus (~200 nm). Using a conductive polymer additive (PANi), we synthesized nanofibers matching this smaller length scale, and showed that MSCs on smaller fibers had a more polygonal cell shape and lower nuclear aspect ratio (NAR) compared to larger fibers.[6] The aim of this study was to consider both MSCs and meniscus cells, and to evaluate their morphology and mechanical response in an engineered microenvironment scaled to match the native tissue.

## Methods

Aligned nanofiber scaffolds were fabricated by electrospinning two different polymer solutions (~350-500 μm in thickness).[2] For 'large' nanofiber scaffolds, a 14% w/v solution of PCL in 1:1 DMF:THF was used. For 'small' nanofiber scaffolds, a 3% w/v solution of polyaniline emeraldine base (PANi) doped with camphosulfonic acid in 1:1 DMF:THF was mixed in a 30:70 v/v ratio with a 14% w/v PCL solution[6] (Fig 1). Scaffolds of each fiber size were coated with fibronectin (2μg/ml) overnight and seeded with either passage 3 bovine MSCs or meniscal fibrochondrocytes (MFCs). Cell-seeded scaffolds (200 cells/mm2) were cultured for 7 days in chemically defined media containing TGF-β3.[2] Cytoskeletal and nuclear morphologies of each cell type were visualized with Actin/DAPI staining. To determine the impact of fiber scale on cell deformation, both cell types and scaffold formulations were subjected to 10% tensile strain after 1 day of culture, prior to Actin/DAPI staining.[4] Projected cell area, cell aspect ratio (CAR) (the ratio of cell length to width), and NAR (the ratio of nuclear length to width) were measured in ImageJ (n=45-50) (Fig 1). Statistical comparisons were made via ANOVA with Fisher's LSD post-hoc test ($p<0.05$).

## Results

Consistent with previous observations,[6] MSCs seeded on larger nanofibers had an elongated cell and nuclear shape, as compared to the same cells seeded on smaller nanofibers. MSCs cultured on larger fibers decreased in cell area ($p<0.05$) with time in culture while MSCs on smaller nanofibers did not change with time. MFCs on larger fibers increased in cell area ($p<0.0001$) and decreased in elongation ($p<0.0001$) during culture, while on smaller fibers, cell area and NAR did not change while cell elongation increased ($p<0.0001$) (Fig 2). With stretch of the scaffold, cell area did not change in MSCs on either scaffold, while MFC cell area increased on small fibers ($p<0.0001$). Cells elongated with scaffold stretch for both cell types on both large and small fibers ($p<0.01$). Interestingly, NAR increased with stretch for both cell types on larger fibers ($p<0.05$), but did not change significantly on small fibers (Fig 3).

## Discussion

All cells take instruction from their surrounding microenvironment, with features such as topography, stiffness, and organization influencing cell behavior. Different cells appear to interpret these signals to differing extents, and the predominance of these signals directing cell behavior will be important in directing new tissue formation. In this study, MFCs seeded on small fibers initially had a more rounded morphology, but elongated with time to adopt a similar morphology to MFCs seeded on larger nanofibers. Conversely, MSC morphology did not change markedly with time. For both MSCs and MFCs, nuclei were less elongated on small fibers compared to large fibers. These changes in

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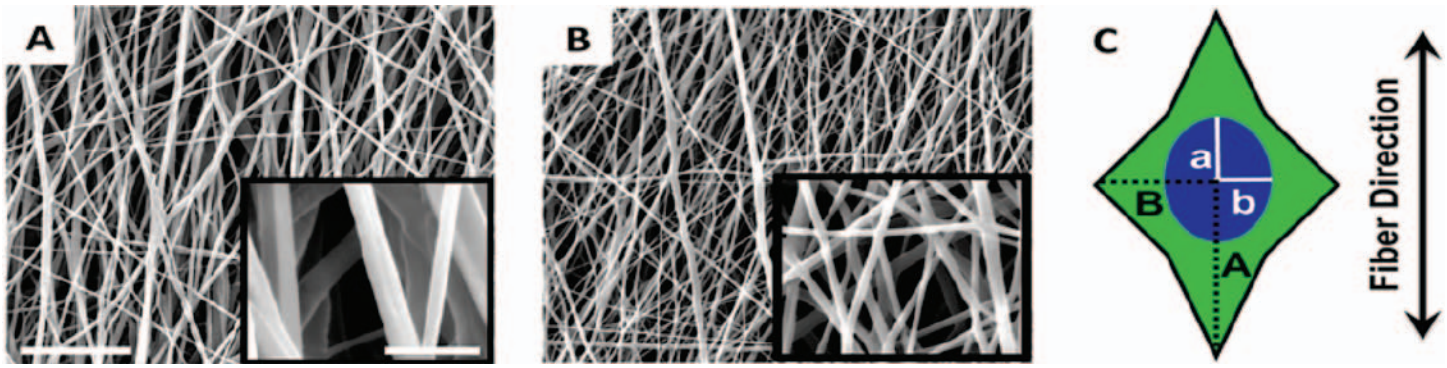


**Figure 1.** SEM images of large **(A)** and small scaffolds **(B)**. **(C)** Schematic of cell measurements. Green is the projected cell area, CAR is the ratio of A/B, and NAR is the ratio of a/b. Scale = 10 μm. Inset scale = 2 μm.

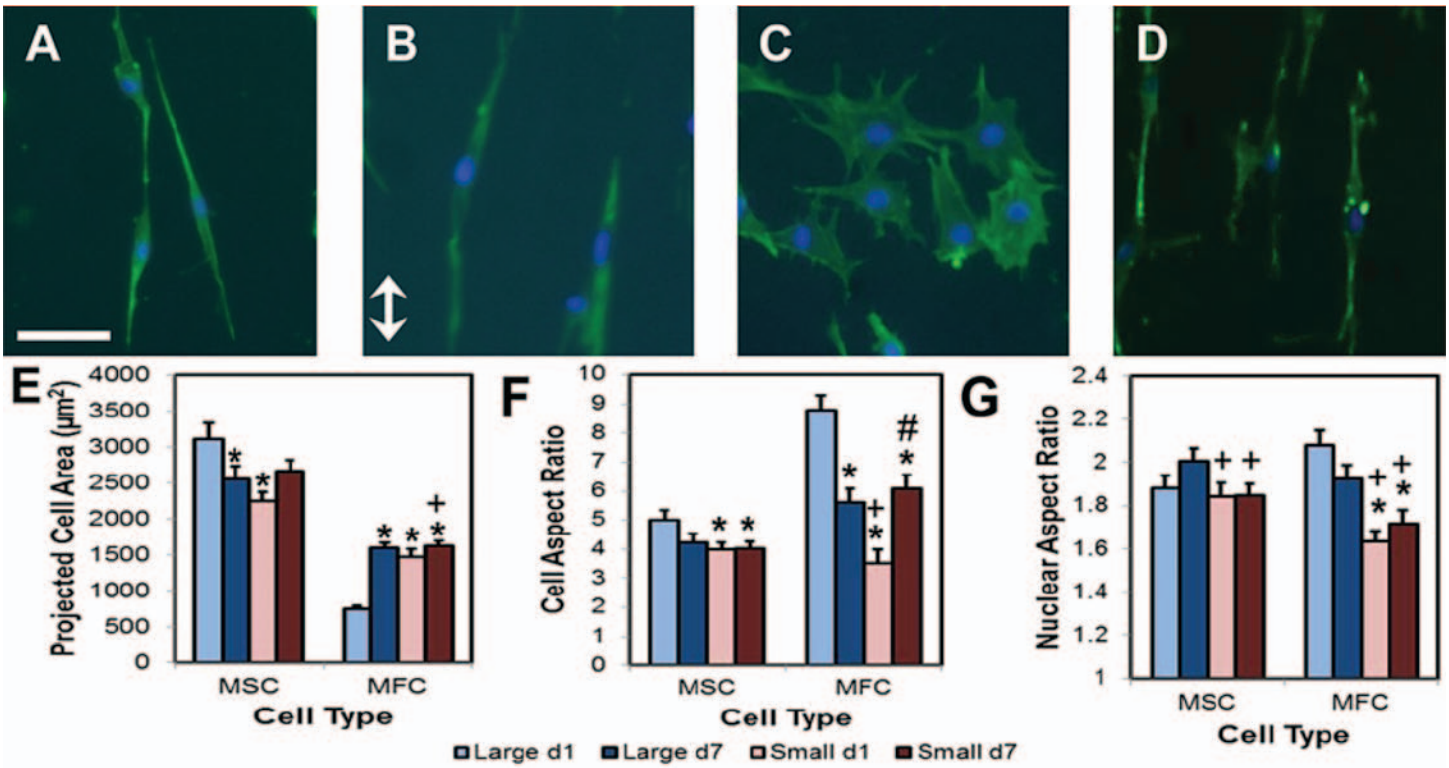


**Figure 2.** MFCs on large **(A,B)** or small **(C,D)** fiber scaffolds after 1 and 7 days in culture. Projected cell area **(E)**, CAR **(F)** and NAR **(G)** as a function of cell type and culture time. Data represents mean ± SEM. Scale bar = 50 μm. Arrow indicates fiber direction.

baseline morphology influenced how each cell type responded to scaffold tensile deformation. While both cell types on small and large fibers elongated in the stretching direction, only cells on larger fibers displayed changes in nuclear morphology with stretch (Fig 3). This sensitivity to nanofiber scale in translation of topographic cues may arise from an increase in the number of contact points for cells on smaller fiber scaffolds, which could alter the assembly of the internal cytoskeleton. Cells on smaller fibers tended to extend over many fibers simultaneously, while on large fibers, cells track along only a few fibers with prominent actin stress fibers. Alternatively, the smaller (and stiffer fibers) may regulate cell contractility, and thereby change load transmission mechanisms. Ongoing studies are exploring how these topographic cues translate into alterations in gene expression for each cell type and with mechanical stimulation. These results highlight the differential interaction of stem cells and fibrochondrocytes with synthetic microenvironments, and will improve tissue engineering approaches for fibrous tissue repair.

## Significance

A better understanding of cell type specific response to native scale fiber morphologies may allow for the optimization of fibrous tissue engineered constructs.

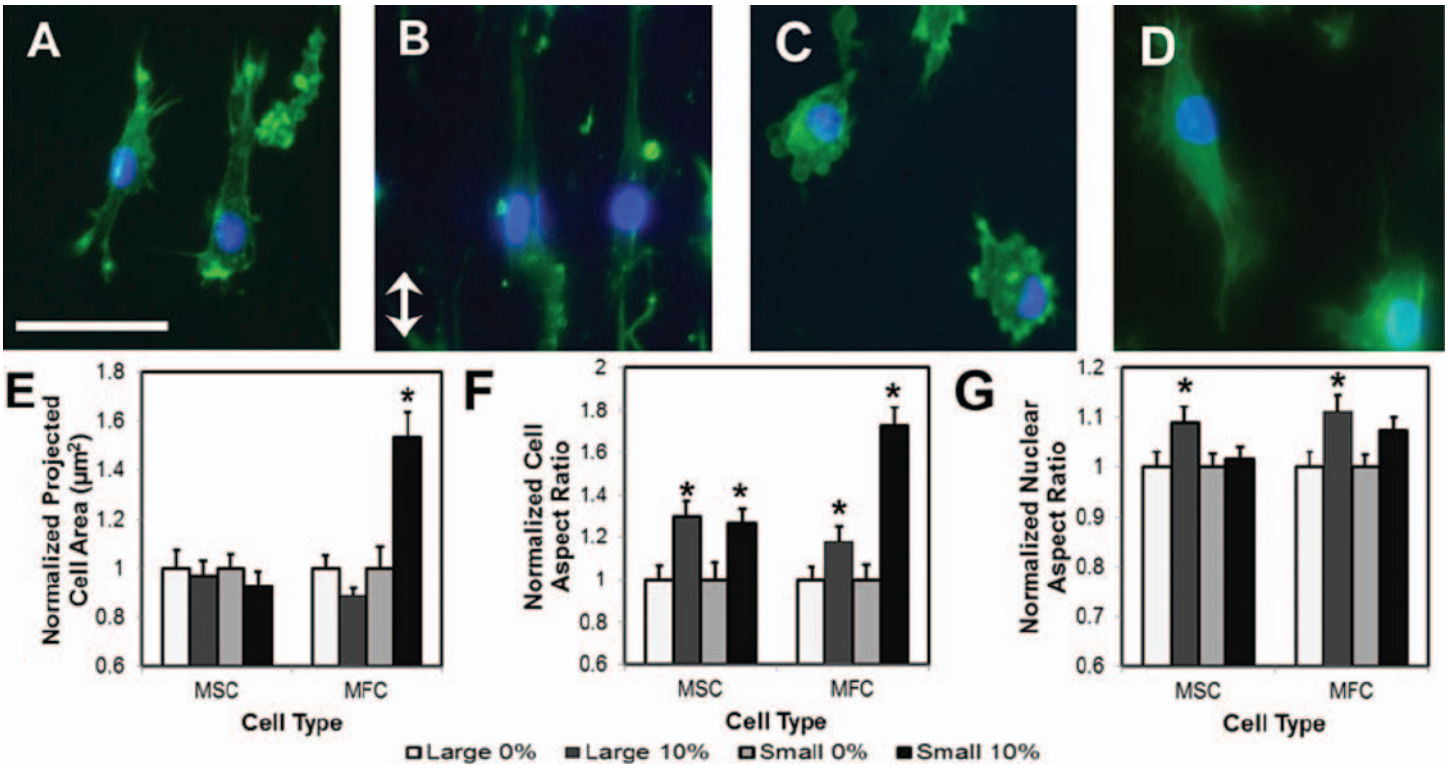


**Figure 3.** MFCs on large **(A,B)** or small **(C,D)** fiber scaffolds after 0% and 10% strain. Projected cell area **(E)**, CAR **(F)** and NAR **(G)** as a function of cell type and normalized to 0% strain. Data represents mean ± SEM. Scale bar = 50 μm. Arrow indicates fiber direction/direction of stretch.

## Acknowledgements

This work was supported by the National Institutes of Health and the Penn Center for Musculoskeletal disorders.

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# Disruption of Thrombospondin-2 Accelerates Ischemic Fracture Healing

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## Introduction

Thrombospondin-2 is a matricellular protein that is highly upregulated during fracture healing. TSP2 regulates vascularity, vascular reperfusion following ischemia, and mice deficient in TSP2 (TSP2-null) show an alteration in fracture healing which is characterized by enhanced vascularization and a shift to an intramembranous bone healing phenotype. An important, yet largely untapped, therapeutic strategy in fracture repair is to enhance vascularization at the fracture site to counteract post-injury ischemia. This can be achieved by either activating angiogenic pathways or by blocking angiogenesis inhibitors. Several angiogenic growth factors have been evaluated in bone repair models such as Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor-2 (FGF2), Platelet Derived Growth Factor (PDGF) and Thrombin-peptide 508. Exogenous delivery of these compounds has been shown to promote angiogenesis. On the other hand, blocking of angiogenic inhibitors has not been researched as intensely. Therefore, we utilized TSP2-null mice to evaluate whether an absence of TSP2 would result in enhanced ischemic fracture healing by increasing vascular reperfusion and callus vascularization.

## Methods

All procedures were approved by the Institutional Animal Care and Use Committee. Male, three month old TSP2-null or wildtype mice (8 or 9 per group) underwent ischemic (femoral artery resection), stabilized tibial fractures and were harvested at 10, 20 or 40 days post-fracture. Tibias were examined using μCT, histology and immunohistochemistry.

