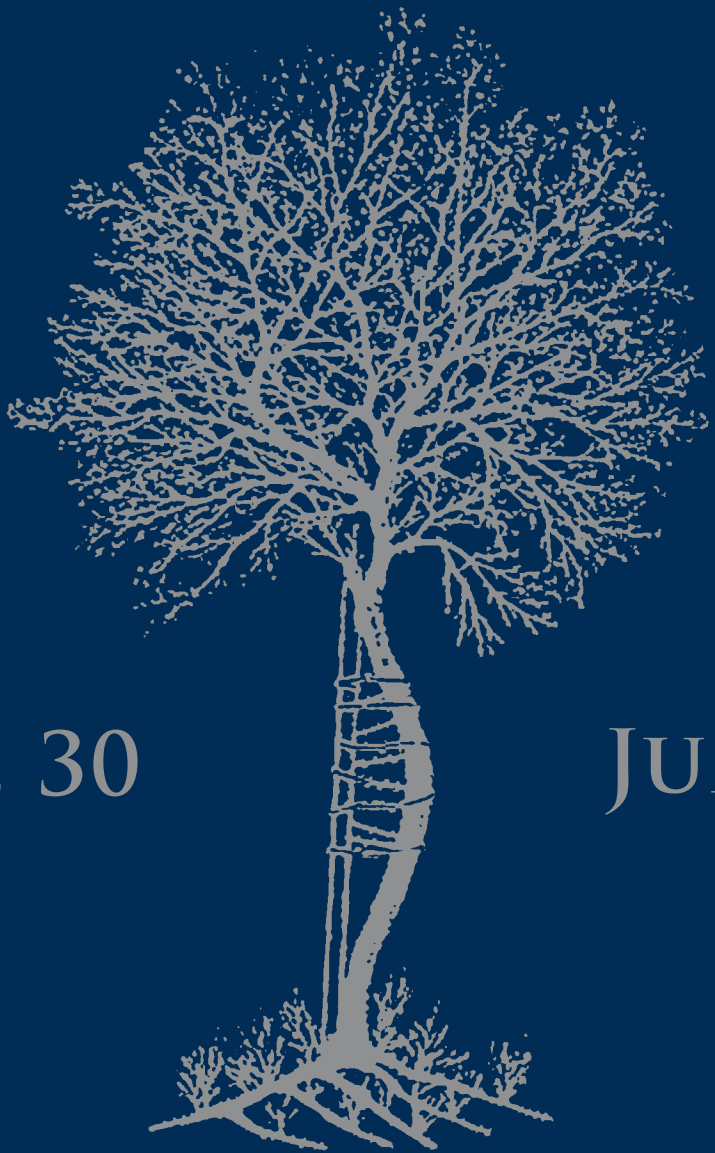
The University of Pennsylvania Orthopaedic Journal



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The University of Pennsylvania Orthopaedic Journal

Volume 30, June 2020

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The University of Pennsylvania Orthopaedic Journal

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Letter from the Editors

George Fryhofer, MD, MTR and Kelsey Bonilla, MD

George Fryhofer, MD, MTR

Kelsey Bonilla, MD

It is our distinct pleasure to present to you the 30th edition of the University of Pennsylvania Orthopaedic Journal (UPOJ). Begun in 1986 under the guidance of Dr. Carl T. Brighton, the UPOJ remains a testament to the Department's commitment to basic science and clinical research—always striving to gain new insights and seek better understanding of the musculoskeletal system, with the ultimate goal of providing the best possible care for our patients.

It is with overwhelming respect and gratitude that we dedicate this 30th edition of the UPOJ to the late Dr. William G. DeLong, Jr. In doing so, we honor Dr. DeLong's treasured legacy at Penn from his time both as a resident and then on the faculty, and also recognize the immeasurable impact both personally and professionally he had in training and supporting so many members of the Penn community over the years.

This year has seen many exciting areas of change and growth for our program, some of which have been highlighted in this year's issue. Though not explicit, the theme for this past year and for this issue is appropriately one of *inclusion* and *collaboration*—that we can both be better and do better together. This past summer, the interns took part in the first-ever city-wide intern "boot camp," led by attendings from six different health systems across the Delaware Valley (see page 37). In the fall, we had the good fortune of welcoming five talented residents and two attendings into our ranks following the closure of Hahnemann. In the spring, despite limitations imposed by the COVID-19 pandemic, our program continued to evolve and to grow and to find new and better ways of fulfilling its educational mission, such as nightly "fireside chat" video fracture conferences (led by Dr. Derek Donegan and Dr. Samir Mehta), which have been a favorite amongst the residents. As we look forward to the future and the possible permanent addition of a new "9th resident," we are grateful for the leadership of our program director Dr. Daniel Farber as well as chief residents for the thoughtful and collaborative process by which our new rotation schedule to accommodate this growth was devised.

We are proud to report that these themes of inclusion and collaboration are not just confined to the residency program, but rather extend into the greater Penn Orthopaedics community as a whole. During her year as President of the AAOS, Dr. Kristy Weber led the Academy on several fronts as it executed on the first year of a five-year strategic plan. Among these accomplishments was devising a strategy for the Academy to increase diversity in its volunteer structure, including increasing awareness, transparency, reporting, and implicit bias training (see page 13). Along similar lines, in their article about the "Perry Initiative," bioengineering PhD students Jaclyn Carslon, Ashley Fung, and Hannah Zlotnick describe their important volunteer work helping to provide young women across the country with early hands-on exposure to orthopaedics (see page 12). And from the Perelman School of Medicine, medical students Joshua Bram and Alejandro Cazzulino shine a spotlight on the newly organized Penn Orthopaedics Summer Scholars (POSS) collaboration with the Leo Leung Orthopaedic Surgery Society (LLOS)—championed by Dr. Jaimo Ahn—which includes the department-funded Orthopaedic Student Scholar Presentation Award that provides travel stipends for Penn medical students to present their orthopaedic research at national meetings (see page 10).

As always, we are grateful for the unwavering leadership of our Chair, Dr. L. Scott Levin, and for the support of the journal's advisors, Dr. Jaimo Ahn and Dr. Samir Mehta. We also would like to thank our section editors. As a fully resident-run publication, the UPOJ would not be possible without their contributions: Lauren Boden (Shoulder and Elbow), Agnes Dardas (Orthoplastics), Michael Eby (Bone), David Falk (Foot and Ankle), Sachin Gupta (Spine), Brandon Haghverdian (Pediatrics), Yudi Kerbel (Arthroplasty), Kendall Masada (Trauma), Lucas Myerson (Hand), Andrew Summers (Oncology), and Eric Pridgen (Sports).

The UPOJ has been financially independent from the Department of Orthopaedic Surgery since 1997, thanks to generous financial support from our advertisers. And so on behalf of the Department, we thank them again for their generosity in supporting the educational and research missions of Penn Orthopaedics.

The journal is viewable for free online and on all mobile devices at www.upoj.org. This year, we have also launched a new digital subscription database and encourage everyone to subscribe at www.upoj.org/subscribe.

It has been our honor to serve as editors for the 30th edition of the UPOJ. On behalf of all of those who contributed this year, we hope that you find this edition educational, rewarding, and thought-provoking.

George W. Fryhofer, MD, MTR
Kelsey Bonilla, MD

Letter from the Chair

L. Scott Levin, MD, FACS

Paul B. Magnuson Professor of Bone and Joint Surgery, Chair of the Department of Orthopaedic Surgery, University of Pennsylvania School of Medicine

I am writing this Chairman's letter at an unprecedented time in the history of modern medicine and the Department of Orthopaedic Surgery at Penn Medicine. Although the pandemic has been front and center on the minds of all of us, I feel that there is so much to be thankful for and would like to share with you the collective success we have had over the past year. First, I have never worked harder to assure that our patients, faculty, residents, fellows, staff and their families remain safe and informed. Second, our commitment to excellence across all missions remains paramount. Our clinics have remained open to evaluate and treat acute and ongoing musculoskeletal issues that require in-person evaluation. We have ramped up our telemedicine efforts dramatically with the help of a committed and skilled administrative staff led by Neil Ravitz. Calvin Jordan has reorganized our operational needs with incredible speed and skill. Our site managers are present and leading our staff. We have adequate PPE and are doing what needs to be done to keep our workforce safe. Our clinical faculty are presenting every urgent or necessary surgical case to me for review and yes – we remain in the operating rooms for orthopaedic trauma cases and staged reconstruction that cannot and should not wait to assure good outcomes for our patients.

Our residency program director Daniel Farber assisted by Vince Moretti have continued to elevate and enhance our educational programs using webinars via Zoom, GoToMeeting, BlueJeans and other digital platforms that have kept us more connected than we ever have been before! Craig Israelite gave his heart and soul as residency program director for more than a decade and we plan to recognize him during a special event in the near future.

Despite our animal labs being closed and our research teams being at home, tremendous work is ongoing in grant writing, manuscript preparation and brainstorming with regards to new basic science projects. This past week, I spoke with Joel Boerckel, Ph.D. about ideas for a new R01 centered around mechanobiology and angiogenesis as it relates to hand allotransplantation. Our watchword in science at Penn —"collaboration"—remains our theme. Lou Soslowsky and our McKay partners have been unwavering in their determination to continue to build Penn Orthopaedic Research. We are now ranked #3 in NIH funding nationally. Our goal is #1!

The hand division continues to be led by David Bozentka and we function here at Penn as an integrated team of orthopaedic surgeons, plastic surgeons and neurosurgeons to effectively provide upper extremity care. Our close collaboration with our shoulder and elbow colleagues and trauma colleagues provides world-class expertise in every aspect of upper extremity surgery. Our transplant team is preparing for our fifth hand transplant that will be performed in a quadmembral amputee we hope sometime this year.

Keith Wapner has asked that we identify a successor for his position as chief of foot and ankle surgery, and we are currently recruiting for a new chief with his help and guidance.

Our adult reconstructive team has been productive across all missions. This year, Dr. Charles Nelson was nominated and elected as a Director of the American Board of Orthopedic Surgery. This is well-deserved and provides another example of Penn faculty leading at the national level. In addition to peer review funding, Craig Israelite and the adult reconstructive division has been named the beneficiary of a $1 million industry grant for the "My Mobility Study" working with Zimmer Biomet and Apple.

The sports medicine division continues to thrive. In a major breakthrough for our department, Penn Medicine and Penn Orthopaedics has been the named the team physicians for the Philadelphia Flyers hockey team. Brian Sennett has been instrumental in negotiating this arrangement and has also been selfless in working with the Philadelphia 76ers and Joel Embiib to coordinate contributions for Penn's efforts fighting the COVID-19 crisis.

The spine division led by Harvey Smith was fortunate to recruit Amrit Khalsa from Hahnemann when that hospital closed. In addition to Amrit, we have welcomed to our faculty Susan Harding from Hahnemann. She is a very well respected orthopaedic traumatologist, consummate educator and skilled clinician. We also enrolled five of the Hahnemann residents into our residency program—all have been outstanding.

The shoulder and elbow division has been active locally and nationally. We were prepared to have the first ASSH-ASES combined society elbow course in May here at Penn in our cadaver laboratory, but this was canceled due to the COVID crisis. We hope to reschedule the course for next year.

The oncology division led by AAOS Past President Kristy Weber continues to expand its reach. Publications in high impact journals such as Cancer Medicine, Science, and Cell are a tribute to her engagement across our health system and School of Medicine. As the first woman president of the AAOS, she led our Academy admirably. Despite us not meeting in person in March in Orlando, she conducted the business of the AAOS at the highest levels of transparency and integrity, and her legacy as the first female President of the Academy is something we all should be proud of.

Our development efforts have again exceeded our goal; and as of this writing we have raised more than $3.5 million in philanthropy for our Penn orthopaedic department. This number does not reflect the soft credit for the recently closed $1.3 million support for COVID-19 research from 76ers player Joel Embiid and owners Josh Harris and David Blitzer.

The department closed a $3 million commitment to support orthopaedic trauma research from the Wyss Medical Foundation. Mr. Hansjörg Wyss has contributed 6.25 million dollars to our department in the past decade. This recent gift was created in memory of Penn orthopaedic alumnus, Dean Lorich who passed away in 2017. The inaugural Lorich Lecture was to be given by David Helfet in April but will be rescheduled soon.

I try to share the achievements of the Penn Orthopaedics team with you each year. The team always comes first. I want to make you aware of a few opportunities that I have had over the last year that have reflected well on Penn Orthopaedics. I completed my term as President of the American Society for Surgery of the Hand in September 2019. I am currently serving as Orthopaedic Regent of the American College of Surgeons and was elected as the Vice Chair of the Board of Regents in July 2019. This is a one-year term, and it has been an honor to lead the regents through the pandemic crisis and to protect and advocate for the entire house of surgery.

I served on the search committee for the new Chair of the Department of Neurosurgery. Daniel Yoshor from Houston will assume the chair position this July. We all wish Sean Grady well. He has been a close friend, confidant and amazing partner in establishing the Penn Spine Center. Our collaborative relationship with Neurosurgery is exemplary and we intend to grow spine clinical care, spine research and education in the years to come working with both Sean and Dan. We were recently recognized as a Blue Cross Distinction+ Center for expertise and efficiency in delivering specialty spine care.

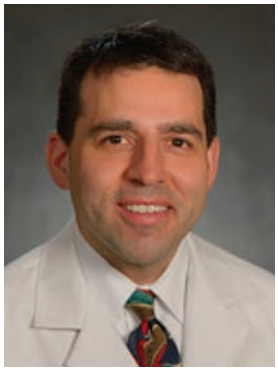
The health system continues to expand in our region and beyond. Penn Orthopaedics has established affiliate relationships as well as placed our orthopaedic faculty at Grandview Hospital, Cape Regional, Bayhealth, Princeton and Chester County Hospital. Growth has been strategic and based on patient demand for our outstanding care and superb outcomes.

Our MSKR service line is hitting on all cylinders, and our disease teams continue to mature and expand, meeting the musculoskeletal health needs of our patients and communities by providing high quality, efficient, and value based care.

As I complete my eleventh year as Chairman of the Department of Department of Orthopaedic Surgery at the University of Pennsylvania School of Medicine, I am humbled by our team's commitment to excellence and high performance year over year. I feel like we are just getting started. The business management author Jim Collins has been referred to many times over the last 11 years. His book "Good to Great" has served many well, and I reflect on our journey of "good to great." We have always been good and great in many ways. Yet our work is never done. We have tremendous opportunities in the next decade to advance our missions and define our legacy further. I have had preliminary discussions with our CEO Kevin Mahoney about our next phases of growth and achievement. It centers around building a new Penn Orthopaedic Hospital on the PPMC campus. While it is a vision for us and a goal, I believe it is achievable. I hope to share the evolution of this concept and conceptual "blueprints" with you the next time we meet. With appreciation for your belief in Penn Medicine and our Penn Orthopaedic Family.

Letter from the Program Director

Daniel C. Farber, MD



It has been a very busy year for the Penn Orthopaedic Surgery Residency Program. I came aboard as Associate Program Director in late June. Over the ensuing months, I have assumed the role of Program Director from Dr. Craig Israelite who has valiantly led the residency program for the past 12 years. That transition became official as of December 1, 2019. Dr. Israelite remains on the team as an Associate PD along with our new Associate PD, Dr. Vincent Moretti. We have added Lauren Johnson as an additional team member and she serves as the administrative assistant to the residency. Rounding out the team is our program coordinator, the indispensable Shannon Savelloni, who has made nothing but positive contributions to the program since her arrival in late 2018.

Our year began with the unprecedented Hahnemann University Hospital bankruptcy which orphaned over 500 residents at that facility including 20 orthopaedic residents. We quickly scrambled and created a compelling application for a temporary complement increase while simultaneously interviewing many of the Hahnemann residents whose future was quite uncertain. From the chaos of that process, 5 residents emerged and were adopted into our program. They have integrated quickly and quite well into the Penn system and thus we now have 9 residents in the PGY2-5 years. We are proud of these new residents and also of all our residents who welcomed their new colleagues with open arms, accommodated rotations, revamped call schedules and made them a part of the team. Because of this unexpected opportunity, we have subsequently applied for a permanent complement increase to 9 residents per year but the outcome of that is still to be determined. The implications of 9 residents in the program means that rotations may change significantly to assure the continued excellent education experience that Penn Ortho provides. We have engaged residents and faculty to help build this new residency world. Meanwhile, we have revamped the medical student application and interview process to focus more holistically on the applicant and who they are as an individual; this is especially timely with the recent decision by the NBME to convert the USMLE Step 1 to a pass/fail exam. Our plan is to truly seek out not just the best and brightest, but also those who are most likely to succeed at Penn and beyond. We continue the work of revamping conference and curriculum formats that is part of an ongoing process of always improving the resident education experience. There are many other projects that we look forward to implementing as the years progress, including enhanced sub-internship experiences for Penn and visiting medical students, more robust feedback mechanisms for residents and faculty, increasing diversity amongst our residents, and more.

We appreciate the tireless work and dedication of this year's administrative chief residents who hold the program together. Mark Hasenauer, Matthew Sloan, and Dan Gittings have been exemplary leaders, and we wish them the best in their fellowship pursuits and into practice.

We couldn't do all we do for the residents and their education without the unwavering support of our chairman, Dr. L. Scott Levin, and all our fantastic faculty who contribute to the education mission every day in their various roles.

Finally, a heartfelt thank you to Craig Israelite, who has served Penn Orthopaedics for many years. Many of you trained under Craig's leadership, mentorship and guidance. We humbly ask you to honor Craig as well as your memories of your time at Penn with a contribution to the newly created Penn Orthopaedic Education fund which directly benefits the current residents' needs.

2019-2020 Dedication & In Memoriam: William George DeLong, Jr., MD (1948-2020)

Christopher T. Born, MD, FACS, FAAOS

William George DeLong, Jr., MD

Dr. William G. DeLong Jr. died unexpectedly from a heart attack at his home in Haddonfield, New Jersey on Friday March 13, 2020. He was 71 years old.

Bill was born in Philadelphia and maintained local and regional roots throughout his personal and professional life. Following graduation from Cardinal Dougherty High School in 1966, he obtained back-to-back undergraduate degrees with honors from Temple University and St. Joseph's College (now University) in Chemical Engineering and Chemistry. He received his MD degree from Temple University in 1978**. Dr. Carl Brighton** recruited him to fulfill his residency training at the University of Pennsylvania which included a year of dedicated orthopaedic research in the department's newly established McKay Orthopaedic Research Laboratory.

As the Chief resident at Penn, he was known to be fearless taking on complex cases during an era when PGY5 residents could run a clinic and an operating room with little or no supervision. This was not false bravado because following his graduation in 1983, he went across the Benjamin Franklin bridge to Cooper Hospital in Camden, New Jersey as the Division Head of orthopaedic surgery. Cooper was the newly formed Level I Trauma Center with a catchment of nine counties in South Jersey. As a freshly minted Associate Professor at the University of Medicine and Dentistry of New Jersey, DeLong started an enviable training program built around a schedule heavily weighted with blunt, high energy trauma cases. The case load was so robust that for many years both Dr. Brighton and **Dr. Richard Rothman** at Thomas Jefferson sent all PGY4s to "The Coop" for their trauma rotations, our own **Dr. Dean Lorich** among them. These residents were fortunate because they also had the opportunity to learn from his other protean skill sets doing sports medicine, total joints, spine, pediatric and hand surgery all the while absorbing many life lessons from this remarkable and consummate practitioner. After 14 years, Bill was recruited to return to Penn and was its Director of Orthopaedic Trauma for six years where he had the opportunity to influence many future Penn residency graduates including **Dr. Samir Mehta**. He ultimately moved back to Temple University in 2003 where he held dual appointments as Professor of Orthopaedic Surgery and Professor of Anatomy and Cell Biology at the time of his death.

Bill was a remarkable visionary with seemingly endless energy. While at Penn, he was asked by Penn's Chief of Trauma and Critical Care, **Dr. Bill Schwab,** to assist in starting a trauma program 70 miles north of Philadelphia at St. Luke's Hospital in Bethlehem, PA. Penn was planning on providing Penn Star life-flight services for St. Luke's new Level I program, and it needed a legitimate orthopaedic traumatologist. Bill would drive from Philadelphia at the end of a long day to do complex cases at St. Luke's Hospital. He instinctively saw a wonderful opportunity and in 2009 partnered with St. Luke's to start an orthopaedic residency program. In part through his leadership and management skills, this small community hospital system has burgeoned to 11 hospitals with a staff of 24 orthopaedic attendings and over 20 physicians' assistants. It offers a teaching platform and research opportunities for MS 2/3/4 Temple University medical students at what has become an adjunct Temple teaching campus. Bill retained his faculty appointment at Temple University, but his primary position for 11 years was that of Network Chairman, Department of Orthopaedic Surgery for St. Luke's University Health Network and the Program Director of its Orthopaedic Surgery Residency. At the time of this death, he was still actively taking trauma call spending 3-4 nights in Bethlehem, returning to his home in Haddonfield at the end of the week.

Bill always gave generously of his time. He sat on numerous hospital and organization committees proving to be a wise and valuable counselor on such disparate topics as education, finance, healthcare reform and science. He was a member of Temple University Hospital's Executive Committee and the Educational Technology Committee of the medical school. DeLong was a very early adopter of computer technology in the 1980's and was prescient about the changes it would bring. He considered the Orthopaedic Trauma Association (OTA) to be the primary organizational platform for his professional life. Although a six-year member of both the American College of Surgeons Committee on Trauma (ACS/COT) and its Board of Governors, Bill dedicated himself extensively to the work of the OTA having become a member in 1990. He served on eight different committees over his 30 year affiliation, and chaired both the committees on Orthobiologics and International Relations. He routinely participated as faculty in the Resident Skills lab at the OTA annual meeting and was twice awarded the Winquist Cup for teaching excellence. Bill understood the importance of surgeon education for response to disasters and served for two terms on the ASC/COT *ad hoc* Disaster

and Mass Casualty Committee. For nearly twenty years he volunteered as a member of the US Department of Homeland Security's Trauma Critical Care Team and participated in deployments following both hurricane Katrina and the Haiti earthquake. The American Academy of Orthopaedic Surgeons awarded him with its Achievement Award for Volunteer Efforts.

Bill DeLong had a long roster of academic and research achievements and held several journal reviewer positions. He was the trauma section editor for **Dr. Robert Fitzgerald's** 2002 textbook, *Orthopaedics*. In 2004, he was the guest editor of a special edition on "Care of the Polytrauma Patient" for Clinical Orthopaedics and Related Research that spotlighted early on the role of cytokines and other factors that promoted the "second hit" in the badly injured patient. He authored over 70 peer reviewed publications and book chapters while giving hundreds of lectures and presentations nationally and internationally.

He loved to teach and to expose young students and physicians to the marvels of surgery and orthopaedics. **Dr. David Halsey**, the immediate past-president of the American Academy of Orthopaedic Surgeons, related to me several months ago how he became captivated with orthopaedics as a career in medicine. During his first week as an MS3 while on an emergency room rotation at Cooper Hospital, DeLong asked him if he wanted to assist fixing a femur fracture in the OR. Bill let him pass the guide wire, carry out the reaming and then insert the nail. Halsey noted, "I was hooked ... we worked closely together on local ortho projects, case reports and he mentored me over the next years including residency selection, first job and life." This was classic Bill DeLong.

Bill radiated energy and always led by example. This was coupled with a wonderful sense of humor especially when telling unbelievable stories about **Drs. Jim Nixon** and **John Gregg** at the Graduate Hospital.

These aspects of his persona are mirrored in comments by his '83 residency classmates. **Russ Windsor, MD:** "…a dynamic individual who was always up." **Paul Lyet, MD:** "…rock steady. His administrative skills and political savvy were evident early in his career and he was always willing to tap resources to accomplish his clinical goals for exemplary patient care." **Steve Sampson, MD:** "Despite the invincible exterior of Bill's persona, he truly had a soft side that was vulnerable to the world around him. He treated everybody as family and always placed himself in harm's way...going the extra mile for those he barely knew." **Co-Chief Resident, Ron Wisneski, MD:** "Bill's enthusiasm was contagious, it impacted favorably on the quality of life for countless patients, innumerable students, his family and all of us who were fortunate to have known him."

Bill was a loving husband and father. He is survived by Ginny, his wonderful wife of 48 years and by his daughter Lauren and son Christian. I know they were the paramount devotion in his life.

Personally, I have lost a dear and loyal friend with whom I practiced for nearly 25 years, surviving together the vicissitudes of orthopaedic surgery and trauma. The orthopaedic community has lost a champion. He will be missed.

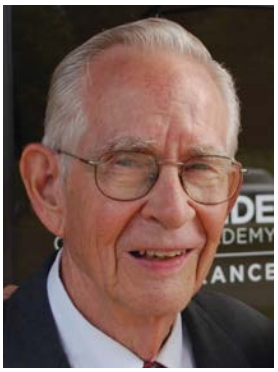
Christopher T. Born, MD, FACS, FAAOS
Intrepid Heroes Professor of Orthopedic Surgery
The Alpert Medical School of Brown University
Emeritus Chief of Orthopedic Trauma and
Director, Weiss Center for Orthopedic Trauma Research
Rhode Island Hospital
Providence, RI

The Residency class of '83 with Dr. Carl Brighton photo courtesy of Dr. Russ Windsor. Left to Right: Mark Kirkland, Steve Sampson, Ron Wisneski, Paul Lyet, Dan Zimet, Dr. Brighton, Manny Soares, Ellen Maiten, Bill Delong, Ron Gerson, Russ Windsor.

Chris Born and Bill DeLong at the October, 2019 OTA meeting. Photo courtesy of Chris Born.

In Memoriam: Carl T. Brighton, MD, PhD (1931-2019)

Marvin E. Steinberg, MD



Carl Brighton, Emeritus Professor of Orthopaedic Surgery, died on July 3, 2019. He was 87.

Carl was born on August 20, 1931 in Pana, IL. He received his B.A. with High Distinction from Valparaiso University in 1953, his M.D. from the University of Pennsylvania in 1957, and his Ph.D. in Anatomy from the University of Illinois in 1969. He took his residency in Orthopaedic Surgery at the U.S. Naval Hospital in Philadelphia and at H.U.P. His interest in teaching became evident early in his career when he taught his fellow residents their basic musculoskeletal pathology, enabling us to pass our Boards!

After serving with the Navy, he returned to Penn in 1968 as Assistant Professor of Orthopaedic Surgery and Director of Orthopaedic Research. He was later given concomitant appointments in Anatomy and Bioengineering. From 1977 until 1993 he served as Chair of Orthopaedic Surgery and Paul B. Magnuson Professor of Bone and Joint Surgery. He founded the McKay Laboratory of Orthopaedic Research and developed it into one of the most renowned and productive in the nation. He established the importance of basic research as an integral part of the residency. Although he is perhaps best known for his basic research, he remained committed to clinical orthopaedics. Many of his residents and fellows went on to hold full-time academic positions. He was a pioneer in using electricity to stimulate bone growth and fracture healing, and in investigating the epiphyseal growth plate.

His presentations, publications, grants, and visiting professorships are too numerous to mention. Carl has received many prestigious scientific honors and awards.These included the Kappa Delta Award, the Shands Lectureship, and the MERIT award and SCOR Grant from the N.I.H. He was a founder and President of the Bioelectrical Repair and Growth Society (BRAGS) and President of the Orthopaedic Research Society. He was also Editor of Clinical Orthopaedics and Related Research (CORR) from 1993 until 2002.

In addition to his professional accomplishments he led an active and gratifying personal and family life, and had many interests outside of medicine. He was a student of History with an emphasis on the Civil War. He enjoyed touch football, tennis, and basketball and routinely hosted pick-up games with our residents at his home. He was an avid gardener and woodworker. Carl remained active in his Church and served as an Elder and bible class leader.

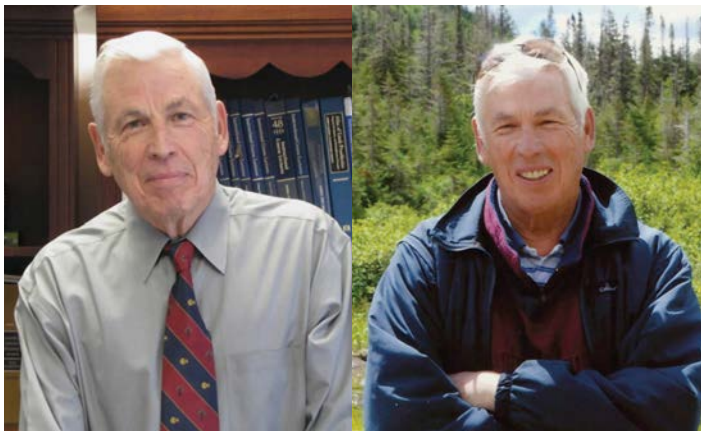
He loved his family and took them on many camping trips and extended vacations. Carl is survived by his wife, Ruth; his children, David, Sue, Andrew, and Joel; 16 grandchildren; and 5 great grandchildren.

Carl and Ruth Brighton and family at their 60th wedding anniversary.

Navy Lt. Cmdr Carl Brighton on USS Sanctuary, 1967.

In Memoriam: Denis Sise Drummond, MD, FRS(C) (1934-2019)

John M. Flynn, MD



Denis Drummond, Chief of Orthopaedics at CHOP from 1985-1996, passed away June 18th 2019 in Toronto, Canada. Our dear friend, colleague, mentor and professional idol left a breathtaking legacy globally. Through his clinical care and research, he bettered the lives of several generations of children; through his teaching and mentoring, he helped train and advise hundreds of surgeons. With his vibrant leadership skills, he improved pediatric care at the University of Wisconsin and Children's Hospital of Philadelphia (CHOP), as President of the Scoliosis Research Society (SRS) and as a founding leader of the Pediatric Orthopaedic Society of North America. Perhaps Denis's greatest impact, however, was on his friends, colleagues and family, for whom his joy of life, positive energy and good old-fashion Irish wit enriched friendships and deepened his love for his family. He is survived by his college sweetheart and loving wife of 60 years Joan, his 4 sons, 10 grandchildren and a number of dogs.

Born on New Year's Eve 1934 in Montreal to Paul and Elizabeth Drummond, Denis grew up loving hockey, football and outdoor activities. Denis received his BA (1957) and MD (1962) from McGill University, and then did his orthopedic training at the University of Toronto. After completing a pediatric orthopaedics fellowship at the Hospital for Sick Children, Great Ormond Street in 1969, Denis joined the Orthopaedic Surgery Department at McGill University and Shriner's Hospital. After 8 years in Montreal, and 7 years as Director of Pediatric Orthopedics at the University of Wisconsin, Denis was recruited to be Chief of Orthopaedic Surgery at CHOP, which he led from 1985-1996 as Professor of Orthopaedics (tenure track).