## Results

Ten days after fracture, TSP2-null mice show 115% more bone volume, 29% greater trabecular thickness, 122% increase in vessel density, and 20% greater cell proliferation in the fracture callus than wildtype (Fig. 1, 2). Twenty days after fracture, TSP2-null mice have 34% greater bone

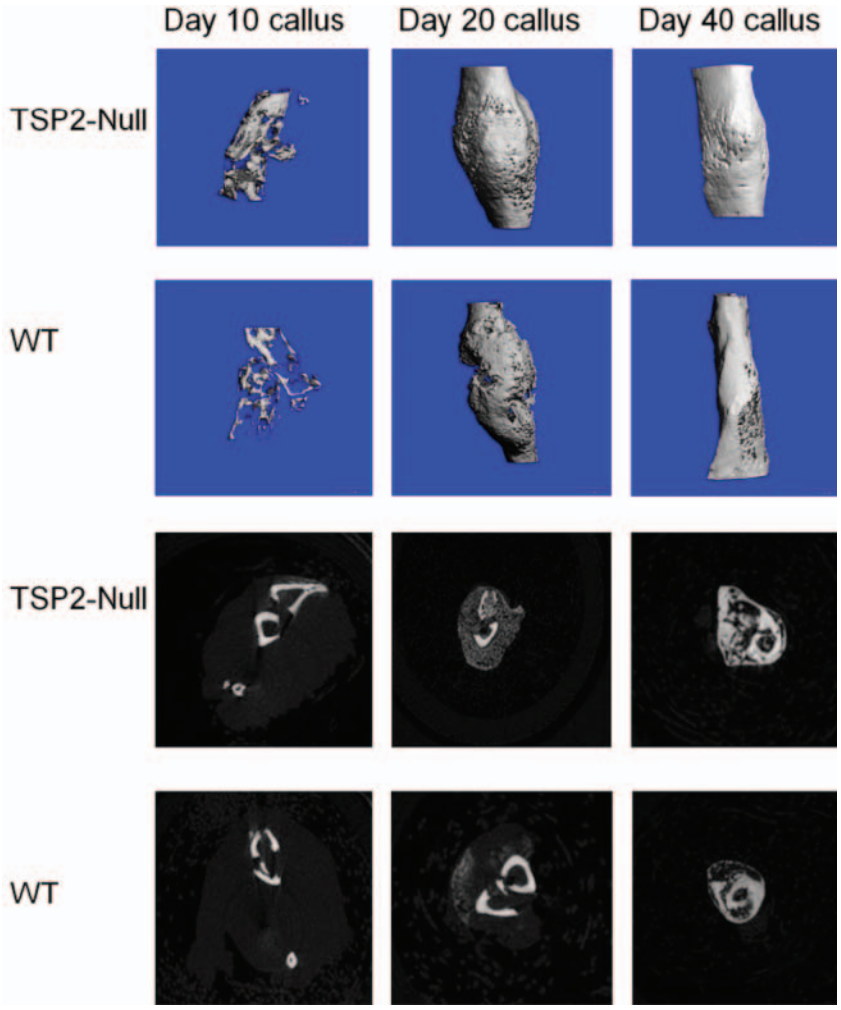


**Figure 1.** Comparison of μCT between TSP2 null and WT mice at days 10, 20 and 40 post-ischemic fracture.

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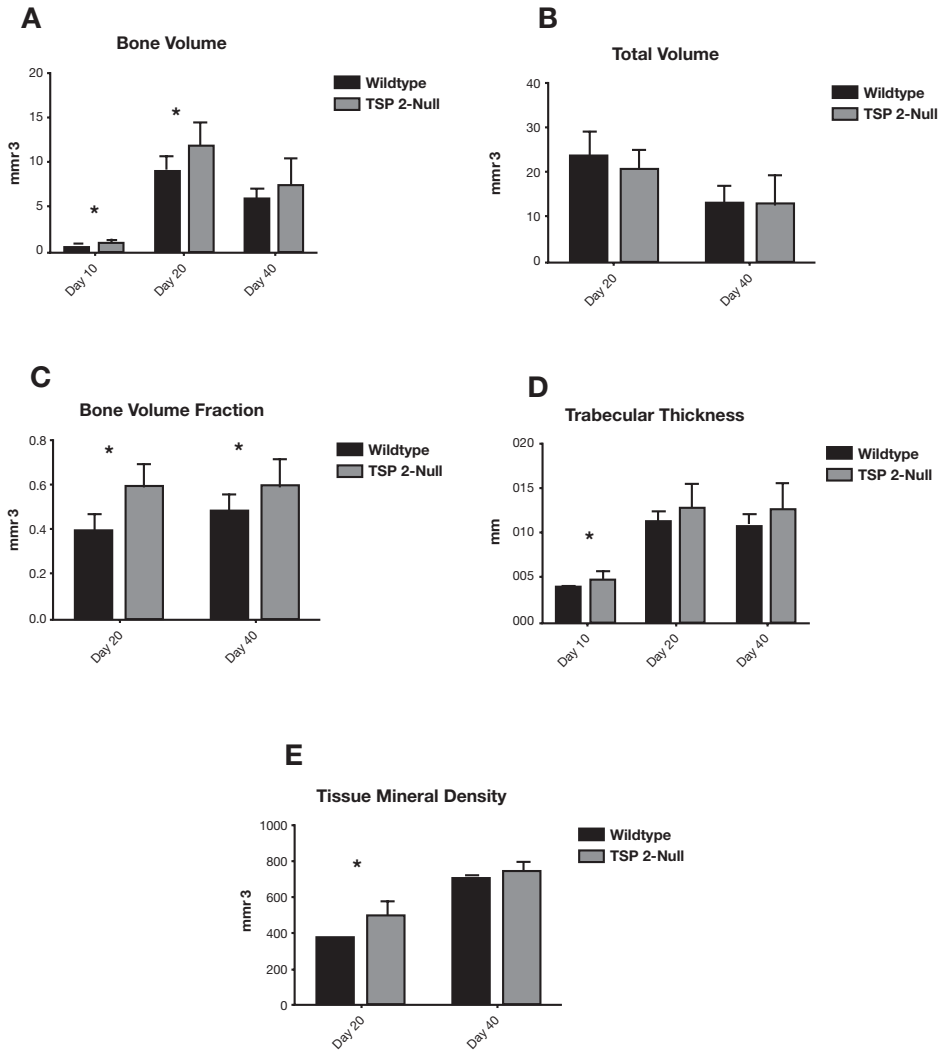


**Figure 2.** μCT scans show TSP-2 null mice have greater bone volume, bone volume fraction and trabecular thickness after ischemic fracture at days 10 and 20. (A) Quantification of bone volume, (B) Total callus volume, (C) Bone volume relative to total callus volume (Bone Volume Fraction), (D) Trabecular thickness, (E) Tissue mineral density. Values are mean ± SD of TSP2-null and WT mice. * $p < 0.05$.

volume, 37% higher tissue mineral density and 51% increase in bone volume fraction relative to wildtype mice (Fig. 1, 2) By 40 days post fracture the TSP2-null mice still have a 24% increase in bone volume fraction, but all other parameters show no significant difference (Fig. 1,2). The fracture callus in both TSP2-null and wildtype mice shows normal cartilage development, with the TSP2-null mice displaying more hypertrophic cartilage at day 10 than WT (results not shown).

## Discussion

The utility of inhibiting TSP2 as a therapeutic agent in compromised fracture healing shows promise. Future directions for this research will include targeting the inhibition of TSP2 specifically during ischemic healing at the time of fracture. It will be important to discern differences in healing between mice that have a complete disruption of the Thbs2 gene (the TSP2-null model used in this study), and those with a disruption of TSP2 at the time of healing. This will allow us to better understand the normal biological significance of TSP2 during bone healing, but also fully establish anti-TSP2 therapy as a viable clinical therapeutic

## Significance

We have established that TSP2 is an important negative regulator of ischemic fracture healing. Inhibiting TSP2 could be a novel therapeutic approach to treating ischemic fracture: TSP2-null tibias show more vessels and greatly increased bone volume during the healing process.

## Acknowledgements

This work was supported by the Foundation for Orthopaedic Trauma (FOT) and the Pennsylvania Center for Musculoskeletal Disorders (PCMD).

# A Mouse Model of Geriatric Fracture Healing: Toward the Elucidation of Aged Fracture Healing Deficiencies

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## Introduction

Fragility fractures represent a significant obstacle in medical care leading to significant morbidity, mortality, and cost both to the individual and society. As the population ages, the incidence of these injuries is expected to increase. It is known that fracture healing capacity decreases with age; an 80 year-old may take months longer to heal the same fracture as an 18 year-old. Improved understanding of the aging process in the skeletal system and advancing technology now allow detailed investigation into the differences in bone healing observed across a lifespan. Currently, no well-established animal model exists to study mechanistic changes responsible for aged fracture healing. The objective of this study was to characterize the phenotypic differences in healing due to chronologic aging in our murine model—and to provide a validated foundation for the rational investigation of the cellular and molecular mechanisms that affect aged fracture healing. Such a model will allow for the identification of pathways that can be manipulated—and therapeutically targeted—to accelerate and improve aged fracture healing characteristics.

## Methods

Model Design: C57BL/6 mice at 5-months of age are reproductively and skeletally mature—"young" adults. 25-month old (m/o) C57BL/6 mice represent the age of 25% survival and therefore a "geriatric" mouse (life expectancy represents 50% survival). All mice were obtained from the National Institute of Aging (NIA Aged Rodent Colonies, Bethesda MD). Surgical Model and Sample Preparation: 84 5-m/o and 85 25-m/o C57BL/6 mice underwent bilateral closed, transverse tibial diaphysis fractures with intramedullary pin fixation (IACUC approved), as previously described1. Tibiae were harvest, at 5, 10, 15, 20, 25, 30, and 40 days post fracture (DPF).

Genetic Analysis: The fracture callus was isolated from the tibial diaphysis at 0, 10, and 20 DPF. RNA was purified with RNeasy system including a DNase digestion. First strand cDNA was then synthesized. Analysis by real-time quantitative PCR (qPCR) was conducted utilizing Fast SYBR Green and the 7500 Fast Instrument (Applied Biosystems). Probes were utilized against target genes including Osteocalcin, Collagen 2a, SOX9, and Osterix. RNA was also sent for microarray analysis.

Histology: Formalin fixed tibiae were decalcified in 15% Formic Acid. Specimens were embedded in paraffin and cut into 5-μm longitudinal sections. Sections were stained with Fast Green FCF/Safranin-O to identify cartilage matrix and Masson's Trichrome to identify bone and osteoid tissue. 2x images were captured with an Olympus BX51 inverted microscope and SPOT Advanced imaging software. Using ImageJ software (NIH), callus size, cartilage area and composition, and bone area and composition were quantified. Two sections per sample were analyzed.

Micro Computed Tomography (μCT Analysis): Using a SancoMedical vivaCT 40 (San Antonio, TX) tibiae were imaged at a voxel size of 21 μm. Callus was spatially segmented from cortical bone. 3D images of the mineralized callus were rendered and callus and connectivity measurements were measured.

Statistical analysis: paired comparisons were performed using two-tailed student t-test with significance set as $p<0.05$(*).

## Results

Histology: 5-m/o mice produce a larger callus ($p=0.03$) with more cartilage area ($p=0.03$) and show a trend towards a larger cartilage per callus area ($p=0.11$) than do 25-m/o mice at 10 dpf. At 20 dpf, 5-m/o mice still have a larger callus ($p=0.02$), but no longer contain more cartilage with the trend of cartilage per callus area reversed toward the 25-m/o mice having a larger percentage ($p=0.17$). No differences in the type of cartilage (hypertrophic, mature, or neo) were observed. Analysis of bone and osteoid tissue did not demonstrate significant differences in the proportion of bony callus between 5-m/o and 25-m/o mice at either 10 or 20 DPF. μCT: 5-m/o mice produce a significantly greater total callus volume (TV) (15, 20, 25, and 30 DPF)

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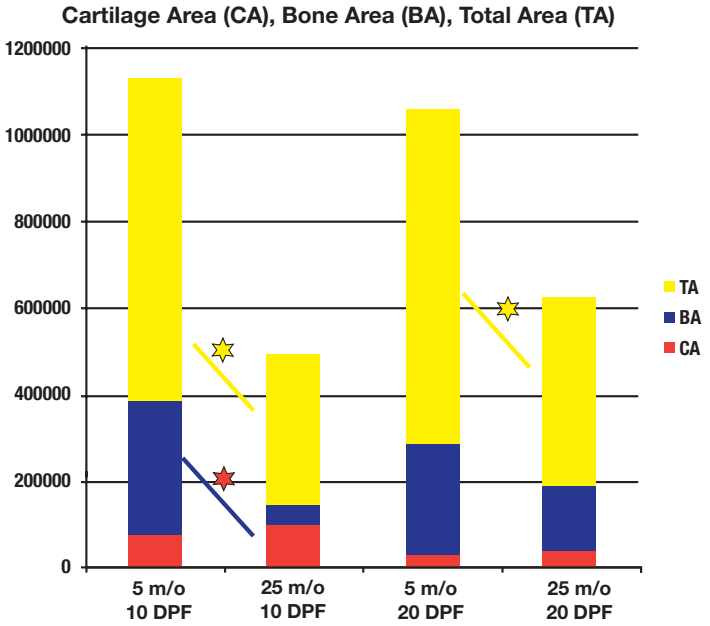


**Figure 1.** Histologic analysis of total area, cartilage area, and bone area of callus in 5 and 25-m/o mice at 10 and 20 DPF.

and bone volume (BV) (10, 15, 20, 25, and 40 DPF) than 25-m/o mice. TV could not be reliably measured at 10 DPF. Calluses formed by 5-m/o mice have a lower degree of anisotropy and a significantly greater polar moment of inertia (PMI) (10, 15, 20 and 25 DPF) than that of 25-m/o mice. Bone mineral content is significantly higher in young mice at 15, 20, 25, 30, and 40 DPF.

Gene Expression: Chondrogenic markers Sox9 and Col2α show upregulation at both 10 and 20 DPF when compared to unfractured 5-month old bone with the greatest upregulation

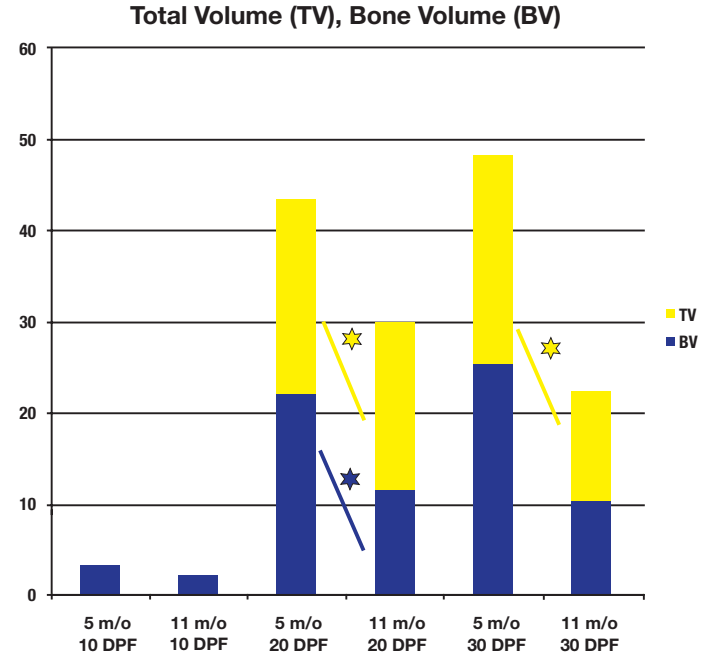


**Figure 2.** μCT analysis of TV and BV of callus in 5 and 25-m/o mice at 10, 20, and 30 DPF.

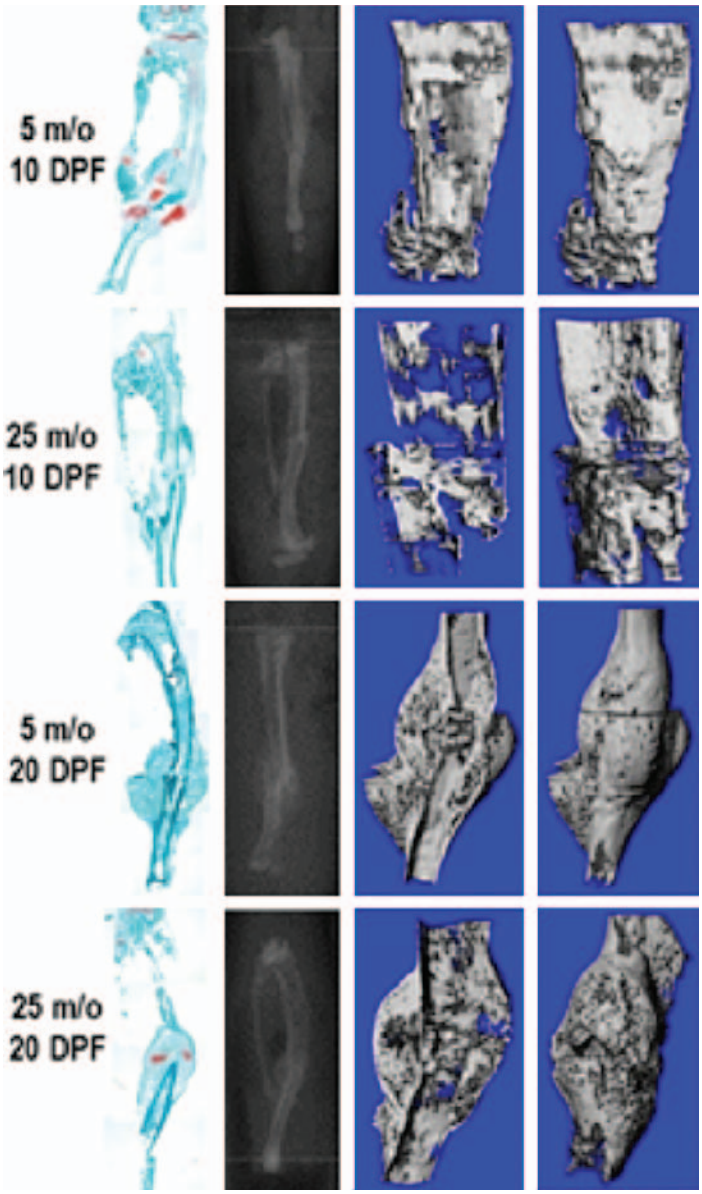


**Figure 3.** Representative images. From left to right: Fast Green/Safranin-O stained, μCT scout, μCT mid-callus and callus 3D reconstruction.

at 10 DPF in both age groups. Osteogenic makers Ocn and Osx also demonstrate upregulation in both age groups at 10 and 20 DPF when compared to 5-m/o unfractured bone. Early microarray analysis indicates there are measurable differences in gene expression patterns (Affymetrix) between young and aged fracture healing.

## Discussion

Our histology demonstrates more robust callus formation in young mice at all time points examined. The observation that cartilage is increased in the callus of young mice at 10 DPF but decreased at 20 DPF relative to aged mice, suggests that 5-m/o mice undergo more robust and rapid remodeling. The μCT data shows significantly greater TV and BV in young mice at most time points. Considering the decreased anisotropy

and increased PMI demonstrated by the young mice suggests that, not only do the young mice produce a more robust healing response, but that this response results in bone of enhanced structural integrity compared with that of aged mice. Preliminary analysis of phenotypic chondrogenic and osteogenic gene expression reveals a profile consistent with formation and resorption of cartilage and formation of bone matrix consistent with endochondral bone formation in both young and old mice. Our characterization reveals a generally intact fracture healing machinery in the geriatric mice but one that remodels into bone more slowly and never to the same quality or extent as seen in the young.This model provides a validated system for further study of the specific age-based differences in fracture—and to test alternations that enhance healing in the elderly. Indeed, initial expression array analysis suggests that there are discernable and significant differences in the gene regulation in these populations, providing targets for further study and potential therapeutic manipulation.