Denis was known as a skilled surgeon, with a particular interest in spine deformity and pediatric cervical spine anomalies and injuries. His pediatric spine thought-leadership was widely recognized, and included both implant design (he was co-holder of 6 patents), surgical technique improvement and outcomes research. He published more than 180 original research studies, 42 chapters, and was a popular invited lecturer, serving in that role more than 50 times. He was legendary for his mentoring of young orthopaedic scholars, vetting ideas and very frankly critiquing project ideas, results and manuscripts; many owe early career success to Denis's commitment to teaching and mentorship. He won the Okagaki Resident Teaching Award at Wisconsin, and was a 6-time winner of teaching awards (Nicholson Award or Dean's Award) at Penn/CHOP.

Denis's signature legacy at Penn Orthopaedics and CHOP was initiating the transformation of Penn's Pediatric Orthopaedics program from a small group of clinicians into the internationally recognized, academic thought-leader powerhouse that it is today. Denis recruited John Dormans and Jack Flynn to the staff, and Ted Ganley and David Spiegel to Fellowship (who later joined the staff)—turbocharging clinical and academic growth of the Orthopaedic Division in the 1990's. Denis started the CHOP Pediatric Orthopaedic Fellowship, which has now trained more than 60 pediatric orthopaedic surgeons to date. He drove the clinical research effort, starting from scratch and inventing the orthopaedics CRC model that has been invaluable to research productivity since the early 1990's. He generously shared his expertise internationally including time with CARE in Tunisia and after the major earthquake in Armenia, and was featured on the PBS show "Nova" as part of one of the very early teams separating conjoined twins. Denis continued his clinical practice at CHOP until 2014, when he retired back to his native Canada, spending time at their summer home on the Saint Lawrence River (Metis sur Mer, 200 miles north of Quebec City), with Joan, family and friends.

Denis played a key leadership role in forming the Pediatric Orthopaedic Society of North America (POSNA). He was President of the Pediatric Orthopaedic Study Group in 1982. In 1983, he was Chair of the Merger Committee of Pediatric Orthopaedic Study Group and the Pediatric Orthopaedic Society that navigated the merger process leading to the birth of POSNA. He was also a leader in the Scoliosis Research Society, serving on the SRS Board of Directors for 10 years, including President 2001-2. He was the co-recipient of the SRS Hibbs Award for best paper (2006) and ultimately the SRS Lifetime Achievement Award (2011).

Perhaps the place Denis impacted the Penn Orthopaedic community most was through his passion for teaching and mentoring young surgeons. A generation of Penn residents benefitted from his wisdom and sage advice. So his legacy of mentoring lives on, and Denis is honored each year with CHOP's annual Denis Drummond Rising Star Visiting Professorship. Initiated in 2016, the program offers an innovative young pediatric orthopaedic surgeon the opportunity to visit CHOP's clinics and ORs and participate in lively interactive education and research sessions.

Denis Drummond left an amazing legacy—for his family, patients, trainees, institutions and organizations. Ultimately, all of us whose lives were warmed and improved by Denis's advice, humor, and joy will carry with us his inspiration to make lives better, as he did.

Ted Ganley, David Spiegel and Denis Drummond.

Denis Drummond at dinner with his wife, Joan.

Dr. Denis Drummond enjoying dinner amongst friends and colleagues, 1996.

Denis honing his future ortho skills in the woodshop.

Orthopaedic Student Interest Group and Departmental Collaboration

Joshua T. Bram BS[1], Alejandro Cazzulino BS[1], Jaimo Ahn MD, PhD[1,2]

[1]Perelman School of Medicine, University of Pennsylvania
[2]Department of Orthopaedic Surgery, University of Pennsylvania

Background

Consistent with the competitiveness of matching in orthopaedic surgery, research productivity has become almost a prerequisite for medical students applying to competitive training programs. Specifically, matched orthopaedic surgery applicants have almost twice (11.5 versus 6.7) the number of research abstracts or publications as unmatched applicants, illustrating that research is an important metric through which students may be distinguished academically during the residency application cycle.[1] The summer between the first and second years of medical school represents an opportune time for students considering orthopaedics to establish research mentors and execute projects. Up to one-third of orthopaedic-bound students have identified an interest in orthopaedics prior to the start of medical school, with many individuals searching for research opportunities early in their education.[2] Unfortunately, opportunities for funded summer research in orthopedics are scarce. As a result, many students are drawn to paid temporary positions in other departments at the University of Pennsylvania Health System (UPHS), the Children's Hospital of Philadelphia (CHOP), or at other institutions rather than within the orthopaedics community at Penn. Despite the prevalence and positive effects of orthopaedic interest groups around the country for increasing student interest in, exposure to, and education about the field of Orthopaedic Surgery, research opportunities associated with funding are still difficult to find.[3,4]

Initial Program Proposal

Therefore, the Leo Leung Orthopaedic Surgery Society (LLOS)—Penn's medical student interest group—proposed in 2017 a summer fellowship for interested and motivated students. In the summer of 2019, and through the collective efforts of LLOS and Dr. Jaimo Ahn, that idea came to fruition with the creation of the Penn Orthopaedics Summer Scholars (POSS) program. The idea for the proposed fellowship program has its roots in several other programs at both Penn and CHOP (Table 1). This program will allow students to defray summertime expenses while purposefully connecting students to the department bringing benefit to both parties.The only comparable established program known to the authors is an 8-week summer research fellowship at the Hospital for Special Surgery. The creation of POSS has, therefore pushed Penn orthopaedics to the forefront of student education and engagement as one of the only university-based orthopaedics department to offer such a summer research program. Beyond the immediate benefits of increased research output from fellowship-sponsored projects, such a program will facilitate relationships between students and faculty/residents, leading to potential future projects and the nurturing of leaders in the field.

Basic Program Structure

As part of the program, Penn medical students interested in orthopaedics are tasked with identifying a faculty mentor and research project for submission. Applications are due in mid-February, with final selection taking place in early March. The application consists of a participant's prior research experience (though prior experience is not a prerequisite), brief description of the applicant's interest in orthopaedic surgery, and a 2-page project proposal. In collaboration with the advisors of LLOS—Drs. Jaimo Ahn, Joseph Bernstein, and Kathryn O'Connor—the upperclass students (MS3 and MS4) of the interest group review individual applications and decide upon the award recipients. The initial program is composed of three funded positions, with each fellow receiving $1,000 for 8-10 weeks of research in the summer. Faculty mentors are encouraged to host their fellows in the clinic and the operating room in addition to hosting regular (e.g. every 1-2 weeks) meetings with the student to review progress and to assess project roadblocks.

Program Outcomes

Scholarship recipients are required to (1) present the work from their primary research project at the Penn Orthopaedics Research Day and (2) submit an article to the University of Pennsylvania Orthopaedic Journal (UPOJ). Awardees will also be expected to be a co-author on at least one project submitted to a national conference and/or a peer-reviewed journal for publication.

Travel Grant

In addition to the challenge of finding summer research funding, many students find it difficult to fund travel to national orthopaedic conferences. With the creation of the POSS program, it will be important to support these students as they submit projects to conferences. Therefore, the Department of Orthopaedic Surgery has also generously contributed funding for the creation of an Orthopaedic Student Scholar Presentation Award. The award funds three $500 travel stipends for Penn medical students providing them with the opportunity to present their research findings at a national orthopaedic surgery conference. Priority is given to abstracts accepted at larger conferences such as AAOS,

Table 1. Example Summer Research Programs at Penn and CHOP

Program Name	Department	Institution	Length	Funding	Spots
Agnew Society Fellowship	Surgery	Penn	6 weeks	$500 (+ $500 travel)	7
Anesthesia and Critical Care Fellowship	Anesthesiology and Critical Care	CHOP	8 weeks	Available	1
Center for Clinical Epidemiology and Biostatistics (CCEB) Fellowship	CCEB	Penn	Summer	$3,000	2-4
Center for Emergency Care Policy Research Summer Fellowship	Emergency Medicine	Penn	8-10 weeks	$2,000	2
Center for HealthCare Improvement and Patient Safety (CHIPS) Internship	CHIPS	Penn	6-8 weeks	$3,000	NA
Clinical Neurosciences Training (CNST) Program	CNST	Penn	6 weeks	$2,400	4
Diagnostic Radiology Summer Fellowship	Radiology	Penn	6 weeks	$1,500	5
Infectious Disease Diagnostics Summer Internship	Infectious Disease	CHOP	8 weeks	$5,000	2
Institute for Translational Medicine and Therapeutics (ITMAT) Internship	ITMAT	Penn	Summer	$3,000	1-2
Interventional Radiology Summer Scholars	Interventional Radiology	Penn	6 weeks	$1,500	5
Joseph Woo, MD Fellowship in Cardiovascular Surgery	Cardiovascular Surgery	Penn	Summer	$2,000	1
Medical Student Health Services and Policy Research Summer Research Fellowship at Penn	Leonard Davis Institute of Health Economics	Penn	Summer	$3,000	1-3
Otorhinolaryngology Summer Research Fellowship	Otorhinolaryngology	Penn	8 weeks	$2,000	2
Pathology Summer Internship	Pathology	CHOP	Summer	$5,000	1-2
Pediatric Cardiology Summer Program	Cardiology	CHOP	6-8 weeks	Available	1-2
Pediatric Center of Excellence in Nephrology (PCEN) Summer Research Scholars Program	PCEN	CHOP	8 weeks	$4,000	NA
Robert L. Mayock Student Fellowship	Allergy, Pulmonology, Critical Care	Penn	8-10 weeks	$3,500 (+ $1,500 travel)	1
Women's Health Innovation Summer Fellowship at Penn	OB/Gyn	Penn	8 weeks	$1,500	1

ORS, and primary subspecialty society meetings (POSNA, OTA, ASSH, etc) as well as to more senior medical students (although medical students from all years can apply).

Conclusion

Penn Orthopaedics stands to benefit from increased medical student involvement in various capacities. Historically, Penn medical students interested in orthopaedics have struggled to find funded, productive research opportunities for the summer between their first and second medical school years. The leaders of LLOS and our faculty advisors believe that the establishment of the POSS program will fulfill the needs of both Penn medical students and the Penn Department of Orthopaedic Surgery. This program has the potential to spur meaningful research and improve trainee career development.

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Perry Initiative: Increasing Diversity in Orthopaedic Medicine and Research

Jaclyn A. Carlson[1,2], MEng, Ashley K. Fung[1,2], MEng, Hannah M. Zlotnick[1,2], BS

[1]McKay Orthopaedic Research Laboratory, University of Pennsylvania, Philadelphia, PA
[2]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA

The Perry Initiative is a non-profit organization with the main mission to inspire young women to pursue careers in orthopaedic surgery and engineering. Women are currently underrepresented in each of these fields (4% of Orthopaedic Attending Surgeons are women[1]), which is undoubtedly a disservice to the diverse orthopaedic patient population. This program is named after Dr. Jacqueline Perry (1918-2013), who was one of the first women in orthopedics. Dr. Perry left an outstanding legacy of treating patients with gait disorders due to cerebral palsy, traumatic brain injury, or stroke. In addition to patient care, she was also known for being an excellent educator, researcher, and author. The Perry Initiative, currently based out of the University of Delaware, was founded in 2009 by Dr. Jenni Buckley, a mechanical engineer at the University of Delaware, and Dr. Lisa Lattanza, an orthopaedic upper extremity surgeon at Yale University.

The Perry Initiative runs outreach events across the United States for women in high school, and also first and second year medical students, to increase early exposure to the field of orthopaedics. The student participants engage in modules using Sawbones, power tools, and hardware to learn about common medical and surgical procedures, such as casting, external fixation, suturing, and total knee reconstruction. During these modules, students are challenged to use an engineering mindset to determine the optimal screw placement, ex-fix positioning, etc. Students also learn from both local female engineers and orthopaedic surgeons, further highlighting the importance of collaborations between clinicians and engineers to progress medical technology, rehabilitation protocols, and ultimately patient care.

As Program Specialists for the Perry Initiative, we have had the fortunate opportunity to witness first-hand the impact this program has on young women during programs hosted at medical centers, universities, and medical device companies across the country. It has also been awesome to have such strong support from former and current members of the Penn Orthopaedics community at these events.

If you are a member of the orthopaedic community, and would like to volunteer for any future Perry Initiative events, we can always use more local volunteers. While the majority of volunteers are women, we welcome men to show their support of women in orthopaedics, and volunteer as well. Additional information about the program can be found at http://perryinitiative.org.

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Reflections on a Year as President of AAOS

Kristy Weber, MD

The theme of the AAOS 2019 year was Breaking Barriers. As the first woman president of the organization in 87 years, and the one leading organizational change, that glass ceiling was certainly broken. I was proud to represent Penn Ortho in this role and appreciate my partners' (especially Robert Wilson's) support during this time.

The year as Academy president built on two prior years in the leadership line spent understanding the issues facing the organization. High functioning organizations have a clear strategic plan that includes unique core values and an adherence to best practice governance. My focus in 2018 was to lead the Board of Directors in the development of a five year strategic plan in order to provide more member value and chart a course for the future. We spent a year with a consultant team and affirmed a new vision and 3 strategic goals. The vision: *"To be the trusted leaders in advancing musculoskeletal health"* is aspirational and requires us to think beyond orthopaedics. The three goals focus on the member experience, quality and value in patient care, and the governance and culture of AAOS. In 2019 we defined new core values for the organization and executed on the first year of the strategic plan.

Key 2019 accomplishments can be found in detail at https://www.aaos.org/about/meet-the-aaos/aaos-annual-report/. I would highlight the focus on free, digital learning opportunities on the AAOS learning platform (learn.aaos.org). The upgraded AAOS Orthopaedic Video Theater (OVT) is an incredible resource for learning and CME, and Penn Ortho was one of the first two academic institutions to have our own 'channel' on this platform. A new Membership Council will join the councils on Advocacy, Research/Quality and Education in 2020. The AAOS developed a new musculoskeletal-focused definition of Quality and Value and continues to develop clinical practice guidelines and appropriate use criteria to help guide surgeons at the point of care. The AAOS Registry Program developed a collaboration with the American Association of Neurological Surgeons to develop an American Spine Registry to add to the American Joint Replacement Registry, the Shoulder and Elbow Registry, and the Musculoskeletal Tumor Registry. The AAOS also outlined a strategy to increase diversity in the volunteer structure which involves increased awareness, transparency, reporting, and implicit bias training.

My goal was to look forward and not back. Our future AAOS members want value, transparency, and inclusion rather than the status quo of an 87 year old organization. Change is hard and requires consistency to keep moving forward. It involves process over personality. It requires courage and integrity. It was an honor to serve in the role for the past year.

Dr. Kristy Weber at the American Academy of Orthopaedic Surgeons 2019 Annual Meeting in Las Vegas, NV.

Celebrating the 40th Anniversary of the McKay Research Laboratory
2019 Penn Orthopaedics Alumni Weekend

George W. Fryhofer, MD, MTR
Robert L. Mauck, PhD

The 2019 Penn Orthopaedics Alumni Weekend last spring coincided with the 40th Anniversary of the McKay Research Laboratory and was a cause for celebration among the entire Penn orthopaedic community, past and present. Alumni journeyed to Philadelphia from all parts of the country to take part in a two-day program full of collegiality, celebration, and scientific discussion.

Attendees included 190 alumni, friends and staff. There were 14 separate speakers, 4 moderators, and 3 keynote speakers (Dr. Joe Iannotti, Dr. Andres Garcia, Dr. Ezekiel Emanuel). Distinguished Alumni Awards were presented to Clark Hung, PhD and John Esterhai, MD.

Leadership at all levels of Penn Orthopaedics, the University of Pennsylvania Health System, and the Perelman School of Medicine were involved in helping make the weekend a success, including Ralph Muller, Jonathan Epstein, Arthur Rubenstein, Scott Levin, Louis Soslowsky, and Robert Mauck.

Ribbon cutting ceremony to mark the official re-opening of newly renovated McKay Laboratory space on the 3rd Floor of Stemmler Hall. Pictured above (left to right): Nathaniel Dyment, Sherry Liu, Lachlan Smith, Foteini Mourkioti, Kyu Sang Joeng, Eileen Shore, Robert Mauck, Jonathan Epstein, Chris Clark, Scott Levin, Ling Qin, Louis Soslowsky, and Joel Boerckel.

McKay 40th reunion attendees included 190 alumni, friends and staff. Group photo above taken during the afternoon reception in the Jordan Medical Educational Center.

Ezekiel Emanuel, MD PhD giving his keynote presentation during the Saturday evening reception at R2L on May 4, 2019.

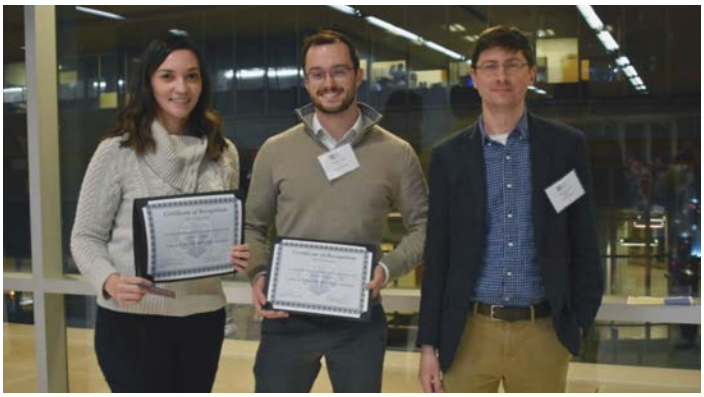
Penn Center for Musculoskeletal Disorders Research Symposium

Kelsey Bonilla, MD

The Penn Center for Musculoskeletal Disorders (PCMD), directed by Dr. Lou Soslowsky, held their 16th annual Scientific Symposium on November 13, 2019 in Smilow Rubenstein Auditorium at the Perelman School of Medicine. The mission of the PCMD is to promote the development of new therapies for musculoskeletal disorders by encouraging collaboration between investigators in the field and supporting cooperative research efforts. Its central focus has been "Musculoskeletal Tissue Injury and Repair," and the annual symposium seeks to celebrate the research being done in this field and to foster connections between researchers.

The 2019 symposium began with its New Member Session, moderated by Dr. X. Sherry Liu, with presentations by Véronique Lefebvre, PhD (Dissecting Genetic Mechanisms Controlling Skeletal Cell Lineage Specification and Differentiation), Peter Noël, PhD (Advancements in CT: More Information with Less Dose), and Shuying Yang, MD, MS, PhD (Regulation of RGS Protein in Inflammatory Arthritis). This was followed by a poster session for other PCMD members to present their research. The presentations for Affiliate Members, introduced by Dr. Robert Mauck, highlighted presentations by Fadia Kamal, PharmD, Msc, PhD (Regulation of GPCR in Cartilage Development and Disease), Nancy Pleshko, PhD (Non-Destructive Applications of Optical Spectroscopy for Assessment of Tissue Pathology and Regeneration), and David Waning, PhD (Skeletal Muscle Weakness: What's bone got to do with it?). The final presentation session for the Pilot Grantees was opened by Dr. Maurizio Pacifici and featured talks by Carla Scanzello, MD, PhD (Time-Dependent Changes in Macrophage Profiles in a Murine Model of Osteoarthritis), Yanqing Anna Gong, PhD (Plasminogen is Critical for Bone Fracture Repair by Promoting the Functions of Periosteal Mesenchymal Progenitors), and Nathaniel Dyment, PhD (Tendon-to-Bone Repair: How do we create the zones?). The second poster viewing session followed these presentations. The symposium then continued with a panel discussion focusing on career opportunities in academics and industry.

The keynote speaker for the 2019 PCMD Symposium was Dr. Anthony Ratcliffe, President and CEO of Synthasome, Inc. who discussed Strategic Approaches for the Translation of Concept to Product in Regenerative Medicine. The symposium concluded with 1st place poster awards to Hannah Zlotnic (Biomechanics), Joseph Collins (Histology), Wei-Ju Tseng (Micro CT), and Elisia Tichy (Miscellaneous). The 2019 symposium was well attended by PCMD members and will undoubtedly continue to facilitate collaborative efforts among investigators in the field.



Penn Orthopaedics Research Day 2019

Kelsey Bonilla, MD

The annual Penn Orthopeaedics Research Day brings together both clinical and research faculty and trainees to showcase the research that is being conducted within the Department of Orthopaedics at Penn Medicine. It is an opportunity to discuss the basic science and translational work that serves as the foundation for the field as well as the clinical impact that it has on our patients. The 2019 Research Day was held on June 10, 2019 in the Smilow Rubenstein Auditorium at Penn Medicine. Dr. Stuart B. Goodman, MD, MSc, PhD, the Robert L. and Mary Ellenburg Professor of Surgery in the Department of Orthopaedic Surgery at Stanford University, was the moderator for the symposium.

The presenters during the first session included Mark Hasenauer, MD; Jay Patel, PhD; Rikesh Gandhi, MD; Joseph Collins, BS; and Nicole Zelenski, MD, and spanned a range of topics from the molecular regulation of ossification centers during embryogenesis to the complications of revision arthroplasty. Following a poster viewing session, the 2019 research residents presented their studies. Dr. Matthew Counihan, MD, MS, discussed the role of "Limited Scar Resection for Chronic Achilles Repair: Use of a Rat Model" and Dr. Liane Miller's, MD presentation focused on "Enhancing Interstitial Cell Migration in Dense Connective Tissues through Nuclear Softening." During this session Alexandra Stanley, PhD also discussed aberrant muscle tissue repair and Andrew Tyler, MD, PhD presented on the effects of local anesthetic in fracture healing.

The morning session concluded with a presentation by Guest Moderator Dr. Goodman who discussed "Osteonecrosis: Past, Present, and Future." The poster presentation session that followed highlighted the wide variety of cutting edge work being done at Penn Orthopedics and provided an opportunity for both participants and judges to engage with the investigators. The afternoon presentation session continued with talks by Julianne Huegel, PhD; Leilei Zhong, PhD; Matthew Sloan, MD, MS; Ryan Charette, MD; Elaine Schmidt, MS; and Matthew Winterton, MD which also spanned the gamut of topics, including discussions of single cell transciptomics in adipocytes, rat models of Achilles tendon injury, the use of tranexamic acid in arthroplasty, and global health opportunities in Madagascar. The afternoon concluded with a final review of posters for awards.

Presentation winners included Liane Miller, MD; Jay Patel, PhD; and Leilei Zhong, PhD, and poster winners were Sonia Bansal, BS; Ana Peredo, BS; Alexandra Stanley, PhD; Blake Meza, BS; and Sarah Gullbrand, PhD.

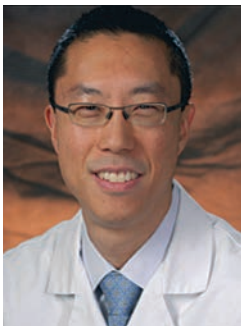
Stuart B. Goodman, MD, MSc, PhD served as moderator for the 2019 Penn Orthopaedic Research Day symposium.

Orthopaedic Trauma & Fracture Service

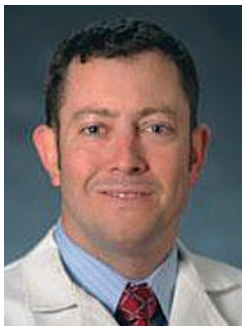
Samir Mehta, MD

Orthopaedic Trauma Faculty

Samir Mehta, MD



Jaimo Ahn, MD, PhD



Derek Donegan, MD, MBA

Susan Harding, MD

The Division of Orthopaedic Trauma & Fracture Surgery continues to be an exceptionally busy and dynamic subset of Penn Orthopaedics. The orthopaedic trauma service, now well settled into its new home at Penn Presbyterian Medical Center, practices at the highest volume Level 1 trauma center in the Delaware Valley, performing nearly 2000 cases annually. The case diversity is expansive, ranging from ankle and distal radius fractures through complex pelvic and acetabular injuries, peri-articular fractures, and management of multiply injured polytrauma patients. The division frequently collaborates with other subspecialties, including plastic surgery for complex revisions and wounds; neurosurgery for spondylopelvic disruptions; and geriatric medicine for optimal care of our geriatric hip fracture population. In addition to strong surgeon leadership, the division succeeds due to the relentless efforts of dedicated advanced practice providers in both the inpatient and outpatient settings, who facilitate management of acute injuries, as well as run an outpatient fracture clinic daily to ensure that new and follow-up patients are seen in a timely and consistent manner. Additionally, orthopaedic trauma is supported by excellent social workers, case workers, physical therapists and nurses who enable our trauma patients to receive optimal care during what is often one of the most challenging times of their lives. Additionally, the life-blood of the orthopaedic trauma program is the resident complement, who continue to support the service line through tireless effort. The trauma program resident complement now includes a PGY-1, two PGY-2s, a PGY-3, a PGY-4, and a PGY-5 as chief resident on the service. Clinical roles and responsibilities are divided amongst all the residents on service with a focus on graduated responsibility and autonomy. Lastly, the trauma service is only able to provide 24-7-365 coverage thanks to the non-trauma faculty who sacrifice time from their family and additional obligations to take call nights and weekends to divide the workload. Because of their sense of responsibility and dedication, our call faculty allow the trauma service to function at a high level at all times.

Innovation in patient care occurs contemporaneously with upholding longstanding division traditions. For example, the trauma division has worked closely with geriatric and emergency medicine to develop a state of the art geriatric hip fracture program, whereupon relevant members of the care team are immediately notified of a geriatric hip fracture patient upon their arrival to the hospital so that the teams can mobilize to provide the patient with streamlined care from ambulance to OR. Geriatric Hip Programs, like that at Penn, have been shown to improve the outcomes of patients suffering from these life-changing injuries. Additionally, the orthopaedic trauma service through the support of Dr. Levin and the Health System is an integral part of the new Penn Orthopaedic Limb Salvage Center (POLSC). The orthopaedic trauma service is offering several limb salvage and reconstruction opportunities, including repair of complex fractures using ring fixation. We have also started the TALLER program—Total Aesthetic Limb Lengthening and Extremity Reconstruction to increase stature. In addition, the division is using 3D printing technology to salvage limbs, including a recent total talus with partial ankle replacement (see x-ray).

The division's presence extends beyond the region and beyond medicine, at large. All of our attendings are deeply involved with the AO Foundation, an international foundation geared towards advancements in fracture care. All Penn traumatologists have chaired a national AO North America course, which attracts hundreds of residents and faculty to learn and to teach the principles of basic and advanced fracture care. Additionally, Drs. Mehta, Donegan, and Ahn each have been involved in international outreach, including Madagascar and the Dominican Republic. Some of their experiences can be followed on Instagram at "pennots". The faculty are also actively engaged with the Orthopaedic Trauma Association, including participating in and chairing committees and courses for the organization.

Clinically, the Division continues to extend its areas of expertise focusing on "elective" orthopaedic trauma care. The

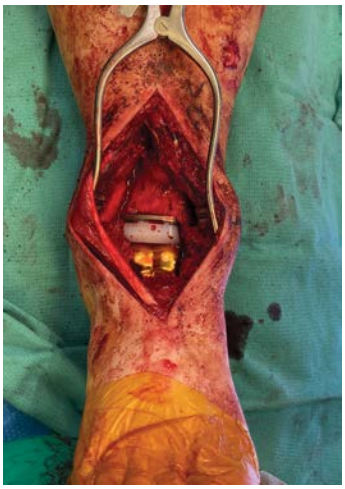
Division has a distinct interest in peri-prosthetic fractures, infection (osteomyelitis), malunions, and non-unions. The division utilizes advanced technology to facilitate the care of these complex patients including ring fixation and lengthening nails. By collaborating with our colleagues within the department, such as shoulder and elbow, adult reconstruction, foot and ankle surgery, orthoplastics, hand, spine, and oncology, the orthopaedic trauma division can provide the highest level of care. Additionally, the division has performed several cases utilizing 3D printing of implants in an effort to salvage extremities in patients with severe injuries.

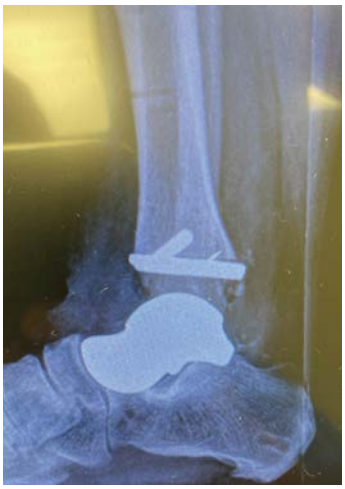
Change, however, is inevitable. With the recent closure of Hahnemann University Hospital, the Penn Orthopaedic Trauma Service was able to grow their family through the hiring of Dr. Susan Harding, an orthopaedic traumatologist. Dr. Harding did her fellowship at Harborview Medical Center and had been in practice in Atlantic City prior to her arrival as Chief of Orthopaedic Trauma at Hahnemann, where she was also the program director. She has been an integral part of the orthopaedic trauma community in Philadelphia for nearly two decades. Dr. Harding is a welcome addition to both Penn Presbyterian Medical Center and also to Cape Regional Medical Center, where she has been empowered to build a Trauma and Fracture program. We are extremely fortunate to have an individual with Dr. Harding's enthusiasm and experience be part of the Penn family.

In addition, it is with a heavy heart that we are seeing one other change to the Penn Orthopaedic Trauma faculty. Dr. Ahn will be leaving to join the University of Michigan as Chief of the Orthopaedic Trauma Service and Vice-Chair of Education at the end of the academic year. While it is a tremendous opportunity for Dr. Ahn, it is a huge loss for our Division. He has been not only a nearly life-long member of the Penn community, but also an integral part of the inception and development of the Orthopaedic Trauma and Fracture Service (see Picture).

The trauma division remains a cornerstone of the residency program's education. Every resident spends 6 to 12 weeks of their year as a member of the busy trauma service, and the rotation is a favorite amongst most residents, regardless of ultimate career goals, due to the high yield learning environment with faculty who value teaching and education. Drs. Ahn, Donegan, Harding, and Mehta all participate in resident morning lectures, department grand rounds, as well as the General Medical Education Committee (GMEC). The attendings also lead every trauma team in a trauma cadaver lab prior to their rotation to engender team unity as well as to practice common procedures and exposures.

In conclusion, the expertise and diversity of the Trauma Division continues to grow, and, despite the change, we are looking forward to another momentous year of patient care, innovation, research, outreach and education.





Spine Division Update

Harvey Smith, MD

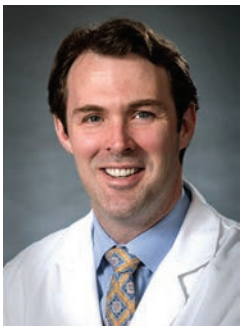
Spine Faculty


Harvey Smith, MD


Vincent Arlet, MD


Amrit Khalsa, MD


Comron Saifi, MD


Michael Murray, MD

The academic year has been one of continued growth for the spine division.