## Significance

Understanding the biological differences in fracture healing in geriatric population will provide a rational basis for potential therapeutic intervention.

## Acknowledgements

These investigations were supported by NIA R03AG040670, Penn Center for Musculoskeletal Disorders (NIAMS P30AR050950), the Jahnigen Scholar in Aging award and the McCabe Foundation.

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# A Closer Look at the Immediate Trabeculae Response to Combined Parathyroid Hormone and Alendronate Treatment

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## Introduction

Aging shifts bone remodeling toward a negative balance between bone formation and resorption, causing bone loss and increased fracture risk. Anti-resorptive agents are commonly used to inhibit bone resorption and stabilize bone mass. While they are effective to prevent further bone loss, there is also a great need for anabolic agents which can reverse bone deterioration and regain lost skeletal integrity. Parathyroid hormone (PTH) is the only FDA-approved anabolic treatment for osteoporosis, which greatly stimulates bone formation. Combined therapy of anti-resorptive treatments, such as alendronate (ALN), and PTH have been proposed and are expected to further increase bone mass. However, studies show conflicting results regarding the effectiveness of combined treatments: some have reported the addition of ALN to impair PTH function,[1] while others suggest an improvement over PTH monotherapy.[2-3] The first objective of this study is to document the immediate changes of individual trabecular structure due to PTH and combined therapy within 12 days using *in vivo* micro computed tomography (μCT). As PTH is typically prescribed for 1 to 2 years to osteoporotic patients, a treatment of 12 days for rats (approximately equivalent to one year of human life) may be more clinically relevant than long-term treatment studies on rats. The secondary purpose of this study was to gain insight into the mechanism of combined versus PTH treatments through a detailed tissue level analysis by using ultra-high resolution *ex vivo* μCT. We hypothesized that PTH and combined treatments would immediately enhance bone formation on the trabecular surface that can be detected by both the structural and tissue level analyses.

## Methods

Seventeen 3-month-old SD rats were assigned to vehicle (Veh) (n=6), PTH (n=8), and combined PTH and ALN (COMBO) treatment (n=3) groups. The Veh group received saline while the PTH and COMBO groups received 80 μg/kg PTH (1-34) daily injections for 12 days. Every 3 days the COMBO group also received injections of 50 μg/kg ALN. The right tibia of each rat was scanned using an *in vivo* μCT system (VivaCT 40, Scanco Medical, 10.5 μm/voxel). A 4 mm region, distal to the proximal tibia growth plate, was scanned. The Veh group was scanned on day 0 and day 12 to minimize radiation exposure. In contrast, the PTH and COMBO rats were scanned every 4 days for 12 days, because PTH exerts a protective effect against radiation to allow multiple scans. This was further confirmed in the current study by a right-left tibia comparison at day 12, which revealed negligible effects of radiation for each group. In addition, the left tibia of each rat was scanned using *ex vivo* μCT (MicroCT 35, Scanco, Medical, 3.5μm/voxel) for high resolution tissue mineral density (Tb.TMD) analysis.

For the *in vivo* scans, a 2.5 mm region of trabecular bone at day 12 was chosen and then the corresponding VOI was accurately identified

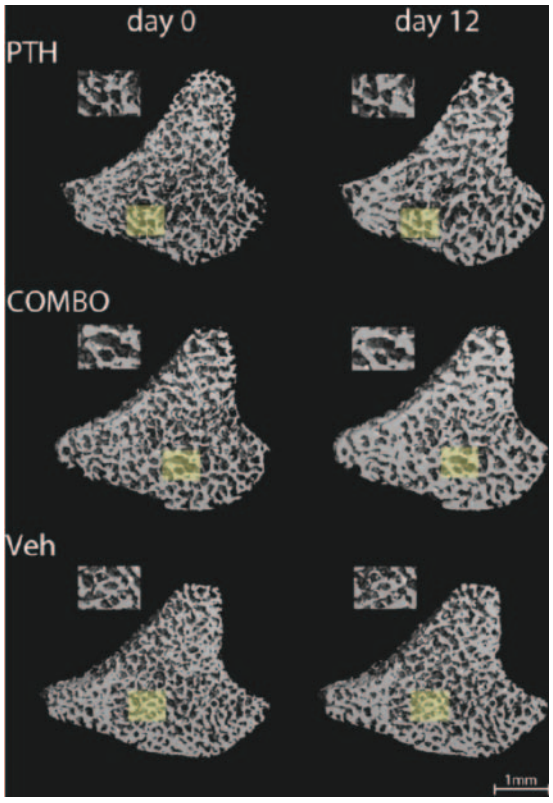


**Figure 1.** Registered trabecular structure at day 0 (Left) and day 12 (Right) of PTH, Combo, and Veh groups.

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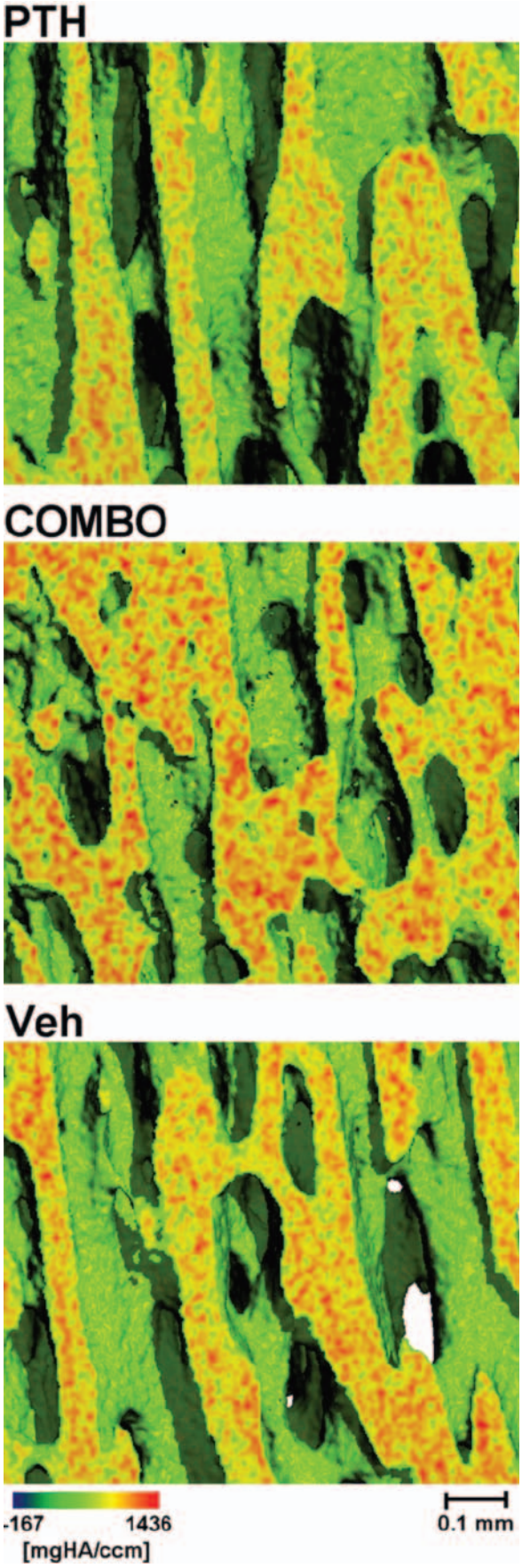


**Figure 2.** Trabecular tissue mineralization distribution.

in the trabecular bone images of day 0, 4, and 8 scans (Fig. 1) by using mutual information-based 3D image registration software (ITK, NLM). Variables of interest included bone volume fraction (BV/TV), structure model index (SMI), trabecular number (Tb.N*), thickness (Tb.Th*), and spacing (Tb.Sp*). Customized microstructural finite element analysis (μFEA) software was used to calculate the trabecular stiffness (Tb.Stiff). In addition, both the mean Tb.TMD and the spatial

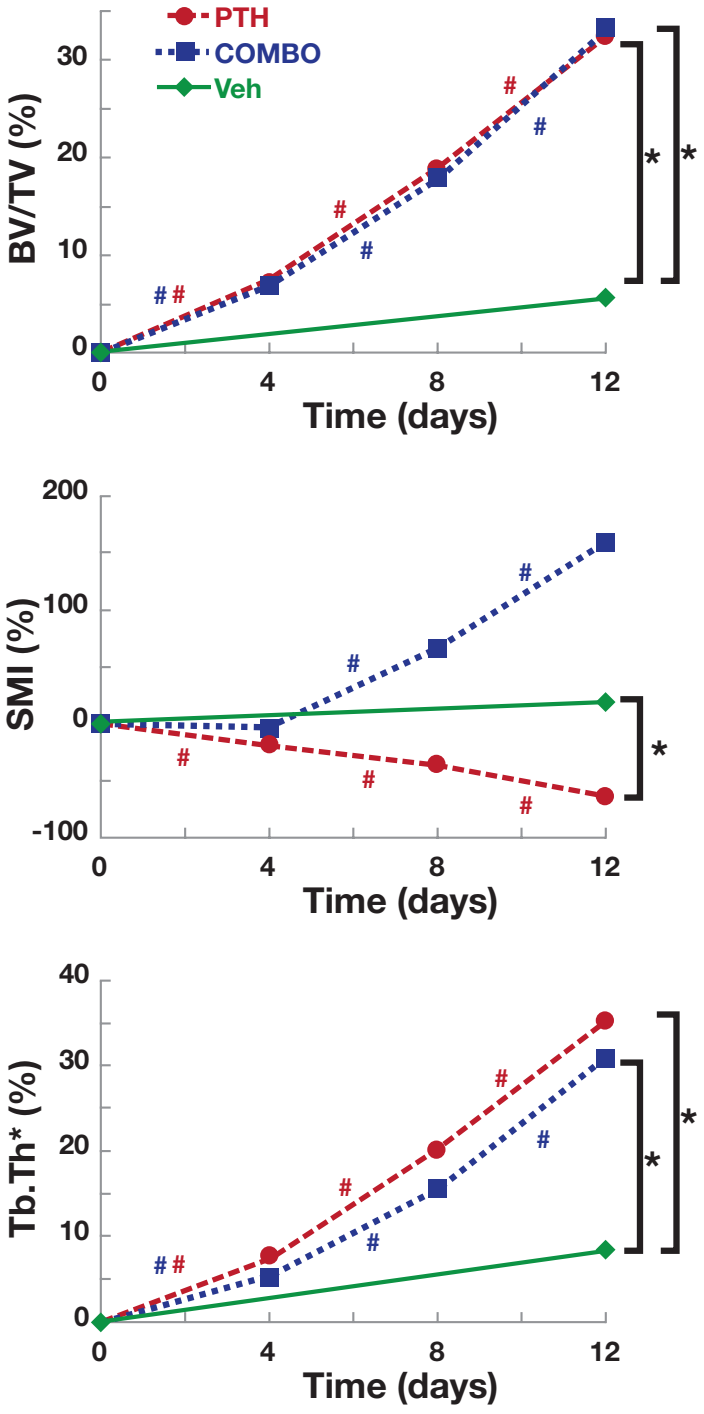


**Figure 3.** % change of BV/TV, Tb.Th*, and SMI over 12 days. # indicates difference over time and * difference between groups.

variation of tissue mineralization (Tb.TMDcv) were calculated based on a 1 $mm^3$ trabecular bone volume of the left tibia scanned at 3.5 μm voxel size (Fig 2).

All variables of interest were compared between time points within groups, and across time, using the %change at day 12 between groups. Student's t-tests were used for all comparisons, with $p<0.05$ considered a significant difference.

## Results

After only 4 days, significant improvements in bone structure were detected in both the PTH and COMBO groups and the improvements persisted through day 12 (Fig 1 & 3). In contrast, no change was detected in Veh group after 12 days. Both treatment groups showed significant improvements over all time points in BV/TV and Tb.Th*, indicating substantial bone formation over the 12 day period. Tb.Sp* showed a 6% reduction in the COMBO group, which was significantly different from the Veh group after 12 days. Tb.N* showed no difference between groups or over time. SMI suggests a 158% increase in rod-like structures in the COMBO treatment group, and a 63% increase in plate-like structures in the PTH treatment group (Fig 3). μFEA revealed 68% increases in Tb.Stiff in both treatment groups and no change in the Veh group over 12 days.

By the end of the 12 day treatment, COMBO group had a 4% higher Tb.TMD compared to the PTH group while Tb.TMD in the PTH group was 2.4% lower than the Veh group (Fig 2). The Tb.TMDcv was different among all groups, with the highest variation in the COMBO group (29%), followed by the PTH group (27%), than the Veh group (25%), indicating a more heterogeneous trabecular mineralization in the treatment groups. Qualitative analysis of Tb.TMD distribution revealed new bone formation with less mineralized tissue on trabecular surface in the PTH group, but highly mineralized bone throughout in the COMBO group, even compared to the Veh (Fig 2).

## Discussion

By using registered *in vivo* μCT imaging we demonstrated an immediate response in trabecular bone microstructure to PTH and combined PTH and ALN treatment starting as early as 4 days after treatment initiation. Over 12 days, continuous increases in BV/TV of both treatment groups were primarily caused by thickened trabeculae, which would suggest excessive formation of new bone on the trabecular surface. However, the Tb.TMD analysis, based on ultra-high resolution *ex vivo* μCT, revealed new anomalies in tissue mineralization. While this study is consistent with previous works which identified increased Tb.TMD from ALN treatment,[4] we did not expect a significant increase after only 12 days. In addition, in the COMBO group we would have expected the thickened trabeculae to have less mineralized tissue at the bone surface as seen in the PTH group. However, our data reveal higher mineralization throughout, including at the bone surface, due to COMBO treatment. Future investigations of the involvement of other types of cells, such as osteocytes, or changes in the biochemical environment of bone may help us to explain this paradox.

## Significance

To our knowledge, this is the first study to examine immediate changes in trabecular structure, stiffness, and tissue mineralization in response to PTH and combined PTH and ALN therapies. Although no additional improvement was found in bone volume, structure, or mechanical stiffness by combined treatment over PTH alone, adding ALN may increase the treatment efficacy by reducing the mineralization lag time and osteoid maturation time.

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U·P·O·J

# 3D Image Registration Is Critical to Ensure Accurate Detection of Longitudinal Changes in Bone Microstructure and Mineral Density Measurements in Rats by *In Vivo* Micro Computed Tomography

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## Introduction

In the recent decade, *in vivo* micro computed tomography (μCT) scanners have become available to monitor longitudinal bone changes in rodents.[1-2] With an isotropic image voxel size up to 10.5 μm, changes in geometry and microstructural properties of rodent bone in response to either disease or treatment can be visualized and quantified over time. In order to detect longitudinal changes, it is critical to understand the precision of *in vivo* μCT measurements. Although reproducibility of *ex vivo* μCT at various volumes of interest (VOI) and resolutions have been reported,[3-4] influences of movement and repositioning of animals, which are associated with *in vivo* scans, have not been well studied. Nishiyama *et al* reported that by 3D image registration, reproducibility can be significantly improved in microstructural measurements at 12.5 μm resolution (precision ~1-5% in rats).[5] However, in their study the follow-up scans were within 2 days where changes to the bone microstructure are negligible. The first objective of the current study was to investigate the short-term reproducibility and long-term precision of bone microstructure and density measurements in the rat tibia by *in vivo* μCT scans at the highest achievable voxel size (10.5 μm). The second objective was to test whether a 3D image registration technique can improve short- and long-term precision.

## Methods

3-month-old female SD rats were used in this study. Rats in the short-term reproducibility group underwent baseline and follow-up scans within the same day (n=15) and those in the long-term precision group were scanned at day 0 and day 14 (n=16). Rats were anesthetized and the right tibiae were scanned by an *in vivo* μCT system (VivaCT 40, Scanco Medical; 10.5 μm voxel size). During the scan, the rat tibia was fixed by a customized holder to ensure minimal motion effect (Fig. 1). A total of 296 μCT slides, corresponding to a 3.1 mm region below the growth plate, were acquired. Between short-term repeated scans, animals were retrieved from the scanner with their tibiae removed from the holder and then replaced for the next scan.

First, 2 mm bone segments starting from the distal ends of the bone were analyzed for each scan. Bone volume fraction (BV/TV), trabecular thickness (Tb.Th*), spacing (Tb.Sp*), number (Tb.N*), structure model index (SMI), connectivity density (Conn.D), bone mineral density (Tb.BMD), and tissue mineral density (Tb.TMD) were evaluated by 3D standard microstructural analysis. A second set of analyses were performed for registered image pairs of both short-term and long-term groups after a 3D image registration procedure. A mutual information-based 3D image registration scheme (ITK, NLM) was applied to the trabecular bone compartments of baseline and follow-up scans to determine the rigid body transformation matrix between the two image coordinates. Then, the VOI of the first scan was located in the 2nd scan through transformation (Fig. 2). All trabecular measurements were calculated for the registered VOIs.