Clinical Growth: Over the past year Dr.Amrit Khalsa joined our division. Dr. Khalsa joined us from Hahnemann, and has already established a significant practice at Penn Presbyterian Medical Center and Radnor.

Research: Our division has been established as a leader in both basic science and clinical spine research. Our translational research is conducted in partnership with the Translational Musculoskeletal Research Center at the VA, developing the first *in vivo* large animal tissue-engineered total disc replacement. Our clinical research division is led by Dr. Comron Saifi who has established an outcomes registry for our complex deformity patients as well as all adult spine patients. This is a large undertaking and he has made significant strides with marked academic output in terms of manuscripts, abstracts, and presentations. Dr. Murray is conducting a number of comparative effectiveness research projects demonstrating the value of MIS surgery. Dr. Khalsa is continuing his research interests in evaluating cost-effectiveness and risk adjustment models in spine surgery. Dr. Arlet continues his role as an international thought leader in complex spinal deformity.

Academic Productivity: Penn Ortho Spine has been represented in over 30 peer-reviewed publications, abstracts and presentations. Our faculty chair committees at North American Spine Society, and have organized Instructional Course Lectures at national and international meetings. The Philadelphia Spine Summit meeting organized in partnership with Thomas Jefferson University is now entering its sixth year and is now one of the largest regional spine meetings.

Outreach Surgery: Under the leadership of Dr. Arlet, Penn Spine maintains an ongoing outreach program in Trinidad managing complex spinal deformities; this program has received national and international recognition. Dr. Khalsa maintains an ongoing outreach program in South America. The spine fellows participate in the outreach program.

Spine Fellowship: Our spine fellowship is entering its fourth year of partnership with the Shriners Hospital of Philadelphia. Our complex spinal deformity fellowship is unique in offering a combined adult and pediatric complex deformity experience.

Sports Medicine Division Update

Brian Sennett, MD

Sports Medicine Faculty


Brian Sennett, MD


James Carey, MD, MPH


John Kelly, MD


Miltiadis Zgonis, MD


Kevin McHale, MD

The Sports Medicine Division at Penn Orthopaedics has continued to grow and expand over the past year. While the Division has continued to excel in their pursuit of clinical care, education and research, the year has been a banner year of relationships and contributions. While the Division of Sports Medicine has traditionally provided medical coverage for Penn Athletics, the University of the Sciences, and many local high schools, the Philadelphia Flyers and the Philadelphia Eagles have reached out to Penn Orthopaedics and the Division of Sports Medicine to provide care for their athletes.

Penn Medicine and Comcast Spectacor, the Philadelphia-based professional sports and live entertainment company, announced a major partnership making Penn Medicine the official health system for the Philadelphia Flyers and Wells Fargo Center. Penn Medicine will also become the team's official medical services provider, including on-ice, orthopaedic, and general practice, as well as the preferred provider for Comcast Spectacor front office employees.

A team of Penn Medicine physicians, led by Gary Dorshimer, MD, section chief of General Internal Medicine at Pennsylvania Hospital, and Brian Sennett, MD, chief of Sports Medicine and vice chair of Orthopaedic Surgery, will be at the ready to care for the Flyers players on the ice at each home game. Dorshimer has been a long-time team physician for the Flyers and will remain a medical provider, while the orthopaedic care of the team will now be led by Sennett. Although Orthopaedic and Sports Medicine care are at the forefront for the new partnership, the team will also have access to many more Penn Medicine providers in areas such as cancer and cardiology.

At the heart of the partnership will be a comprehensive community program that will have a lasting impact on Philadelphians. Among the highlights of the community program will be annual events promoting both partners' dedication to cancer research and treatment, as well as cardiovascular health. In addition, Penn Medicine will become the presenting partner of the Gritty 5K, the highly-popular event launched in 2019 that benefits Flyers Charities. Furthermore, the partnership will include PSAs featuring Flyers players and a social media series highlighting the importance of healthy lifestyles, physical fitness, and proper eating habits.

In addition to the partnership with the Philadelphia Flyers, the Philadelphia Eagles reached out and selected Dr. Arsh Dhanota to be both the Head Team Physician and Chief Medical Officer of the Philadelphia Eagles in 2019. He was initially signed to a 3-year agreement which has already been extended to a 5-year commitment. He has been the guiding medical force behind the Philadelphia Eagles. In his first year at the helm, he significantly decreased soft tissue injuries and improved the team's ranking in the category of "games missed due to injuries". He has done a stellar job in his first year not only in decreasing injuries but in transforming the medical care provided.

While the fight against COVID 19 has taken center stage this year, you would not traditionally expect the Division of Sports Medicine to have much of an impact as almost all organized sports have come to a crashing halt. However, several faculty members have had significant impact in Penn's fight against COVID -19. Dr. Kris Fayock served as a Deputy Director of Triage Medicine at Penn Presbyterian Medical Center during the crisis. He has worked tirelessly during this period of time and is a faculty member that we are very proud of due to his tremendous medical knowledge and organizational prowess. In the area of philanthropy, the division played crucial roles in assisting with the donations made by local teams, owners, and players. Dr. Arsh Dhanota played a pivotal role in in providing guidance to Mr. Jeffrey Lurie, the principal owner of the Philadelphia Eagles, in understanding the Penn difference and secured 1 million dollars of funding from Mr. Lurie to establish the COVID-19 Immunology Defense Fund for Penn. He continues to work with Mr. Lurie to secure additional funding through relationships with donors looking to contribute to the fight against COVID-19. Dr. Brian Sennett played an equally pivotal role in providing guidance to Joel Embiid, the All-star basketball player of the Philadelphia 76ers, in making a significant contribution to set up a program of antibody testing for COVID-19 in front-line health care workers. This effort was quickly joined by two of the owners of the Philadelphia 76ers, Mr. Joshua Harris and Mr. David Blitzer. Joel and the two owners generously donated 1.3 million dollars to provide support to the front line workers.

Combining all of these efforts, 2.3 million dollars was donated to fight COVID 19. This was a tremendous contribution from members of the Eagles and the 76ers.

While the new professional team affiliations have dominated the news around the division, the cornerstone of cartilage restoration has continued to be one of the primary focuses with respect to all three areas of clinical care, research, and education. Dr. James Carey, Director of the Penn Cartilage Center currently serves as the lead Principal Investigator and Chairperson of the Clinical Steering Committee for the MACI Pediatric Study – PEAK (PEdiatric Autologous cultured chondrocytes treatment of cartilage defects in the Knee).

In addition, Dr. Carey, Dr. Mauck, Penn Sports Medicine, and the Penn Cartilage Center hosted the International Cartilage Repair Society (ICRS) Traveling Fellows and their godfather Dr. Tom Minas in late September 2019. In the area of research, a landmark study entitled "Autologous Chondrocyte Implantation as Treatment for Unsalvageable Osteochondritis Dissecans: 10- to 25-year Follow-up" has been accepted for publication in the American Journal of Sports Medicine. Dr. Carey traveled to Gothenburg, Sweden twice to work on this project. This study reports the longest follow-up of outcomes following autologous chondrocyte implantation.

Other areas of expansion have continued with the addition of orthopaedic and sports medicine coverage to Drexel University and expansion at Penn Medicine at Radnor. With the new expansion of Penn Medicine at Radnor, the footprint of sports medicine is growing. Dr. John Vasudeven, who along with Alexis Tingan provide coverage of our largest running events, will expand clinical and educational experiences for patients at the new Radnor facility.

It has been a busy year in the Division of Sports Medicine and we are looking forward to getting back on the ice, fields, and courts. No matter what comes our way, we are ready to be teammates for Penn Medicine and all athletic individuals across the Tri-State region.

Hand Division Update

David Bozentka, MD

Hand Surgery Faculty


David Bozentka, MD


David Steinberg, MD


L. Scott Levin, MD, FACS


Benjamin Gray, MD


Robert Carrigan, MD


Apurva Shah, MD, MBA


Stephen Liu, MD

It has been another exciting year for the hand and upper extremity section. The program continues to provide the highest quality service in its clinical and academic missions. Our success is due to the exceptional teamwork and commitment of the entire group. We see this collaboration daily with a remarkable effort from our staff, residents and fellows.

Our chairman, L. Scott Levin MD has completed his year as president of the American Society for Surgery of the Hand at the annual meeting in Las Vegas, Nevada. He gave an inspiring presidential speech while reviewing the history and future of the practice of hand surgery. Angela Duckworth, professor of psychology at the University of Pennsylvania, gave the presidential guest lecture presenting her work on "grit" – the tendency to pursue long-term goals with perseverance and passion.

Under the leadership of Dr. Benjamin Gray MD, the hand surgery section has further developed its robust clinical research program. The hand and upper extremity research team includes Annamarie Horan PhD, Director of Orthopedic Clinical Research, and our Clinical Research Coordinators Mary Dooley, Ashley Iwu and Evan Bannister. The team has been instrumental in advancing the numerous ongoing clinical research projects. The group is completing patient enrollment to evaluate digital tomo-synthesis for the detection and case management of scaphoid and distal radius fractures with a comparison to MRI or computed tomography. Enrollment is also coming to a close for the Axogen-sponsored study: A Multicenter, Prospective, Randomized, Subject and Evaluator Blinded Comparative Study of Nerve Cuffs and Advance Nerve Graft Evaluating Recovery Outcomes for the Repair of Nerve Discontinuities.

The hand transplant team has successfully performed bilateral upper extremity transplantation for four patients with quadra-membral amputations. Two patients have required a transatlantic coordination with the patients travelling from France to Philadelphia for their procedures. The group meets on a regular basis performing cadaveric rehearsals and honing procedure checklists to prepare for our fifth bilateral upper extremity allotransplanation.

The clinical productivity of the hand section has exceeded budget predictions again this year. Dr. Stephen Liu's practice at Chester County Hospital is growing rapidly. The hospital will be welcoming trainees in the next academic year which will add a community dimension to our training program. The Radnor office will be moving across the street to a new multi-specialty outpatient facility once construction is completed this spring. The building will provide expanded services to include an outpatient OR in the future.

The hand surgery fellowship continues its strong tradition under David R. Steinberg MD as the director and Ines Lin MD as the associate program director. Our three hand surgery fellows have had a solid clinical and academically productive year. Erin Weber M.D., Ph.D. completed her plastic surgical residency at the Keck School of Medicine of the University of Southern California. Her goal is to become an academic surgeon-scientist combining a practice in hand and upper extremity reconstruction with research in tissue engineering, focusing on nerve and muscle regeneration. Ketan Sharma MD obtained a Master in Public Health at the University of North Carolina-Chapel Hill and completed his plastic surgical residency training at Washington University School of Medicine in St. Louis, Missouri. He plans to utilize his epidemiology skills in an academic career in hand surgery. Dr. Jonathan Lundy MD is a military general surgeon serving as a trauma surgeon at Fort Hood, TX. After fellowship he plans to return as the hand surgeon for the United States Army Institute for Surgical Research Burn Center and join the upper extremity team at the adjoining San Antonio Medical Center.

The hand and upper extremity service could not function without the outstanding support from our superb advance practice providers, nurses and administrative assistants. With this exceptional support and collaboration, the hand surgery section looks forward to another successful year.

Shoulder and Elbow Division

David Glaser, MD

Shoulder & Elbow Faculty

David Glaser, MD

G. Russell Huffman, MD, MPH

Andrew Kuntz, MD

It has been another outstanding year for the Shoulder and Elbow division of the Department of Orthopaedic Surgery in the Perelman School of Medicine at the University of Pennsylvania. With continued commitment to manage the most complex cases, the section's tertiary referral network has dramatically increased along with the complexity of cases. In FY20, the group performed over 12,000 visits and performed over 1000 surgical cases with revision shoulder arthroplasty and elbow surgery seeing increased volume.

As director of research, Andy Kuntz is leading our research effort, with close collaboration with Louis Soslowsky and others in the McKay Research Laboratory. Together, we help form one of the largest shoulder research laboratories in the world. We would like to recognize Andy for his continued focus as a clinician-scientist, providing world class clinical care, while contributing to all aspects of our research mission-clinical, translation and basic science. Through his leadership we are actively enrolling patients in five sponsored clinical trials, including stemless reverse arthroplasty, and a multi-center trial, which is the direct result and translational follow-up to basic science research performed in the McKay Lab. Russ is participating in an early release trial of a cementless elbow arthroplasty. The multimodal pain protocol for outpatient shoulder surgery that we developed is now being utilized at other Penn sites. In conjunction with Mike Hast in the Biedermann Lab, new biomechanical testing apparatus and protocols have been used to study reverse glenoid baseplate fixation.

For Andy's efforts, he has been elected to the Orthopaedic Research Society (ORS) board of directors and is Chair of the ORS membership committee and Community Council while also being active in the ASES. Together the group has published 14 papers.

Now in its fourth year, and in collaboration with our French colleagues, we offer our fellow an opportunity to visit world leaders in shoulder surgery. Current fellow Rob Williams (F'20) will follow Greg Gomez (F'19), Josh Rogozinski (F'18), and Chad Myeroff (F'17), and spend three weeks visiting academic centers in Monaco and France. Director of our Fellowship, Russell Huffman continues to coordinate the next generation of academic surgeons, with our last several fellows joining teaching programs. Past fellow, Mohit Gilotra (F'15) won the 2018 ASES Charles Neer award and Chad is in academic practice at the University of Minnesota. The Penn shoulder and elbow faculty presented 10 abstracts at national meetings and gave 14 talks at international, national, regional and local meetings in 2019/20.

Adult Reconstruction Division Update

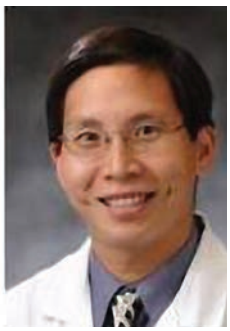
Charles Nelson, MD

Arthroplasty Faculty

Charles Nelson, MD

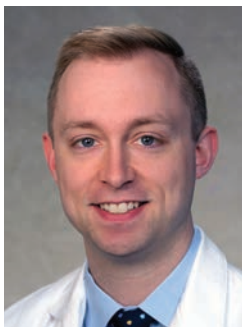
Craig Israelite, MD

Eric Hume, MD



Gwo-Chin Lee, MD

Neil Sheth, MD



Christopher Travers, MD

Vincent Moretti, MD

The 2019/2020 academic year has been an outstanding year for Penn Orthopaedics and the Adult Reconstruction Division. The adult reconstruction division has continued to increase surgical volume while improving quality, ranking at or near the top in observed to expected mortality among more than 150 participating hospitals. The annualized surgical volume this year for the total joint division was over 3000 surgical cases at the two downtown hospitals.

In addition to clinical excellence, our faculty have been active in clinical education nationally and internationally, as well as in leadership and volunteer positions within most of the important national orthopaedic organizations including: the American Academy of Orthopaedic Surgeons; The Hip Society, The Knee Society, the American Associaton of Hip and Knee Surgeons, the American Orthopaedic Association, and the American Board of Orthopaedic Surgeons. Our faculty were involved with more than 40 peer reviewed publications in 2019 and more than 60 scientific presentations or lectures by invitation.

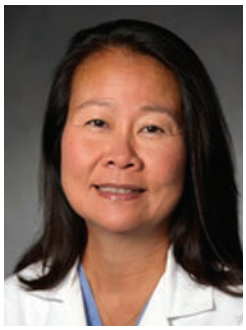
Our current Adult Reconstruction Faculty include Dr. Eric Hume, Dr. Craig Israelite, Dr. Gwo-Chin Lee, Dr. Vincent Moretti, Dr. Charles Nelson, Dr. Neil Sheth, and Dr. Christopher Travers. In addition, we look forward to the addition of Dr. Christopher Anthony, who will be joining us in August 2020 as part of our Adult Reconstruction Division with an interest in Hip Preservation.

Foot and Ankle Division Update

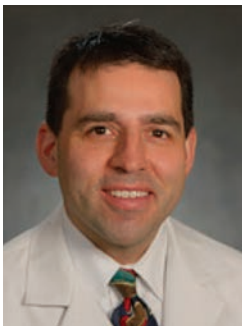
Keith Wapner, MD

Foot & Ankle Faculty

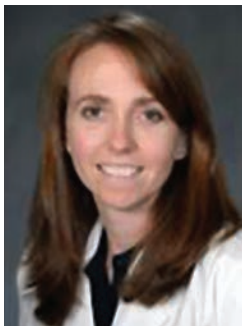
Keith Wapner, MD



Wen Chao, MD



Daniel Farber, MD



Kathryn O'Connor, MD, MSPT

The Foot and Ankle Division has had another productive year. Our current faculty includes Keith Wapner, Wen Chao, Kathryn O'Connor, and Daniel Farber. We continue to serve Center City and beyond with locations at the Farm Journal Building, PMUC, Cherry Hill, Radnor, and Exton and perform surgical procedures at Pennsylvania Hospital, Penn Presbyterian, the surgery center at PMUC, and at Chester County Hospital.

Dr. Keith Wapner has represented Penn Orthopaedics with presentations around the world and nationally. He has presented at the AAOS, AOFAS and Orthopedic Summit meetings, the Global Foot and Ankle Symposium in Annecy, France as well as serving as Visiting Professor at University of Arizona and Louisiana State University. Dr. Wapner has announced his plans to step down as Chief of Foot and Ankle at Penn as he begins his plans towards retirement.

Dr. Daniel Farber continues to lead the fellowship and research components of the division and in the past year has taken on the role of Residency Program Director. He serves on the AOFAS Education committee and on the AAOS Resolutions committees as well as continuing to help develop the AOFAS fellowship accreditation process. This past year he served on a mission trip with the AOFAS in Kijabe, Kenya and represented the AOFAS at the SICOT meeting in Muscat, Oman. Further, he is a regular lecturer at the Maine Orthopaedic Review.

Dr. Wen Chao remains an Orthopaedic Consultant to the Pennsylvania Ballet. She serves on the Public Education Committee for the AOFAS. She is an active reviewer for the journals Foot and Ankle International and Foot and Ankle Orthopaedics.

Dr. Kathryn O'Connor continues to run the resident foot and ankle education curriculum and the monthly foot and ankle resident and fellow cadaver labs. She was awarded an AOFAS grant for her Achilles Research as well as her ongoing McCabe Award. She serves on the AOFAS Evidence Based Medicine Committee.

The division's research endeavors continue to expand. We are currently concluding a clinical study on opioid use in foot and ankle surgery and actively investigating Achilles tendonitis treatments and Achilles rupture treatments. Current national studies include completion of an ongoing study of the STAR ankle replacement (PI: O'Connor, Wapner), an investigation of the use of bone stimulators for acute operatively treated ankle fractures (PI: Farber), and one on a novel tri-planar correction of hallux valgus deformities (PI: Farber). The division is also involved in collaborative investigations with the department of radiology looking at the use of weight bearing CT in hallux valgus, arthritis and other conditions. We continue to work closely with Josh Baxter, PhD of Penn's Human Motion Laboratory exploring treatment of chronic Achilles pathology as well as acute Achilles ruptures for which he recently received a K01 award and awaits a decision on an R01. We are also nearing publication of a collaboration with the Biedermann lab and Mike Hast, PhD exploring the compression properties of a new plate for fusions of the hindfoot. Collaborating is ongoing with the McKay Lab and Lou Soslowsky, PhD investigating early return to activity after repaired and non-repaired Achilles ruptures with several publications as well as a study on chronic Achilles rupture treatments in a rat model that is nearing conclusion. We are also collaborating on an application for a new R01 grant exploring the effect of rehabilitation on Achilles ruptures.

The division has presented at multiple meetings over the past year, including the AOA and AOFAS and had presentations planned for the unfortunately cancelled AAOS and IFFAS meeting. We have multiple new publications in print and more have been submitted to leading foot and ankle journals.

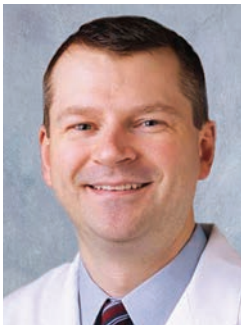
Penn's Orthopaedic Foot and Ankle division has had another successful year with more achievements to come. We look forward to another year of growth with the anticipation of a new division chief and other staff and will continue to provide excellent patient care, outstanding service to the orthopaedic community and meaningful research to foot and ankle science.

Orthopaedic Oncology Division Update

Kristy Weber, MD

Orthopaedic Oncology Faculty

Kristy Weber, MD, FACS



Robert Wilson II, MD

Musculoskeletal Oncology at Penn: Building a Comprehensive Team

The Orthopaedic Oncology clinical service at Penn is comprised of Dr. Kristy Weber and Dr. Robert Wilson as well as Sarah Borgia, MHA, Administrative Coordinator; Kate Barrie, PA; and April Chambers, RN. We are part of a larger multidisciplinary team who care for patients of all ages with bone and soft tissue tumors.This includes the care of patients with benign and malignant primary tumors as well as patients with metastatic bone disease.

The multidisciplinary clinical team that treats patients with bone or soft tissue sarcomas continues to meet weekly on PCAM South 12 for a clinical care videoconference to discuss the presentation and differential diagnoses of new patients as well as the ongoing multimodal therapy for existing patients. A Sarcoma leadership group meets monthly to work on quality initiatives and clinical pathways to improve the overall delivery of care to our patients. Our primary quality metric this year is 'time to biopsy' as we focus on providing expedient care for our patients. Most of our patients can now get a 'same day' biopsy which facilitates their overall care.

There have been critical additions to the Penn Sarcoma team this year. Robert Maki, MD, PhD joined the team in January, 2020 as the Director of the Medical Oncology Sarcoma program. He is an international leader in the clinical management and research of sarcomas. He has extensive experience in drug development and has been instrumental in the evaluation of various treatments for sarcoma and gastrointestinal stromal tumors. Dr. Maki serves nationally as the Director of Translational Research with the Sarcoma Alliance for Research through Collaboration (SARC). Patrick Grohar, MD, PhD as joined the CHOP team in July, 2019 as Director of Translational Research for the Center for Childhood Cancer Research. He is a basic and translational scientist focused on developing innovative therapies for children and adolescents with Ewing sarcoma. He most recently worked at the Van Andel Institute and Helen De Vos Children's Hospital in Grand Rapids, MI. The addition of these two oncologists will allow us to more effectively move ideas from the laboratory to the clinic and engage in innovative clinical trials.

The core sarcoma research team continues their work and has been productive with new publications, grants and awards. Drs. Karin Eisinger and Malay Haldar are progressing with their RO1-funded projects in sarcoma. Dr. Haldar recently had a publication accepted to *Cell* on his work with the immune microenvironment. There are ongoing clinical trials for patients with soft tissue sarcoma with the SARC trial combining pembrolizamab and IMRT as well as a clinical trial for patients with desmoid tumors using nirogacestat. Dr. Sebro's hypoxia imaging trial for sarcoma is still accruing patients. The canine trial for dogs with soft tissue sarcoma using an NFκB inhibitor is also up and running.

Finally, philanthropic support from grateful patients is critical for our research efforts and we are thankful for their generosity. Our patient and family Sarcoma Advocacy group is in their 6th year of organization and planning to support sarcoma research at Penn Med/Penn Vet/CHOP. In 2019, over $140,000 was raised and over 1000 people attended the annual Walk/Run. This year the event is May 31, 2020 at Wilson Farm Park in Wayne, PA. www.stepstocuresarcoma.com/

Orthopaedic Oncology sites and upcoming lecture:

Patients are seen 4 days per week with clinic locations at PCAM and Radnor. Surgeries are performed at HUP, the Philadelphia VA Hospital, and CHOP (with Dr. Alex Arkader). A collaboration with the Philadelphia Shriners Hospital to evaluate and treat patients with bone or soft tissue tumors has continued this year. The Penn Orthopaedic Oncology Visiting Professor for 2020 is Dr. Carol Morris, Chief of Orthopaedic Oncology at Johns Hopkins.

Recent Publications:

Lewis DM, Pruitt H, Jain N, Ciccaglione M, McCaffery JM, Xia Z, Weber K, Eisinger-Mathason TS, Gerecht S: Feedback loop between hypoxia and matrix stress relaxation increases oxygen-axis migration and metastasis in sarcoma. Cancer Res 79:1981-1995, 2019.

Gomez-Roca CA, Italiano A, Le Tourneau C, Cassier PA, Toulmonde M, D'Angelo SP, Campone M, Weber KL, Loirat D, Cannarile MA, Jegg AM, Ries C, Christen R, Meneses-Lorente G, Jacob W, I, Ooi CH, Watson C, Wonde K, Reis B, Michielin F, Rüttinger D, Delord JP, Blay JY: Phase 1 study of Emactuzumab single agent or in combination with Paclitaxel in patients with advanced/metastatic solid tumors reveals depletion of immunosuppressive M2-like macrophages. Ann Oncol. 2019 May 22 (epub ahead of print).

Jain V, Venigalla S, Sebro RA, Karakousis GC, Wilson RJ 2nd, Weber KL, Shabason JE: Association of health insurance status with presentation, treatment and outcomes in soft tissue sarcoma. Cancer Med., 8:6295-6304, 2019.

Folkert IW, Devalaraja S, Linette GP, Weber K, Haldar M: Primary bone tumors: Challenges and opportunities for CAR-T therapies. J. Bone Min Res., 34:1780-1788, 2019.

Neuro-Orthopaedics Division Update

Keith Baldwin, MD, MPH, MSPT

Neuro-Orthopaedic Faculty

Keith Baldwin, MD, MPH, MSPT

David Spiegel, MD

Comprehensive Care in a Complex Population

The Neuro Orthopedics service at Penn is a dynamic multidisciplinary service that cares for patients with complex orthopedic needs that span multiple traditional disciplines. The service is a "lifespan" service, caring for patients across the lifespan at both the Clinical Practices of the University of Pennsylvania, and the Children's Hospital of Philadelphia. Keith Baldwin, MD, MPH, MSPT is the chief of Neuro Orthopaedics at Penn and is one of a handful of orthopaedic surgeons nationally who cares for the spectrum of neuromuscular disorders in both adults and children. Dr. Baldwin works alongside Katie Walizer, PA, Ross Lenzi PA, and Kerry Howry, PA to provide timely care to adults who have suffered a traumatic brain injury, spinal cord injury, multiple sclerosis, cerebral palsy and a variety of other conditions. This includes direct work with well-known rehabilitation services both inside and outside the system including Penn Good Shepard partners, Moss Rehabilitation, Magee Rehabilitation, and Bryn Mawr rehabilitation among others.

On the Pediatric side, Dr. Baldwin works with David A. Spiegel MD to address the musculoskeletal needs in children with a variety of disorders such as Cerebral Palsy, Spina Bifida, Charcot Marie Tooth, Spinal Muscular atrophy, and others. They are supported by Kathy Abel CRNP, Emily Stegonshek CRNP, and Jessica Staschak, who play a key role in serving this challenging population. Treating neuromuscular disorders is a team sport, and the neuro orthopedic team is large. The service partners with many other services within Penn Orthopedics to provide cutting edge and high-level care by partnering in the last year with the Adult Reconstruction service, the Hand and Upper Extremity Service, the Ortho Plastics Service, the Orthopedic Oncology Service, the Sports Medicine Service and the Trauma Service. The adult Neuro Orthopedic Service was also invited to provide clinical training to a physiatry fellow last year and provides a supportive role in the education of Foot and Ankle Fellows. We were also lucky enough to host an international foot and ankle fellow from the United Kingdom who was interested in the surgical treatment of spasticity.

On the pediatric side last year we welcomed a new chief of Physical Medicine and Rehabilitation, Dr. Sally Evans, MD. We look forward to building the service further with Dr. Evans. Additionally, Laura Prosser PhD, PT, has spearheaded a mobile gait lab which provides innovative gait lab services which can be brought "on the go" for clinical evaluations. Outreach to outlying institutions has been highly successful. Penn has become the "go to" service for neuro orthopedic care for much of the surrounding area with referrals coming from all major rehabilitations in the area. Effort is ongoing to build a more regional and national presence on the adult and pediatric side., Using our referral network and harnessing the nurse navigator program at CHOP the neuro orthopedic service have treated patients from many states and foreign countries.

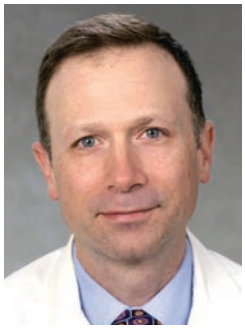
The research program in neuromuscular orthopedics has been on the rise as Drs Spiegel and Baldwin are currently exploring pelvic obliquity and its measurement reliability. We are also continuing a line of investigation assessing nutrition in patients with neuromuscular scoliosis. Additionally, a joint paper with Dr. Flynn and Dr. Baldwin using humeral growth stage to correlate with curve progression in neuromuscular scoliosis won the Jacqueline Perry award this year. Ongoing research in neuromuscular hip surgery, multicenter studies on neuromuscular foot reconstruction and neuromuscular spine surgery have increased the profile of the program and its thought leadership nationally.

David Spiegel continues his service abroad and has presented nationally and internationally on topics relating to neuromuscular care of children. The neuro orthopedic service at Penn continues to grow and provide one of a kind care that is not matched in the region.

Orthoplastic Limb Salvage Division Update

Meghan E. Wilson, RN, Stephen Kovach, MD, and L. Scott Levin, MD, FACS

Orthoplastic Limb Salvage Faculty



Stephen Kovach III, MD

L. Scott Levin, MD, FACS

Samir Mehta, MD

Since its official launch in July 2018, the Penn Orthoplastic Limb Salvage Center (POLSC) has been steadily increasing its patient population into a more defined center. POLSC is headed by Dr. Scott Levin, Dr. Samir Mehta, and Dr. Stephen Kovach, and now has the full-time assistance from an Orthoplastic fellow and Orthoplastic nurse coordinator. Our unique program is still one of only a few formal limb salvage centers across the country that combines the coordination of plastic reconstructive surgery and orthopedics in an effort to reconstruct non-functional extremities and save those at risk for amputation.

Our physicians' liaisons and marketing team continue to work to promote awareness of the program locally to encourage referrals and transfers for limb salvage. In the past year, POLSC has been very active with over 200 new patient referrals specifically for limb salvage or extremity reconstruction. These referrals come from all over; they include internal Penn Medicine recommendations, local outside healthcare facilities who have been steadily referring these challenging cases, self-referring patients who have found us through word-of-mouth and online promotion, as well as international patients coming in through Penn Global Medicine. In 2019, there with over 150 surgical procedures performed under POSLC criteria, including local tissue rearrangements in conjunction with orthopedic reconstruction and vascularized free tissue or bone transfers. 2019 saw a 17% increase in POLSC volume since 2018!

For those cases where amputation is the only solution for a functional of limb outcome, Dr. Stephen Kovach continues to expand his Targeted Muscle Reinnervation (TMR) practice in amputated limbs. TMR works by taking the nerves severed during the amputation and rerouting them into the muscles of the residual limb. This process has significantly decreased patients' complaints of phantom limb pain as well as reduces neuropathic pain in the stump including any occurrence of neuromas.