To evaluate the short-term reproducibility, individual coefficient of variance (CV) was calculated, and the root mean square average of the %CV (RMSCV) was derived for each parameter for unregistered and registered image pairs. To evaluate the long-term precision,

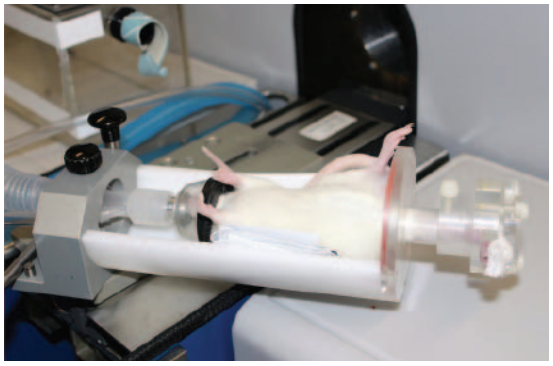

**Figure 1.** *In vivo* μCT scan of a rat under anesthesia with the right tibia held by customized jig.

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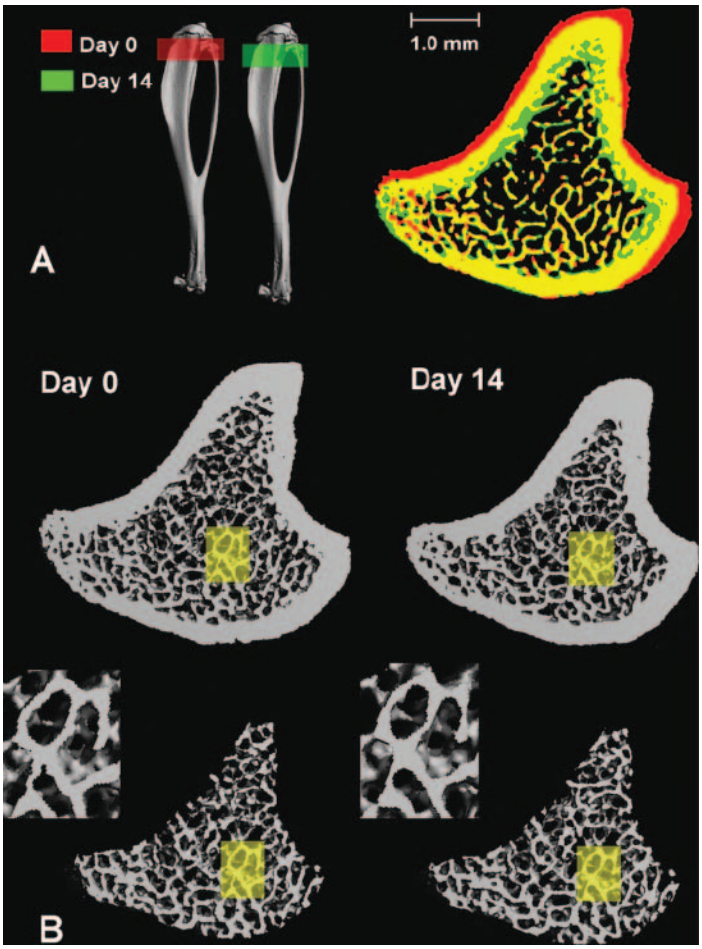


**Figure 2. (A-B)** Overlapped registered bone structure of day 0 (Red, also shown in B left) and day 14 (Green, also shown in B Right). Yellow: common bone area.

percent change of each parameter between day 0 and day 14 was evaluated for registered and unregistered image pairs. Paired Student's t-tests were performed with $p<0.05$ indicating a significant difference.

## Results

Short-term precision: Prior to image registration, reasonable reproducibility was found for most parameters. The precision errors associated with BV/TV, Tb.N*, Tb.Th*, Tb.Sp*, Tb.BMD, and Tb.TMD ranged between 0.85% and 2.65% (Table 1). Precision error was higher for SMI and Conn.D measurements (4.29% and 7.49%). Precision errors of most measurements decreased with registration. However, improvement in reproducibility of microstructural parameters by 3D registration did not reach statistical significance.

Long-term precision: Prior to image registration, by using the growth plate as reference, comparisons between VOIs at day 0 and 14 suggested significant increase in BV/TV, Tb.N*, Tb.Th*, Conn.D, and Tb.BMD and decrease in Tb.Sp* and SMI (Table 1). However, 3D registration indicated new bone generated from the growth plate in 14 days, which was pushed from the growth plate toward the mid shaft region (Fig 2). Percent change in each parameter from registered comparisons were significantly different from that calculated based on unregistered scans. Registered results suggested that in 14 days the registered trabecular VOI had a significant increase in BV/TV and Tb.BMD, primarily caused by increased Tb.Th* and Tb.TMD. In addition, there was a significant decrease in Conn.D, as compared to an increase based on unregistered results.

## Discussion

We tested short-term and long-term precision of microstructural and density measurements of an *in vivo* μCT scan protocol of the rat tibia. For the short-term study, reasonable reproducibility can be achieved by standard scan and analysis procedure for most measurements. 3D registration tended to reduce precision errors but improvements were not significant. This result differs from that reported by Nishiyama *et al* which demonstrated improved short-term precision by 3D image registration.[5] However, by using a customized jig to minimize motion artifact and reposition errors during *in vivo* scans, reproducibility of most trabecular microstructure and

**Table 1. Short term RMSCV and long term % difference of registered and unregistered scans.**

| | Short-term RMSCV Without Registration | Short-term RMSCV With Registration | Long-term % Difference Without Registration | Long-term % Difference With Registration |
|---|---|---|---|---|
| BV/RC | 2.65% | 2.37% | 10.48%* | 6.30%* |
| Tb.N* | 2.49% | 2.01% | 7.70%* | −1.30% |
| Tb.TH* | 1.20% | 0.97% | 4.15%* | 10.07%* |
| Tb.Sp* | 1.76% | 1.33% | −8.02%* | 1.82% |
| SMI | 4.29% | 4.01% | −6.05%* | −0.87% |
| Conn.D | 7.49% | 7.01% | 10.07%* | −12.51%* |
| Tb.BMD | 1.14% | 1.01% | 7.90%* | 5.49%* |
| Tb.TMD | 0.85% | 0.75% | 1.31% | 3.22%* |

* indicates significant difference between baseline and followup scans.

density measurements in our study were within 3%, a similar level of registered precision reported by Nishiyama *et al.* This may explain the minimal improvement by adding 3D image registration in our study.

In the 14-day study, 3D registration had a significant impact on the accuracy of all measurements. Due to the continuous growth in rodents, without image registration the differences between the baseline and follow-up scans were driven by changes due to bone growth instead of local remodeling. In the current study, unregistered comparison results exaggerated the changes in trabeculae and wrongly suggested significant improvements in every structural and density parameter. After image registration, the comparison results indicated thickened and more mineralized trabeculae caused by local bone remodeling over 14 days.

## Significance

Our results suggested that 3D image registration is a critical step to ensure accurate detection of longitudinal changes in rodent trabecular bone microstructure by *in vivo* μCT imaging.

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# The FOP R206H Alk2 Mutation Enhances BMP-Induced Chondrogenic Differentiation

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## Introduction

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disease characterized by heterotopic endochondral ossification within soft connective tissues and is caused by mutations in ALK2/ACVR1, a BMP type I receptor. The most common mutation, R206H, causes dysregulation of canonical BMP signaling, a key regulator of chondrocyte commitment, proliferation, and maturation.

## Methods

Primary mouse embryonic fibroblasts (MEFs) were harvested from wild-type and heterozygous knock-in Alk2R206H/+ embryos to examine the effects of the mutation on chondrogenic differentiation.

## Results

Consistent with previous results, Alk2R206H/+ MEFs have increased canonical BMP signaling in both the presence and absence of BMP ligand, as detected by phosphorylation of Smads1/5/8. Chondrogenic media containing BMP ligand was used to induce differentiation as TGFα alone did not induce chondrogenesis of wild-type or mutant MEFs. In the absence of BMP, Alk2R206H/+ MEFs did not spontaneously differentiate, despite increased BMP signaling; however, in the presence of BMP show increased sensitivity toward chondrogenesis. Alk2 mRNA is most abundant in undifferentiated MEFs and decreases upon differentiation, suggesting a role in early differentiation events. Consistent with our results, Alk2R206H/+ MEFs have accelerated onset and increased abundance of early chondrogenic transcripts during differentiation corresponding to the earlier appearance of chondrocyte morphology. Proliferation was quantified but showed no differences between wild-type and Alk2R206H/+ MEFs either prior to or during early chondrogenesis. Implants of MEFs into hind limbs of wild-type mice demonstrate that robust *in vivo* heterotopic endochondral ossification is induced by the combination of BMP ligand with Alk2R206H/+, but not wild-type, MEFs.

## Conclusion

Our data demonstrate that heterozygous expression of R206H Alk2 enhances chondrogenic differentiation of progenitor cells and suggests Alk2 plays an important role early during chondrogenic differentiation. The requirement for BMP ligand to activate differentiation of Alk2R206H/+ MEFs both *in vitro* and *in vivo* suggests that an increased sensitivity to BMP signals during early stages of chondrogenesis is a critical mechanism to promote heterotopic endochondral ossification in the presence of the R206H Alk2 FOP mutation.

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# Functional Consequences of Fibrodysplasia Ossificans Progressiva-associated Mutations ACVR1$^{R206H}$ and ACVR1$^{Q207E}$ in Comparison to Constitutive Active ACVR1$^{Q207D}$

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## Introduction

Fibrodysplasia ossificans progressiva (FOP, MIM 135100) is a rare genetic disorder characterized by postnatal transformation of soft connective tissues into bone throughout life in a periodic and progressive manner. Mutations within the BMP type 1 receptor ACVR1 (activin A receptor, type 1; *ALK2*, *ActR1A*) were identified as the genetic cause, with R206H (c.617G>A) found to be the most frequently occurring mutation in patients. Patients with R206H develop a classic clinical FOP phenotype that is characterized by congenital great toe malformation and ectopic bone formation. Several other rare ACVR1 mutations have also been associated with an atypical FOP presentation.

## Methods

A patient with FOP-type ectopic ossification and atypical severe growth retardation was found to carry a Q207E (c.619C>G) mutation. We performed functional analyses to investigate differences between R206H and Q207E receptors that could reflect differences in phenotype. Viral-mediated over expression of each mutant receptor in chicken embryos induced similar skeletal abnormalities (e.g. joint fusion, formation of ectopic elements) analogous to those found in FOP patients. Effects on cell differentiation were analyzed *in vitro* using chick limb bud micromass cultures.

## Results

Infection with wild-type ACVR1 did not alter cell fate decisions. By contrast, both R206H and Q207E mutations similarly enhanced chondrogenesis and osteogenesis and additionally exhibited anti-myogenic activity. Of note, a ligand-independent and strongly constitutively activating ACVR1 mutation, Q207D, has previously been identified. In all assays we found that both R206H and Q207E FOP mutations induce less severe responses compared to Q207D, an interesting result given that Q207E and Q207D affect the same amino acid residue.

To examine the ligand responsiveness of R206H and Q207E, we co-expressed the BMP antagonist Noggin in micromass cultures and, in contrast to Q207D which is not inhibited by Noggin, we observed reduced chondrogenesis in cultures with R206H and Q207E, supporting that both mutant FOP receptors act in a ligand-sensitive manner.

## Conclusion

Our data show that the R206H and Q207E FOP mutant receptors have similar functional effects on cell differentiation assays, suggesting that the atypical phenotype associated with Q207E occurred coincidentally, and additionally support that FOP ACVR1 mutations are ligand-responsive and more mildly activating than the constitutively active Q207D mutation.

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# Penn Orthopaedics in Nicaragua

Adam T. Griska, MD and Jaimo Ahn, MD, PhD

In the fall of 2012, the University of Pennsylvania Department of Orthopaedic Surgery participated in a series of medical volunteering trips in partnership with Health Volunteers Overseas. During the first trips, faculty and residents traveled to Managua, Nicaragua to work alongside local orthopaedic surgeons treating an underserved population. The following are a few glimpses into our experiences and observations:

## Day 1, Sunday, 11/18/12

***Tengo hambre = "I am hungry"***

That's pretty much all we felt as we disembarked our planes and stepped into Managua, Nicaragua. We were hungry for food, yes, but also to teach to learn and to absorb and see this new place that we knew so little about. We're soon transported to Casa Naranja ("Orange House"), a little oasis of an Inn in an eclectic neighborhood that includes a variety of restaurants and the Taiwanese embassy. My two-week home feels lush and tropical though it's temperate now.

Over dinner we talk about the Nicaraguan three tiered health system–public, which is free welfare at designated hospitals, "social security" which is contracted cared based on employment, but still government funded, and private, which is only for those who can specifically afford it. Total charge for knee arthroplasty: $8k.

## Day 2, Monday, 11/19/12

***Mucho gusto = "Nice to meet you"***

National Hospital or Hospital Escuela Roberto Calderón Gutierrez is one of the two largest public hospitals in Nicaragua. It serves those who have nowhere else to go. As soon as we enter, I know we're somewhere "else."


As part of the introduction, we were led through a sea of patients waiting to be treated in the fracture clinic to a small, dilapidated exam room where we met the acting director of orthopaedics. We then went on rounds through one of the hospital's crowded wards. There were 6-8 people per room, many in skeletal traction, no privacy curtains between patients. We stood at the bedside, looked at the x-rays, and they asked us what we would do with each fracture. Many of the fractures were difficult, highly comminuted, and frequently days or weeks old. It seemed that most of the patients would be treated with traction or immobilization for extended periods of time, due to a lack of implant availability.

To give you a more vivid picture, two of the patients are in skeletal traction–hard films show a 2-week old pilon with persistently swollen soft tissues. They are unsure about plating or an external frame because they don't know when they'll have the resources. Films from patient 2 reveal an anterior pelvic separation (still out of place) with a posterior pelvic fracture. He is resting comfortably in bed with no IV pain medication. He also happens to have a serious open fracture that is also awaiting treatment. Timing? Uncertain, again because of resources. They hope to get to the open fracture first.

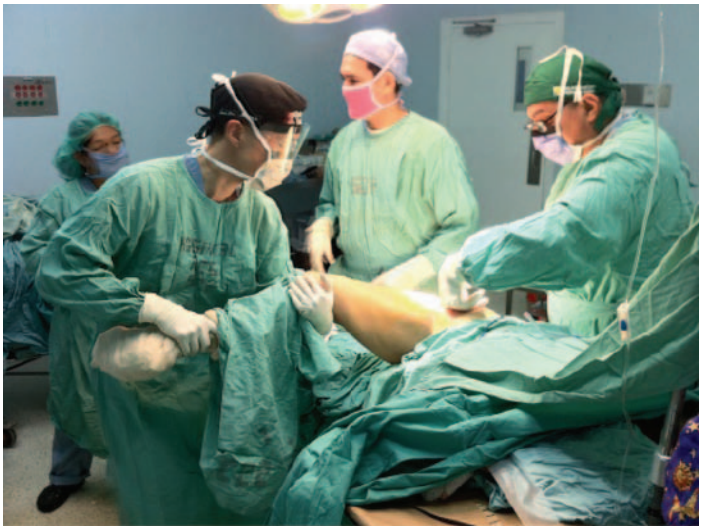
We are soon whisked to the OR. The first case is a fragmented tibia-fibula fracture. They move efficiently–especially considering their limited tools. The amazing thing: no live x-ray! n the U.S., the case does not start until we have this. But after 2 hours and zero x-rays, the case is complete. It's not perfect–screws have to be manually cut to length–but it was just right for the situation.

## Day 3, Tuesday, 11/20/12

***¿Ya llegamos? = "Are we there yet?"***

Our second day at the hospital was every bit as eye-opening as the first. We started the day with a total knee replacement. The surgery went well and actually was not hindered by any significant lack of equipment. The instruments were a current set from Zimmer using the intramedullary femoral guide and extramedullary tibial guide. The implant itself was a posterior stabilized design from a Brazilian company Impol, which are apparently less expensive.

We're really looking forward to the next patient's case. A subcapital femoral neck fracture in an 84 year-old edentulous woman. The implant of choice: a Thompson prosthesis or rather, the Impol version of the implant which became popular circa 1950. Jaimo had to scrub this one just for the anachronistic experience of history!



Our afternoon cases were a true departure. Jaimo worked on a subluxated Weber C ankle fracture, without fluoro, and with only one plate choice. Adam helped with a comminuted pertrochanteric femur fracture, which we put a sliding hip screw into, also without fluoro, and with severely limited choices of screw lengths. We palpated the femoral neck and placed the guide wire manually, in a trajectory matching that of the neck, as best as we could tell. We then placed the longest sliding screw available (85mm). We won't see the results of our efforts until tomorrow, when they will obtain the post-op x-rays. So for tonight, we just have to reflect on the procedures and hope for the best.

Are we there yet? Yes, we are. This is a lesson in humility.

## Day 5, Thursday, 11/22/12

***Cosas nuevas puede ser humillante = "New things can be humbling"***

First case is hemiarthroplasty for a femoral neck fracture. Dr. Jimenez says "this is your case." We try to explain to him that we do it very differently and I am a little suspicious of our ability to make this look smooth without our team, our instruments, implants. He is not to be dissuaded. He wants to see it our way. We become very accustomed to what works with what is familiar… As the case starts, communication is earnest but still sparse and hit or miss. To start, we feel for landmarks and cut; no marking pen. Electocautery is used instead of the preferred knife. It takes at least 15 seconds to explain Cobb elevator. Then things progress until we're ready to take off the posterior external rotator tendons. They have no "c" or double angle retractor. Hmm…. During the neck cut, the battery dies so it is finished with an osteotome. Curette instead of a canal finder. No box osteotome… The Thompson, which we've only seen in books and in Dr. Steinberg's display shelf is secured with hand-mixed and packed cement. Pull pull pull and "thok"–success! Stable as she can be. That thing is never coming out. But oh, how humbling.