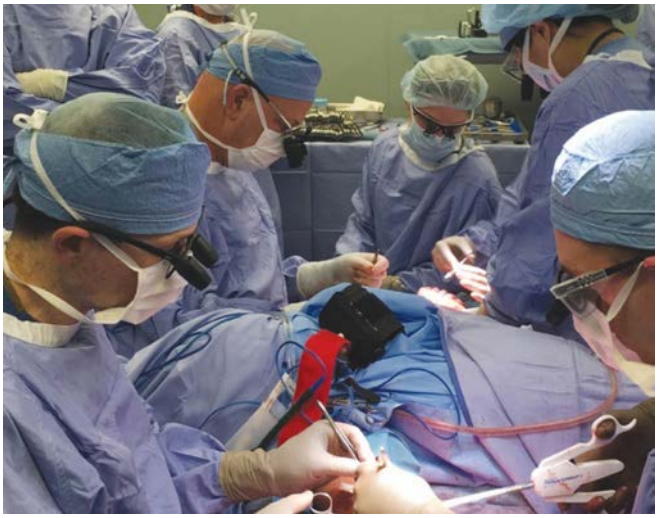
Dr. Samir Mehta continues to manage limb length differences by practicing limb lengthening using a magnetic lengthening nail in our Total Aesthetic Limb Lengthening & Extremity Reconstruction (TALLER) program. Over the past year, the company that created the internal limb lengthening nail has developed a fully weight bearing lengthening rod called the STRYDE nail. Dr. Mehta is able to utilize this nail to correct malunions, nonunions, osteomyelitis, and limb length differences by performing an osteotomy and implanting this magnetic nail. The patient is then able to go home and walk on the affected extremity immediately after surgery. At home, they use an external hand held device where they can manually lengthen the extremity 2-3 times a day up to 1mm per day until the desired length is achieved. This nail is much more patient friendly than the bulky external fixators. In addition to using this new technology on functional issues, Dr. Samir Mehta continues to promote the aesthetics portion of this program for individuals who wish to discreetly gain 3-6 inches of height in an elective bilateral limb lengthening surgery.

The POLSC also works in close conjunction with our orthopaedic joints team. Collaboration with this team includes many limb salvage surgeries after failed or infected total knee arthroplasties done here or elsewhere. We have managed to save and reconstruct several knee joints by clearing infection, if present, and then providing free flap or local tissue coverage with a total knee revision. Dr. Gwo Lee also continues to work closely with Dr. Scott Levin performing free vascularized fibular grafts (FVFG) to hips where avascular necrosis is present. They have had great success in this hip preservation surgery, helping many young healthy adults avoid a total joint prosthetic. Including FVFG and prosthetic knee reconstruction, Dr. Gwo Lee has assisted POLSC with over 30 cases in 2019!

In addition to close collaboration with our joints team, POLSC also works with our Foot & Ankle specialists, orthopaedic oncology surgeons, and vascular surgeons. The

Foot and Ankle service has seen an increase in joint cases with Dr. Daniel Farber, Dr. Keith Wapner, Dr. Kathryn O'Connor, and Dr. Wen Chao over the past year. Dr. Robert Wilson and Dr. Kristy Weber continue to be in close collaboration with POLSC in patients who have osteosarcomas with large soft tissue and orthopaedic deficits after resections. Dr. Benjamin Jackson, Dr. Timothy Clark, and Dr. Venkat Kalapatapu also work closely with POLSC to help ensure adequate blood flow to compromised limbs. Dr. Scott Levin has also increased his work in upper extremity bypass to restore adequate flow in conjunction with performing sympathectomies for severe cases of Raynaud's.

In other news, the Penn Medicine Hand Transplant program successfully performed their 3rd bilateral hand transplant in February of 2019. The vascularized composite allograft (VCA) program is run by Dr. Scott Levin and Dr. Benjamin Chang, and continues to grow as we keep getting inquiries and listing new candidates for donors. Some additional updates for POLSC include adding designated orthoplastic OR time at Presbyterian hospital. This will create uniformity in our complex patients who need more than one surgical specialty during the case. We now have access to efficiently schedule these joint cases and make limb salvage surgery more routine with Penn Medicine. We are also looking forward to the annual Penn Flap course which is a two-day long course in August held in the human tissue lab which focuses on the variety of free flaps available to use for extremity reconstruction. We have shared stories of our patient testimonials on Instagram and Facebook @ PennOrthoplastic. We hope to hold an Orthoplastic Conference at Penn Medicine within the next year and look forward to what great things the next 12 months will bring.



Dr. Scott Levin and Dr. Stephen Kovach working side by side during a bilateral hand transplant case in February 2019.

Children's Hospital of Philadelphia Update

Divya Talwar, PhD, MPH and John Flynn, MD

Pediatric Faculty


John Flynn, MD


Jason Anari, MD


Alexandre Arkader, MD


Keith Baldwin, MD, MPH, MSPT

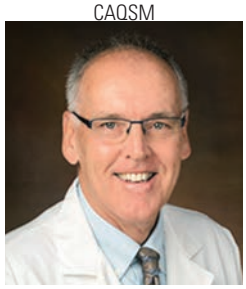

Naomi Brown, MD, FAAP, CAQSM


Patrick Cahill, MD


Robert Carrigan, MD


Benjamin Chang, MD, FACS


Richard Davidson, MD


Vincent Deeney, MD


Malcom Ecker, MD


Theodore Ganley, MD


B. David Horn, MD


J. Todd Lawrence, MD, PhD


Ines Lin, MD


Kathleen Maguire, MD


Christina Master, MD, FAAP, CAQSM, FACSM


Christopher Renjilian, MD


Wudbhav Sankar, MD


Apurva Shah, MD, MBA


David Spiegel, MD


Brian Vernau, MD, FAAP, CAQSM


Kristy Weber, MD, FACS


Lawrence Wells, MD


Brendan Williams, MD


Jennifer Winell, MD

Introduction

The Division of Orthopaedic Surgery at the Children's Hospital of Philadelphia (CHOP) had another successful and productive year of significant growth, accomplishment, and innovation. Upholding our mission and vision to provide the most comprehensive care to our patients, we have continued to expand our clinical, research, and teaching programs.

In 2019, CHOP Orthopaedics continued the Nicholson Visiting Professorship, welcomed two pediatric orthopaedic surgeons on our team, hosted major conference meetings for Food and Drug Administration (FDA) reviewers, maintained enrollment of FDA Phase IIIb investigational drug trial and a feasibility device trial, expanded our research coordinator team, obtained significant extramural funding from major funding agencies such as National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and National Science Foundation (NSF).

Clinical Program

Our orthopaedics faculty continues to expand and is currently comprised of twenty-nine Faculty, nineteen specially trained pediatric orthopaedic surgeons (fifteen operative and four non-operative), five sports medicine-trained pediatricians, two active plastic surgeons, and three transition-to-adult care faculty. Our division welcomed two new faculty members, Dr. Brendan Williams, MD (Figure 1) and Dr. Katherine Maguire, MD (Figure 2). Both Drs. Williams and Maguire joins our program as new Attending Orthopaedic Surgeon with specialization in sports medicine.

Figure 1. Brendan Williams, MD

Figure 2. Katherine Maguire, MD

Education Program

CHOP Orthopaedics currently funds four one-year clinical fellowships and one one-year research fellowship. The 2019-2020 clinical fellows are Alexa Karkenny, MD (Figure 3); Matthew Landrum, MD (Figure 4); Brian Piazza, MD (Figure 5); and Margaret Wright, MD (Figure 6). This year's research fellow is Dr. Soroush Baghdadi, MD from Iran (Figure 7). While at CHOP Dr. Baghdadi has focused his research efforts on between basic science projects related to cartilage regeneration and clinical research focused on pediatric trauma, neuromuscular conditions, and sports injuries.

To celebrate the graduation of the 2018-2019 clinical fellows, the Division hosted the Nicholson Visiting Professor Program and Fellows Graduation & Reunion in June 2018. This year's Visiting Professor was Dr. David Skaggs, of Orthopedic Surgery at the Keck School of Medicine of the University of Southern California and Chief of Orthopaedic Surgery at Children's Hospital Los Angeles. He is a nationally recognized expert in pediatric spinal deformity and trauma and currently holds the Associates Endowed Chair of Pediatric Spinal Disorders at Children's Hospital Los Angeles. The program consisted of a mix of short lectures and discussions, a cocktail reception, and research and end-of-the-year remarks from the four fellows.

Figure 3. Alexa Karkenny, MD

Figure 4. Matthew Landrum, MD

Figure 5. Brian Piazza, MD

Figure 6. Margaret Wright, MD

Figure 7. Soroush Baghdadi, MD

The 2018 Drummond Rising Star Visiting Professor was Raymond Liu, MD. Dr. Liu, an Associate Professor of Pediatric Orthopaedics at Rainbow Babies and Children's Hospital in Cleveland, Ohio, with a specialization in complex hip and limb deformity and holds the Victor M. Goldberg Endowed Chair in Orthopaedics. He gave excellent talks on maturity and predicting growth—critical to most areas of pediatric orthopaedics. The Division also continued to host visiting scholars to provide them with an opportunity to observe clinical care of pediatric patients in a high volume, academic setting.

Research Program

Basic Science and Translational Research

This past year, our basic and translational medicine researchers led by Maurizio Pacifici, Ph.D. have made impressive progress and generated novel, exciting, and far-reaching insights on key aspects of skeletal biology and growth and pediatric musculoskeletal pathologies. Our pediatric musculoskeletal research lab continues to solidify its standing with research work from Dr. Fanxin Long and Dr. Veronique Lefebvre. Our faculty members and their associates, including postdoctoral fellows, visiting scientists and research technicians, continued to tackle and fulfill the goals of several current NIH R01 grants and one Department of Defense (DOD) grant. These biomedical research projects aim to

advance current understanding of basic cellular, biochemical and genetic mechanisms that regulate the behavior and function of skeletal forming cells. These basic and key insights and observations are used to predict what may subtend and lead to pediatric pathologies including Multiple Hereditary Exostoses (MHE), Fibrodysplasia Ossificans Progressiva (FOP), Temporo-mandibular Joint dysfunction, Lamb-Shaffer syndrome, Hjadu-Cheney syndrome, and spondyloarthritis. The research Program is currently supported by 11 RO1 grants from the National Institutes of Health and generous donations from private foundations.

Center for Thoracic Insufficiency Syndrome (CTIS) Frontier Translational Research Program

Through funding from the Frontier Program, the Division's Center for Thoracic Insufficiency Syndrome (CTIS) continued developing innovative projects in translational research. The CTIS program strives to develop novel imaging techniques, construct new metrics for clinical outcomes, and establish reliable evidence to support innovative surgical strategies and devices through its research. These efforts are made possible by the collaboration of a multidisciplinary team of specialists from clinical research, image processing, informatics, and basic sciences/biomechanics. Currently, the CTIS Basic Science Lab is developing an animal model of TIS that will provide a platform for testing novel devices. The animal surgeries and biomechanics testing will be performed at Penn Vet's New Bolton Center. In addition, the CTIS team in collaboration with Medical Image Processing Group were awarded NIH R01 grant to develop novel dynamic functional metrics for TIS patients by establishing a comprehensive normative database of dMRI images and anatomic and functional models and metrics, and to translate these to develop biomarkers of TIS and of its corrective-surgery outcomes.

With the generous philanthropic support, Dr. Campbell's legacy was strengthened with the establishment of *Wyss/ Campbell Center for Thoracic Insufficiency Syndrome*, enabling CHOP to discover countless more breakthroughs in research and care for TIS children.

Genetic Research

CHOP Orthopaedics continues to work in collaboration with the Center for Applied Genomics (CAG), led by Dr. Hakon Hakonarson and Dr. Struan Grant, to compile a registry of DNA and RNA samples. These samples are obtained from patients and families with a variety of orthopaedic conditions including adolescent idiopathic scoliosis (AIS), osteochondritis dissecans (OCD) of the knee, and multiple hereditary exostoses (MHE). The team is investigating further genetic characterizations of the EXT1/EXT2 mutations harbored by each exostosis and identify second hit(s) across exostoses from the same patient. This pilot project represents the first biomedical research focused on MHE and will provide novel and broadly relevant information. The goal is to translate the findings to prognostic tools based on the severity of the disease and to identify therapeutic means to counter the effects of EXT1/EXT2 plus "second hit" mutations.

Orthopaedic Engineering

Dr. Saba Pasha, Director of Orthopedic Engineering, continues her research on the application of 3D imaging and computer simulation in surgical planning, use of predictive models in surgical decision-making, and the exploration of gait and motion analysis for a more personalized treatment. For her research, Dr. Pasha is supported by grants from POSNA and SRS.

With new emerging technology, such as the EOS x-ray imaging system, comprehensive information about a patient's condition is now readily available. Dr. Pasha's work utilizes advanced imaging and motion analysis to collect data on a range of conditions and patient populations.

Clinical Research

The Division of Orthopaedic Surgery is currently conducting more than 200 IRB-approved clinical research projects. This includes 80 prospective and observational studies. CHOP Ortho faculty are also members of a number of multicenter study groups, including the Harms Study Group (HSG), Research in Osteochondritis Dissecans of the Knee (ROCK), SCFE Longitudinal International Prospective Registry (SLIP), The Fox Pediatric Spinal Deformity Study (Fox PSDS), Pediatric ACL: Understanding Treatment Operations (PLUTO), Medial Epicondyle Outcomes Multicenter (MEMO) study and International Hip Dysplasia Institute (IHDI). Investigators within the division have been awarded funding from both internal and external sources to conduct these studies. In 2018, the Division published over 150 articles in major orthopaedic journals, including *JBJS, Lancet Neurology, JPO*, and *CORR*. Members across our division presented more than 150 presentations at international and national conferences last year alone.

The Division successfully continues to award the annual Benjamin Fox Fellowship Award for medical students who are interested in conducting a year of clinical research within orthopaedics. In July, Joshua Bram (Perelman School of Medicine at the University of Pennsylvania), Lacey Magee (Rutgers-Robert Wood Johnson Medical School) and Nishank Mehta (Rutgers New Jersey Medical School, Newark), were awarded with the fellowship (Figure 8-10).

Recognition and Achievements

Our faculty have assumed several leadership roles within the pediatric orthopaedic community over the past year.

Figure 8. Joshua Bram

Figure 9. Lacey Magee

Figure 10. Nishank Mehta

Jason Anari, MD served as international faculty member at the Salzburg Medical Seminar in Pediatric Orthopedics in Salzburg, Austria. Dr. Anari also received a new grant as co-PI from Penn Institute for Translational Medicine and Therapeutics (ITMAT) titled, "*Development and testing of deep learning algorithms for segmentation on 4D MRI to understand changes in normal thoracic dynamics during childhood maturation"*.

Alexandre Arkader, MD was the Vice Chair for the Pediatric Orthopaedic Society of North America (POSNA) Educational Course Committee and faculty member for *XITROIA Congresso Brasileiro de Trauma Ortopedico Pediatrico* in Brazil. He also serves as sub-committee chair for Global Courses. Dr. Arkader continues to serve as a reviewer for *Journal of American Academy of Orthopaedic Surgeons, Journal of Bone and Joint Surgery Essential Surgical Techniques, BMC Musculoskeletal Disorders, Journal of Pediatric Orthopaedics B and Journal of Children's Orthopaedics*. He received funding from RSNA Research & Education Foundation Seed Grant as a Co-PI for grant titled "*Osteosarcoma Imaging with UTE MRI: Validation and Optimization with CT and Histopathology Correlation*." Dr. Arkader is an active member of CORTICES study group.

Keith Baldwin, MD, MSPT, MPH is the Associate Director of Orthopaedic Trauma in the Division of Orthopedic Surgery. He currently serves as a reviewer for a number of journals including the *BMC Medical Education, BMC Musculoskeletal Disorders, BMJ Open, Journal of Pediatric Orthopaedics, Annals of Internal Medicine, Journal of Bone and Joint Surgery—American*, and the *American Academy of Pediatrics*. He also serves as an associate editor for *Journal of Orthopedic Trauma* and an editorial board member of the *American Journal of Orthopedics, Current Orthopaedic Practice* and *World Journal of Orthopedics*. Dr. Baldwin is an active member of CORTICES study group and CORTICES Research Committee.

Patrick Cahill, MD started his term as Board of Director for Pediatric Cervical Spine Study Group. He serves as Chair for Health Policy Committee and member of Governance Council at Scoliosis Research Society. He is also a member of POSNA's Quality, Safety, Value Initiative Committee. He continues to serve as an Associate Editor for *Spine Deformity Journal* and as a reviewer for the *Journal of Bone and Joint Surgery – American* and the Thrasher Research Fund. Dr. Cahill is an active member in the Harms Study Group, Pediatric Spine Study Group, and Fox Pediatric Spine Deformity study group, which are multi-center groups prospectively researching care improvements for complex pediatric spine deformities. Dr. Cahill received a new grant as co-PI from Penn Institute for Translational Medicine and Therapeutics (ITMAT) titled, "*Development and testing of deep learning algorithms for segmentation on 4D MRI to understand changes in normal thoracic dynamics during childhood maturation*". He is the Director for *Wyss/Campbell Center for Thoracic Insufficiency Syndrome*.

Robert Carrigan, MD continues to serve on the ASSH Fellows Conference Committee, AAOS Appropriate Use Committee, and POSNA Resident Newsletter Committee. He also serves as a reviewer for *Journal of Hand Surgery* and *Clinical Orthopaedics and Related Research.*

Richard Davidson, MD has continued to serve as an associate editor for Foot & Ankle, International. He also serves as a reviewer for *Clinical Orthopedics and Related Research* and *Advances in Orthopaedic Society*.

B. David Horn, MD continues to serve as a reviewer for journals, such as *Clinical Orthopaedics and Related Research (CORR), Pediatric Emergency Medicine, and Pediatrics*.

Jack Flynn, MD, Chief of the Division of Orthopaedics, continues to serve his 10-year term as a Director of the American Board of Orthopaedic Surgery. Dr. Flynn is a co-editor of *Lovell and Winter's Pediatric Orthopaedics, Rockwood's Fractures in Children, Operative Techniques in Pediatric Orthopaedics*. He is a core member of Pediatric Spine Study Group and Harms Study Group, a multicenter collaboration of researchers studying care improvements for pediatric spine deformity surgery, and serves on the Board for the Children's Spine Foundation. He also received *William Potsic Mentoring Award* from the Department of Surgery. In the past year, Dr. Flynn was also invited as the visiting professor at Northwell/LIJ Medical Center, St. Justine/University of Montreal, University of Alabama Birmingham, Vanderbilt University and Hospital for Special Surgery. He was invited as Visiting Lecturer for the Silver Anniversary of POSICON, Mumbai, India.

Theodore Ganley, MD is the Sports Medicine Director at CHOP, continued growth of clinical, research initiatives. Dr. Ganley has continued in several leadership roles with national organizations, such as the chairman for the POSNA Evidence Based Practice Committee, second vice president of the Pediatric Research in Sports Medicine (PRISM) group, co-founder and executive board member for the Research in Osteochondritis Dissecans of the Knee (ROCK) group, executive committee member for the American Academy of Pediatrics, advisory board member for the International Pediatric Orthopaedic Symposium, and program chair for the Philadelphia Orthopaedic Society. Along with his leadership roles, he continues to be actively involved in biomechanical studies utilizing cadaver specimens in collaboration with the *Biedermann Lab for Orthopaedic Research* and *Human Motion Lab*. He is leading a nationwide initiative on Tibial Spine prospective study group with 14 sites currently participating. Dr. Ganley was invited as a Visiting Lecturer for Silver Anniversary of POSICON, Mumbai, India. Additionally, he is the site leader for the FDA clinical trial for studying the efficacy and safety of autologous cultured chondrocytes on porcine collagen membrane (MACI).

John Todd Lawrence, MD, PhD continued his collaborative work with Dr. Leo Han at Drexel University. Funded by the National Science Foundation, the project focused on conducting in vitro studies for a novel cartilage repair strategy. Dr. Lawrence is an active member of sports medicine multicenter research groups such as PLUTO and he leads a 12-site study group called MEMO. He continues to serve as a reviewer for the *American Journal of Sports Medicine (AJSM)* and *Journal of Shoulder and Elbow Surgery (JSES)*.

Dr. Lawrence received a new grant as co-PI from NIH titled "*A Low-Cost, Collaborative Tool for the Tracking of Youth Activities to Reduce Risk of Physical Injury*".

Wudbhav Sankar, MD is the Director of the Young Adult Hip Preservation Program at CHOP. Dr. Sankar currently serves as the chair of the POSNA Fellowship committee and co-director of the International Hip Dysplasia Institute. He remains active in several study groups including Academic Network of Conservational Hip Outcomes Research (ANCHOR), SCFE Longitudinal International Prospective Registry (SLIP) and International Perthes Study Group (IPSG). Dr. Sankar is currently a reviewer for the *Journal of Bone and Joint Surgery, Journal of Pediatric Orthopaedics,* and an Editorial Board Reviewer of *Techniques in Orthopaedics*. Dr. Sankar was also the recipient of *POSNA Special Effort and Excellence Award.*

Apurva Shah, MD, MBA continues his tenure as the Director of Clinical Research. He continued to serve as co-PI on the grant from Orthopaedic Trauma Association titled, "*Opioid utilization after rotational ankle fractures*". He continued to serve as the team leader and traveled to Sigua Tepeque, Honduras for a pediatric hand surgery medical mission. Dr. Shah is currently a reviewer for the *Journal of Bone and Joint Surgery* and *Journal of Pediatric Orthopaedics.* Dr. Shah served as international faculty member at the Salzburg Medical Seminar in Pediatric Orthopedics in Salzburg, Austria.

David Spiegel, MD continued his work with the Children's Hospital of Philadelphia Global Health Pilot Grant. He currently is the chair for International Scholars Program at the American Academy of Orthopaedic Surgeons (AAOS). He served as a visiting lecturer at McGill University. Dr. Spiegel continued to be an active academic internationally, giving lectures in Iraq, Nepal and Pakistan.

Lawrence Wells, MD is the Associate Director of the Sports Medicine Performance Center at CHOP and Director of Quality, Safety, Value, and Patient Experience in the Division of Orthopaedic Surgery. Dr. Wells currently serves as the President of Board of Directors for the Philadelphia Orthopaedic Society.

Chief's Corner: Academic Chief Update

Mark D. Hasenauer, MD, Matthew Sloan, MD, and Daniel Gittings, MD

Another year has quickly come and gone, and collectively, we feel privileged to have served as the academic chief residents for 2019-2020. First, we would like to thank Drs. Levin, Farber, Israelite, Ahn and Moretti for their support and leadership throughout the year. Special recognition is reserved for Dr. Israelite, who stepped down from his long-standing tenure of Program Director this year. Dr. Farber has quickly transitioned into his new role of Program Director with the help of Dr. Moretti who will be serving as Assistant Program Director. We would also like to thank the faculty, staff and our co-residents for their hard work while continuing to work every day to make Penn Orthopaedics a great place to train. This year has certainly been a unique one, but one in which our residency has been able to accomplish several changes in our educational curriculum, expansion of our residency program, and the continuation of our robust visiting professor curriculum.

The biggest update and change came at the beginning of the academic year. With the closure of Hahnemann Hospital, we welcomed five additional residents to our program. They were quickly integrated into the department and have played an integral role throughout the year. The new residents provided us with a unique opportunity to permanently expand our resident complement to nine residents which would allow for increased flexibility and the opportunity for new rotations. We are hoping to hear back in the near future regarding our request to a permanent expansion of nine residents per year. We hope to implement additional rotations including dedicated research blocks, elective opportunities and the potential for further international work with the addition of a ninth resident per year.

The resident education program has seen many positive signs of growth. Utilization of the Penn Human Tissue Lab has drastically increased. This year we have more than doubled the number of cadaver led sessions and increased the number of specimens per session, allowing each resident increased hands-on participation. We have had sessions ranging from peripheral nerve microsurgery techniques to upper and lower extremity osteosynthesis to primary and revision arthroplasty.

International orthopaedic work continued this year, where two chief residents (Ryan Charette and Rikesh Gandhi) accompanied Dr. Samir Mehta with a group out of Rush University in Chicago to provide orthopaedic care in the Dominican Republic for the second year in a row. While there, they were able to take care of those underprivileged patients who would otherwise be unable to receive care.

Our robust visiting professor curriculum continued this year, with leaders in the field coming from across both the United States and the globe to lecture and educate the department. Each of the speakers provided our department with stimulating lectures and enhanced resident education with cadaveric dissection or technique demonstrations, case presentations, or journal clubs. We were delighted and honored to have these giants in the field and thoroughly enjoyed having them visit.

At the end of our Chief year, we were confronted with the COVID-19 pandemic. A new schedule was devised and put into place that limited resident exposure while still allowing us to provide care for our orthopedic patients. While case volume decreased due to cessation of elective procedures, we worked with the newly elected rising chiefs to design a virtual daily education curriculum which included daily subspecialty conferences, journal clubs, and "fireside chats" on the fracture of the night with Drs. Mehta and Donegan. We would like to thank the faculty for their support and help with the education schedule.

As our tenure as academic chief residents is coming to a close, we would personally like to thank all of the Penn Orthopaedic surgery residents for their dedication and hard work. We would also like to express our gratitude to our program leadership and faculty who have been excellent mentors and leaders during our time here at Penn. We wish the best for next year's chiefs and look forward to the growth and new heights the program will reach.

Sincerely,

Mark Hasenauer, MD
Matthew Sloan, MD
Daniel Gittings, MD

2019 Intern Bootcamp

Stephen R. Barchick, MD

As is standard practice, new interns arrived in Philadelphia for orientation during the first week of June. This year, however, our newly minted and motivated physicians enjoyed the addition of an introductory orthopaedic course. Dr. Derek Donegan, MD, MBA (Penn Orthopaedic Trauma) coordinated a city-wide course entitled *Future Leaders: OrthoCamp 2019.* The course co-director was Dr. Chris Haydel, MD, from Temple University Orthopaedic Trauma Service and was offered to interns from five orthopaedic residencies programs (Drexel, Einstein, Penn, Temple, PCOM).

The two-day course was hosted with the assistance of DePuy Synthes and the Johnson and Johnson Institute. Training occurred at The Convene in Center City Philadelphia on June 14-15th, 2019. The event featured attendings from six health systems across the Delaware Valley.

On Friday after introductions, the course began with a team-building exercise focused on using stability design principles. The junior residents collaborated quickly to construct their designs (blinded for future academic use), and then deconstruct the design advantages and disadvantages while discussing relevant principles of fixation used in orthopaedic surgery. The most important part of the evening came next with a dialogue led by Dr. J. Milo Sewards, MD (Temple University Hospital) on the qualities and expectations of junior residents. Dr. Seward emphasized developing productive team-building habits early in one's career as a physician.

Dr. Jaimo Ahn MD, PhD (Penn Orthopaedic Trauma) led a section of lectures on "Keeping Patients Alive". Topics included bleeding, thromboembolism and myocardial infarction, necrotizing fasciitis, and a lecture by Dr. Donegan on pelvic ring stabilization. A second series of lectures followed on "Saving Limbs" which stressed management of a pulseless extremity. Dr. Kathryn O'Connor (Penn Foot and Ankle Service) added instruction on compartment syndrome diagnosis and management. The formal events for the evening concluded with an opportunity to utilize virtual reality orthopaedic training simulators (Image #1). Following this, the attendings took the junior residents to *Spin* for a chance to relax, build camaraderie, and test hand-eye coordination playing ping-pong.

To acquaint the new physicians with the expectations of working hard late and being ready to rise before sunrise to accomplish the days tasks, Saturday started early. The day's events included additional lectures, but the emphasis was on closed reduction and management of injured limbs, and simulations of internal fixation using Sawbones®. The residents were given short lectures and each type of splint and then given the opportunity to practice its application. Wrist and forearm splints including management of distal radius fractures, coaptation splits for humeral shaft fractures

Dr. Andrew Summers simulates open reduction internal fixation as Dr. Kelsey Young observes.

(Image #2), ankle fracture splinting including both long and short-leg splints were utilized.

Following the splinting lab, focus was turned to methods of internal and external fixation used in orthopaedic surgery

Dr. Jordan Cohen mid-phase coaptation splint application by Dr. Steven Zhang.

Dr. Jaimo Ahn supervises fracture fixation and motivates the interns through his selected instructional attire.

today. A presentation on external fixation of the lower extremity, with a lab placing a knee-spanning external fixator was conducted (Image #3). This was followed by Sawbones® skill development for lag screw placement utilizing both by design and by technique methods. Dr. Donegan demonstrated employing compression plating in the operating room. The morning concluded with discussion between residents over lunch.

The first session of the afternoon underscored different problems physicians face in the management of musculoskeletal disease by sub-specialty area. Dr. Ahn led a course focused on management of pelvis and hip problems which junior residents can expect to encounter in the first years of residency. Dr. Stephen Liu MD (Penn Hand Surgery) instructed the learners on some of the cases they can anticipate fielding from the emergency departments across Philadelphia when holding the consult pager. Additional courses included: assessing a polytrauma patient, neurovascular examinations of upper and lower extremities, knee, shoulder and elbow, and pediatric examination and parental management

Dr. O'Connor led the seminar on "Urgent Conditions", as other faculty contributed with a variety of lectures. Junior residents received lectures on fracture/dislocations, pediatric emergencies, urgent spine issues, and femur emergencies including young adult and geriatric hip fractures. Dr. O'Connor concluded with some thoughts on how to best management the expectations for junior residents with emphasis on

2019 intern class: (L to R) Dr. Barchick, Dr. Weintraub, Dr. Summers, Dr. Young, Dr. Zhang, Dr. Masada, Dr. Myerson, Dr. Cohen.

approaching each situation with humility and a focus on increasing one's knowledge.

The final education block of the course was led by Dr. Liu, with a plethora of courses focused on the art of being a good physician, good surgeon, and a good team member. Dr. Sewards, the Temple University Residency Program Director discussed professionalism and collegiality—which are of utmost importance in residency. Junior residents also enjoyed classes on active learning tips and tricks and emotional intelligence. The block concluded with a thought-provoking discussion—filled with patent pauses—led by Dr. Ahn. While much was learned, as has been the case during his tenure at Penn, interns left asking more questions than they had before the lecture. One might suspect this was his intent all-along.

The event concluded with final review and feedback led by the course leads from Penn and Temple. The intern class is thankful for all the effort Dr. Donegan put into organizing this two-day course. It offered the opportunity to gain additional exposure to orthopaedic management before the official start of clinical duties in a controlled and guided setting. This year's intern class (Image #4) started early in building camaraderie and developing a collaborative culture occur because of events like this. We are fortunate to have so many faculty members who value education and are willing to share their time and expertise for all members of the residency program regardless of their learning level, especially Dr. Ahn, Dr. Liu, and Dr. O'Connor.

Penn Faculty:
Dr. Jaimo Ahn, MD, PhD (Trauma and Fracture Division)
Dr. Derek Donegan, MD, MBA (Trauma and Fracture Division)
Dr. Stephen Liu, MD (Hand Division)
Dr. Kathryn O'Connor, MD, MSPT (Foot and Ankle Division)

Programs in Attendance:
Albert Einstein Health System
Hahnemann University
University of Pennsylvania
Philadelphia College of Osteopathic Medicine
Temple University

June 27, 2019: Leung Lectureship

Dr. John G. Seiler, III

Tendon repair and reconstruction of wrist, elbow, and brachial plexus at Georgia Hand, Shoulder & Elbow; Clinical Professor of Orthopaedic Surgery at Emory University

Born in Louisville, KY, Dr. Seiler attended medical school at the University of Louisville and completed his Orthopaedic Surgery training at Vanderbilt University. After a fellowship at Harvard he settled in Atlanta, GA where he has been in practice since 1990.

Now a Clinical Professor of Orthopaedic Surgery at Emory University in the Department of Orthopaedic Surgery, he is also the managing partner at Georgia Hand Shoulder and Elbow and Georgia Surgical Center on Peachtree.

He is a director of the Orthopaedic Surgery Service Line at Piedmont Hospital where he manages the program for quality metrics in Orthopaedic Surgery and was the 54th President of the American Board of Orthopaedic Surgery. He is the President of the American Foundation for Surgery of the Hand and a member of the Council for the American Society for Surgery of the Hand.

A continuously active clinician, Dr. Seiler's research interests have focused on tendon and nerve repair after injury. He was the recipient of the Marshall Urist Award for his work on Flexor Tendon Grafting that elucidated differences in tendon survival characteristics after transfer to the synovial space.

The University of Pennsylvania Department of Orthopedics was honored to welcome Dr. Seiler as speaker for the Leung Lectureship on June 27, 2019. In "It's Only a Stinger," Dr. Seiler spent his first hour discussing the epidemiology, anatomical considerations, and treatment options related to "stinger" injuries in high school, college, and professional athletes. His lecture highlighted how serious these injuries can be, but also pointed towards several treatment strategies employed by his group and by other specialists in the field.

Dr. Seiler offered a valuable perspective in his second lecture "Think About How You're Thinking," and then finished the morning by leading anatomical dissection and demonstration of flexor tendon repairs with the residents in the human tissue lab.

June 27, 2019: "It's Only a Stinger," Dr. John Seiler speaking during the Leung Lectureship for University of Pennsylvania Department of Orthopaedic Surgery Grand Rounds

Dinner on June 26, 2019. Left to right: Benjamin Gray, MD; Stephen Liu, MD; David Steinberg, MD; John G. Seiler III, MD

August 7, 2019

Dr. Bauback Safa

Reconstructive microsurgeon and hand surgeon at the Buncke Clinic; Clinical Assistant Professor of Surgery at Stanford and UCSF divisions of plastic surgery

Dr. Safa is a reconstructive microsurgeon and hand surgeon at the Buncke Clinic. He studied music at the University of Virginia as an Echols scholar, completed medical school and plastic surgery at Stanford, followed by a fellowship in hand and microsurgery at the Buncke Clinic where he has been on staff since 2008. His clinical focus is on complex reconstruction of the hand, peripheral nerve surgery, lower extremity reconstruction, and phalloplasty. Dr. Safa is the 2019 American Society for Reconstructive Microsurgery Godina Fellow.

The University of Pennsylvania Department of Orthopedics was honored to welcome Dr. Safa for Grand Rounds on August 7, 2019.

Dr. Safa's talks included "Advances in Replantation: Revisiting Conventional Wisdom" and "Decision-Making in Complex Upper Extremity Reconstruction: Thinking Beyond Step One."The cases and papers presented by Dr. Safa showed just how wide a breadth of upper extremity injuries may be replanted with excellent cosmetic as well as functional outcomes and truly did challenge the "conventional wisdom" of what might have once been thought possible. Dr. Safa also provided valuable insight into his experience in helping set a high bar for what can be thought of as the standard of care for these injuries, utilizing a methodical, forward-thinking team- and systems-based approach to optimize efficiency and communication both inside and outside the operating room to ensure the best outcome for the patient not just for that day, but also for down the road.

Dr. Safa concluded the morning by leading the residents in the human tissue lab in anatomical dissection, with review of intrinsic hand flaps as well as other upper extremity reconstruction options.

August 7, 2019: "Advances in Replantation: Revisiting Conventional Wisdom," Dr. Bauback Safa speaking at University of Pennsylvania Department of Orthopaedic Surgery Grand Rounds.

September 12, 2019

Dr. David Lowenberg

Clinical Professor of Orthopaedic Surgery at Stanford University

David W. Lowenberg, MD is Clinical Professor of Orthopaedic Surgery at the Stanford University School of Medicine and served as the Chief of the Orthopaedic Trauma Service at Stanford from June 2010 until January 1, 2016. He is a past President of the Limb Length-ening and Reconstruction Soc-iety of North America, Past President of the Foundation for Orthopaedic Trauma and immediate Past-President of the Osteosynthesis and Trauma Care Foundation International (OTC International) which is composed of 22 chapters around the world with a membership of over 4,000 orthopaedic traumatologists. His clinical and research interests are in the treatment of osteomyelitis and nonunions, fracture biomechanics, and basic science of musculoskeletal infections and biofilm. He is well published in the field of limb salvage and the treatment of devastating limb injuries. He is also co-director of the Buncke Microsurgical Research Laboratory, where his research was on perfecting techniques for limb transplantation via immunotolerance. He has over 50 peer reviewed articles and book chapter publications and over 400 regional, national, and

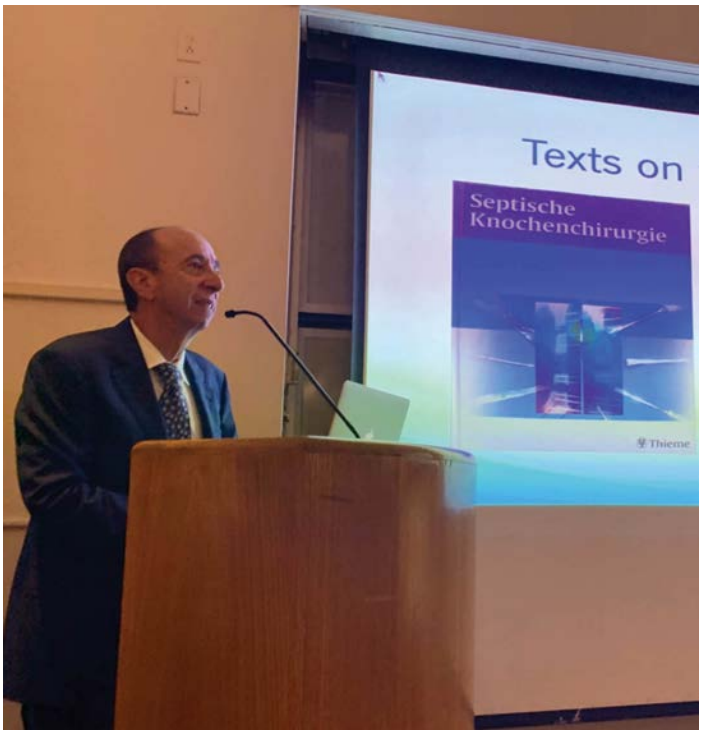
international lectures on osteomyelitis, nonunions, malunions, and trauma. He has an active basic science research lab studying musculoskeletal infection and biofilm physiology and modulation.

Dr. Lowenberg received his undergraduate degree at UC Davis, his medical degree at UCLA and did his internship and residency in orthopaedic surgery at UCSF.

The University of Pennsylvania Department of Orthopedics was honored to welcome Dr. Lowenberg for Grand Rounds on September 12, 2019.

Dr. Lowenberg's talks in the first half of the morning included "Antibiotic Stewardship in the Treatment of Chronic Osteomyelitis: Entering the Post-Antibiotic Era" and "My Last 1,000 Nonunions: What I Have Learned." Dr. Lowenberg provided valuable insight into his experience in the management and treatment of traumatic injuries complicated by acute or chronic infection and challenged the notion of six or more weeks of intravenous antibiotics being a "one-size-fits-all" treatment for osteomyelitis – on the contrary, and in the right patient, he argued, a much shorter course could be sufficient. Dr. Lowenberg also highlighted the body's own role in fighting, or at other times achieving homeostasis with bacterial organisms.

Dr. Lowenberg concluded the morning with lively case presentation and discussion with the residents.



September 12, 2019: Dr. David Lowenberg speaking at University of Pennsylvania Department of Orthopaedic Surgery Grand Rounds.

November 21, 2019

Dr. Thomas Wright

Frank P. Glowczewskie Professor of Orthopaedic Surgery at the University of Florida, Director of Interdisciplinary Center for Musculoskeletal Training & Research; Division Chief, Hand and Upper Extremity

Dr. Thomas W. Wright obtained his MD degree from the University of Florida in 1983. He completed his Orthopaedic Residency from the University of Florida in 1989. Dr. Wright was given an Appointment as a Clinical Instructor with the University of Florida from 1988-1989. He completed his Hand Fellowship training in 1990 at the Mayo Clinic in Rochester, Minnesota. Dr. Wright is ABOS certified and has a Certificate of Added Qualifications for Surgery of the Hand.

The University of Pennsylvania Department of Orthopedics was honored to welcome Dr. Wright for Grand Rounds on November 21, 2019.

Dr. Wright's talks in the first half of the morning included "Intra-Operative Surgical Navigation: Is it Worth the Fuss?" and "Proximal Humerus Fractures – Avoiding Complications – Technical Tips."

Dr. Wright shared his experience with utilizing intra-operative surgical navigation for shoulder arthroplasty, detailing his observations and patient outcomes both before and after he began to incorporate surgical navigation into his practice. He then went on to present several cases of patients presenting with proximal humerus fractures, which served to highlight several key learning points regarding management of these injuries that can sometimes be deceivingly tricky.

Dr. Wright concluded the morning with lively case presentation and discussion led by the residents.

January 16, 2020: Annual Gentchos Lectureship

Prof. Andrew Carr

Nuffield Professor of Orthopaedics, Director of the Musculoskeletal BRC Theme, Director of the Botnar Research Centre

Professor Andrew Carr DSc FRCS FMedSci is the Nuffield Professor of Orthopaedic Surgery at the University of Oxford where he founded and directs the Botnar Research Centre, one of the world's leading musculoskeletal disease research Institutes.

Professor Carr has focused his research on the development and evaluation of surgical implants and technologies, including joint replacements, minimally invasive surgery and tissue engineering scaffolds. He has pioneered the importance of patients' views in assessing the outcome of surgery and the Oxford Scores, which he co-invented and are now used globally to assess patient outcomes and direct health policy. He is author of over 450 papers and review articles including more than 20 in the Lancet and BMJ which have been cited over 26,000 times. He has been chief investigator of multicentre randomised controlled trials of surgery and has improved the National infrastructure for clinical trials of surgery in the UK. His clinical trial research has included defining the indications for, and ethics of, placebo surgery controls in surgical trials.

He has held senior leadership positions in the University and NHS sectors in the UK and was Divisional Director of the Nuffield Orthopaedic Centre during the merger of all Oxford's hospitals to form Oxford University Hospitals NHS Foundation Trust. He has held trustee and advisory roles with charities Universities and Research Councils internationally.

The University of Pennsylvania Department of Orthopedics was honored to welcome Professor Andrew Carr for Grand Rounds on January 16th, 2020 for the annual Gentchos Lectureship.

Prof. Carr's talks in the first half of the morning included "Improving Evidence for Orthopaedic Surgery" and "Bioactive Surgical Implants: The Journey from Laboratory to Clinic."

Prof. Carr's shared his research experiences, which ranged from laboratory-based basic science research, to large scale multi-center randomized clinical studies. His clear leadership on these fronts served as an unspoken call to action for those in the audience—a challenge to encourage everyone to push the old boundaries of orthopaedic research from what previously might have been thought "feasible" or "practical" and to raise the bar to keep finding better answers to clinical questions that are critical for providing the best patient care possible.

Prof. Carr concluded the morning by moderating an exciting ethical debate amongst the residents regarding the usage of placebo controls in randomized surgical trials.

February 27, 2020

Dr. Edward McDevitt

Captain (Retired), US Navy; former Chief of Sports Medicine and Brigade Medical Officer at the United States Naval Academy and Chief of Surgery at Anne Arundel Medical Center

Edward R. McDevitt M.D. a native Clark NJ, attended Bucknell University, and is a graduate of Hahnemann Medical College. His Orthopaedic training was done at Portsmouth Naval Hospital and 12 of his 24 years of active duty service were spent at the United States Naval Academy as Chief of Sports Medicine and Brigade Medical Officer He continues as a volunteer Team Physician for the Navy men's and women's basketball teams. For 12 years he was the Orthopaedic Surgeon for the US Congress and the Supreme Court. He was previously the Chief of Surgery at Anne Arundel Medical Center. He is on the Editorial Board of the American Journal of Sports Medicine and serves on positions of Leadership on multiple Orthopaedic Organizations.

As a medical history buff, he has given talks about the Plague in Florence, the American Civil War to physicians in the US, and Ireland, and World War II injuries in France, on D-Day. His latest talks include the Dangers of Opioids, Concussions, Electronic Cigarettes, and Physician Suicide, a growing epidemic. He teaches courses on the History of Medicine at the University of Maryland, College Park and the University of Maryland Medical School. He presently works in the Annapolis Hand Center.

The University of Pennsylvania Department of Orthopedics was honored to welcome Dr. Edward McDevitt for Grand Rounds on February 27th, 2020.

Dr. McDevitt's talks in the first half of the morning included "Is Football Too Dangerous?" and "Physician Suicide: Time to

Act." These topics are not necessarily the easiest to discuss – but they are important – and the candid and heartfelt manner in which Dr. McDevitt shared his experiences and thoughts related to both subjects was welcome by all.

Dr. McDevitt concluded the morning with an informal discussion with the residents in which he recounted some of the eye-opening and humbling experiences he had during his time serving as Orthopaedic Surgeon for the US Congress and the Supreme Court for 12 years. He also took a few moments to impart insights from medical history, such as describing how events like the Civil War were actually instrumental in revolutionizing healthcare delivery as it had been known at the time and how those changes helped to bring about the modern healthcare system as we know it today.

Class of 2010 Alumni Residents—Where are they now?

Kelsey Bonilla, MD

Meira Z. Yeger-McKeever, MD

Fellowship: Sports Medicine at Union Memorial Hospital (Baltimore, MD)
Current Employment: Mohawk Valley Health System (Utica, NY)

How has training at Penn impacted your practice?

My experience at CHOP inspired me to become a pediatric sports medicine specialist, which is an area of expertise that is new to my community. I carry a lot of principles I learned from Dr. Flynn and Dr. Mehta into my practice as well.

What have you learned in the first decade of practice?

The first decade of practice has taught me that you never stop learning—from your patients and your peers.

What advice would you give residents?

I would tell residents, surgery is fun but don't underestimate what you learn from clinic. Soon you will be on your own and have to figure out what to do with your patients after you've diagnosed them or after you've operated on them.

Julia Kenniston, MD

Fellowship: Hand & Upper Extremity at Brown University/ Rhode Island Hospital
Current Employment: Plymouth Bay Orthopedic Associates (Plymouth, MA)

How has training at Penn impacted your practice?

Being at Penn helped give me the solid foundation for being successful in my practice on many levels. The Socratic method of teaching (while painful at the time) taught me critical and creative thinking, which is essential during difficult OR cases or determining complex diagnoses. Being a resident on busy services also helped me to be more efficient and effectively multitask. In addition, the Penn 'network' is great to be a part of and I was fortunate to work with many amazing and talented co-residents, fellows, and attendings. They are not only wonderful people, but also great resources.

What have you learned in the first decade of practice?

There are many things that I have learned over the past 10 years that are too numerous to list here, so I'll include the most noteworthy learning points. The first is that it is significantly more stressful being the attending than being in training. Every patient that you see is directly affected by the decisions that you make and become a part of you. It makes the highs higher and the lows lower. Second, there is a vast amount of the 'business of orthopedics' that I was unaware of and am learning as I go. The third is the importance of being involved with the community that you serve and using your role to affect change. This is true at the local, national, and global level.

What advice would you give residents?

Enjoy and appreciate your time at Penn. You are on the path to a successful and happy life and career. It is a remarkable place with amazing attendings. There is much to be learned there. At times, it can seem crazy and overwhelming, but it makes you more resilient and able to more easily manage life after residency. Finally, life balance is essential to maintain. While work is takes up the majority of our waking hours, the most important part of life is family and friends. Take time to enjoy and relax with your colleagues, friends, and family.

Jonathan P. Van Kleunen, MD

Fellowship: Mississippi Sports Medicine and Orthopedic Center
Current Employment: University Orthopedics Center (Altoona, PA)

Nirav Pandya, MD

Where did you do fellowship?
Rady Children's Hospital in San Diego

Where are you currently practicing?
I am currently the chief of pediatric orthopedics at UCSF.

How has training at Penn impacted your practice?
Penn tremendously impacted the manner in which I practiced orthopedic surgery. Through mentors such as Dr Ganley, Dr Metha, and Dr Sennett, I was prepared to become an academic orthopedic surgeon. I learned to operate independently, practice efficiently, and build an academic career. Without Penn, this would not have occurred.

What have you learned in the first decade of practice?
I think more than anything else is that you are constantly learning and adapting to the patients in front of you. It is important to be humble and learn from your mistakes.

What advice would you give residents?
Never stop learning. Understand your limitations. Prepare for every surgical case you are going to do. Don't be afraid to ask for help.

Stephan G. Pill, MD

Where did you do fellowship?
Steadman Hawkins Clinic

Where are you currently practicing?
Prisma Health (Greenville, SC)

How has training at Penn impacted your practice?
The high complexity of cases and exceptional work ethics of all attendings prepared me for a "turn key" successful orthopaedic practice. After 7 years in private practice, I returned to the academic sector due to the long-lasting mentors I made at Penn. I live everyday to try and emulate the teaching of the Penn faculty. I'm forever in debt to my friends and teachers there.

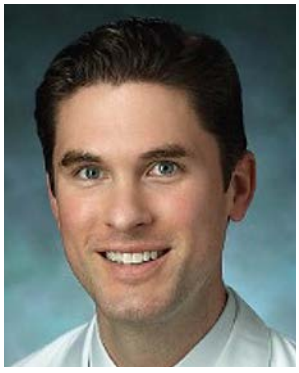
What have you learned in the first decade of practice?
It is harder to teach well than do surgery well.

What advice would you give residents?
It is best to always have more questions than answers. Never stop the passion for questioning and learning.

Derek Dombroski, MD, MS

Fellowship: Parkland Health and Hospital System (Dallas, TX)
Current Employment: Island Orthopedics (Honolulu, HI)

J. Stuart Melvin, MD



Fellowship: Orthopeadic Trauma at Carolinas Medical Center, Hip and Knee Reconstruction at OrthoCarolina
Current Employment: Washington Orthopaedics and Sports Medicine (Washington, DC)

Jesse Torbert, MD

Where did you do fellowship?
Shock trauma

Where are you currently practicing?
VCU (Richmond, VA)

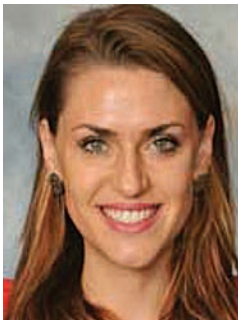
How has training at Penn impacted your practice?
The attention to detail that the Penn residency (and the litigious nature of practicing in Philadelphia) instilled in me is an asset to my practice.

What have you learned in the first decade of practice?
Just try to do the right thing, treat people like family, and you will have no shortage of patients.

What advice would you give residents?
Read more, see more cases, scrub cases you are not interested in, learn everything you can while you have someone above you to teach you.

Current Residents

Clinical Year 5 Resident Spotlight



Blair Ashley, MD*

Hometown: Pittsburgh, PA
Undergraduate: The College of William & Mary
Medical School: University of Pittsburg School of Medicine
Residency Highlights: Getting to work with—and to befriend—my two classes, an enlightening year in the lab with Drs. Mauck and Dodge, and the unmatched clinical opportunities and amazing mentorships that enabled me to become a confident and capable surgeon.
Future Directions: Rothman Institute for Adult Reconstruction Fellowship

Annie Ashok, MD

Hometown: Philadelphia, PA
Undergraduate: University of Pennsylvania
Medical School: Thomas Jefferson University–Sidney Kimmel Medical College
Residency Highlights: The opportunity to work with a group of highly motivated and talented residents, and the privilege of learning from exceptional mentors and leaders in the field.
Future Directions: Hand Surgery Fellowship at Baylor

Ryan Charette, MD

Hometown: Springvale, ME
Undergraduate: University of Connecticut
Medical School: University of Connecticut School of Medicine
Residency Highlights: When Sloan forgot to show up for his second day of Step 3 and had to retake and repay for the test.
Future Directions: Adult reconstruction fellowship at Columbia

Rikesh Gandhi, MD

Hometown: Roslyn, NY
Undergraduate: Boston College
Medical School: Duke University School of Medicine
Residency Highlights: Mission trip to the Dominican Republic, operating with my co-residents, PGY5 year
Future Directions: Hand and Upper Extremity Fellowship at Beth Israel Deaconess Medical Center

Daniel Gittings, MD*

Hometown: Portsmouth, RI
Undergraduate: Providence College
Medical School: Boston University School of Medicine
Residency Highlights: Learning and developing lifelong friendships with colleagues and mentors during residency
Future Directions: Hand Fellowship at University of Southern California

Mark Hasenauer, MD

Hometown: Rochester, NY
Undergraduate: Boston College
Medical School: New York Medical College
Residency Highlights: Getting to know, learning from, and operating with my co-residents.
Future Directions: Adult Reconstruction Fellowship at Anderson Orthopaedic Clinic

*Indicates Resident is in the 6-year Research Track

Matthew Sloan, MD, MS

Hometown: Beverly, MA
Undergraduate: University of Massachusetts
Medical School: University of Massachusetts Medical School
Residency Highlights: Learning from leaders in every subspecialty of orthopedics, side by side with the brightest residents in the country. Getting married, having my first child, and spending 5 years in Philadelphia, which was an amazing city.
Future Directions: Fellowship at Brigham & Women's Hospital in adult reconstruction, hoping to stay in the greater Boston area to practice and be near family

Andrew Tyler, MD, PhD

Hometown: Dallas, TX
Undergraduate: Harvard University
Medical School: University of Texas - Dallas Southwestern Medical School
Residency Highlights: Harper Tyler, born 3/10/19. Beers with co-residents. Snowstorm intern year. AO Basic in Chicago. The OTA/EOA circuit. FOT in Las Vegas.
Future Directions: Orthopaedic trauma fellowship at Vanderbilt University in Nashville, Tennessee.

Matthew Winterton, MD

Hometown: Atlanta, GA
Undergraduate: Brigham Young University
Medical School: Perelman School of Medicine at the University of Pennsylvania
Residency Highlights: Receiving over $350,000 in grants and starting a biomedical device company with Dr. Levin
Future Directions: Rush University for Hand Surgery Fellowship

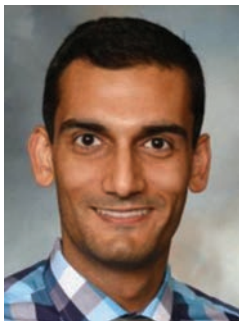
*Indicates Resident is in the 6-year Research Track

Clinical Year 4 Residents

Gerald Andah, MD

Undergraduate:
University of Pennsylvania

Medical School:
Perelman School of Medicine University of Pennsylvania



Adnan Cheema, MD*

Undergraduate:
University of Missouri-Kansas City

Medical School:
University of Missouri-Kansas City School of Medicine

Michael Eby, MD, MS*

Undergraduate:
University of Pennsylvania

Medical School:
Georgetown University School of Medicine

Chelsea Hendow, MD, MS

Undergraduate:
Univ. of CA—Los Angeles

Medical School:
New York Medical College

Christina Nypaver, MD

Undergraduate:
Univ. of Notre Dame

Medical School:
Loyola Univ.—Chicago Stritch School of Medicine

William Ryan, MD

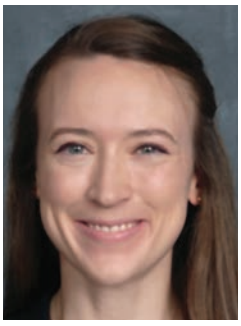
Undergraduate:
Muhlenberg College

Medical School:
Drexel University

Christopher Scanlon, MD, MS

Undergraduate:
Univ. of So. Carolina—Columbia

Medical School:
Drexel University College of Medicine



Kimberly Stevenson, MD, MS

Undergraduate:
Univ. of Delaware

Medical School:
Georgetown University School of Medicine

Matthew Webb, MD

Undergraduate:
Harvard College

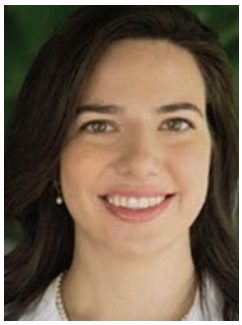
Medical School:
Yale School of Medicine

*Indicates Resident is in the 6-year Research Track

Clinical Year 3 Residents

Sarah Blumenthal, MD
Undergraduate:
Harvard University
Medical School:
University of California–Los Angeles

Matthew Counihan, MD, MS*
Undergraduate:
Univ. of Richmond
Medical School:
Drexel University College of Medicine



Agnes Dardas, MD, MSc
Undergraduate:
Harvard University
Medical School:
Washington University in St. Louis

Martin Griffis, MD
Undergraduate:
Temple University
Medical School:
Drexel University

Brandon Haghverdian, MD
Undergraduate:
University of California–Irvine
Medical School:
University of California–Irvine

Yehuda Kerbel, MD
Undergraduate:
La Salle University
Medical School:
Drexel University

Liane Miller, MD*
Undergraduate:
Univ. of CA—Santa Barbara
Medical School:
Univ. of CA—San Francisco School of Medicine

Eric Pridgen, MD, PhD
Undergraduate:
University of Delaware
Medical School:
Stanford University

Ivan Zapolsky, MD, MS
Undergraduate:
Tulane University
Medical School:
Tulane University

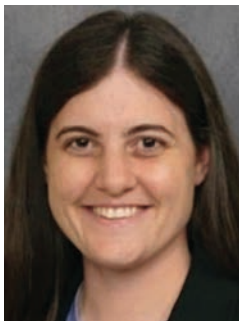
Research Year

Kelsey Bonilla, MD*
Undergraduate:
Rutgers University
Medical School:
Perelman School of Medicine at University of Pennsylvania

George Fryhofer, MD, MTR*
Undergraduate:
Harvard University
Medical School:
Perelman School of Medicine at University of Pennsylvania

*Indicates Resident is in the 6-year Research Track

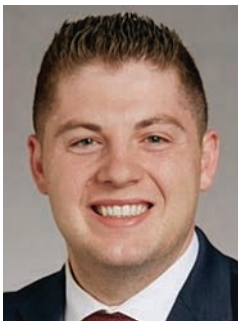
Clinical Year 2 Residents



Lauren Boden, MD

Undergraduate:
Pomona College

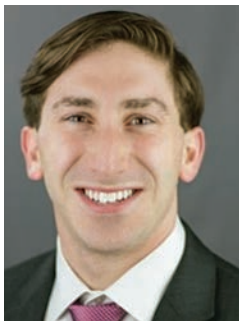
Medical School:
Emory University



Ryan DeAngelis, MD

Undergraduate:
The College of New Jersey

Medical School:
Cooper Medical School of Rowan University



David Falk, MD

Undergraduate:
University of Michigan

Medical School:
George Washington University

Sachin Gupta, MD*

Undergraduate:
George Washington University

Medical School:
George Washington University

Joseph Koressel, MD

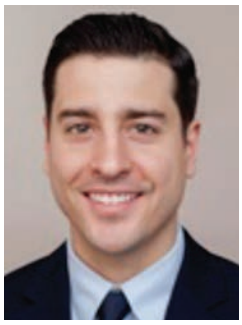
Undergraduate:
University of CA - Davis

Medical School:
Weill Cornell

Viviana Serra Lopez, MD, MS

Undergraduate:
Mass. Inst. of Technology

Medical School:
University of Puerto Rico



Gregory Minutillo, MD

Undergraduate:
James Madison University

Medical School:
Tulane University

Brian Perez, MD

Undergraduate:
Rutgers University

Medical School:
Albert Einstein

Matthew Stein, MD, MS*

Undergraduate:
Univ. of Maryland

Medical School:
Georgetown University

*Indicates Resident is in the 6-year Research Track

Clinical Year 1 Residents

Stephen Barchick, MD

Undergraduate:
Harvard University

Medical School:
Duke University

Jordan Cohen, MD*

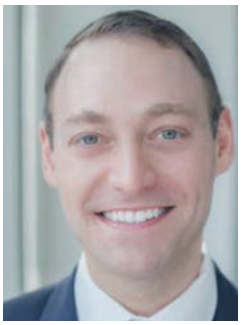
Undergraduate:
University of Maryland

Medical School:
George Washington University

Kendall Masada, MD*

Undergraduate:
University of Texas

Medical School:
University of Texas Health Science Center



Charles Lucas Myerson, MD

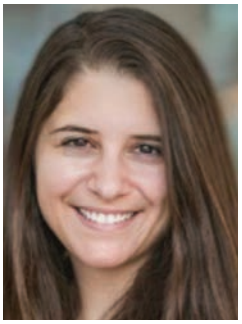
Undergraduate:
University of Southern California

Medical School:
Tulane University

Andrew Summers, MD

Undergraduate:
Portland State University

Medical School:
Oregon University



Sara Weintraub, MD

Undergraduate:
University of Pennsylvania

Medical School:
Perelman School of Medicine at the University of Pennsylvania

Kelsey Young, MD

Undergraduate:
Cornell University

Medical School:
Cornell University

Steven Zhang, MD

Undergraduate:
Cornell University

Medical School:
Stanford University

*Indicates Resident is in the 6-year Research Track

U·P·O·J

Current Fellows

August 1, 2018–July 31, 2019

Ketan Sharma, MD
Hand Surgery

Erin Weber, MD, PhD
Hand Surgery

Richard Boe, MD
Adult Reconstructive Surgery

Chris Hoedt, MD
Adult Reconstructive Surgery

Robert Williams, MD
Adult Reconstructive Surgery – Shoulder & Elbow

Wonyong Lee, MD
Foot & Ankle Surgery

Dan Prat, MD
Foot & Ankle Surgery

Christopher Caruso, MD
Spine Surgery

Terrence Ishmael, MD
Spine Surgery

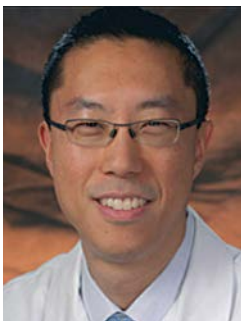
Sherif Sherif, MD
Spine Surgery

Itai Gans, MD
Sports Medicine

Robert Parisien, MD
Sports Medicine

Corporal Michael J. Crescenz Philadelphia VA Medical Center

Richard E. Grant, MD


Jaimo Ahn, MD, PhD


Joseph Bernstein, MD


Richard E. Grant, MD


Eric Hume, MD


Andrew Kuntz, MD


Vincent Moretti, MD


Harvey Smith, MD


David Steinberg, MD


Robert Wilson, MD

Orthopaedic Surgery at the VA is led by Dr. Richard E. Grant as Chief and consists of a talented team of surgeons including Dr. Jaimo Ahn, Dr. Joseph Bernstein, Dr. Eric Hume, Dr. Andrew Kuntz, Dr. Vincent Moretti, Dr. Harvey Smith, Dr. David Steinberg, and Dr. Robert Wilson.