## Day 6, Friday, 11/23/12

***Tijeras = "scissors"***

Today we had conference with a visit from the chief of surgery. X-rays were reviewed including the Thompson (whew, looks good, though a touch long), the sliding hip screw is contained in the bone with a good center position.

Our complete Spanish incompetence was psychologically bothersome today more than before. Yes, Endress, we miss you. So we decided to at least try to say the instrument names, Nicaraguan style. Dos-zero Vee-creel, Tijeras, right!

The last case of the day was a young man with a large knife wound to his palm from a week ago with index flexor tendon injuries as well as nerve injuries. As we began to prep for the case, it became clear that they were going to rely heavily on us to perform this case. We have our own little conference, and decided that together we could do this.

It's dingy but we clean it nice. Both tendons definitely out, no cascade, no tension. Found both ends of the severed FDS and FDP as well as the severed common digital nerve. The tendons were repaired primarily with core sutures and epitendonous sutures. We have a cascade again and full passive motion shows no gapping. Love it. They did not have the tools or suture to do micro style nerve repair, so a 4-0 nylon, just to approximate the ends. Wash again.

This was definitely one of the biggest, most difficult, but most rewarding cases for Adam and as primary surgeon. The residents say that the patient will get hand therapy, but it is hard to imagine him receiving the follow-up that we would like and we're a little concerned about his outcome.

## Day 10, Tuesday, 11/27/12

***Dame = "Give me"***

Jaimo gave a lecture at morning conference on semi-extended parapatellar tibial nailing. The major advantage to the surgeons here would be that they would not need to hang the operative leg off the side of the table, limiting the potential for contamination. The presentation generated a lot of discussion, and as luck would have it they had a tibial nail scheduled today for Dr. Somarribba. He agreed to let Jaimo do the semi-extended approach.

The tibia does not look technically difficult. Just past

midshaft, nearly isthmic… we go through the parapatellar approach with them, which not surprisingly, is easier and nice for demonstration with no geniculate branches blurring your field. We can see the intact synovium and they all palpate the subretinacular tissue plane and the lateral border of the patellar tendon. Nods all around. Entry reamer—dame! Nice try. So we ask for the awl, which we are happy using but a little tentative about doing so without any x-ray. The lateral border of the tendon is a good guide. Dig, push, dig push. Need the guide wire now—dame! No ball tip, no bend. It doesn't pass. Instead we have to use a sharp canal finder. Okay it passes… Ahhh, the neck of their jig is not long enough to get around the patella—dame! But we make it work. Both locking screws go in with no problem including the no-x-ray perfect-circle distal screw in one shot by Dr. Somarriba. The case went well but we wonder if they will adopt it.

If any of you have the opportunity to come here–or another under-resourced site–observe carefully, because there is so much to see. This hospital, for instance, may be in need of many repairs but the floors are the cleanest anywhere. Someone seems to be cleaning all the time. As I write this at 1:00pm, mopping has occurred at least twice and will again soon.

## Day 13, Friday, 11/30/12

***En la selva, de la selva fuerza = "In the jungle, the mighty jungle…"***

For our send off, the theme appears to be super-malunion. The bilateral ankles/pilons have been sitting, waiting for 23 days and the 2nd wrist is 5 weeks old. Independent of the cases, we're feeling mildly guilty that our linguistic incapacity has kept us from becoming lifelong friends with the folks here. To make up for it, we ordered a big lump of food for the staff from La Terraza Peruana, our now favorite little Peruvian place in Mangua.

A lot of mixed emotions on our last day in the hospital. It has been eye-opening in many ways. The patients, the staff, the techniques, the resources (and lack there of), have given us a new perspective on our specialty, and have made us consider for the first time–what is the essence of what we do? What is required to do what we do successfully? What can we do to help the patients here? At the same time, we cannot deny that these two weeks have also exhausted us, and we are looking forward to returning to the relative luxury of our hospitals at home…

# New Facilities Planned for Penn Presbyterian Medical Center

Alyson Cole, MPM, Assistant Executive Director for Professional Services at Penn Presbyterian Medical Center

In September 2012, Penn Presbyterian Medical Center announced the plans for two new buildings on the hospital's campus: the Penn Center for Specialty Care and the Advanced Care Pavilion. These 300,000+ square-foot facility expansions at Presbyterian support the new physical foundation of the *Penn Musculoskeletal Institute* by providing significant investments in patient centered care design and upgrades to ancillary, emergency, critical care and operative facilities for the musculoskeletal patient.

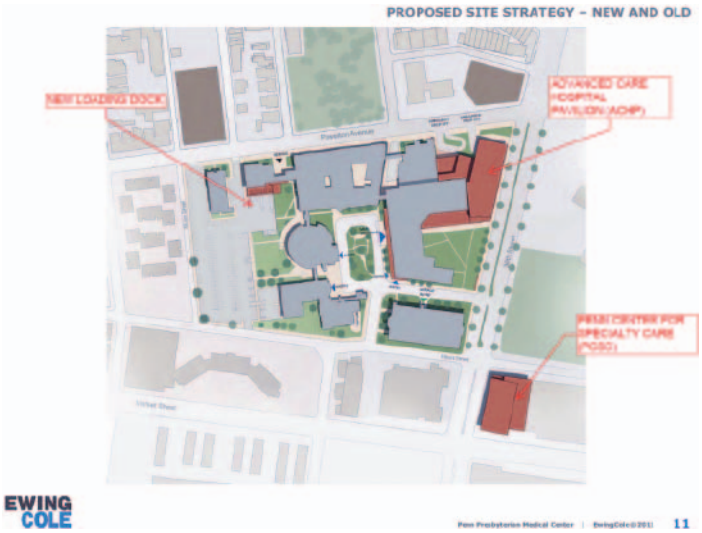



**Figure 1.** Penn Musculoskeletal Institute proposed site strategy.

## Penn Center for Specialty Care

Construction began in September, 2012 on the Penn Center for Specialty Care and will be complete by 2014. The Penn Center for Specialty Care will be a modern 11-story tower located at 3737 Market Street to provide patients seamless, integrated care, for same-day specialty consultations, testing and treatment options. This building will add more than 150,000 square feet of outpatient care and surgical space to the Penn Presbyterian Medical Center campus.

This state-of-the-art building will house nearly 110 exam rooms, six outpatient operating rooms, and an outpatient radiology center. The Penn Center for Specialty Care will also house the multidisciplinary *Penn Musculoskeletal Institute*, the first of its kind in Philadelphia. The Penn Musculoskeletal Institute will transform the already exceptional care offered by Penn Orthopaedics, Rheumatology, Physical Medicine and Rehabilitation, Pain Medicine, Musculoskeletal Radiology and Good Shepherd Penn Partners (GSPP). In addition to the clinical footprint, the Center for Specialty Care will unite the cross-campus footprint for the Department of Orthopaedic Surgery academic offices on the 6th floor of the building. Faculty, administrative staff, and residents will move in to the new offices and the clinic spaces in the fall of 2014.

## Advanced Care Pavilion

Scheduled to open in the winter of 2015, the Advanced Care Pavilion will also expand and enhance the services offered by Penn Presbyterian Medical Center. The new acute care building will feature overall upgrades and enhanced capacity for emergency, surgical, trauma and critical care patients at PPMC. This will be coupled with an expansion of the PENNStar flight program with an additional helipad ensuring rapid


**Figure 2.** Penn Center for Specialty Care: view from 38th and Market Streets.


**Figure 3.** Penn Center for Specialty Care: patient entrance.


Figure 4. Penn Center for Specialty Care: lobby.

access to state-of-the-art resources for all critically ill patients. The project also includes an expansion of the Cupp Pavilion building at the corner of 38th Street and Powelton Avenue as well as several significant renovations within Cupp itself.

Renovations will upgrade the capacity and efficiency of the emergency and radiology departments. In addition to added emergency bay capacity, a new state-of-the art trauma resuscitation area will be dedicated to the evaluation and stabilization of critically injured patients.The project will also facilitate improvements in centralized patient flow and newly designed treatment spaces for the Radiology and Preoperative Services areas.

## New Concourse

Finally, a new concourse will be created which will extend from the main lobby in Myrin Circle through the heart of the hospital, terminating at 38th Street. The concourse will provide a location for family, patients, and staff to gather and provide an exceptional thoroughfare for way finding. The exterior of the PPMC campus will also be developed to feature a landscaped green space in the 38th Street courtyard to provide an additional aesthetic element to the PPMC campus and the surrounding community.

The hospital campus has grown tremendously since its opening more than a century ago. This multi-year project will provide the PPMC campus and the Department of Orthopaedics with the facilities and clinical programs to better serve Philadelphia, and adjoining communities as a tertiary center while significantly increasing Penn Medicine's overall capacity.

# A Tribute to Dr. Clifford H. Turen

Sarah M. Yannascoli, MD, Andrew H. Milby, MD, and Samir Mehta, MD

On behalf of Penn Orthopaedics, we would like to both acknowledge a great loss and honor the memory of Dr. Clifford H. Turen, who passed from our ranks on January 13th, 2013 at the age of 55. As an internationally renowned orthopaedic traumatologist, many of the faculty, staff, and friends of our community knew him well. His overwhelming professional and personal accomplishments will extend well beyond his years.

Born in Brooklyn and raised in Roslyn, NY, Dr. Turen graduated from the Wheatley School in East Williston, NY, and attended college at Johns Hopkins University, graduating with the class of 1979. He earned his medical degree in 1983 from SUNY Upstate Medical University in Syracuse, NY, and completed his internship and residency at Long Island Jewish Medical Center in New Hyde Park, NY. Dr. Turen subsequently completed his trauma fellowship at the R. Adams Crowley Shock Trauma Center in Baltimore, MD in 1988.

Dr. Turen first became a member of the Penn orthopaedic family through our partnership with BayHealth Medical Center in Dover, DE, where he maintained his most recent practice. This position was preceded by a position as the Director and Chair of the Georgia Orthopaedic Trauma Institute in Macon, GA, and a 20-year career as the Chief of Orthopaedic Trauma Services and the Director of the Orthopaedic Traumatology Fellowship Program at Shock Trauma Center in Baltimore, MD. Dr. Turen also served for 28 years as a Commander in the Medical Corps of the U.S. Navy Reserve, acting as a medical officer for the U.S. Navy Seals when on active duty. His 20 year membership in AO North America and the AO Trauma Foundation afforded him numerous opportunities to serve as faculty, chairman, and senior trustee. He participated as an educator, firefighter, fire officer, and dive team member for the Emergency Medical Services community with the Maryland Fire and Rescue Institute, the Washington DC Fire Department, and the Howard County, MD Fire and Rescue Department. His work as a former Special Deputy US Marshal further led to the establishment of the tactical EMS program for the National Capital Region Antiterrorism Task Force. Dr. Turen is survived by his wife Bethanne, sons Jonathan and Jason Turen, stepchildren Jessica Webster, Margaret Sutton (William), and Zach Webster, step-grandson Alex Webster, his mother Georgia Lo Prete, and his sister Anita Davidson (Robert Friedman).

With Dr. Turen's passing, we have lost a truly passionate educator, a dedicated and hard-working orthopaedic surgeon, and a great friend. His impact and his legacy live on through the countless orthopaedic trauma fellows and residents he has touched over the years with his commitment to the care of the injured. Dr. Turen will be greatly missed by all at Penn Orthopaedics and our thoughts are forever with his family.

# Chief Residents

### Eileen A. Crawford, MD

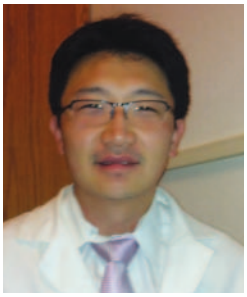
**Hometown** - Wilmington, Delaware
**Undergraduate Institution** – Princeton University, AB in Ecology and Evolutionary Biology
**Medical School** – University of Pennsylvania
**Fellowship** – Sports Medicine, University of Michigan
**Penn Highlights** – The birth of my daughter, Charlotte, and just being a part of the amazing Penn Ortho family. No matter how hard we work, I've never had a day here when I didn't laugh.
**Future Directions** – Hopefully back to the Philadelphia area.

### Andre (Nic) Gay, MD

**Hometown** – Dallas, TX
**Undergraduate Institution** – University of North Texas, BS in Biology
**Medical School** – Baylor College of Medicine
**Fellowship** – Foot & Ankle Adult Reconstruction, Roger Mann, MD, Oakland, CA
**Future Directions** – To return to Texas to practice.

### Jason E. Hsu, MD

**Hometown** – Warren, Ohio
**Undergraduate / Medical School** – 7 year BA/MD program at Northwestern University, BA in Biochemistry
**Fellowship** – Shoulder and Elbow, Washington University in St. Louis
**Penn Highlights** – Administrative Chief, UPOJ Editor, Post-doctoral research fellowship with Dr. Lou Soslowsky
**Future Directions** – Academic orthopaedics.



### Tae Won B. Kim, MD

**Hometown –** Born in Seoul, South Korea; Grew up in Tenafly, NJ.
**Undergraduate Institution –** Massachusetts Institute of Technology
**Medical School –** Albert Einstein College of Medicine
**Fellowship –** Orthopaedic Oncology, Memorial Sloan-Kettering Cancer Center
**Penn Highlights –** Having my parents see me in a white coat during intern year; meeting my wife during residency.
**Future Directions –** Looking forward to being in academic medicine, working with residents and fellows, and publishing papers to push the boundaries of oncologic care.

## Amun Makani, MD

**Hometown** – Born in Easton, PA; Grew up in Petersburg, WV.
**Undergraduate Institution** – Northwestern University, BS in Medical Engineering, concentration in Tissue Engineering
**Medical School** – Northwestern University
**Fellowship** – Sports Medicine, Massachusetts General Hospital
**Penn Highlights** - Recipient of the Jacqueline Perry Research Award, section editor of the UPOJ, my trip to Tanzania where I performed volunteer orthopedic care in Arusha, and working with extremely talented attendings and residents who took the time to teach and mentor me throughout residency. Most importantly, I got married to my amazing wife Neeharika.
**Future Directions** – I would like to work with residents in my future practice and be able to share the education and skills that I have been fortunate to receive during my training at Penn.

## Min Jung Park, MD

**Hometown** – Seoul, South Korea
**Undergraduate Institution** – Brown University, BA, MMSc
**Medical School** – Brown University
**Fellowship** – Hand and Upper Extremity, Robert A. Chase Hand Center at Stanford University
**The Future –** Hopefully somewhere on the West Coast.

## Amy E. Sewick, MD

**Hometown** – Western Michigan and Boston, MA
**Undergraduate Institution** – Harvard University, AB in Philosophy
**Medical School** – University of Michigan
**Fellowship** – Sports Medicine, University of California Los Angeles
**Penn Highlights** – engaged to be married as soon as we can afford it!
**Future Directions** – Focus on injury prevention in recreational and elite athletes; team physician for college hockey and rugby teams.

## Roshan P. Shah, MD, JD

**Hometown** - Camden, NY, a small town north of Syracuse by about 40 miles.
**Undergraduate Institution** - Dartmouth College, BA in Chemistry
**Graduate Education –** Stanford University Law School, JD
**Medical School** – Yale University
**Fellowship** - Reconstructive Arthroplasty, Rush University
**Penn Highlights** – Post-doctoral research fellowship with Dr. Rob Mauck. Proud parent of two boys, Niko and Riv, with my wife Arthi.