There have been some exciting changes this year at the VA. From a facilities standpoint, the VA has made available dedicated rooms for the long-awaited VirtaMed simulators for all surgical subspecialties, including Orthopaedic Surgery. The surgical simulator device is to be positioned and confirmed this spring. The surgical simulator will assist our orthopaedic residents with pre-operative surgical skills related to orthopaedic procedures, especially in the area of arthroscopy of the knee and shoulder. The department is also excited to be onboarding a new physician assistant, Mr. Bialkkowski, who will assist with orthopaedic clinical care at Wilmington, DE and Coatesville, PA.

Dr. Smith leads the VA spine service. He currently teaches medical students and residents at Penn and also works with graduate students and postdoctoral fellows in his research group. His current research activity continues to involve work on a tissue-engineered disc replacement in a large animal model, and his team just submitted a provisional patent application on the technology. His team currently has a VA Merit grant for funding, and Dr. Smith recently completed a 5-year VA CDA-2 award. Dr. Smith serves as a mentor for Dr. Gullbrand's CDA award (Sarah Gullbrand, PhD) and is on the thesis committee of Beth Ashinsky (MD, PhD Candidate from Drexel University working in our research lab at McKay and the VA). Dr. Smith also continues to serve as chair of the NASS Research and Biologics Committee and as chair of the FDA's advisory panel on Orthopaedic Devices.

Dr. Kuntz heads the shoulder service at the VA and continues to provide clinical care to veterans as well as educational opportunities to the residents. There is a weekly shoulder clinic that provides care to veterans with all types of shoulder pathology from the Philadelphia area and surrounding satellite VA facilities. Following shoulder clinic, a didactic teaching session is held with the residents to review and discuss various shoulder pathologies, treatments, and practice-associated factors related to orthopaedics. Residents are exposed to arthroscopic shoulder surgery and shoulder arthroplasty in the OR. Dr. Kuntz also participates in pre-clinical research related to clinical shoulder pathology. Work on VA-funded (RR&D SPiRE and Merit grants) was recently completed, investigating the effects of localized delivery of bFGF or Ibuprofen in the rat rotator cuff repair model. These studies utilized a novel BiLayer Delivery System (BiLDS), developed in collaboration with Rob Mauck and Lou Soslowsky in the TMRC and McKay Labs. This line of research has resulted in

multiple abstract presentations at national meetings as well as one recently published manuscript and another in the later stage of review.

Dr. Steinberg continues to run the hand service at the VA, with weekly surgery and hand clinics.

Dr. Steinberg just received an "intent to fund," along with his co-PI Robert Mauck and their team of investigators from Penn, for a four year VA Merit Grant. That grant, titled "Knee Joint Resurfacing with Anatomic Tissue Engineered Osteochondral Implants," is an evolution of the research they have been performing over the past 8 years.

In addition to providing educational opportunities for residents, the VA remains a major outpost of our department's teaching efforts for medical students. The Perelman School of Medicine required clinical clerkship, Orthopaedic Surgery 200, is anchored at the VA. The didactic session on orthopaedic treatments and rotation's final examination are led by Joe Bernstein. In addition, in the past academic year, 157 students completed the course. PSOM students are also actively participating research projects based at the VA. In 2020, we look forward to additional instructional efforts using the surgical simulator.

Dr. Bernstein was supported by a VA Merit grant, collaborating with Dr. Soslowsky, Dr. Mauck, Dr. Kuntz and other members of the McKay Lab. The group recently published a paper in the Journal of Orthopaedic Research, "Localized delivery of ibuprofen via a bilayer delivery system (BiLDS) for supraspinatus tendon healing in a rat model." Dr. Bernstein's other peer-reviewed publications for 2019 were "Measurement of cultural competency: A pilot study of nurses' knowledge of religious practices. (Journal of Nursing Education and Practice, Vol. 9, No. 8, August 2019 DOI: https://doi.org/10.5430/jnep.v9n8p74); "Randomized Controlled Trials for Geriatric Hip Fracture Are Rare and Underpowered: A Systematic Review and a Call for Greater Collaboration" ("J Bone Joint Surg Am. 2019 Dec 18;101(24):e132. doi:10.2106/JBJS.19.00407) and "Price dispersion of generic medications" (PLoS One. 2019 Nov 18;14(11):e0225280. doi: 10.1371/journal.pone.0225280) Dr. Bernstein also writes the *Not The Last Wor*d column in CORR. In 2019, titles included "Roll Them Bones-Selecting Orthopaedic Surgery Residents by Lottery" ; "High-value Health Care and the Assassination of George Washington"; "Prizes for Cures"; "Why Can't I Set Fractures in Vermont?"; "Pre-arthritis Syndrome"; and "Big Data Will Make You Confront Big Ethical Questions-Here's Why."

Pennsylvania Hospital

Neil Sheth, MD

Pennsylvania Hospital (PAH) has a rich history in Philadelphia as the nation's first hospital. Founded in 1751 by Benjamin Franklin and Dr. Thomas Bond, the hospital was intended as a safe haven for the care of the "sick-poor and insane of Philadelphia." Located in the heart of South Philadelphia, its brand name draws thousands of patients annually to receive their care at the corner of 8th and Spruce Streets.

Residents are typically in the operating room three to four days per week, with dedicated clinic time in multiple sub-specialties. Over the past year, a PGY-5 resident from Hahnemann was added to the resident complement at Pennsylvania Hospital, covering the adult reconstruction, hand and consult services. With a continuing commitment to resident education, conferences have been video conferenced from PMUC. Weekly sub-specialty specific conferences include spine and foot and ankle.

The administration at Pennsylvania Hospital continues to be extremely supportive of the expanded presence of orthopaedic faculty and residents. The hospital system has increased the number of physician extenders, doubled the OR block time for the department, and increased physical space for clinical work and administrative duties. Their continued support is critical as the orthopaedic volume continues to grow, allowing PAH to maintain its reputation in the region as a first-class hospital.

The Department of Orthopaedic Surgery at the University of Pennsylvania now staffs seventeen attending surgeons from various sub-specialties to populate the orthopaedic clinic in the Cathcart Building and the Farm-Journal Building. Among the sub-specialties represented are adult hip and knee reconstruction, foot and ankle, hand/plastic surgery, neuro-orthopaedics, shoulder and elbow, spine/deformity, sports medicine, and trauma. Notable for this past year, Dr. Vincent Moretti and Dr. Wudbhav Sankar began operating one to two days per month at Pennsylvania Hospital. We are preparing for the arrival of two new Attendings in September 2020 to increase the complement of providers on the adult reconstruction and spine services.

With the continued increase in operative volume, PAH continues to be staffed by a PGY-1, PGY-2, PGY-5 and the Adult Reconstruction Fellow at all times, complemented by a team of nurse practitioners and physician extenders that assist with patient clinical care and floor work. The Orthopaedic Intern spends a portion of the week on the Foot and Ankle Service, as well as assisting the PAH team with patient care issues on the floor. The PGY-2 resident is now dedicating a portion of the week to Sports Medicine under the guidance of Dr. Miltiadis Zgonis. Starting in August 2020, the Adult Reconstruction service will have 3 Fellows, spending 4 months each at PPMC, PAH and Virtua.

With the continually changing healthcare environment, we continue to grow the outpatient total joint arthroplasty program which started three years ago. We have implemented and continue to refine the dedicated rapid recovery program – the 9th floor extended stay unit opened in October 2019. This service is to be expected to start at Tuttleman sometime in 2020. In addition, a new robotics platform is to be offered at Pennsylvania Hospital by the start of the second quarter. Pennsylvania Hospital is poised to be successful in the region as we continue to evolve.

Figure 1. Surgical Amphitheater at Pennsylvania Hospital (constructed in 1804).

Penn Center for Musculoskeletal Disorders

Louis J. Soslowsky, PhD

Founding Director of the Penn Center for Musculoskeletal Disorders

The Penn Center for Musculoskeletal Disorders (PCMD) was initiated in 2004 with a goal to bring musculoskeletal researchers across campus together at the University of Pennsylvania. In 2006, the National Institute of Arthritis and Musculoskeletal Skin Diseases of the NIH funded our center grant proposal at which time we became one of five such NIH-recognized Centers in the country (www.med.upenn.edu/pcmd). In 2011, this Center grant was renewed for another five years and was the only one of the three up for renewal that was re-funded that year. Through the review by the NIH, Penn scored a perfect "ten" and was hailed as "exceptional" by the review panel! In 2016, we received another "exceptional" score, highest ranked in the country, by the NIH review panel and were renewed for another five years. We are the longest running such center in the country.

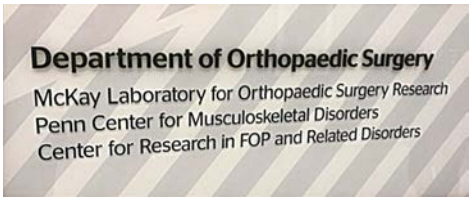
The overall goal of this Center is to promote cooperative interactions among investigators, accelerate and enrich the effectiveness and efficiency of ongoing research, foster new collaborations and new research, and ultimately, translate our research efforts into better and new therapies for musculoskeletal disorders. The central theme of the Center continues to be "Musculoskeletal Tissue Injury and Repair". This theme is broad (as it includes all musculoskeletal tissue types, such as bone, cartilage, disc, ligament, meniscus, muscle, and tendon), focused (as takes advantage of commonalities in approaches across tissue types), and clinically significant (as it fosters development of assays, procedures and knowledge in pre-clinical animal and human models of translational relevance). It is important to note that our PCMD is not a "bone center" nor is it a "muscle center". Rather, it is truly a "musculoskeletal center" and has emerged as the recognized home for musculoskeletal research across the Penn campus and as a technical and intellectual resource for the broader Philadelphia musculoskeletal research community. Thus, the primary overall aims of this Center are to enhance and advance the research productivity of investigators in musculoskeletal tissue injury and repair by: 1) Providing innovation within critical resource core facilities in areas that cross disciplines, length scales, and hierarchies. These core facilities are mCT Imaging, Biomechanics, and Histology, 2) Developing a pilot and feasibility grant program for investigators, with direct mentorship, whereby new approaches, ideas, and collaborations can be developed prior to seeking extramural funding, and 3) Developing educational and research enrichment programs spanning tissue types, research approaches, and paradigms, through which members can learn from national leaders and from each other. High quality musculoskeletal research is currently being conducted by many groups at Penn. While many bring sophisticated approaches to bear on musculoskeletal problems, few groups have the required expertise and facilities to perform high quality and specialized assays in their own labs. Furthermore, most investigators are not aware of approaches utilized, and results obtained, in other tissues that may have direct relevance on their research questions. Ultimately, close cooperation, communication, and collaboration among researchers across musculoskeletal tissue types and from a wide variety of disciplines will significantly enhance the research of our members. The Center will provide opportunities to integrate multi-disciplinary techniques to determine mechanisms for tissue function, injury, degeneration, repair, and regeneration, with the ultimate goal of advancing the diagnosis, treatment, and prevention of diseases and injuries of the musculoskeletal system.

The Center currently has a membership of more than 158 faculty across five schools at Penn (Perelman School of Medicine, School of Engineering and Applied Science, School of Veterinary Medicine, School of Dental Medicine, and School of Arts and Sciences). We also now have 54 affiliate faculty members for more than 16 Philadelphia-area institutions as we expand the reach and impact of our Center. For more information on the PCMD, please visit our website at www.med.upenn.edu/pcmd.

McKay Orthopaedic Research Laboratory

Robert L. Mauck, PhD and Louis J. Soslowsky, PhD

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 over 22,000 sq. ft. of newly renovated space on the 3rd Floor of Stemmler Hall. There are more than 120 full- and part-time staff and trainees now in the labs. McKay is an active, thriving research and educational community committed to advancing basic and translational musculoskeletal research.



The McKay labs have recently completed a transformation both in terms of physical space and faculty. Our home, Stemmler Hall, underwent a > $120 million dollar renovation, completed in 2019, which resulted in a fully modernized facility in which to grow our laboratory space, faculty, and research and training endeavors. We were also excited this year to recruit Dr. Su Chin Heo as our newest Assistant Professor, who is developing a program in musculoskeletal mechanobiology and tissue engineering supported by a K01 Award from the NIH. Finally, we have just completed an exhaustive search to recruit a senior scientist as the inaugural holder of our new endowed Professorship in Orthopaedic Surgery. We are delighted to announce that Dr. Ernestina Schipani, MD, PhD, will be joining us in the fall of 2020 as the WW Smith Professor of Orthopaedic Surgery! Welcome to McKay, Stina!

In addition to these exciting developments in our faculty, the lab continues to expand its activities and funding. Currently, McKay has an annual research budget from extramural grants, gifts, and endowments of > $14 million, and continues to rank within the top 5 orthopaedic programs in the country in terms of funding from the National Institutes of Health (NIH), with a 2019 ranking of #3. This past year has seen a very impressive and continued rise in new grants awarded to our faculty. To highlight just a few, Dr. Foteini Mourkioti was awarded two (!!) new NIH R01s and a grant from NASA to support her research program. Dr. Joel Boerkel was also awarded two (!!) new R01s and was recognized with the Alice L. Jee Young Investigator Award by the Orthopaedic Research Society. In addition to the above-mentioned new grants this year awarded to our junior faculty, each of the McKay Laboratory faculty members remains well-funded through ongoing and newly awarded research grants from federal agencies and industrial sponsors.

Our faculty and trainees also continue to represent the department at major international meetings and via national and international recognitions. Sherry Liu was selected as a spotlight speaker at the 2020 Orthopaedic Research Society Annual Meeting and Ling Qin and Robert Mauck were named a Fellows of International Orthopaedic Research (FIOR) at the International Combined Orthopaedic Research Society Meeting. Dr. Mauck was also named a Research Career Scientist by the Department of Veterans Affairs. Our trainees also won numerous awards and prizes over the last year, including multiple Section Awards and New Investigator Recognition Awards at the 2020 Orthopaedic Research Society Meeting, a Young Investigator Award at the 2019 American Society for Bone and Mineral Research Annual Meeting, and several winners of the PhD and Masters Competitions at the 2019 Summer Bioengineering Conference, to name just a few.

Growing musculoskeletal research in the Department of Orthopaedic Surgery and across the Penn campus has been a primary objective for our program, and this effort has been particularly fruitful in the past year. Last spring marked the 40th year of operation of the McKay labs, and we were excited to celebrate this occasion with ~ 200 of our current members and alumni at the Ortho Alumni Weekend and McKay 40th Celebration this past May. In the last dozen years alone, we have more than doubled in terms of lab faculty (100% increase), lab personnel (100% increase), lab space (110% increase), and research expenditures (140% increase). With our 40 years of leadership, training, and scientific contributions to musculoskeletal research, we are excited for what the future will bring.

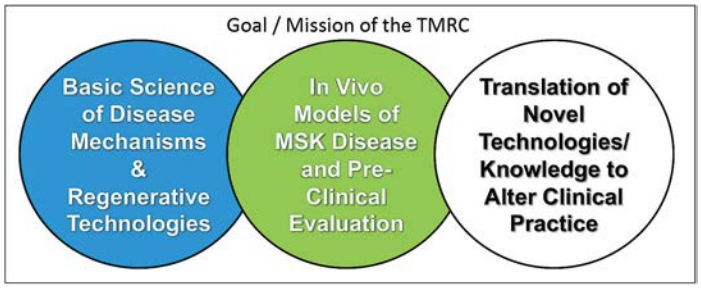
The Corporal Michael J. Crescenz VA Medical Center's Translational Musculoskeletal Research Center

Directors: George R. Dodge, PhD and Robert L. Mauck, PhD

Musculoskeletal (MSK) conditions are part of normal life and aging however occur more frequently in individuals after a variety of injuries. MSK conditions and joint diseases, such as osteoarthritis, as well as spine and disc degeneration also may arise as a consequence of the high risk physical activity typical of military service and with associated combat trauma. In fact, MSK diseases and related disabilities are more prevalent in Veterans than in the general population. Furthermore, while improvements in armor and "in theater" medical care has introduced incredible life-saving technologies, an increasing number of our wounded soldiers return home with damaged limbs and joints. Also, as with any population, when veterans age, there is an increasing tendency to develop arthritis and various degenerative joint diseases, each of which can significantly compromise quality of life. In response, the Department of Veterans' Affairs has focused research efforts to improve our understanding of the function of MSK tissues and injuries that occur to them. In particular, in 2014 the VA created an enterprise located at the Corporal Michael Crescenz VA Medical Center (CMC VAMC) with a focus developing novel technologies to enhance tissue repair, regeneration, and ultimately function. This was named the Translational Musculoskeletal Research Center (TMRC) and has grown over these past 6 years to be a research enterprise comprised of 18 Principal Investigators including 2 new junior members, 10 full-time VA employees and more than 35 WOC employees.

In keeping with the goal of improving Veteran musculoskeletal health, the last several years have witnessed a dramatic growth in VA-sponsored MSK research across the nation, with one of the largest increases occurring at our CMC VAMC in Philadelphia. The TMRC is a collaborative multidisciplinary group of physician investigators, basic scientists, and engineers at the CMC VAMC, together with colleagues from the University of Pennsylvania from many disciplines, including Orthopaedic Surgery, Rheumatology, Physical Medicine and Rehabilitation, Bioengineering, and Neurosurgery. Currently there are more than 15 current research projects being carried out within the TMRC focused on the injury and repair of MSK tissues, including tendons, ligaments, disc, bone, meniscus, and cartilage.

Critical to our research mission is to keep the research we do focused on the outcomes that relate to improving regenerative and rehabilitative approaches that ultimately will translate into improving the lives of Veterans. To carry out our mission, we are an integral part of the Research Enterprise at the CMC VAMC, including the Shared Instrument Core which is comprised of high tech state-of-the-art imaging and analysis instrumentation. Physically, we are all under one roof, in approximately 9,000 sq. ft. of renovated research space. Drs. George Dodge and Robert Mauck co-direct this enterprise with input, advice, and support from a joint CMC VAMC / Penn TMRC Advisory Committee and local and central office leadership. This year has seen several new grants from both VA and NIH sources including a new Career Development Award-2 (CDA-2) to Dr. Sarah Gullbrand that is focused on novel disc and spine regenerative approaches and a CDA-1 Award to Dr. Jay Patel, focused on cartilage repair. Dr. Robert Mauck was also awarded a VA Career Scientist Award, and both Drs. Sarah Gullbrand and Dr. Mauck were awarded SPiRE Awards. Dr. David Steinberg was recently notified of the award of a new Merit Award focused on articular cartilage regeneration. In keeping with collaborative nature of our center, we have several new projects funded in 2019-2020 involving 8+ PI's in the TMRC in the form of new or renewed VA Merit awards, a NIH R21, and an NIH R01. Of particular note is the new R01 grant to study the mechanism that contributes to osteoarthritis, awarded to Dr. Carla Scanzello, a clinical scientist who is also Division Chief of Rheumatology at the CMC VAMC. Grant funding at the VA TMRC totals more than $2.5 million dollar in direct costs.



The ultimate goal of the TMRC is to develop a focused, internationally recognized research center at the CMC VAMC and to emerge as a VA Center of Excellence, which is an ongoing goal and application process. The TMRC continues as a center for MSK translational research both at the VA along with partners and collaborators at Penn, CHOP, Drexel and Temple Universities. We will continue to focus on the Veteran MSK issues and do so by bringing new resources and regenerative technologies to all service members, past and present. Overall, the TMRC is on an upward trajectory, with a vibrant multi-disciplinary team of investigators and significant new funding directed towards making possible new discoveries in musculoskeletal repair and regeneration. We are committed to our goal of translating this research into life-changing improvements in patient care and quality of life for Veterans as well as the general population.

The Biedermann Lab for Orthopaedic Research

Elaine Schmidt, MS, Kayley Dear, MSE, Danielle Cristino, PhD, and Michael Hast, PhD

Since opening in 2015, the Biedermann Lab for Orthopaedic Research has developed a substantial body of work involving biomechanical characterization of human tissue and orthopaedic implants. Research from within the Lab spans a wide variety of orthopaedic injuries and often involves multidisciplinary methods of investigation. By combining expertise in mechanical testing, motion analysis, and computational modeling, the Lab primarily seeks to provide comprehensive assessments of interactions between implants and their musculoskeletal environment. Over the last calendar year, the Lab has presented 14 abstracts at national meetings and published 10 full-length manuscripts. Topics have included trauma implant performance, osteoporotic fracture fixation, ligament biomechanics, and orthopaedic applications for additive manufacturing

The Biedermann Lab has recently partnered with several industrial sponsors in an effort to elucidate the relationships between trauma implant designs, construct biomechanics, and clinical outcomes. Studies have demonstrated the importance of implant design and surgical technique. For example, it was found that two screws provided increased stability in talonavicular arthrodesis in comparison to a plate with an integrated compression screw (study supported by Stryker Orthopaedics). Separately, it was found that Nitinol staple augmentation in clavicle fracture repair may improve healing in comparison to traditional plating techniques (supported by DePuy Synthes). Interestingly, these biomechanical studies continue to reinforce a common theme of our research: synthetic models do not faithfully recapitulate the failure mechanisms of cadaveric, particularly osteoporotic, bone. In the upcoming year, the Lab is excited to pursue more funded biomechanical experiments with DePuy Synthes,Acumed, and Integra LifeSciences.

The Lab has an established track record of internal and external academic collaborations, and that trend continued over the last year. The Biedermann Lab has an ongoing relationship with Josh Baxter and the Human Motion Lab here at the University of Pennsylvania. Most recently, the two labs conducted an AOFAS-sponsored study focused on quantitative ultrasound examination of cyclically fatigued cadaveric Achilles tendons. It was found that mean echogenicity may be a promising marker for evaluating fatigue damage in these tendons and could be readily incorporated into clinical predictive models for tendon injury.The Lab's partnership with Surena Namdari at the Rothman Institute also continued.This team developed a computational shoulder model that assesses

Instron machine set-up at the Biedermann Lab for Orthopaedic Research

relationships between greater tuberosity avulsions and range of motion restrictions. Most recently, the Biedermann Lab formed a new collaboration with Hannah Dailey's lab at Lehigh University. The two labs aim to explore relevant fracture-based questions using a combination of benchtop tests and finite-element models. Recently, the group presented an abstract at the 2020 ORS meeting which examined the sensitivity of specimen malalignments in benchtop biomechanical testing.

Additive manufacturing has become a major interest the Biedermann Lab.This was recently highlighted by our work on 3D printed fracture models for resident education, which was selected as a finalist for a New Investigator Recognition Award at the 2020 Orthopaedic Research Society conference. This Bach Fund sponsored study showed that providing resident physicians with preoperative 3D models of bone fractures significantly improved performance within the operating room. In this arena, the Lab has teamed with Drs. Guha Manogharan and Gregory Lewis at the Pennsylvania State University and recent work has resulted in four full-length publications. Most recently, the team secured a grant from the PA Manufacturing Fellows Initiative, related to the design and manufacture of patient-specific, additively manufactured rib implants.

The team at the Biedermann Lab is excited about the future of the Lab, as we feel that that our research continues to have a direct impact on clinical orthopaedic practice. Importantly, we appreciate the generous donations from the Biedermann family, which makes the aforementioned research possible.

Human Motion Lab

Josh Baxter, PhD

The Human Motion Lab continues to work closely with our clinical colleagues to address unmet clinical needs. Using custom sensors, motion capture, ultrasound imaging, and musculoskeletal modeling, we have established exciting new frameworks to continuously monitor structural and functional progress in patients who are treated in the Orthopaedic Surgery clinics at Penn Medicine. In the past year, we've been busy. Our group has collaborated with clinicians and scientists at Penn to identify governing factors following Achilles tendon injuries,[1–3] automate medical image analysis,[4] improve musculoskeletal simulations,[5] predict function following tendon injury,[6,7] discover predictors of ankle function,[8,9] and developed novel paragigms to monitor patioen biomechanics using low-cost sensors.[10–12]

The Human Motion Lab is focused on establishing itself as a leader in the field of Achilles tendon health. Using motion capture, ultrasonography imaging, and musculoskeletal modelling we are beginning to explain the biomechanical factors that explain functional outcomes in these patient cohorts. With strong collaborations around the Department of Orthopaedic Surgery, we are excited for the future of the Human Motion Lab.

Our group is developing new clinical paradigms for monitoring and guiding rehabilitation after Achilles tendon injuries. Working closely with Drs. O'Connor and Farber in the Foot and Ankle division, we have identified novel mechanisms that explain functional outcomes in patients after Achilles tendon ruptures. To improve the structural response of both muscle and tendon to these injuries, we have developed exciting new techniques to quantify Achilles tendon loading when patients begin to load their healing tendons.[12] This work is currently supported by the American Orthopaedic Foot and Ankle Society.

In addition to collaborating with orthopaedic surgeons, we also utilize musculoskeletal simulations and small animal models to experimentally determine the interplay between Achilles tendon injuries, muscle-tendon changes, and functional outcomes.[1,8] With support from the National Institutes of Health, we will work with Dr. Soslowsky to experimentally determine rehabilitation loads that stimulate muscle-tendon healing. By leveraging the strengths of the McKay Orthopaedic Research Laboratory, we expect to accelerate the translation of basic discovery to clinical care.

In addition to studying Achilles tendon health, we work closely with orthopaedic trainees to advance the educational mission of Penn Orthopaedics. This past year, we worked with Drs. Gandhi (PGY-5) and Serra López (PGY-2) to develop and deploy a wearable sensor to quantify thumb motion in patients with carpometacarpal joint arthritis. Our exciting preliminary results confirmed that quantifying functional outcomes can be part of routine clinic care.

We are excited to continue our clinically-focused work to improve patient care, advance our fundamental understanding of musculoskeletal biomechanics, and educate the next generation of leaders in clinical care and research.

Recent Work

1. **Baxter JR, Farber DC, Hast MW.** Plantarflexor fiber and tendon slack length are strong determinates of simulated single-leg heel raise height. J Biomech. 2019 Mar 27;86:27–33.
2. **Hullfish TJ, O'Connor KM, Baxter JR.** Gastrocnemius fascicles are shorter and more pennate throughout the first month following acute Achilles tendon rupture. PeerJ. 2019 Apr 23;7:e6788.
3. **Hullfish TJ, O'Connor KM, Baxter JR**. Medial gastrocnemius muscle remodeling correlates with reduced plantarflexor kinetics 14 weeks following Achilles tendon rupture. J Appl Physiol. 2019 Aug 8;127(4):1005–1011.
4. **Drazan JF, Hullfish TJ, Baxter JR**. An automatic fascicle tracking algorithm quantifying gastrocnemius architecture during maximal effort contractions. PeerJ. 2019 Jul 2;7:e7120.
5. **Hast MW, Hanson BG, Baxter JR**. Simulating contact using the elastic foundation algorithm in OpenSim. J Biomech. 2019 Jan 3;82:392–396.
6. **Bachner EM, Schmidt EC, Chin M, Namdari S, Baxter JR, Hast MW.** Parameterization of proximal humerus locking plate impingement with in vitro, in silico, and in vivo techniques. J Shoulder Elbow Surg [Internet]. 2019 Feb 13 [cited 2019 Feb 15];0(0). Available from: https://www.jshoulderelbow.org/article/S1058-2746(18)30892-9/abstract
7. **Schmidt EC, Hullfish TJ, O'Connor KM, Hast MW, Baxter JR.** Ultrasound Echogenicity is Associated with Achilles Tendon Fatigue Damage in a Cadaveric Loading Model. BioRxiv Prepr. 2019 Nov 21;849943.
8. **Baxter JR, Hast MW**. Plantarflexor metabolics are sensitive to resting ankle angle and optimal fiber length in computational simulations of gait. Gait Posture. 2019 Jan 1;67:194–200.
9. **Drazan JF, Hullfish TJ, Baxter JR**. Muscle structure governs joint function: linking natural variation in medial gastrocnemius structure with isokinetic plantar flexor function. Biol Open. 2019 Dec 15;8(12):bio048520.
10. **Hullfish TJ, Qu F, Stoeckl BD, Gebhard PM, Mauck RL, Baxter JR.** Measuring clinically relevant knee

motion with a self-calibrated wearable sensor. J Biomech. 2019 May 24;89:105–109. PMCID: PMC6249046

11. **Hullfish TJ, Baxter JR**. Novel instrumented insole algorithm accurately approximates plantar flexor loading. BioRxiv Prepr [Internet]. 2019 Dec 23 [cited 2020 Jan 2]; Available from: http://biorxiv.org/lookup/doi/10.1101/2019.12.20.885228

12. **Hullfish TJ, O'Connor KM, Baxter JR.** Instrumented immobilizing boot quantifies reduced Achilles tendon loading during gait. BioRxiv Prepr. Cold Spring Harbor Laboratory; 2020 Feb 27;2020.02.27.968495.

Clinical Research Section

Annamarie D. Horan, MPA, PhD

In 2020, the Penn Orthopaedics Clinical Research Program marks its 10th Anniversary. Clinical Research activity at Penn Orthopaedics encompasses retrospective and prospective cohort studies as well interventional studies and clinical trials. This writing intends to celebrate and highlight the accomplishments of the program and of each Division.

Table 1. Summary of Clinical Faculty Research Activity 2010-Present

	Funded Projects (Total)	Pubs (Total)	Protocols (Current)	# Faculty (Current)
Adult Reconstruction	24	183	56	6
Foot & Ankle	4	17	14	4
FOP	8	81	8	2
Hand	6	178	22	4
Oncology	1	38	3	2
Shoulder & Elbow	5	68	15	3
Spine	2	52	12	5
Sports Medicine	9	133	32	4
Trauma	25	282	59	3
	84	1032	221	33

Table 1 shows the extent of activity that has occurred in the past decade in Penn Orthopaedics. For the period 2001 – 2010, there were only 4 funded Clinical Research awards from any source. Since 2010, each Division has significantly increased Clinical Research activity in the form of funded projects, the number of all types of protocols approved by the University of Pennsylvania Institutional Review Board (IRB), and the number of publications. Increased funding from grants and industry sponsored projects has allowed the program to hire Clinical Research Coordinators (CRCs) to support the faculty in the conduct of funded studies and other projects, and enables Clinical Research to take on new and exciting projects. We currently have 10 full time staff members supporting the 221 protocols active in the Department.

Adult Reconstruction has had 24 funded projects initiate at either Penn Presbyterian (PPMC) or Pennsylvania (PAH) Hospitals since 2010, 11 of which are still active. The 11 studies are distributed among all 6 faculty in this Division, each whom serve as the Principal Investigator (PI) on one or more ongoing funded clinical research projects. Our CRCs connect with patients at PPMC, PAH, Radnor, Cherry Hill, and Valley Forge locations as needed for each study. The primary CRC for Adult Reconstruction is Helena Moses. Helena has been with the team for 6 years and works out of PPMC. She also is actively working toward a Nursing Degree. In addition, Adult Reconstruction is served by both Christine Wojciechowicz at PPMC and Warren Harding at PAH. Christine has worked with the team for 10 months. She will be attending Geisinger Commonwealth School of Medicine in the Fall of 2020. Warren Harding has been with the team for 8 months and plans to begin a PhD program in Fall 2022. The largest ongoing study in Adult Reconstruction is myMobility (NCT03737149) (PI, Dr. Israelite). The myMobility study is a post-market prospective, multi-center longitudinal study to determine if mobile application-guided education and exercise paired with accurate and sensitive activity monitoring, captured from consumer wearables, can provide a viable, and potentially improved, alternative to current standard of care physical therapy for hip and knee arthroplasty. This winter saw the completion of enrollment for the first phase of the study: a randomized controlled trial. We successfully enrolled 92 of our target 100 subjects and are now working towards enrolling a further 500 subjects in the second phase of the study.

Foot & Ankle has had 4 funded projects initiate since 2010. There are 3 active funded projects in this Division. The primary site for Clinical Research is on the PAH campus at the Farm Journal Building (FJB). The CRCs in service to the Foot & Ankle Division are a shared resource with other Divisions (Warren Harding and Dr. Mary Dooley). In the past fiscal year, Foot & Ankle initiated a funded study sponsored by Treace Medical Concepts Inc. entitled "Early Weight-Bearing After the Lapiplasty Procedure (ALIGN3D)" (NCT03740282). This study evaluates the outcomes of the Lapiplasty® Procedure for patients in need of hallux valgus surgery. Foot & Ankle has also seen a surge in the past year of unfunded studies comprised of prospective Division initiatives and retrospective chart reviews. The CRCs support the conduct of these studies that give residents, fellows, and medical students the opportunity to participate in a strong research program.

FOP continues its track record of success in the search for therapies to ameliorate symptoms of FOP and perhaps, someday, to even cure the disease. Currently under the leadership of Drs. Kaplan and Al Mukaddam, there are 3 active studies in FOP supported by 2 different sponsors. There are 2 staff who exclusively support FOP Clinical Research, Project Manager Katherine Toder and CRC Renee Jurek. Both Katherine and Renee have been on staff for about 4.5 years, are in the Penn Masters of Regulatory Affairs Program, and we are lucky they will be with our team for the foreseeable future. In addition, Mrs. Kamlesh Rai is an essential part of the team as well. Kay has been with the Department for over 30 years. The FOP team has been working for several years on the Clementia program and is more recently also engaging in a study with a different sponsor, Regeneron ("LUMINA-1",

NCT03188666). Additional sponsors are taking interest in the FOP disease state and we anticipate increased research activity in this population in the near future.

Hand Surgery has initiated six funded clinical research projects in the past 10 years and they are all currently active. The Division is supported by 2 CRCs, Dr. Mary Dooley and Ashley Iwu. Mary is coming up on 2 years of service and Ashley is approaching 10 months. We are happy to report that both of them plan to stay with us for some time. All 4 faculty in this Division have at least one funded clinical research project. Dr. Bozentka serves as PI for a randomized prospective trial that all Division faculty members participate in through patient enrollment. Entitled "Comparison of Processed Nerve Allograft and Collagen Nerve Cuffs for Peripheral Nerve Repair" (NCT01809002), this study compares the performance of a specially processed human allograft vs. a collagen nerve cuff in nerve injuries. As this trial draws to a close and is anticipated to finish enrollment during FY21, we are celebrating the accomplishment of being the #4 site nationwide in terms of enrollment and completion. This is a double success for our team because while Dr. Bozentka is the local PI, Dr. Levin serves as the Global PI. We are looking forward to seeing the results.

Shoulder & Elbow has developed a strong Clinical Research presence over the past 10 years with 5 funded studies currently ongoing. The Division is supported by Evan Bannister in the CRC role. Evan has been with the Department for 6 years and is expected to graduate with a Masters in Regulatory Affairs in May 2020 (Penn). Evan plans to stay with our team for the near term. Currently, all studies in Shoulder & Elbow are led by Dr. Kuntz as PI, though there are pending projects for Dr. Huffman anticipated for FY21. The featured study for this year is the OrthoFix RCStim Study (NCT03339492). This study investigates the safety and efficacy of treating full thickness rotator cuff repairs with pulsed electromagnetic fields (PEMF). We are excited to participate in a clinical study that parallels the research completed by our McKay Lab colleagues on PEMF technology for tendon repair.

Spine currently has 2 active funded studies: "An ACDF Multi-center Study Using ViviGen Cellular Bone Matrix" (NCT02814825) and "An Assessment of P-15L Bone Graft in Transforaminal Lumbar Interbody Fusion with Instrumentation" (NCT03438747), with additional studies at the preparatory phase. The Spine Division also has a large unfunded research arm involving both prospective and retrospective study designs. At the moment, we do not have a dedicated Spine CRC, but Dr. Mary Dooley and Warren Harding both assist to cover Spine at PPMC, PAH, and Valley Forge. The 2 current funded studies are led by Dr. Smith as PI with the pending studies split between Drs. Smith and Saifi. It will be very exciting to revisit this Division and their progress next year.

Sports Medicine has 6 active funded projects shared amongst 3 faculty as PIs. Dr. Carey is the Local and Global PI on the Vericel sponsored PEAK study (NCT03588975) entitled "A Study of MACI in Patients Aged 10 to 17 Years With Symptomatic Chondral or Osteochondral Defects of the Knee". This study compares the efficacy and safety of MACI® vs arthroscopic microfracture in the treatment of patients aged 10 to 17 years with symptomatic articular chondral or osteochondral defects of the knee. Dr. Carey has long been interested in knee cartilage defects and their repair and regrowth possibilities, and it is great to see that he has been recognized with this leadership role. Dr. Carey has been supported by Shawn Simmons as CRC. Shawn joined our team about 2 years ago and will be leaving us to attend Medical School at Columbia in the Fall.

Ortho Trauma has been a very strong Division these past 10 years. There have been an astounding 25 funded projects in Ortho Trauma over the 10 years with 3 currently funded studies active and more on the horizon. This team has also had the most comprehensive funding mix of federal, foundation, philanthropy, and industry sponsorship. Currently, Dr. Mehta is the PI on 2 multicenter trials and 1 single site trial investigating the diagnosis, prevention, and management of surgical site infections in the Ortho Trauma population. At the moment, we do not have a dedicated Trauma CRC, but Dr. Mary Dooley and Ashley Iwu both assist to cover this Division.

We also want to recognize the outstanding collaboration that occurs within Divisions and across the Clinical Research Programs in the Departments of Orthopaedic Surgery and Anesthesia and Critical Care. Highlights include a study led by Dr. Farber and sponsored by DJO, "CMF Bone Stimulation as Adjunct to Surgical Treatment of Ankle Fractures" (NCT02688855), which both the Foot & Ankle and Ortho Trauma faculty support recruitment for; the PCORI sponsored REGAIN Trial (NCT02507505) (PI, Dr. Neuman) that incorporates a well-integrated team of Orthopaedic Surgery and Anesthesiology & Critical Care faculty; and an investigator

Samir Mehta, MD
Chief, Division of Orthopaedic Trauma, Medical Director of Clinical Research
Associate Professor of Orthopaedic Surgery

Annamarie Horan, MPA, PhD
Director of Clinical Research
Orthopaedic Surgery and Anesthesiology & Critical Care

initiated trial (PI, Elkassabany in collaboration with Dr. Glaser) studying the effects of liposomal bupiviane injected prior to surgery in the Shoulder Elbow patient population. These and other anesthesia studies are supported by a team including Project Manager Aliaksei Basatski and CRCs Annie DiLisio, Nnamdi Ilonzo, Anmol Madaan, and Cassandra Dinh.

Thank you to all the named and unnamed staff and faculty on our team, the residents, fellows, and other clinical support staff, and the leadership of Penn Orthopaedics and Anesthesiology & Critical Care for their ongoing support of our team. Specifically, we thank the Chairs, Drs. Levin and Fleisher, the Vice-Chairs for Research, Drs. Soslowsky and Eckenhoff, as well as the Chief Operating Officers, Neil Ravitz and Dennis Harris for your ongoing guidance and support in every way throughout the year.

Figure 1 Top row: Evan Bannister, Aliaksei Basatski, Mary Dooley, Annie DiLisio, Cassandra Dinh. Middle row: Warren Harding, Nnamdi Ilonzo, Ashley Iwu, Renee Jurek, Anmol Madaan. Bottom Row: Helena Moses, Kamlesh Rai, Shawn Simmons, Katherine Toder, Christine Wojciechowicz.

Human Tissue Lab

Lorianne Kish-Burdsall

The Human Tissue Laboratory ("HTL") opened its doors in August of 2011 under the direction of Dr. L. Scott Levin, chair of the division of Orthopaedic Surgery at the University of Pennsylvania.

The original mission of the lab was to provide an opportunity for residents and surgeons to practice and explore the vast arenas of surgery, review anatomy and learn new approaches and techniques as they are developed that ultimately lead to better patient results and recovery. While the mission has not changed, it has expanded to include assisting authors of medical anatomy books, hosting international courses and workshops to inspire young minds. Since 2011, the human tissue lab has hosted hundreds of courses, comprised of internal training courses and industry partnered events. Departments from all areas of Penn Medicine now use the facility as this type of training is invaluable.

The HTL and the teachings of the Penn faculty is what sets the Penn residency program apart from many others in the world. The administration of the HTL continues to reinvest in the lab with improvements, additions and upgrades to equipment. Currently the lab has two full time staff members to ensure availability 7 days a week, day or evening. Penn is proud to offer the same quality experience as is available in a commercial lab. The 14 station HTL offers an HD overhead camera for the lead surgeon, OR quality surgical lights, live streaming capabilities, flat screens for participant viewing, arthroscopy towers, specimen holders, a full complement of arthroscopic trays, a full-size C Arm, peg board positioners, hand held power saws and drills, ancillary instrumentation, disposables, scrubs, locker room and a sterilizing dishwasher. Again this year, the HTL volume and genre of educational events has expanded. The HTL will continue to reinvest in its equipment to enhance the experience of the attendees.

Poised for Growth and Expansion

Neil Ravitz, MBA

Chief Operating Officer
Chief Administrative Officer, Musculoskeletal Service Line

The Penn Medicine Health System continues to grow and expand and for many, they would hardly recognize the new landscape and locations being constructed. At the current HUP location we are building a $1.5 billion new pavilion that will have about 500 beds and about 50 operating rooms slated to open in 2021. At the same time, we have a new patient Pavilion opening at Chester County Hospital in April of 2020 that will modernize that campus and provide needed infrastructure. Meanwhile, in Radnor there is a new ambulatory facility opening in June of 2020 that will more than double the overall footprint of the building and more than double the clinical space for the Musculoskeletal and Rheumatology Service line. It is hard to look around Penn Medicine right now and not see the signs of growth and expansion.

Fundamentally, the expansion is positive for the Department as it represents modernization for both our patients and our physicians. It also enables us opportunities to see more patients and bring the expertise of Penn Orthopaedics closer to patients in the suburbs. One of the challenges that exist is trying to find enough people and space to see those patients, so in addition to building efforts, we also are innovating new ways to provide access to patients. Several years ago we began hiring more Advanced Practice Providers (APPs) who are usually Physician Assistants and have now grown to over 40 in the Department. This past year we focused on getting each of these APPs to see independent sessions, usually while their physician counterpart is in the OR, to help expand our access. In this fiscal year, we anticipate that more than 33,000 patients will be seen by our APPs and non-operative colleagues. We are also extending hours in Cherry Hill in the evening and weekends with some of our APPs in hopes of providing additional options to working adults to get access to the finest care in the region. Of course this growth and expansion cannot be accommodated only with existing faculty. We are also recruiting heavily across five of our division currently. We are focused on finding people who provide great clinical care and match the culture of our department.

We also announced an exciting partnership this year with the Philadelphia Flyers. The marketing component of the five-year deal began in January of 2020 and the Orthopedic care of the team will begin in September of 2020 with the start of the new season. Dr. Brian Sennett is leading this effort for the department and we think it is a tremendous opportunity to promote that growth and get our brand in front of hundreds of thousands of people in the Philadelphia region and beyond.

We had several new clinical faculty members join the Department in the past year. Dr. Amrit Khalsa joined the Spine division in September of 2019. Dr. Khalsa completed his residency at Hahnemann and a fellowship at Scripps in California. He had already been in practice in the Philadelphia area for a couple of years before joining the Department. Dr. Susan Harding also joined the faculty this past year as a partner to Dr. Kevin McHale and Dr. Stanley Michael down at Cape Regional Medical Center. She is a member of the Trauma division and is spending about 20 percent of her time at PPMC. Dr. Harding built her career at Hahnemann where she was an extremely well regarded clinician and educator. We are happy to have her join our department and she has provided a nice continuity for the residents that came from Hahnemann. Finally, Dr. Vince Moretti began seeing patients with the Department in a part time capacity. While he has been with the Department at the VA for the past two years, he was interested in setting up a new location for us in Woodbury, NJ and began practicing out there one day a week helping to expand the Adult Reconstruction division into a new market. We welcome all three of them to the Department and look forward to their continued success and contributions. They are key to our growth and expansion!

Continued Evolution of the MSKR Service Line

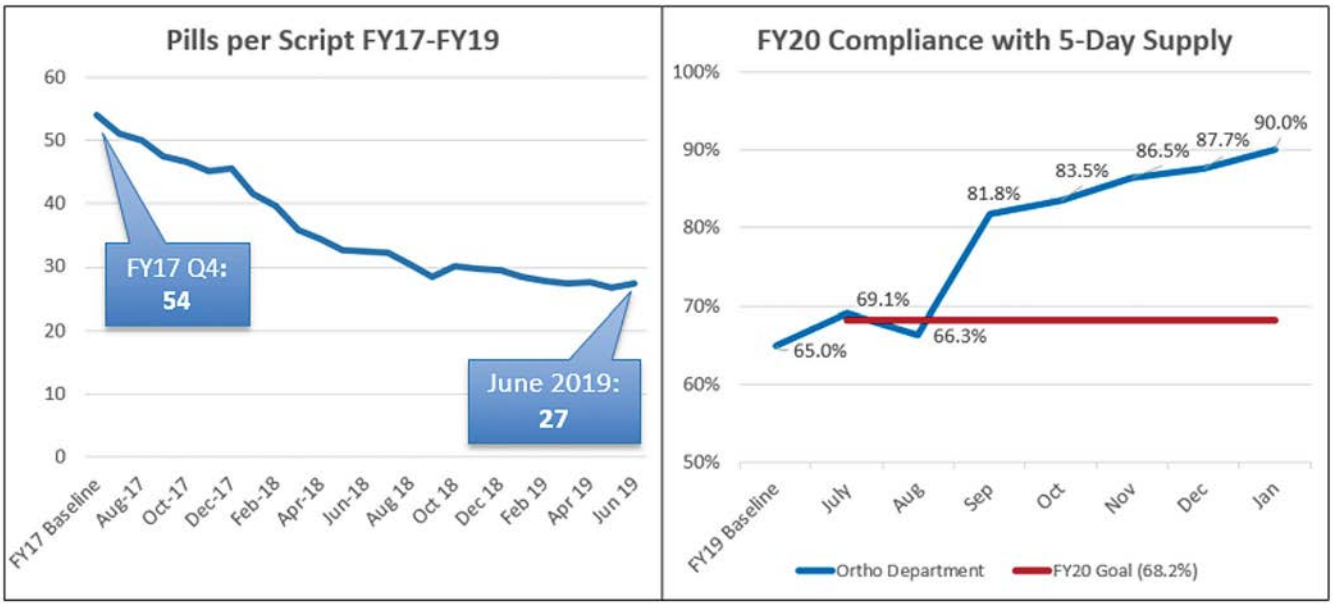
Sean Looby, MHA

Director, Service Line & Network Integration, Musculoskeletal & Rheumatology Service Line

The Musculoskeletal and Rheumatology Service Line continues to work to enhance connections and advance care across the departments, divisions, and hospitals that serve our patients. As we navigate the constantly changing local and national healthcare landscape, we are proud of our accomplishments and are poised to tackle the challenges ahead.

Opioid Stewardship

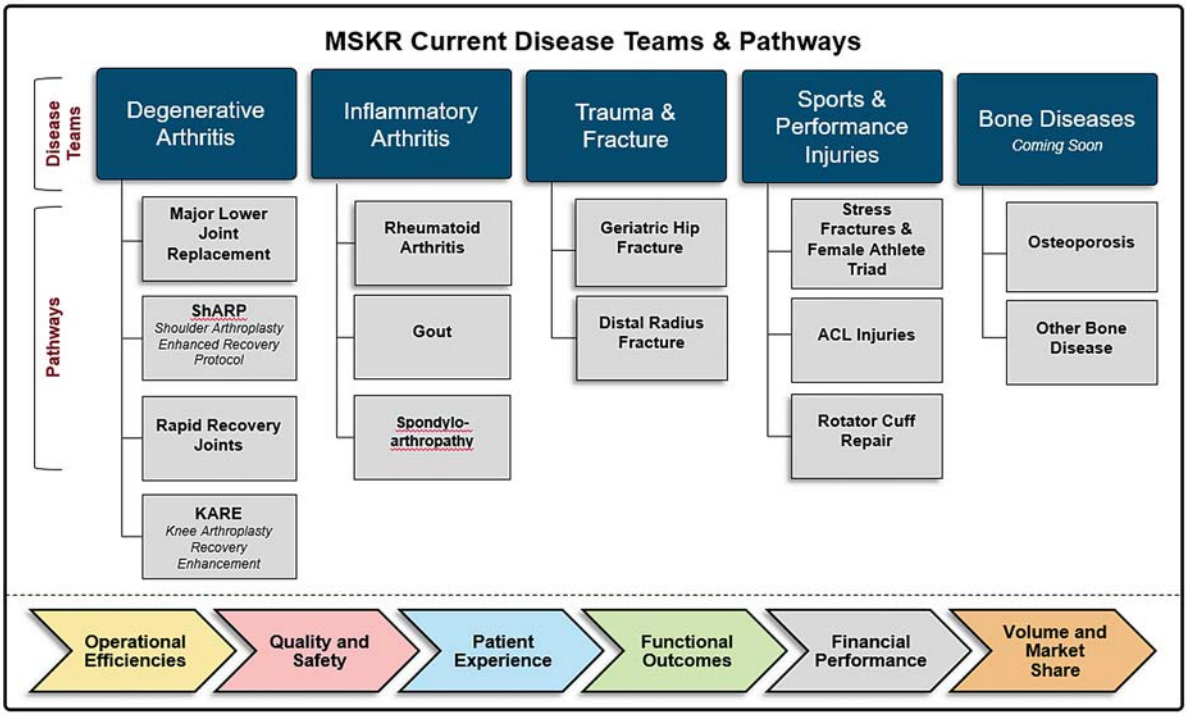
The MSKR Service Line has made significant contributions to reducing the use of opioids in support of health system and national agendas in fighting the opioid epidemic. For the past several years the Department of Orthopaedics has focused on pills per outpatient script, which have been reduced 50 percent from FY17 through FY19. For FY20, we have shifted our focus on complying with the 5-day supply recommendations, and in the first half of the fiscal year have improved from 65% to 90% of all prescriptions being for a 5-day supply or less. These are significant strides, showcasing the commitment of our surgeons, and strong partnership efforts with pain management and other colleagues across the health system. These successes are coupled with other efforts to continue to move the needle, including development of opioid-sparing peri-operative pain protocols, as well as participation in research studies to better understand patient opioid consumption patterns.



Improving Care for Patient Populations

The service line multidisciplinary disease teams continue to be the vehicles used to drive advancements forward in care for distinct patient populations. One of our key focus areas has been length of stay reduction efforts, with our Degenerative Arthritis disease team working to get patients home faster and safer through work on care pathways related to hip, knee, and shoulder replacement surgery. We have worked closely with our hospital partners to improve early mobility through enhanced physical therapy resources and protocols, develop pathways for same-day unilateral knee replacement surgery, and improve patient selection and compliance for total shoulder replacement enhanced recovery efforts. The policy and reimbursement environment continues to evolve related to procedures that can be done on an outpatient basis, and we are working diligently to ensure we remain ahead of the curve.

We are in the planning stages of launching a new disease team for Bone Diseases, focusing on improving care for patients at-risk of, or with Osteoporosis, as well as other bone diseases. Given the aging population and the increasing prevalence of fragility fractures being cared for by our orthopedic surgeons, this is an underserved area with significant opportunity to enhance how patients are screened and treated. This will truly require a multidisciplinary approach, inclusive of rheumatology, orthopaedics, primary care, endocrinology, pharmacy, radiology, and others. We are excited to move this work forward and tackle the challenges of optimizing care for these patients.



Affiliate Network Development

The MSKR Service Line continues to develop our affiliate network of external hospitals and physician groups, aimed at enhancing care and access in local communities beyond our traditional service area. In the summer of 2019, we welcomed Grand View Health as an affiliate of our Orthopaedic Specialty Network. Located in Sellersville, PA, about an hour northwest of Philadelphia, Grand View is an independent community health system with a small employed orthopaedic group. We are working closely with the Grand View team to assist them in continuing to enhance the quality of care provided to patients of Bucks and Montgomery Counties, while streamlining care for complex patients referred to our specialists downtown.

We also bolstered our relationship with Cape Regional Medical Center, located on the New Jersey coast, by adding a third faculty member to the Penn Orthopaedics at Cape Regional practice. Susan Harding, who was previously the orthopaedic trauma lead at Hahnemann University Hospital, has joined the group and is providing a full spectrum of fracture care as the first fellowship trained orthopaedic traumatologist on their medical staff.

Orthopaedic Advanced Practice Providers

Christine McAndrew, PA-C

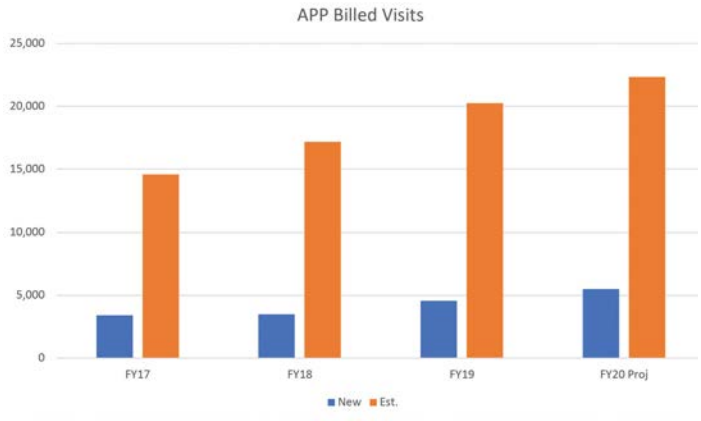
Penn Medicine Advanced Practice Providers (APP) have been an integral member of the healthcare team since the 1970's. They have supported the health system's ability to increase access to quality healthcare for the communities we serve.

Within the department of Orthopaedic Surgery our APP group continues to grow. We currently have 37 APPs within our department. In the past year we have added two new positions: a float PA and an additional PA to the foot and ankle team. In addition, we have also hired Brian Fletcher who is our independent joints APP. Brian has 9 independent clinic sessions per week supporting the joints division. He is seeing new, return and post-operative patients. Brian has been a wonderful addition to the team and has tremendously helped with access to care.

Our float physician assistant is Kerry Howey. Given the growth of the APPs, as well as the integral role they play in clinical operations, the float PA provides an additional layer of support for the team. The role of the float PA is to run independent sessions, focused in general Orthopaedics and be made available for coverage of other advanced practice providers when needed. Kerry has clinic schedules at PMUC, PAH and Cherry Hill while also covering extended hours clinic in Cherry Hill predominantly on Wednesdays.

The Orthopaedic Extended Hours of Cherry Hill has been open for a little over one year now. The clinics are APP run and supported by Dr. Samir Mehta as attending physician. Hours of operation are now Wednesday 4-8pm and Saturday 8-12pm. Appointments can be made ahead of time or walks ins are available. This has provided options for patients after business hours, has opened access to care, and has captured a patient population for the department that would otherwise prove difficult to attain. It allows us to streamline care to ensure that patients are getting treated in a timely manner and getting directed to the correct surgeon or practitioner.

The Orthopaedic APP's have had a remarkable impact on patient care here at Penn Medicine. They are on the front lines making significant strides to improve clinical care. They continue to increase access to care while supporting a heavy clinical demand, and manage continuity and continuum of care. They drive safety, quality, cost and satisfaction to our patients. The vast majority of our APPs all run independent sessions which range from post-operative patients, return and new patients, as well as minor procedures. They also do the majority of the history and physicals and prepare the patients for surgery. They are also seeing many of the post-operative patients to free up the physician's schedules for new patients. Each year we continue to see an increase in total visits by our APPs. In FY19 they saw a total of 4,554 new patients and 20,253 established patients.



The APPs continue to support department initiatives, including most recently telehealth. The APPs are in the midst of preparing to help with our telehealth initiative by choosing appropriate post-operative patients and offering them a telehealth visit with them. While telehealth will not benefit most, we are excited about the opportunity for those who will benefit from this type of visit.

This past fall Marcus Nartey was nominated for the Advanced Practice Provider Clinical Excellence Award. Marcus was honored at the APP Awards Ceremony which was held during Advanced Practice Provider week. We congratulate Marcus on this very special nomination and thank him for his continued dedication to our practice and patients. He has been an integral part of the growth in the spine division.

In conclusion, the advanced practice providers are major contributors to the success of the department. With a strong focus on superior patient outcomes, they serve as highly valued members of the clinical care team. I am beyond grateful to work with such an amazing group of advanced practice providers.

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References: 1. Stoffel K, Zderic I, Gras F, Sommer C, Eberli U, Mueller D, Oswald M, Gueorguiev B. Biomechanical evaluation of the femoral neck system in unstable Pauwels III femoral neck fractures: a comparison with the dynamic hip screw and cannulated screws. *J Orthop Trauma*. 2017; 31(3):131-137. **2.** DePuy Synthes Report: Static Cut Through Rotation Test in Bone Foam. 2018. Ref: 0000277853. **3.** DePuy Synthes Report: FNS Design & Procedure Comparison. 2018. Ref: 0000274963.

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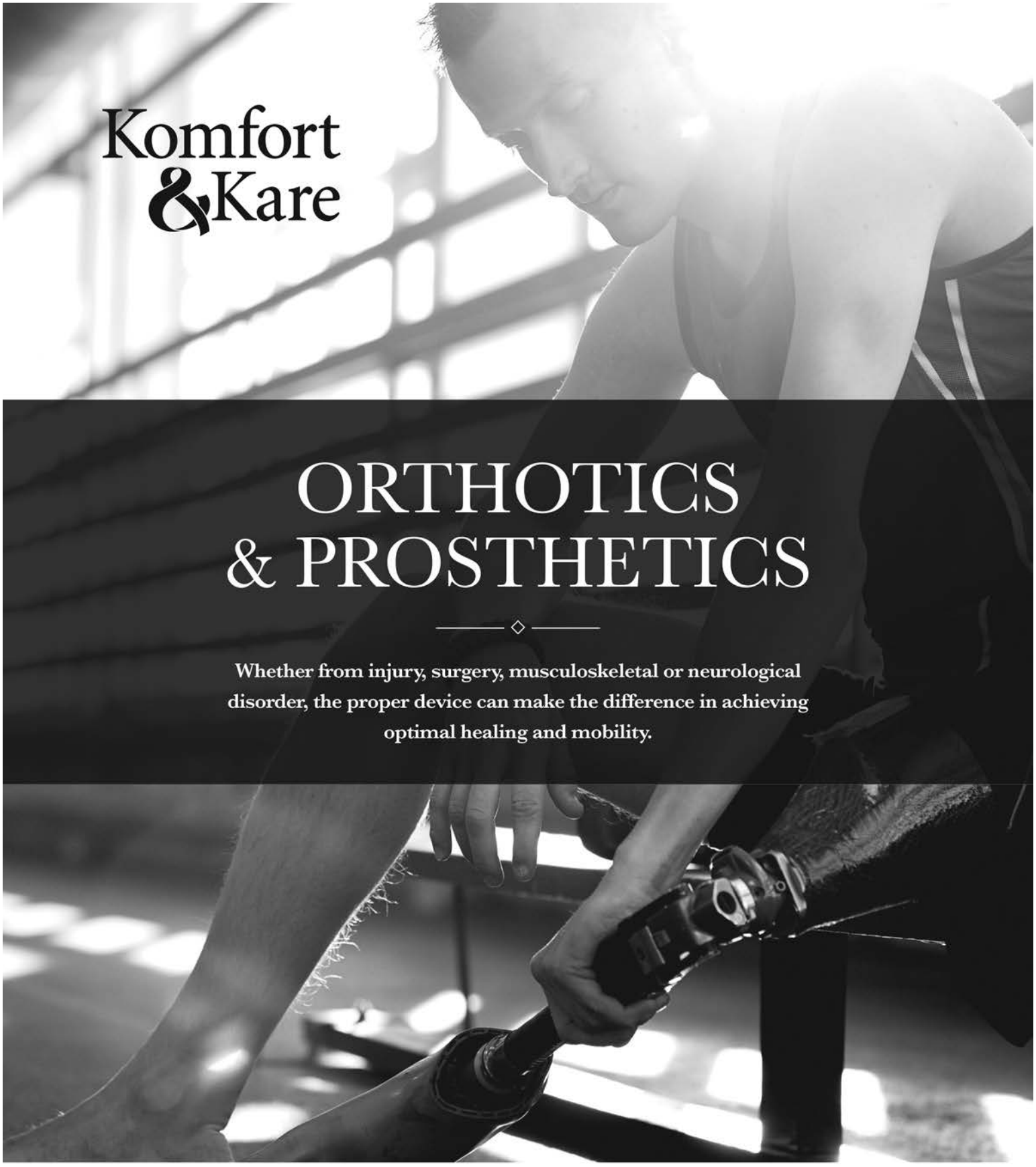

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University of Pennsylvania Orthopaedic Journal

2019-2020 Clinical and Basic Science Research

The following sections highlight clinical and basic science research conducted at the University of Pennsylvania in the field of Orthopedics, including work from the Department of Orthopaedic Surgery, The McKay Laboratory for Orthopaedic Research, Children's Hospital of Philadelphia, the Philadelphia Veterans Affairs Translational Musculoskeletal Research Center, The Biedermann Laboratory for Orthopaedic Research, and the Human Motion Lab. In addition to research, each clinical section is preceded with a "Tips & Tricks" article highlighting case reports or surgical techniques for education and to display the breadth of musculoskeletal disease seen and treated in our hospital system.