# Current Residents

## Clinical Year 4

**Hassan Alosh, MD**
*Undergraduate:* University of Maryland
*Medical School:* Johns Hopkins University

**Christina F. Endress, MD**
*Undergraduate:* University of Michigan
*Medical School:* University of Michigan

**Chancellor F. Gray, MD***
*Undergraduate:* Princeton University
*Medical School:* Thomas Jefferson University

**Adam T. Griska, MD**
*Undergraduate:* Brown University
*Medical School:* Tufts University School of Medicine

**Sunil S. Jani, MD**
*Undergraduate:* University of Pennsylvania
*Medical School:* UMDNJ – Robert Wood Johnson

**Mara L. Schenker, MD***
*Undergraduate:* University of Pittsburgh
*Medical School:* University of Chicago

**Rehan S. Shamim, MD**
*Undergraduate:* Princeton University
*Medical School:* UMDNJ – Robert Wood Johnson

## Clinical Year 3

**Nicole S. Belkin, MD***
*Undergraduate:* University of Florida
*Medical School:* University of Florida

**John G. Horneff III, MD**
*Undergraduate:* Rutgers University Honors College
*Medical School:* University of Pennsylvania

**Kevin J. McHale, MD**
*Undergraduate:* LaSalle University
*Medical School:* Thomas Jefferson University

**Christos D. Photopoulos, MD**
*Undergraduate:* McGill University
*Medical School:* Dartmouth Medical School

**Matthew P. Sullivan, MD**
*Undergraduate:* Tufts University
*Medical School:* Boston University

**Ryan M. Taylor, MD**
*Undergraduate:* Dartmouth College
*Medical School:* UT Southwestern Medical School

**Stephen J. Torres, MD**
*Undergraduate:* University of Florida
*Medical School:* Albert Einstein College of Medicine

**Pramod B. Voleti, MD***
*Undergraduate:* Princeton University
*Medical School:* SUNY – Downstate

## Research Year

**Andrew H. Milby, MD***
*Undergraduate:* Washington University in St. Louis
*Medical School:* University of Pennsylvania

**Sarah M. Yannascoli, MD***
*Undergraduate:* Cornell University
*Medical School:* Albert Einstein College of Medicine

***Six Year Research Track***

## Clinical Year 2

**P. Maxwell Courtney, MD**
*Undergraduate:* Washington and Lee University
*Medical School:* Georgetown University

**Joshua A. Gordon, MD***
*Undergraduate:* Pitzer College
*Medical School:* UCLA – David Geffen School of Medicine

**Stephen Y. Liu, MD**
*Undergraduate:* Tufts University
*Medical School:* Tufts University

**Michael H. McGraw, MD**
*Undergraduate:* Howard University
*Medical School:* Howard University

**Christopher M. Melnic, MD**
*Undergraduate:* Boston College
*Medical School:* Tufts University

**Nicholas Pulos, MD**
*Undergraduate:* University of Pennsylvania
*Medical School:* Perelman School of Medicine

**Vishal Saxena, MD***
*Undergraduate:* Northwestern University
*Medical School:* University of Chicago

**Jonathan B. Slaughter, MD**
*Undergraduate:* University of Pennsylvania
*Medical School:* Wright State University

## Interns

**Jason B. Anari, MD**
*Undergraduate:* The College of New Jersey
*Medical School:* UMDNJ – Robert Wood Johnson

**Tyler R. Morris, MD***
*Undergraduate:* University of Pennsylvania
*Medical School:* Drexel University

**Alexander L. Neuwirth, MD***
*Undergraduate:* Rutgers University
*Medical School:* UMDNJ – Robert Wood Johnson

**Philip A. Saville, MD**
*Undergraduate:* University of Leicester
*Medical School:* University of Leicester

**Russell N. Stitzlein, MD**
*Undergraduate:* Miami University
*Medical School:* Cleveland Clinic Lerner College of Medicine

**Michael T. Talerico, MD**
*Undergraduate:* University of Notre Dame
*Medical School:* Saint Louis University

**Nathan A. Wigner, MD PhD**
*Undergraduate:* University of North Carolina
*Medical School:* Boston University

**Chase Woodward, MD MPH**
*Undergraduate:* Northwestern University
*Medical School:* Northwestern University

** Six-Year Research Track*

# Dedicated Lectureship Series: Academic Year 2012–2013

Each year, the Department of Orthopaedic Surgery is privileged to host several distinguished professors in honor of individuals who have demonstrated extraordinary talent and tireless devotion in the name of family, friends, and orthopaedic surgery. It is in commemoration of these individuals – Mrs. June Wapner, Dr. Edgar L. Ralston, Dr. Ernest Gentchos, and Dr. Leo Leung – that we highlight these special events.

*The First Annual June Wapner Endowed Lectureship*
*May 24th, 2012*
*Guest Lecturer: Dr. Roger Mann, MD*
*Director of the Foot and Ankle Fellowship Program,*
*Professor of Orthopaedic Surgery*
*Oakland Bone & Joint Specialists, Oakland, CA*
Covered by: Joshua Gordon, MD


**Dr. Roger Mann**

The June Wapner lectureship was founded as a tribute to Mrs. June Wapner, cherished wife of Dr. Keith Wapner, director of the Foot and Ankle department at Pennsylvania Hospital. As conveyed in Dr. Wapner's meaningful opening remarks, Mrs. Wapner left behind a legacy of love and courage. Dr. Wapner met his wife-to-be while he was an intern. She was a clinical lab manager, and Dr. Wapner fondly recalled finding numerous creative ways to make his way to the lab to confirm results or otherwise tend to patient care in the chemistry lab. Their two children inherited Mrs. Wapner's strength and perseverance; one is currently working on Capitol Hill and the other is studying at Temple Law School. Mrs. Wapner is remembered by all who knew her as a loving wife and mother and as a woman of tremendous fortitude.

Dr. Roger Mann served as the inaugural guest speaker. Dr. Mann is counted among the most prominent Foot and Ankle surgeons of his time. Among his countless accomplishments, Dr. Mann has published over 120 scientific journal articles, nearly 100 book chapters and is the co-author of one of the most widely used textbooks on Foot and Ankle surgery. Dr. Mann began his first lecture with an excellent review of the diagnosis and operative treatment of Pes Cavus. He also drew on his over 40 years of expertise to succinctly describe the indications for surgical intervention for Pes Planus. He continued with a second lecture on the use of the Scandanavian Total Ankle Replacement (STAR) system. His perspective as the lead investigator on the FDA clinical trials for the system brought to light the findings of these extensive studies for prosthetic evaluation. He presented a brief history of total ankle arthroplasty and a thorough discussion of surgical technique, outcomes, and optimal use of the system.

It was a privilege and a pleasure to learn from Dr. Mann. His inspiring lectures were a fitting beginning to the June Wapner Endowed Lectureship. They did great justice to the memory of a fine and beloved woman.

*The Edgar L. Ralston Lectureship Series*
*January 24th, 2013*
*Guest Lecturer: Dr. Alexander Shin, MD*
*Professor of Orthopaedic Surgery*
*Mayo Clinic, Rochester, MN*
Covered by: Sarah M. Yannascoli, MD


**Dr. Alexander Shin**

This year we welcomed Dr. Alexander Shin for our Ralston Lectureship series, a tradition held in tribute to our former chairman, Dr. Edgar Lee Ralston. Dr. Ralston was born in Dubois, Pennsylvania, earned a bachelor's degree from Muskingum College in New Concord, Ohio, and received his medical degree from the University of Pennsylvania in 1937. He completed his residency and fellowship at New York Orthopaedic Hospital Columbia / Presbyterian Medical Center in New York City and eventually joined the Penn faculty in 1947. Dr. Ralston was the Chairman of the Department of Orthopaedic Surgery at the University of Pennsylvania from 1960 – 1977. During his tenure, he grew the department from one hospital, 5-6 faculty members, and several interns to a robust department which covered 6 hospitals, carried 30 faculty members and taught 40 residents. Dr. Ralston is best known for his staple textbook, *The Handbook of Fractures*, which is still carried in every orthopaedic resident's pocket on a daily basis. We owe much of what our department has become today to the hard work, perseverance, and love of orthopaedic surgery left behind by Dr. Ralston. This lectureship series is a small token of our appreciation.

Dr. Shin earned his medical degree from the University of Pennsylvania, recalling a number of fond and humorous memories working with Dr. Sennett as the orthopaedic intern and Dr. Heppenstall in the operating room. He went on to complete his Orthopaedic Residency at Naval

Regional Medical Center in San Diego, CA and his Hand and Microvascular fellowship at the Mayo Clinic in Rochester, MN where he currently practices. Dr. Shin shared his passion and enthusiasm for microvascular and complex brachial plexus repair and reconstructive surgery. A unique field, many of his presented cases left the audience awestruck at his courage in the operating room, and his dedication to helping patients whom other physicians had refused further treatment. He spoke specifically about traumatic adult brachial plexus injuries, demonstrating numerous incredible videos of success despite the tremendous odds working against his patients. To say the least, Dr. Shin's visit was inspiring and opened our eyes to a new frontier of orthopaedic surgery.

It was our pleasure to host such a unique, dedicated, and extraordinary orthopaedic surgeon to the University of Pennsylvania in honor of Dr. Edgar L. Ralston.

*The 12th Annual Ernest Gentchos Lectureship*
*March 14th, 2013*
*Guest Lecture: Dr. Laurence Higgins, MD*
*Chief of Sports Medicine / Shoulder Service at Brigham and Woman's Hospital*
Covered by: Sarah M. Yannascoli, MD


**Dr. Laurence Higgins**

In tribute to the great educator and clinician, Dr. Ernest Gentchos, the University of Pennsylvania was proud to host Dr. Laurence Higgins as the 2013 speaker for the 12th annual Ernest Gentchos Lectureship series. Dr. Gentchos has been a dedicated member of the Penn Orthopaedic Family for many years, never ceasing to demonstrate his exceptional and fierce dedication to orthopaedic surgery. After growing up in Greece, Dr. Gentchos completed medical school at St. Louis University School of Medicine, served in the medical battalion of the US Army Air Cavalry during the Vietnam War, and completed his residency training at the University of Pennsylvania. Since that time, Dr. Gentchos has continued to serve as a dedicated faculty member, resident mentor, and an exceptional clinician. Among countless noteworthy academic contributions, he has provided endowed scholarships for high school, college, and medical school students, and made a profound impact on Penn Orthopaedics through his sincere avocation of superior patient care.

This year our dedicated lectureship speaker was Dr. Laurence Higgins. Dr. Higgins completed his medical degree at the State University of New York at Stony Brook School of Medicine, attended residency at the Hospital for Special Surgery, and completed his Sports fellowship at the University of Pittsburgh. He has served as the team physician for both Duke and Pittsburgh University athletes, the Pittsburgh Steeler's, and currently as the team physician for Brookline High School in Massachusetts. His talk on the evolving management of shoulder instability and value-driven healthcare exhibited his experience as a clinician, and passed on a level of wisdom worthy of honoring Dr. Gentchos.

Each year we hope that we can commemorate Dr. Gentchos's continual contribution to education. We are grateful to Dr. Higgins for imparting his experience and knowledge to our department and echoing the sentiments of our beloved faculty member, Dr. Ernest Gentchos.

*The 9th Annual Leo Leung Memorial Lecture*
*April 18th, 2013*
*Guest Lecture: Dr. Dan Nagle, MD*
*Professor of Clinical Orthopaedic Surgery, Northwestern Center for Surgery of the Hand, Chicago, IL*
Covered by: Sarah M. Yannascoli, MD


**Dr. Dan Nagle**

The Leo Leung Memorial Lectureship is held annually as a dedication to Dr. Leo Leung, former chief resident at the University of Pennsylvania. Dr. Leung grew up in Hong Kong, receiving his undergraduate degree at Brown University and his medical degree from the University of Pennsylvania. In 2002, Dr. Leung passed away suddenly during his final year of residency. Throughout his years as a resident, he developed an enthusiasm for the field of hand and upper extremity and was being actively recruited by many competitive fellowships at the time of his passing. He was often warmly referred to as "Leo the Lion" and "The Iron Leung" for his profound loyalty and remarkable work ethic. Through this lectureship series we hope to honor Dr. Leung's life and contributions to the Penn orthopaedic family.

Our invited speaker for this year's lectureship series was Dr. Dan Nagle from Northwestern University. Dr. Nagle completed his orthopaedic surgery residency at Northwestern University, receiving subspecialty training in hand and microsurgery in Louisville, Kentucky with Dr. Harold Kleinert and Dr. Joseph Kutz. He has been a long-standing, dedicated faculty member at Northwestern University since 1984, and it was only fitting that he was our invited speaker in memory of Dr. Leung. He lectured passionately about thermal devices and their uses in wrist arthroscopy, CMC arthroplasty, and medical-legal issues facing today's orthopaedic surgeon. Dr. Nagle shared many pearls from his extensive clinical experience and emphasized the need for continued innovation despite the cost-cutting climate of our current and future healthcare system.

We sincerely thank Dr. Nagle for taking the time to visit the University of Pennsylvania and sharing his experience and insight. It was a true asset to our education and a tribute to the memory of Dr. Leo Leung.

# Hospital of the University of Pennsylvania

John L. Esterhai, Jr., MD, Jaimo Ahn, MD, PhD, Derek Donegan, MD, Keith Baldwin, MD, MSPT, Kristy Weber, MD, R. Bruce Heppenstall, MD, L. Scott Levin, MD, FACS, and Samir Mehta, MD

As the Department of Orthopaedic Surgery has continued to expand and further subspecialize, the focus at the Hospital of the University of Pennsylvania has expanded beyond orthopaedic trauma and fracture care to include neuro-orthopaedics and orthopaedic oncology.

Over the last decade, orthopaedic trauma has "come of age." At its most basic level, the care of the traumatically injured patient is at the core of being an orthopaedist. The ability to deliver care to this unique and often underserved patient population is truly at the heart of being a physician. However, being a successful Level I trauma center is centered on the concept of the "team." At a macroscopic level, the team consists of hospital administrators, physicians, nursing staff, and tangible structures (like ICUs and resuscitation bays) coming together to create an environment to care for those that sustain traumatic injuries and put into place mechanisms which will facilitate this process.

Upon this foundation, Level I trauma center triage and care requires intense interaction with more services than most elective practices: emergency medicine; diagnostic and interventional radiology; trauma, vascular and plastic surgery; anesthesia; critical care; nursing; general internal medicine; infectious disease; rehabilitation medicine, physical therapy and occupational therapy; and social work.

It is in our very busy rotating night and weekend call schedule that we best demonstrate our collegiality and depth of caring for one another within our department. With an increased eye towards outcomes and quality improvement, we have started to "close" the call system and deliver care based on algorithms for various injury patterns. Several of the non-trauma faculty share call, 24/7/365—at no small personal sacrifice—to meet the burden of emergency orthopaedic care for our region.

Patient ward in Managua, Nicaragua, as visited in collaboration with Health Volunteers Overseas.

In addition to the faculty support, we have Adele Hamilton, CRNP as our inpatient orthopaedic trauma nurse practioner to improve the comprehensive nature of our inpatient service. Ms. Hamilton's tireless effort is second-to-none and her acute management of our complex patient population has furthered our ability to provide world-class care. To support our growing outpatient practice, the orthopaedic trauma service has added Angela Millier, CRNP and Katie Marine, PA. They have been a tremendous asset in their short time on 2 Silverstein, measured by the dramatic increase in patient satisfaction. They have also initiated "Own the Bone" through the American Orthopaedic Association, along with collecting outcomes on our trauma patients. In addition, the Division of Orthopaedic Trauma has continued to grow its clinical research efforts through the work of Kelly McGinnis as our clinical research coordinator for orthopaedic trauma in conjunction with Dr. Horan, director of our clinical research efforts. Through their combined efforts, the orthopaedic trauma service continues to be a departmental leader in prospective funded studies.

The Division of Orthopaedic Trauma welcomed Derek Donegan, MD back to the University of Pennsylvania. Dr. Donegan, former chief resident at the University of Pennsylvania,

completed his trauma fellowship at UMDNJ-Newark with Drs. Reilly, Sirkin, and Liporace. His interests in arthroplasty and trauma have truly enhanced the service's ability to manage the increasing burden of periprosthetic fractures.

The didactic portion of the Division of Orthopaedic Trauma has expanded to include weekly fracture conference where a review of all operative cases from the week prior is done in the Socratic Method. In addition, weekly fracture conference reviews topics of interest and is a combination of journal clubs, classic literature, resident and faculty presentations, and CEQI. Furthermore, the Division of Orthopaedic Trauma has been working diligently on an international component which came to fruition this year through the support of the Biedermann family. Through their generous gift, we were able to send three residents and three faculty members to Managua, Nicaragua via Health Volunteers Overseas. Their experience was nothing short of remarkable.

Orthopaedics at HUP also added Keith Baldwin, MD to the mix. Dr Baldwin, former Penn resident, completed a fellowship at Children's Hospital of Philadelphia. As part of his fellowship, he has taken on the surgical management of adult patients with neuro-orthopaedic conditions – a legacy of Dr. Mary Ann Keenan. This unique skill set is coupled with his drive and enthusiasm in collaborative research efforts to expand our understanding of orthopaedics.

Most recently, we had the distinct privilege of bringing orthopaedic oncology to HUP via the addition of Kristy Weber, MD. Dr. Weber, a well-established orthopaedic oncologist from Johns Hopkins and leader in the orthopadeic community, brings her knowledge, enthusiasm, and experience to the Department of Orthopaedic Surgery and to the University of Pennsylvania Health System.

Despite all of the additions, one of the most exciting (and anxiety provoking) developments is the transition of the trauma center from the Hospital of the University of Pennsylvania campus to the expanded Penn Presbyterian Medical Center site. With the groundbreaking ceremony complete, the transition is slated for the middle of 2015.

Each of us who works with patients who have these difficult injuries realizes that it is not our personal skill that cures. Year after year, participating in the care and watching the healing is a humbling experience. We are reminded of how truly lucky we are and how important the entire team is in making this a reality.

# Penn Presbyterian Medical Center

David J. Bozentka, MD

Chief of Orthopaedic Surgery, Penn Presbyterian Medical Center

The Department of Orthopaedic Surgery at Penn Presbyterian Medical Center (PPMC) had another very successful year as considering the academic productivity, program awards, expansion of the clinical staff, and the construction of new facilities.

We are fortunate to welcome back Dr. Andrew Kuntz to PPMC. Dr. Kuntz obtained his medical degree from the University of Virginia School of Medicine prior to completing his orthopaedic surgical residency at the University of Pennsylvania. He then spent a year of fellowship in shoulder and elbow surgery at the Thomas Jefferson University Hospital and the Rothman Institute. Dr. Kuntz is the current director of the shoulder study group at Penn and is a member of the American Orthopaedic Association Emerging Leaders Program. Dr. Kuntz will split his time between the McKay Orthopaedic Research Laboratory and his clinical practice of shoulder and elbow arthroscopy and replacement.

We also welcome Dr. Harvey Smith MD to the Department of Orthopaedic Surgery at PPMC. Dr. Smith with be taking over the care of patients with disorders of the spine. He obtained his undergraduate degree at Harvard University and medical school training at the Pennsylvania State University College of Medicine. His residency and fellowship training were completed at Thomas Jefferson University Hospital and the Rothman Institute. After completing his fellowship, Dr. Smith served as an attending physician at the Weill Cornell Medical College Methodist Hospital in Houston Texas, followed by time at Tufts University School of Medicine New England Baptist Hospital in Boston, Massachusetts. Dr. Smith's clinical interests include complex surgery of the cervical, thoracic, and lumbar spine. His research interests include degenerative disc disease, minimally invasive surgery, and image-guidance navigation systems, as well as tracking and measuring the outcomes of spine surgery.

The Joint Replacement Service at PPMC has earned The Joint Commission's Gold Seal of Approval for hip and knee replacement. The Joint Commission's Disease-Specific Care Certification Program began in 2002 and evaluates a clinical programs' continuum of care. Three core areas are evaluated, including compliance with consensus-based national standards, effective use of evidence-based clinical practice guidelines to manage and optimize cases, and an organized approach to performance measurement and improvement activities. The certification process was coordinated by Dr. Eric Hume. There was a rigorous on-site survey by the Joint Commission who assessed the department for compliance of their strict standards including infection prevention, leadership, and medication management.

Penn Presbyterian Medical Center was once again named a Blue Distinction for Hip and Knee Replacement by Independence Blue Cross. This is a nationwide program that identifies programs demonstrating expertise in delivering quality health care. An extensive evaluation of the program's clinical data is used to assess the facility's program structure, processes and outcomes of care. Programs that are chosen have been found to outperform their peers in quality safety and efficiency. These awards are a testament to the excellence of care provided and pre-eminence of the program at PPMC.

The Bach fund research awards were recently announced with the Department of Orthopaedic Surgery at PPMC garnering four of the six grants. The winning projects included: Dr. Eric Hume and Dr. Laura Kosseim for Pre-Operative screening for sleep apnea in patients undergoing hip or knee arthroplasty; Dr. G. Russell Huffman and Dr. Judith O'Donnell for a pilot study to evaluate the bacterial diversity of the shoulder joint during revision arthroscopy microbial genomics versus standard care cultures; Dr. Nabil Elkassabany, Dr. Andrew Kuntz, Dr. G. Russell Huffman, and Dr. David Glaser for development and evaluation of a multimodal analgesia protocol for postoperative pain management following shoulder surgery; and Dr. Eric Hume, Dr. Craig Israelite, Dr. Gwo-Chin Lee, Dr. Charles Nelson, and Dr. Neil Sheth for collection of patient reported outcomes, joint outcomes, and implant data in a PPMC joint registry to support arthroplasty clinical care, education, and research.

Construction has begun for the Penn Center for Specialty Care located at 3737 Market Street. The 11 story facility with 150,000 square feet of space will include a comprehensive interdisciplinary center for musculoskeletal care. The center will have nearly 110 exam rooms for the ambulatory practice, physician offices, along with physical therapy exam space and therapy gym. In addition a the facility will hold a state of the art ambulatory surgery center with six operating suites and outpatient radiology services. This state of the art facility will allow cutting edge multidisciplinary integrated care for our patients and foster collaborative research efforts.

The Penn Medicine Trauma Center will transfer its operations at the Hospital of the University of Pennsylvania to PPMC. The approximately 1,900 trauma patients entering the Penn System will be treated at PPMC which will become the Level 1 Regional Trauma Resource Center for Penn Medicine. The 178,000 square foot PPMC Advanced Care Hospital Pavilion will be located on Powelton Avenue and 38th street. The facility will include a helipad, critical care beds, perioperative services, emergency department, and trauma bays. It is slated to open in 2015.

The future is very bright for the Department of Orthopaedic Surgery at PPMC as we look forward to another exciting year through our commitment to excellence in clinical care and academic productivity.

# Pennsylvania Hospital

Vincent M. Arlet, MD

Director, Penn Orthopaedic Spine Center at Pennsylvania Hospital

Pennsylvania Hospital continues to maintain its proud tradition of healthcare excellence as the nation's first hospital while reinventing itself to suit changing times. This year has marked the departure of the Booth, Bartolozzi, and Balderston practice from Pennsylvania Hospital, leaving tremendous opportunities in terms of surgical and patient care capacity for Penn Orthopaedics. We are also fortunate to have retained Dr. David Nazarian as clinical assistant professor of orthopaedic surgery, who will continue his high-volume hip and knee replacement practice under the banner of Penn Orthopaedics.

The addition of Dr. Neil Sheth will also ensure that Pennsylvania Hospital remains a center for excellence in joint replacement. Dr. Sheth returns to Penn Orthopaedics as an assistant professor following residency training at Penn, fellowship at Rush University in Chicago, and several years in practice with OrthoCarolina in Charlotte. Dr. Derek Donegan's practice of trauma and total joint replacement and Dr. Keith Baldwin's practice of neuro-orthopaedics both continue to grow steadily. Other established faculty are also expanding their clinical activities at Pennsylvania Hospital. Our chairman Dr. L. Scott Levin now maintains a busy outpatient and surgical practice here, and Dr. Charles Nelson and Dr. James Carey have begun shifting surgical volume here as well. Dr. Bruce Heppenstall has moved his clinical practice from HUP to Pennsylvania Hospital where he sees patients in the clinic space from Monday to Thursday. Dr Heppenstall stopped operating this year after 40 years of practice within Penn. The orthopaedic foot and ankle service also remains as busy as ever, as Drs. Wapner, Chao, and Steiner continue to provide specialized care to patients with the most complex foot and ankle disorders.

The Penn Orthopaedic Spine Center continues to grow in close collaboration with our colleagues in the department of neurosurgery. Minimally-invasive spine surgery as well as complex spinal deformity corrections are performed on a regular basis. We are pleased that Dr. Harvey E. Smith has joined our ranks as assistant professor and is already clinically active at Pennsylvania Hospital while maintaining an appointment at the Philadelphia Veterans Affairs Medical Center. Dr. Smith underwent residency and fellowship training at Thomas Jefferson University Hospital, and brings with him a wealth of experience from years in practice at New England Baptist Medical Center in Boston.

Penn Orthopaedics at Pennsylvania hospital offers a comprehensive clinical program where all orthopaedic subspecialties are represented. In addition to changes within our ranks, the transition at Pennsylvania Hospital is visible with the construction of the Penn Medicine at Washington Square facility. This 153,000 sq. ft. expansion will aid in the transformation of Pennsylvania Hospital into a fully-modernized acute care hospital with all private rooms. These changes will all enable Pennsylvania Hospital to continue providing world-class orthopaedic care for the centuries to come.

# The Children's Hospital of Philadelphia

John P. Dormans, MD[1] and Jennifer A. Talarico, MS[2]

[1]Chief, Division of Orthopaedic Surgery, Children's Hospital of Philadelphia, Professor of Orthopaedic Surgery, Perelman School of Medicine at the University of Pennsylvania
[2]Clinical Research Coordinator, Division of Orthopaedic Surgery, Children's Hospital of Philadelphia

Hello from the Division of Orthopaedic Surgery at the Children's Hospital of Philadelphia (CHOP)! The CHOP orthopaedic faculty had another exceptional year, excelling in both our clinical and research programs. We are also pleased to announce that CHOP Orthopaedics has been ranked again as the number one Pediatric Orthopaedic Surgery Program in the United States and shares the number one spot with Children's Hospital Boston as the top pediatric institutions in the country, as determined by the 2012 US News and World Report.

## Clinical Program

Our orthopaedic faculty (Figure 1) continues to expand and is currently comprised of twenty one total providers, including eighteen specially trained pediatric orthopaedic surgeons (thirteen operative and five non-operative), and three pediatricians with sports medicine training.

**Figure 1.** Members of the CHOP Orthopaedic team and visiting professor Dr. Peter Waters, MD during the Jesse T. Nicholson Visiting Professorship event in June, 2012.

CHOP Orthopaedics is thrilled that Keith Baldwin, MD, MSPT, MPH (Figure 2A) joined the department in August of 2012 as an attending surgeon after completing his clinical fellowship here at CHOP in 2011-12. Dr. Baldwin obtained his medical training at Robert Wood Johnson Medical School in New Brunswick, NJ, and completed his residency at the University of Pennsylvania. Dr. Baldwin has a highly specialized skill set and is working with Dr. David Spiegel in adult and pediatric neuromuscular disease and trauma. Dr. Baldwin is splitting his time with University of Pennsylvania and is establishing a transitional program from pediatric to adult treatment.

Additionally, we are excited to announce the new collaboration with Dr. Helen Horstmann, MD (Figure 2B) as a part-time, non-operative pediatric orthopaedic surgeon.

A B

**Figure 2 (A-B).** From left to right, A) Dr. Keith Baldwin and B) Dr. Helen Horstmann.

Dr. Horstmann joins us from University of Pennsylvania and specializes in neuromuscular scoliosis.

CHOP has also recently developed a partnership with Virtua Hospital to provide pediatric services at Virtua's facilities in Voorhees and Mount Holly. Orthopaedics, in particular, provides both outpatient clinic visits as well as day surgery at Virtua's Speciality Care Center in Voorhees (Figure 3).

Our department also staffs twelve nurse practitioners, two registered nurses, six physician's assistants, four cast technicians, and two athletic trainers who are able to evaluate, diagnose, and treat the full range of musculoskeletal disorders, as well as an additional staff of 41 office personnel.

## Teaching

CHOP Orthopaedics currently funds four one-year clinical fellowships, and four one-year research fellowships. The 2012-2013 **clinical fellows** are Martin Morrison, MD (Figure 4A); Laura Gill, MD (Figure 4B); Sean Kearney, MD (Figure 4C); and Nanjundappa Harshavardhana, MD (Figure 4D). This year's **research fellows** are Dino Colo, MD from Utrecht, Netherlands (Figure 5A); Hooman Bakhshi, MD from Iran (Figure 5B); Indranil Kushare, MD (a fellow of the CHOP/SICOT fellowship) from Mumbai, India (Figure 5C); and Bibek Banskota, MD from Kathmandu, Nepal (Figure 5D). Following completion of their clinical fellowships, Dr. Morrison is seeking an academic position in Orthopaedic Surgery on the West Coast along with his wife, who is a pediatrician; Dr. Gill, originally from Barbados, is currently looking for an academic position in pediatric Orthopaedic Surgery; Dr. Kearney will practice Pediatric Orthopaedic Surgery in the U.S. Army (location to be determined); and Dr. Harshavardhana

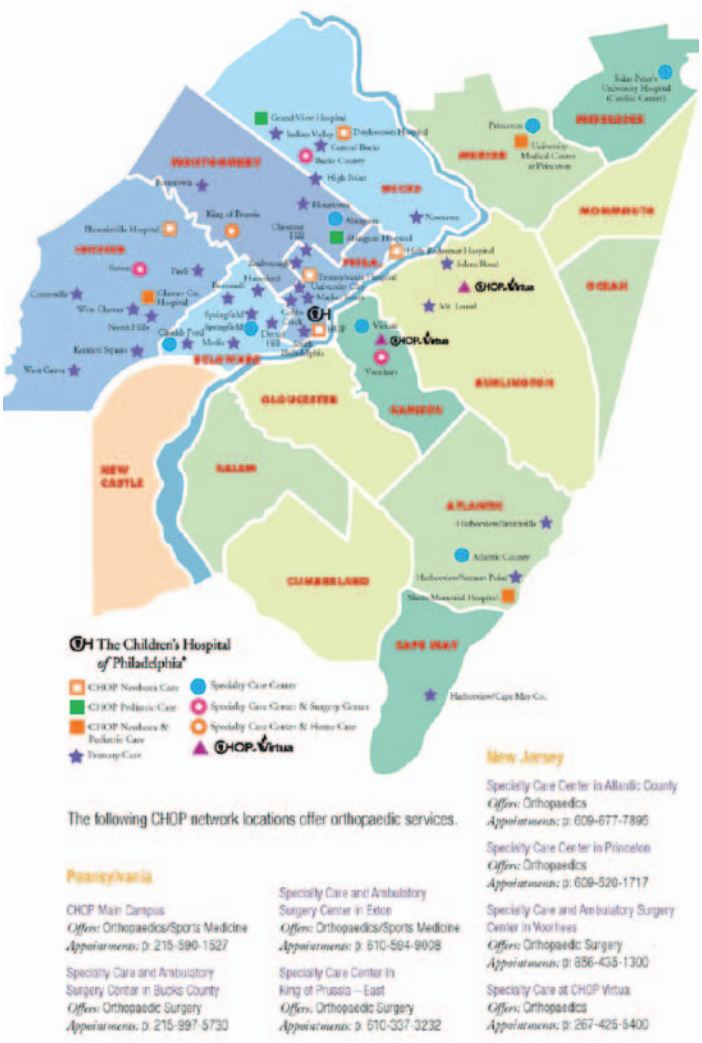



**Figure 3.** Map of CHOP's network locations that offer orthopaedic services.

would like to pursue another clinical fellowship in Pediatric Orthopaedics or spinal surgery in the U.S. After completing his research fellowship, Dr. Colo plans to return to the Netherlands to finish his PhD and his orthopaedic training; Dr. Bakhshi plans to continue research, concentrating in the field of pediatric spine, musculoskeletal tumors, and orthopaedic infection; Dr. Kushare is pursuing a clinical fellowship in the United States before returning to Mumbai; and Dr. Banskota will return to Nepal where he works with underprivileged

A B C C

**Figure 4 (A-D).** From left to right, the CHOP Orthopaedic 2012-2013 clinical fellows: A) Dr. Martin Morrison, B) Dr. Laura Gill, C) Dr. Sean Kearney, and D) Dr. Nanjundappa Harshavardhana, MD.

A B C C

**Figure 5 (A-D).** The CHOP Orthopaedic research fellows, from left to right: A) Dr. Dino Colo from the Netherlands, B) Dr. Hooman Bakhshi from Iran, C) Dr. Indranil Kushare from India, and D) Dr. Bibek Banskota from Nepal.

children with physical disabilities under a non-profit charitable organization called Hospital and Rehabilitation Center for Disabled Children (HRDC), the only pediatric orthopedic care facility in Nepal.

The Division of Orthopaedic Surgery continues to reach out to the international community of specialists by participating in the Visiting International Scholars Program (VISP), a program designed to provide international orthopaedic surgeons with the opportunity to observe clinical care of pediatric patients in a high volume, university, academic setting. Over the past year, CHOP Orthopaedic Surgery has had numerous Visiting International Scholars, including Alaa Azmi Ahmad from Palestine, David Farrington from Spain, Indranil Kushare from India, Juan Pretell from Peru, Chasanal Rathod from India, Josip Vlaic from Croatia, Ziming Zheng from China, Liu Zhenjiang from China, Jacky Hua from China, Muayad Kadhim from Syria, Li Lianyong from China, and Harska Kanumalla from India. Some of our Visiting International Scholars have gone on to be accepted as a Research or Clinical fellow here at CHOP, or another institution in the United States.

## Research Program

The past year has been an exciting and productive one for our Orthopaedic Basic Research Program, led by Maurizio Pacifici, PhD, (Figure 6) with many activities and research initiatives

**Figure 6.** A group picture of the CHOP Orthopaedic Translational Research team led by Maurizio Pacifici, PhD. From left to right (back row): Masahiro Iwamoto, Colleen Larmour, Cheri Saunders, Kenta Uchibe, Rebekah Decker, Julianne Huegel, Eiki Koyama and (front row): Motomi Enomoto-Iwamoto, Agnese DiRocco, Maria Elena Candela, Leslie Cantley, Jiyeon Son, Federica Sgariglia, Maurizio Pacifici, Jennifer Rosa.

related to a number of skeletal pathologies. Our faculty members and their associates continue to work diligently on the aims of our several current NIH R01 grants to understand the pathogenic mechanisms of pediatric and adult conditions including Heterotopic Ossification (HO), Fibrodysplasia Ossificans Progressiva (FOP) and Multiple Hereditary Exostoses (MHE), and to clarify processes including tendon and cartilage repair. An exciting new development is that one of our faculty members, Dr. Masahiro Iwamoto, has recently received a new grant from the Muscular Dystrophy Association to study skeletal muscle repair and regeneration, thus linking nicely current efforts on the overall musculoskeletal system. The new data and insights have generated publications in top peer-reviewed journals.

In our efforts to strengthen the position and resources of our Division in MHE's clinical and research fields, we organized and hosted the 4th International Research Conference on MHE here at CHOP/Penn from November 1 to 4, 2012. The Conference was attended by more 60 researchers and clinicians from all over the world gathered at The Inn at Penn for an intensive three day workshop that allowed presentations of the most recent findings but also many opportunities and time for lively discussions about future goals and possible treatments for this and related diseases. The Conference was co-sponsored by the National Institutes of Health, the MHE Research Foundation, the CHOP Research Institute, the Division of Orthopaedic Surgery at CHOP, and Shriners Hospitals for Children, a demonstration of the strong interest, importance and broad relevance of this biomedical research field. We have also been working hard to strengthen our ties with other research groups –including one from the University of California San Diego and one from UCSF- to coordinate and encourage research on MHE on a national level.

A similarly exciting biomedical development this year is that our basic research on HO and FOP has made advances toward possible clinical trials. Papers we published in 2010 and 2011 showed that synthetic agonist ligands for the nuclear retinoic acid receptors are very potent inhibitors of HO/FOP in experimental subcutaneous, intramuscular and genetically-driven mouse models of the diseases. A Canadian-based pharmaceutical Company is now working closely with us and with our colleagues at the Penn FOP Foundation to organize and implement a phase 2 trial in the very near future.

**Figure 7.** A group photo at the 4th Annual Multiple Hereditary Exostoses Research Conference in Philadelphia in November, 2012.

We are also finalizing collaborative plans with a Swiss pharmaceutical company to test the efficacy of synthetic sulfated polymers in our mouse models of MHE. The outcome of these experiments could provide proof-of-principle that exostosis formation can be inhibited or even blocked altogether by pharmacological means.

CHOP Orthopaedics is also working in collaboration with the Center for Applied Genomics (CAG) to compile a database of DNA samples obtained from patients and families with a variety of orthopaedic conditions, including targeting families with multiple individuals affected with adolescent idiopathic scoliosis (AIS). In 2011, CAG and Orthopaedics won the Scoliosis Research Society (SRS) Russell Hibbs Award for Best Basic Science Paper in 2011 for their study entitled "A Genome Wide Association Study Identifies IL17RC as an Adolescent Idiopathic Scoliosis Locus." Currently, whole exome sequencing is being performed on familial AIS blood samples with the goal of further understanding the influence of genetics on the development of AIS.

CHOP Orthopaedics, in collaboration with the Center for Childhood Cancer Research (CCCR) and the Ambramson Family Cancer Research Institute (AFCRI), has developed a position to establish, maintain, and oversee extramurally funded research projects in basic mechanisms of sarcoma pathogenesis and progression.

The CHOP Orthopaedic Surgery division is currently conducting 93 ongoing, active clinical research and basic science projects. Investigators within the division have been awarded funding from both internal and external sources to conduct these studies. In the past two years, the division has published over 100 articles in major orthopaedic journals, including (but not limited to) *JBJS*, *Spine*, *JPO* and *CORR*.

Our pediatric orthopaedic faculty continues to present research studies at orthopaedic conferences around the world, including the American Academy of Orthopaedic Surgeons (AAOS), the Pediatric Orthopaedic Society of North America (POSNA), the European Pediatric Orthopaedic Society (EPOS), the Scoliosis Research Society (SRS), the American Orthopaedic Society for Sports Medicine (AOSSM), the Musculoskeletal Tumor Society (MSTS), the Societe Internationale de Chirurgie Orthopedique et de Traumatologie (International Society of Orthopaedic Surgery and Traumatology, SICOT) and many more.

In 2009, our department initiated an annual Benjamin Fox Scholarship Award for current medical students who are interested in conducting a year of clinical research within Orthopaedics. In June, our department awarded Itai Gans, an upcoming fourth year medical student at the Perelman School of Medicine at the University of Pennsylvania and Eric Sarkissian, a fourth year medical student at Drexel University with this scholarship (Figure 8). While at CHOP, Itai has concentrated his research on developmental dysplasia of the hip (DDH), tibial eminence fractures, osteochondritis dissecans (OCD), and quality, safety, and value of Orthopaedic Surgery procedures. Eric is focusing on anterior cruciate

ligament tears in children, and healing mechanisms in patients with osteochondritis dissecans.

## Recognitions and Achievements

Our Attendings have assumed several leadership roles within the pediatric orthopaedic community over the past year.

Robert Campbell, MD was recently recognized by the Federal Drug Administration (FDA) as one of 30 Heroes who have made clinical, research, advocacy, and regulatory contributions over the 30 years since the enactment of the Orphan Drug Act for his work with the VEPTR. His Center for Thoracic Insufficiency Syndrome at CHOP continues to expand clinically and new research initiatives are ongoing.

Denis S. Drummond, MD, CHOP Orthopaedic's Chief Emeritus, currently serves as the co-director of the CHOP Orthopaedic Fellowship Program. Additionally, Dr. Drummond was the director of clinical research until December, 2012.

John M. Flynn, MD will assume his role as President of the Pediatric Orthopaedic Society of North America (POSNA) in the Spring of 2014 and he will host the 46th Annual meeting of POSNA in Hollywood, California. Dr. Flynn also recently completed his last year of 4 years as the chair of the International Pediatric Orthopaedic Symposium (IPOS). Dr. Flynn has recently been selected Chair of the American Academy of Orthopaedic Surgeons CME Courses Committee. He also ran the Scoliosis Research Society (SRS) Grants Committee, and he currently serves as the Vice President of the Chest Wall and Spinal Deformity Study Group.

Theodore J. Ganley, MD, is the Sports Medicine Director at CHOP supporting the clinical, research and outreach initiatives which continue to expand, including the new planned sports medicine center in King of Prussia. Dr. Ganley collaborated on the creation of a new sports medicine fellowship, the Penn/Children's Hospital of Philadelphia orthopedic sports medicine fellowship which will commence in August of 2013 with Dr. Sennett as well as departmental chairmen Drs. Levin, and Dormans. He was selected as moderator or instructor at instructional course lectures for the following annual meetings: the American Academy of Orthopedic Surgeons, American Academy of Pediatrics, American Orthopedic Society for Sports Medicine, International Pediatric Orthopedic Symposium, and Pediatric Orthopedic Society of North America this past year. He was an advisory board member for IPOS and ran the sports medicine section of their first annual Surgical Simulation lab. Dr. Ganley was also the Presidential Guest Speaker at the Pediatric Orthopaedic Club of New York.

**Figure 8.** 2012-2013 Benjamin Fox Research Fellows, Eric Sarkissian (left) and Itai Gans (right). Eric and Itai are upcoming fourth year medical students who have taken a year to do clinical research in pediatric orthopaedic surgery at CHOP.

B. David Horn, MD is the editor of the 2013 Pediatric Orthopaedic Special Interest Examination to be published by the American Academy of Orthopaedic Surgeons (AAOS) in March, 2013.

John Todd Lawrence, MD, PhD was American Board of Orthopaedic Surgery Board Certified this year. He also completed an OmeGa Core Competency Grant for the 2011-2012 academic year. This funding will support resident education as it pertains to fracture care through the development and implementation of a simple distal radius fracture reduction and casting simulation-based teaching program.

Wudbhav Sankar, MD continues to build and direct the adolescent and young adult hip program at CHOP, and has established a comprehensive clinical hip database. Additionally, Dr. Sankar and the Division of Orthopaedic Surgery was recently awarded a Scholler Foundation grant to fund a portable ultrasound machine.

David Spiegel, MD traveled to Somalia twice this year to Hargeisa and Mogadishu, both as a World Health Organization consultant. He also traveled to Nepal and China. Additionally, he was appointment to the American Academy of Orthopaedic Surgery's international committee and was appointed to the Board of Orthopaedics Overseas. Along with his professional achievements this year, Dr. Spiegel and his wife welcomed their first child, a daughter named Sophia, on March 6, 2012.

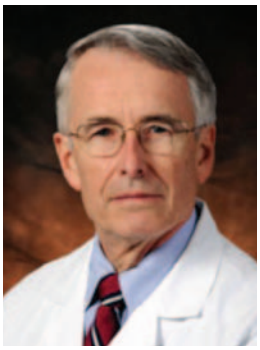
Lawrence Wells, MD is the section editor for the orthopaedic section of Nelson's Textbook of Pediatrics 20th edition. Dr. Wells is also the program chair elect for the Philadelphia Orthopaedic Society and is a member of the executive committee for the Section on Orthopaedics for the American Academy of Pediatrics.

John P. Dormans, MD, FACS, Chief of Orthopaedic Surgery at CHOP, was elected into the Presidential Line of the Scoliosis Research Society (SRS) and will host the SRS 50th Anniversary meeting as president in Minneapolis, Minnesota in 2015. Dr. Dormans completed his term as *President of Société Internationale de Chirurgie Orthopédique et de Traumatologie (SICOT) – United States* last year. He also completed his term as President of the Pediatric Orthopaedic Society of North America in 2010. Dr. Dormans is President Elect of the *World Orthopaedic Concern (WOC)* for the 2014-2016 term.

# Philadelphia Veterans Affairs Medical Center

John L. Esterhai, MD

Chief of Orthopaedic Surgery, Philadelphia Veterans Affairs Medical Center



Today, one in ten Americans is an armed forces veteran. Seventy-five percent served during at least one war time period, and more than 3.6 million women and men have served during the time that we have been involved in the Middle East.

Our first President knew that, "The willingness with which our young people are likely to serve in any war, no matter how justified, shall be directly proportional to how they perceive the veterans of earlier wars were treated and appreciated by our nation."

The Philadelphia VA Medical Center provides health care to 90,000 veterans living in America's fifth largest metropolitan area. Our four-fold mission is to honor America's veterans with world-class health care, advance medical knowledge through research, train health care professionals, and be prepared to serve in the event of a crisis.

We are a tertiary referral center with more than 135 acute care beds, 95 of which are medicine-surgery beds, and total yearly operating budget of more than $380 million. It is an eight-minute walk from the Hospital of the University of Pennsylvania. Our orthopaedic residents and faculty are honored to help care for those who have served their country. Abraham Lincoln articulated the primary mission of the Veterans Administration Penn Orthopaedic Service more than a century ago:"To care for him who shall have borne the battle."

The University of Pennsylvania Orthopedic rotation at the Philadelphia VAMC allows our PGY-2 and PGY-5 residents to care for veterans in an intensive, general orthopedic practice setting under the direct supervision of Drs. Bernstein, Ecker, Esterhai, Hume, Kelly, Kuntz, Sheth, Smith, and Steinberg. Dr. Levin volunteers without compensation. Those few veterans who require care at a level of sophistication that we cannot provide are referred to subspecialists within the University of Pennsylvania Health System at Pennsylvania Hospital or Penn Presbyterian Medical Center.

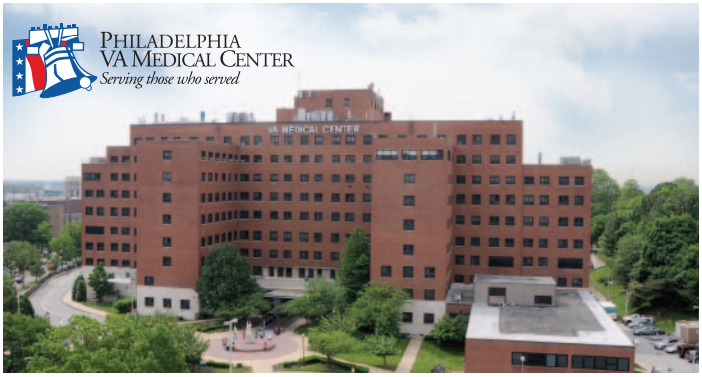
In addition to their dedication to direct patient care and resident education, Drs. Bernstein, Esterhai, Sheth, and Steinberg have each applied for or been awarded research funding through the Veterans Administration competitive grant system. They collaborate actively with intra and extra mural physicians and basic scientists including Drs. Jonathan Black, Jason Burdick, Paul Ducheyne, Dawn Elliott, Matthew Fisher, Kurt Hankenson, Russ Huffman, Robert Mauck, Samir Mehta, Lachlan Smith, and Lou Soslowsky.

Current grants include:

- *Timed-release of Local Anesthetic from Sol Gels for Post-Op Pain Control*
  - PI: Sheth, Co-PIs: Ducheyne, Cowan, Radin ($655,091)
- *Engineered Multi-Functional Nanofibrous Meniscus Implants*
  - PI: Esterhai, Co-PIs: Mauck , Schaer, Huffman, Burdick ($678,157)
- *Disc Degeneration in the Lumbar Spine of a Small Animal Model*
  - PI: Mauck, Co-PIs: Smith, Elliott, Dodge, Burdick ($739,817)
- *Cartilage Preservation with Stem-Cell Laden Hyaluronic Acid Hydrogels*
  - PI: Steinberg, Co-PIs: Mauck, Fisher, Belkin ($1,100,000)

Mitchell (Chip) Staska and John Wheeler, our superb Physician Assistants, provide seamless, exemplary, tender care from initial patient referral through appropriate triage, outpatient evaluation, scheduling of appropriate testing and consultations, surgery, and post hospitalization care. After 15 years in private practice and a decade at the PVAMC, Chip continues to provide immediate, timely interaction with referring physicians and outside consultants, coordination of pre-bed evaluations, surgery scheduling, interaction with the primary care providers, liaison with VA referral health centers, and acute and chronic pain management. John has had the daunting task of coordinating all orthopaedic spine care as Dr. Smith integrates into our system.

We have patient office hours on Mondays, Wednesdays, and Fridays allowing us to provide more than 5200 patient visits each year. New patients are scheduled within thirty days of their



primary physician's request for consultation. The Emergency Room is very busy. We perform surgery four days each week, averaging more than 450 major procedures yearly. Orthopedics performs more major surgeries than any other service. None of this would be possible without the professional expertise and wisdom of the Chief of Surgery, Kris Dumon, the Vice President for Surgery and Anesthesia, John Wylie, and the nurses, administrative support personnel, and physician staff of the PVAMC. In this time of increasing financial restraint and federal budget review we will likely be called upon to deliver more direct care and perform more research with less.

Many of the veterans for whom we care commute a long distance from central and northeastern Pennsylvania, southern New Jersey and Delaware. Many have significant medical comorbidities and difficult psychosocial environments. Many have had multiple operations making reconstructive surgical approaches and wound healing more difficult. Not infrequently they have had a difficult time reintegrating into society after their military service. Providing Philadelphia-level, state of the art, complication free, compassionate care requires extra special diligence. It is a worthy goal to which we are fully committed.

# McKay Orthopaedic Research Laboratory

Louis J. Soslowsky, PhD

Director, McKay Orthopaedic Research Laboratory

The McKay Orthopaedic Research Laboratory of the Department of Orthopaedic Surgery in the Perelman School of Medicine continues to explore important problems in musculoskeletal research. The research facility, including labs and offices, occupies just over 15,000 sq. ft. of space on the 3rd, 4th and 5th Floors of Stemmler Hall. There are over 80 full- and part-time staff and trainees now in the labs. It is an active, thriving research and educational environment.

Currently, the lab has an annual research budget from extramural grants, gifts, and endowments over $7,000,000 and are in the number 4 position in NIH rankings for orthopaedic surgery departments in the country in terms of funding from the National Institutes of Health (NIH). This past year has seen a very impressive and continued rise in new grant activity amongst the faculty.

We have had several new grants awarded this year. These are:

George Dodge, PhD
- PI of a Merck grant titled, "Role of FGF-18 in Cartilage Repair"

Matthew Fisher, PhD
- PI of a Musculoskeletal Transplant Foundation Jr. Investigator grant titled, "Controlled Release of Enzymes Using Nanofibrous Scaffolds to Improve Integration and Healing following Meniscal Injury"

Robert Mauck, PhD
- PI of an AO Foundation supplement titled, "Production of High Throughput Mechanical Screening (HTMS) Devices for the ACI Consortium"

Ling Qin, PhD
- PI of a NIH R03 grant titled, "EGFR Signaling in Growth Plate Development"

Eileen Shore, PhD
- PI of a Progressive Osseous Heteroplasia Association grant titled, "Molecular Pathophysiology of Progressive Osseous Heteroplasia (POH): The Molecular Biology of GNAS Expression in POH".

Louis Soslowsky, PhD
- PI of a NIH R01 supplement titled, "Mature & Aging Tendon: Extracellular Matrix Interactions in the Injury Response"
- PI of an Amniox Medical grant titled, "Studies of Amniotic Membrane for Tendon Healing"
- PI of a subcontract with Nemours Foundation titled, "Extracellular Matrix Structure and Function in Diabetic Wound Healing"

In addition to the above-mentioned new grants this year, each of the McKay Laboratory faculty remains well-funded through existing research grants not identified in this new grants list. Further, there were several new grants and clinical trials for our surgeon faculty this year. These are:

Craig Israelite, MD
- PI of an OREF Residency Enhancement grant
- PI of an OMeGA Residency grant

Samir Mehta, MD
- PI of a DOD grant titled, "A Randomized, Controlled, Ascending Dose Clinical Trial of a Bismuth-Thiol (BT) Topical Anti-Infective Drug for Treatment of Post-Surgical Orthopedic Infections"

Mara Schenker, MD
- PI of an AO North America Kramer Award titled, "Development of a Nanofibrous Scaffold with Biphasic Antibiotic Release for Treatment of Musculoskeletal Infections"

Brian Sennett, MD
- PI of a Histogenics Corporation clinical study titled, "A Randomized Comparison of NeoCart to Microfracture for the Repair of Articular Cartilage Injuries in the Knee"

David Steinberg, MD
- PI of a VA grant titled, "Cartilage Repair with Stem-Cell Laden Hyaluronic Acid Hyrogels"

Keith Wapner, MD
- PI of Small Bone Innovations study titled, "2-Year Post-Approval Study to Investigate the Star Ankle under Actual Conditions of Use".

Sarah Yannascoli, MD
- PI of an OREF grant titled, "Influence of Locally and Systemically Delivered Ibuprofen on Rotator Cuff Healing in a Rat Model"

We have also received several grants from DePuy Synthes for residents to attend various courses.

This year, we continued recruitment for additional research faculty through funds provided by the Perelman School of Medicine, in coordination with our Penn Center for Musculoskeletal Disorders. Growing musculoskeletal research, not only within the Department of Orthopaedic Surgery, but across the Penn campus has been a primary objective for our program and these efforts have been particularly successful thus far. We look forward to another exciting year.

Gina, 20, received spinal surgery at CHOP at age 15 to correct idiopathic scoliosis.



# We've got your back.

The Children's Hospital of Philadelphia's Division of Orthopedics has one of the best teams in the nation, with expertise in pediatric spine tumor, hip, foot and ankle, upper extremity, and hand surgery, as well as sports medicine. We provide safe and effective care for patients from diagnosis through recovery, performing nearly 3,500 surgeries and handling over 59,400 outpatient visits a year. We boast one of the most robust clinical research programs in the country, and have pioneered breakthroughs that offer greater hope to children with adolescent idiopathic scoliosis and improve safety during complex spine surgery.

**Appointments are available in eight locations in PA and NJ. Visit www.chop.edu/ortho or call 215-590-1527 for more information about our services and how to refer.**

CH The Children's Hospital *of* Philadelphia®

**DIVISION OF ORTHOPEDICS**

Ranked No. 1 in the nation for orthopedic surgery in *U.S.News & World Report*'s 2012–13 survey of Best Children's Hospitals.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VANAE

UNIVERSITY OF PENNSYLVANIA ORTHOPAEDIC JOURNAL VOLUME 23