Clinical Research Sections:

Trauma

Spine

Sports

Hand

Pediatrics

Shoulder and Elbow

Arthroplasty

Foot and Ankle

Oncology

Orthoplastics

Basic Science Research Sections:

Bone & Development

Cartilage, Meniscus, & Muscle

Tendon & Ligament

Trauma Tips & Tricks: Nail Plate Combination Fixation for Distal Femur Fractures

Kendall M. Masada, MD[1]
Gregory T. Minutillo, MD, MPH[1]
Derek J. Donegan, MD, MBA[1]

1Department of Orthopaedic Surgery, University of Pennsylvania, Philadelphia, Pennsylvania

Background

Distal femur fractures account for less than 1% of all fractures and between 3% and 6% of all femur fractures.[1] These fractures follow a bimodal distribution between high-energy mechanisms such as motor vehicle accidents in the younger population and low-energy mechanisms such as fall from standing in the elderly and osteoporotic populations. Their incidence is increasing with the rising geriatric population and periprosthetic knee arthroplasty fractures.[2]

Distal femur fractures are significant injuries that can be technically challenging to operatively treat. The main goals of management of distal femoral fractures are 1) anatomic reduction of the articular surface, 2) restoration of length, alignment, and rotation 3) stable fixation construct to allow early knee range of motion, and 4) preservation of the soft tissue attachments to bone fragments to reduce the risk of nonunion.[3]

Nonsurgical management is reserved for non-ambulatory patients with medical comorbidities that place them at unacceptably high risk of surgical/anesthesia complications. Nonsurgical management involves protected weight or non-weight bearing in a hinged knee brace. Complications of nonsurgical management, including decreased mobility, decubitus ulcers, and thromboembolic disease, generally outweigh the risks of surgical intervention in most patients.[4]

Surgical fixation has consistently demonstrated superior outcomes as compared with nonsurgical treatment.[4] Potential methods of fixation include external fixation, plates (fixed angle blade, locking), retrograde intramedullary nail (IMN), and distal femoral replacement. Of those options, plates and intramedullary nail are most commonly used. Biomechanical studies demonstrate locking plates are more stable than IMN to loading forces in osteoporotic bone, however they have a greater incidence of sudden periprosthetic fracture.[5,6] The increased stability is thought to be due to increased distal fixation with the locking plates compared to IMNs. Nonunion rates are similar for locking plates and IMNs.[7] The use of either a locking plate or IMN alone usually warrants a protected weight-bearing status.

The nail plate combination (NPC) technique offers more stable fixation while allowing for immediate weight bearing and early mobilization, which is of particular importance in the treatment of geriatric fractures. The rationale in combining plate and IMN fixation is the stress forces are more evenly distributed between the bone and the implants.[8] Biomechanical studies have shown NPC is more resistant to failure in axial and torsional load tests, and load to failure tests compared with both locking plate and IMN alone. [9] However, in a study comparing dual plating and NPC, dual plating provided stiffer fixation to axial and torsional loading. The study hypothesized the difference was due to an inability to use all distal interlocking bolt positions within the nail or all distal screw positions within the plate in the NPC construct. [10] While dual plating provides stiffer fixation, there is a soft tissue cost of an additional surgical incision and potential effect on fracture healing that must be taken into consideration.

Below, we highlight the NPC technique using an example case of Patient X.

Perioperative Assessment

Perioperative assessment should include history-taking (baseline function, prior injuries, prior surgeries, congenital deformity to the limb) and physical exam (compartments, vascular assessment with distal pulses and ankle-brachial indices given potential popliteal artery injury). Obtain orthogonal radiographs of the femur, knee, and hip. Evaluate for an ipsilateral femoral neck fracture, particularly with high-energy mechanisms.[11] As intra-articular extension can be difficult to visualize on radiographs alone, CT imaging is usually indicated. Attention should be paid for possible Hoffa fragment (intra-articular fracture in the coronal plane of the condyle).[12]

Initial stabilization can be achieved with a knee immobilizer to ensure support proximal and distal to the fracture site without creating fulcrums for further deformity. Alternatively, a long leg splint may be applied. Distal femoral traction is not advised, even with evidence of no intraarticular extension, given the distal nature of the fracture and deformity. Proximal tibial traction may be considered unless ipsilateral ligamental knee injury is suspected. External fixation may be used as a temporizing measure for length unstable fractures with overlying soft tissue concerns and/or vascular injuries.

Example Case

Patient X, 73-year-old female with history of dementia, prior strokes with residual right sided weakness, end-stage renal disease on hemodialysis, and diastolic congestive heart failure who presented with right knee pain after an unwitnessed fall from standing position. She was a home ambulator with a walker at baseline and used a wheelchair outside of the home. Physical exam demonstrated a closed injury with a shortened and internally rotated well-profused right lower extremity. X-rays revealed a right-sided comminuted extra-articular distal third femur fracture with valgus and apex posterior deformities (Figure 1). No intra-articular extension was evident on CT imaging. She was stabilized with a knee immobilizer.

She was a good candidate for surgical intervention given her baseline ambulatory status and the morbidity of non-operative management with her multiple medical co-morbidities. NPC offered stable fixation technique for her comminution and poor distal bone quality and early mobilization with immediate weight bearing for her age and co-morbidities.

Surgical Technique

The patient was placed supine on a radiolucent table with fluoroscopic imaging on the contralateral side of the table. A small bump was placed under the ipsilateral buttock to ensure the patella was facing upwards. Next, a radiolucent triangle was placed under the injured distal thigh to bring the knee into approximately 30 degrees of flexion. Radiographs were obtained of the contralateral, uninjured, knee and femur to act as a reference for alignment and rotation.

The right femur was first approached by performing closed reduction using skeletal traction, which corrected the length and valgus deformity (Figure 2A). The radiolucent triangle aided in reducing the apex posterior deformity (Figure 2B). Having restored length, alignment and rotation, attention was turned to making a transtendinous infrapatellar incision. Sharp dissection was taken down. Patella tendon was identified and incised in line with the incision. Starting point was achieved and confirmed fluoroscopically. The guidewire was then taken into distal femur in the appropriate trajectory. The distal femur was opened with reamer and the ball-tip guidewire was then taken into the distal femur across the fracture into the proximal femur. Reaming then began sequentially up to a size 11.5 reamer. The length was measured to be just around the 360 mm. The decision was made to place a 10x360 mm nail. The nail was assembled on the back table on the jig. That trajectory through the jig was checked. The nail was then introduced over the ball-tip guidewire into the distal femur across the fracture and into the proximal femur. Appropriate depth was confirmed fluoroscopically (Figures 2C and 2D). Three distal interlocking screws were placed through the jig (Figure 2E). Two proximal interlocking screws were placed using the perfect circle technique (Figure 2F). The most distal interlocking screw was then removed in order to link the plate to the nail. Fluoroscopic evaluation revealed good length and rotation of the femur with appropriately placed hardware. Due to the poor bone quality, the decision was made to supplement with a laterally based plate.

Plate length was estimated by overlaying it on the skin under fluoroscopic imaging and determining the length

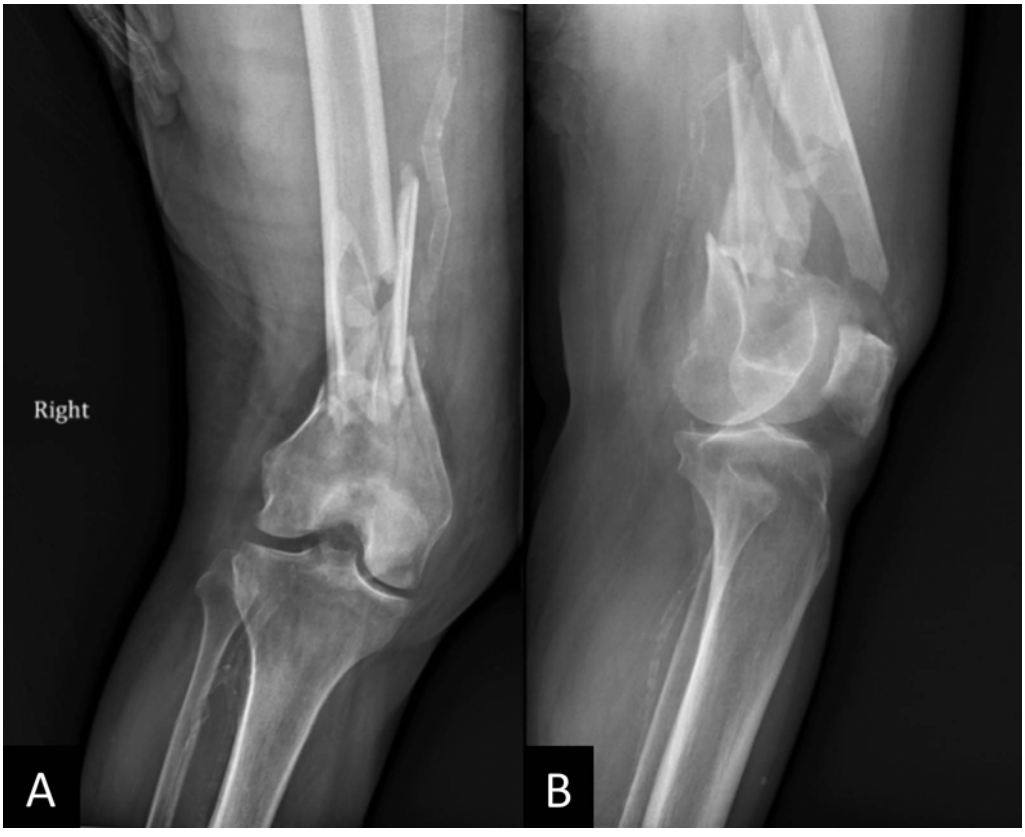

Figure 1. Patient X's injury radiographs demonstrating a right-sided comminuted extra-articular distal third femur fracture. **(A)** AP radiograph demonstrating valgus deformity. **(B)** Lateral radiograph demonstrating shortening and apex posterior deformity.

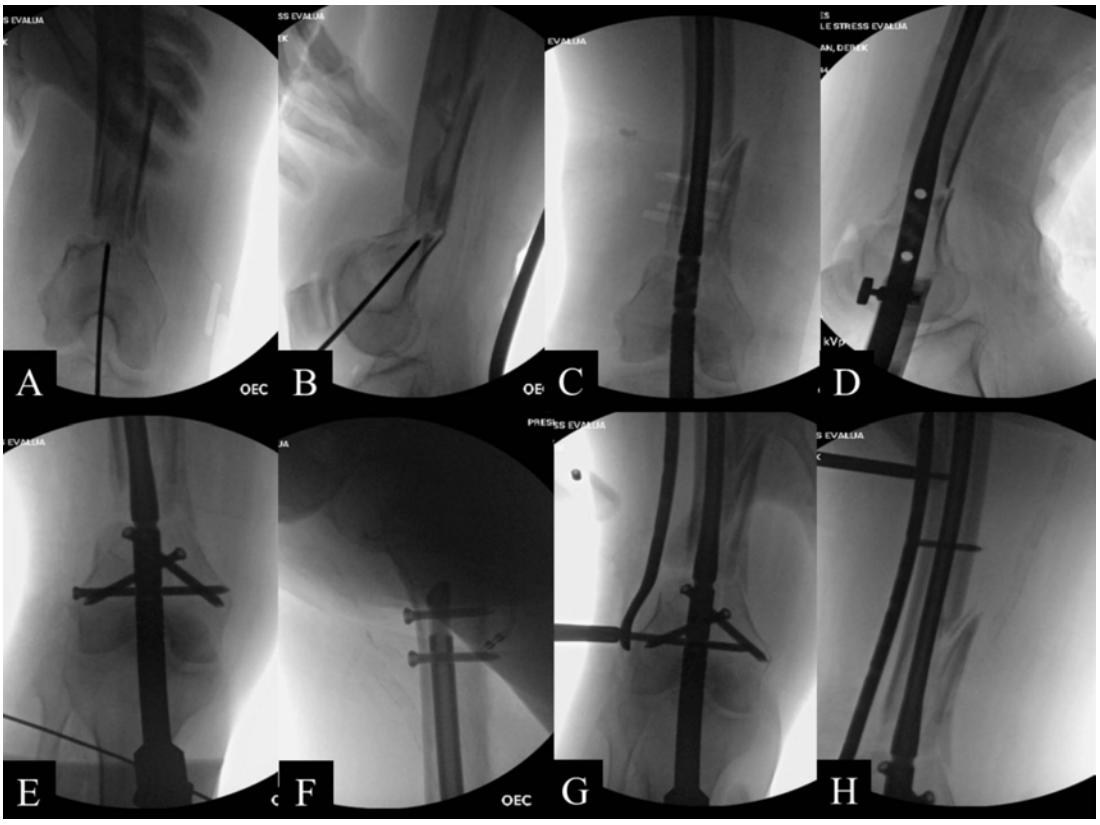

Figure 2. Patient X's intra-operative fluoroscopy. **(A)** AP distal femur demonstrating correction of the length and valgus deformity with skeletal traction. **(B)** Lateral distal femur demonstrating use of the radiolucent triangle to help correct the apex posterior deformity. **(C)** AP distal femur demonstrating final position of the retrograde IMN. **(D)** Lateral distal femur demonstrating correction of the apex posterior deformity after IMN placement. **(E)** AP distal femur demonstrating three distal interlocking screws placed through the jig. **(F)** AP proximal femur demonstrating two distal interlocking screws placed using perfect circle technique. **(G)** AP distal femur demonstrating replacement of the most distal interlocking screw through the plate to link the plate and IMN. **(H)** AP proximal femur demonstrating placement of distal screws through the plate around the IMN.

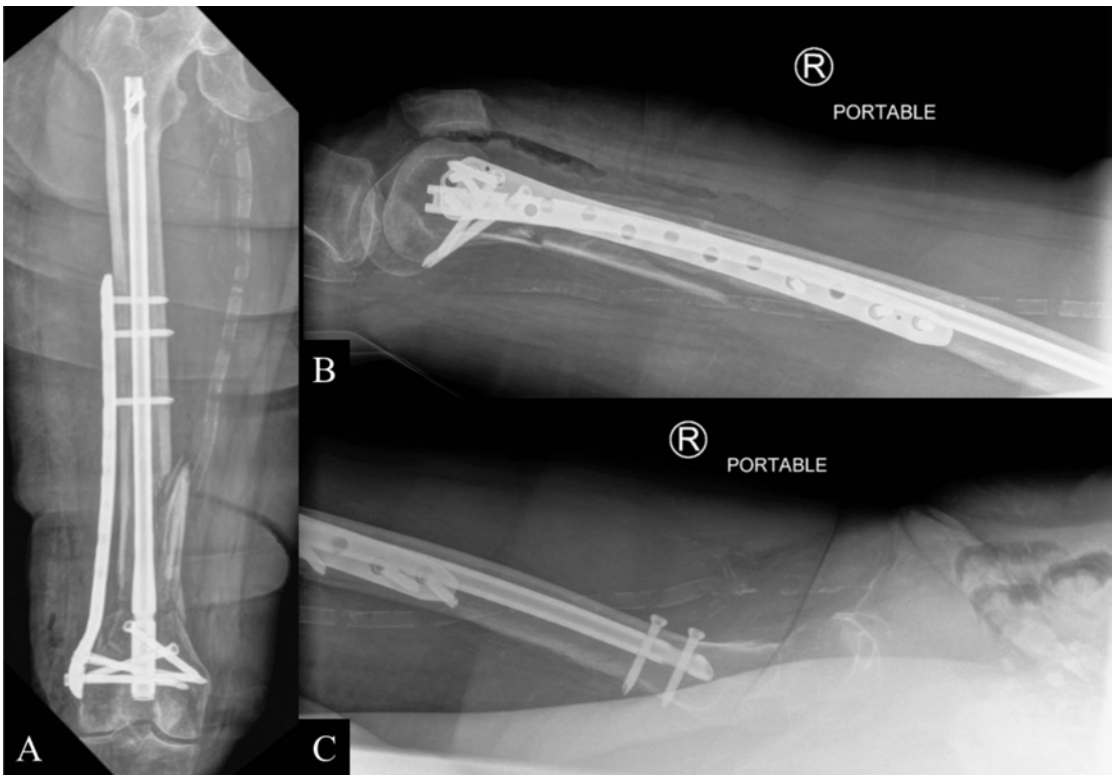

Figure 3. Patient X's final radiographs demonstrating NPC with Zimmer retrograde femoral nail and Zimmer NCB distal femur plate. **(A)** AP of the whole femur. **(B)** Lateral of the distal femur. **(C)** Lateral of the proximal femur.

necessary to achieve three screws proximally. A Zimmer distal femur NCB plate was selected. Next, a separate mid-lateral subvastus incision was made over the distal femur starting from Gerdy's tubercle. Sharp dissection was taken down. The iliotibial band was identified and incised in line with the incision. The femur was identified and the vastus lateralis was lifted off the intermuscular septum exposing the lateral aspect of the femur. This "proximal window" allows for direct

visualization and mid-axial placement of the plate, which was slid under the vastus lateralis, from the distal incision. The plate was balanced with K-wired in place. The plate was then secured with nonlocking screw distally through the plate and the nail using the jig for the nail to link the constructs and a nonlocking screw proximally around the nail to compress the plate to bone (Figures 2G and 2H). The plate was further secured with hybrid fixation with locking screws distally and non-locking screws proximally around the nail. Final fluoroscopic evaluation revealed good length, alignment and rotation of the femur with appropriate placed hardware (Figure 3).

Post-operative Care

Initiation of early physical therapy post-operatively is essential to prevent stiffness and loss of function. Traditionally with either nail or plate fixation, partial or non-weight bearing precautions are maintained for 6–12 weeks after surgery or until evidence of radiographic fracture healing. NPC allows for immediate weight bearing as tolerated. In the case of Patient X, she was made weight bearing as tolerated with a walker post-operative day one. She progressed well with physical therapy and was recommended for inpatient rehabilitation to improve functional mobility and maximize independence.

Conclusion

In summary, NPC offers a reliable technique for early mobilization after distal femur fractures. While plating and nailing alone usually require protected weight bearing, using NPC allows for immediate weight bearing. This can help improve outcomes and maintain baseline function, particularly in the growing geriatric population.

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Improving the Neer and AO Classifications of Greater Tuberosity Fractures: A Computational Framework

Michael W. Hast, PhD[1]
Kayley A. Dear, MS[1]
Josh R. Baxter, PhD[2]
Surena Namdari, MD, MS[2]

[1]Biedermann Lab for Orthopaedic Research, University of Pennsylvania, Philadelphia, Pennsylvania

[2]Rothman Institute, Thomas Jefferson University, Philadelphia, Pennsylvania

Introduction

Proximal humerus fractures are painful and debilitating injuries with an incidence rate that is expected to triple over the next thirty years.[1] Greater tuberosity (GT) fractures account for roughly 20% of proximal humerus fractures, and the vast majority of these injuries involve relatively small displacements of the GT bone fragment.[2] Traditionally, Charles Neer and the AO have classified the GT fragment as displaced (i.e. requires surgery) if it translates more than 5 mm from its anatomic position.[3] However, the Neer and AO classification systems do not take into account patient-specific anatomy, nor do they consider fragment orientation within the joint. The purpose of this study was to create a computational model that was capable of predicting subacromial impingement in patient-specific models. We hypothesized that the Neer and AO classification systems would not be able to accurately predict impingement in controlled simulations of GT fractures.

Methods

Eight intact fresh-frozen upper extremity cadaveric specimens were utilized in this preliminary study (3F, 1M; 60-70 y.o). Specimens were scanned in the anatomic pose with a clinical CT scanner using 0.5 mm axial slice thickness. Humeral and scapular geometries were segmented into 3-D renderings. Using a custom Matlab script, virtual bones were aligned to the International Society of Biomechanics shoulder coordinate system.[4] 3-D geometries were then inserted into a validated OpenSim shoulder model, which includes scapular rhythm during dynamic activities.[5] Virtual joints were adjusted to ensure they recapitulated patientspecific anatomy captured with CT scans. Specifically, we ensured that the humeral head was centered in the nadir of concavity of the glenoid and appropriate space was afforded between the proximal most point of the humerus and the inferior surface of the glenoid. Displaced GT fragments were created by slicing the humeri in the sagittal plane, 8mm medial to the lateral-most point of the GT. The GT fragments were systematically moved relative to the humerus with 4 different displacements (2.5, 5.0, 7.5, 10.0 mm) at 8 angles (0°, 45°, 90°, 135°, 180°, 225°, 270°, 315°) (Fig 1A). Once models were assembled, passive ROM tests were performed. Specifically, the models sequentially performed abduction from 0°-180° at 22 different elevation planes (-90° – 120°) (Fig 1B). For each motion, a binary determination of contact between the GT fragment and the acromion was determined with the onboard elastic foundation subroutine within OpenSim.[6] The probability of impingement for each ROM test was calculated by dividing the number of positive impingement motions by the total number of motions in a ROM test (22).

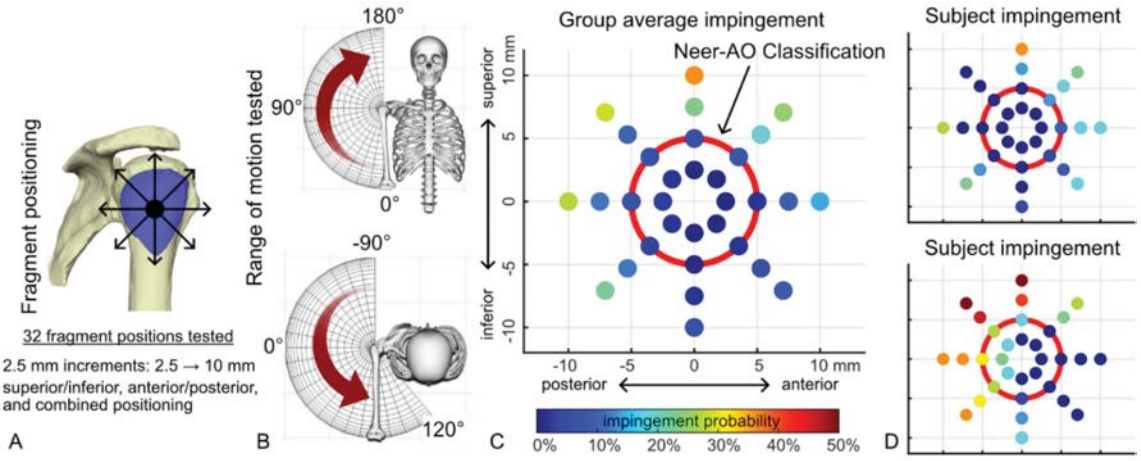

Figure 1. (A) The greater tuberosity fragment was iteratively positioned in 2.5 mm increments **(B)** and contact was simulated by creating abduction motions (top) in 22 different planes (-90° - 120°, bottom). **(C)** On average, fragment positioning of 5 mm or less from the anatomical position did not increase impingement probability. (D) While some individual specimens (top) had similar impingement profiles as the group average, other specimens bottom) experienced impingement with changes in fragment position as small as 2.5 mm.

Results

When averaging results from all 8 specimens, the average probability of impingement was 0.9%, 4.2%, 11.6%, and 21.1% for GT fragment displacements of 2.5, 5.0, 7.5 and 10.0 mm, respectively (Fig 1C). The majority of subacromial contact events occurred when arms were abducting in the 20°- 50° elevation planes. 7 out of 8 specimens did not experience impingement when the GT fragment was displaced 2.5 mm (Fig 1D, top). 2 out of 8 avoided impingement with 5.0 mm of GT fragment displacement. One specimen experienced impingement at all GT fragment displacement levels, but no impingements were detected when the fragment moved anteriorly, or antero-inferiorly (Fig 1D, bottom).

Discussion

The low values of 0.9% and 4.2% for average probability of impingement for the 2.5 and 5.0 mm displacements suggest that the Neer and AO classification systems may provide reasonable clinical guidelines for assessing displaced GT fractures.This finding somewhat nullifies our initial hypothesis, but it should be noted that several specimens in this small cohort of specimens clearly violated these guidelines. In this preliminary study there were large variabilities associated with measurements between specimens, which is to be expected with a human population. Further work is being done to incorporate a larger sample size.This model does not account for internal/external rotation of the humerus, muscle forces, or translation of the glenohumeral joint.All of these issues will be addressed in future iterations of the study.

Significant/Clinical Relevance

Subacromial impingent is difficult to predict with current standards of care, which include planar radiographs and rules-of-thumb that utilize gross displacement of the GT fragment. Precision medicine approaches, which may include 3-D imaging and computational modeling within the clinic, may allow for the accurate prediction of shoulder function following GT avulsions.

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U·P·O·J

Low Risk, High Impact: 3-D Printed Fracture Models for Resident Education

Danielle M. Cristino, PhD[1]
Kayley A. Dear, MS[1]
Elaine C. Schmidt, MS[1]
Michael W. Hast, PhD[1]
Samir Mehta, MD[1,2]

[1]Biedermann Lab for Orthopaedic Research, University of Pennsylvania, Philadelphia, Pennsylvania

[2]Department of Orthopaedic Surgery, University of Pennsylvania, Philadelphia, Pennsylvania

Introduction

As additive manufacturing (AM) becomes more ubiquitous, orthopaedic standards of care are also evolving towards patientspecific precision medicine.There exists a wide spectrum of clinical uses for AM within the operating room -from patient-specific implants, to single-use custom cutting guides.[1] The educational utility of 3-D printing should not be overlooked. For cases involving trauma, 3-D models of bone fractures can be created quickly and cheaply using CT or MR images.These models can serve as valuable teaching tools, as they allow learners to manipulate and reduce the fracture in a low-risk, low stress scenario. This may improve confidence and visuospatial skills that are required during surgery. Currently, there is a lack of data describing the impact of these tools on resident trainee competence.[2,3] The objective of this study was to quantify the influence of tactile learning on resident trainee performance during a variety of trauma-based operations. It was hypothesized that pre-operative utilization of AM models by a resident population would lead to improvements in confidence, accuracy, and efficiency in the operating room, as indicated by Ottawa Surgical Competency Operating Room Evaluations (O-Scores).[4]

Methods

This preliminary (Institutional Review Board-approved) study involved 7 learners that performed a total of 34 surgical procedures. Trainees performed the same procedure on two separate patients.The first surgery (n = 17) was performed in the absence of supplemental learning tools (i.e. AM models). For the second surgery, cases were randomly assigned to either receive a 3-D printed physical model of the fractured bone (n = 11) or to omit it (n = 6). Briefly, the following procedure was used for "second surgeries": An algorithm randomly determined whether the trainee would receive a 3-D printed model of the fracture or if they would serve as a control. If selected for an AM model, pre-operative CT scans of fractures were scrubbed of all patient-identifying information and submitted to the research lab. CT scans were segmented, converted into 3-D renderings, and printed with 0.125 mm resolution. The physical models were provided to the trainees at least 24 hours before surgery. Following surgery, the attending surgeon evaluated the ability of the trainee to independently perform the surgical procedure with an O-Score. This scale uses a 1-5 rating in 8 different categories. An overall average score of 1 indicates that the trainee needed total hands-on guidance from the attending surgeon or was unable to perform the procedure. An average score of 5 indicates that the learner performed the procedure without any guidance. Shapiro-Wilk tests were performed to test for normality. For non-Gaussian data, a MannWhitney-Wilcoxon Test was performed to identify potential differences between groups. Otherwise, two-tailed, equal variance t-tests were used to assess unknown responses across groups.The significance level was set at $p < 0.05$ and post-hoc Bonferroni corrections were used.

Results

A significant improvement in O-Score was observed between the first and second case for resident trainees who received physical models (P-value = 0.0004, Table 1). Specifically, the average O-score was 2.43 ± 0.91 for the first case

Table 1.

Category	Control Case 1	Control Case 2	AM Model Case 1	AM Model Case 2
Preprocedure Plan	2.83 ± 0.98	2.83 ± 0.75	2.09 ± 0.83	3.73 ± 0.65
Case Preparation	2.67 ± 0.82	2.67 ± 0.52	2.36 ± 0.67	3.55 ± 0.52
Knowledge of Procedural Steps	2.83 ± 1.17	3.00 ± 0.63	2.45 ± 1.13	3.73 ± 1.01
Technical Performance	2.83 ± 0.75	2.83 ± 0.75	2.36 ± 1.12	3.73 ± 1.01
Visuospatial Skills	1.67 ± 0.52	1.67 ± 0.52	1.82 ± 0.75	4.18 ± 0.87
Postprocedure Plan	3.33 ± 0.82	4.00 ± 0.00	3.55 ± 1.04	3.82 ± 0.40
Efficiency and Flow	2.67 ± 0.82	2.50 ± 0.55	2.27 ± 0.79	3.55 ± 0.82
Communication	2.67 ± 0.52	2.67 ± 0.52	2.55 ± 0.93	3.55 ± 0.69
O-score	2.69 ± 0.80	2.77 ± 0.53	2.43 ± 0.91	3.73 ± 0.75

and 3.73 ± 0.75 for the second case. A significant difference in O-score was not observed for the control cases (p-value = 0.799), with small changes in average scores between first and second cases (2.69 ± 0.80 and 2.77 ± 0.53, respectively). Significant increases in sub-scores were observed in 7 of 8 categories for the group that received physical models. Most notably, visuospatial skills showed the greatest increase in rating for the physical model groups, with average ratings increasing from 1.82 ± 0.75 to 4.18 ± 0.87 between the first and second case (p-value = 0.0001). In addition, pre-operative planning ratings were greatly improved in the physical model group between the first and second case, with the average ratings increasing from 2.09 ± 0.83 to 3.73 ± 0.65. The only rating that did not significantly improve in this group was "post-operative plan," which only increased marginally. There were no significant differences in ratings for all 8 categories in the control group.

Discussion

The results from this study suggest that AM models are an excellent addition to the education curriculum for resident surgeons. The immense improvement in visuospatial rating in particular, which involves mastery of positioning instruments as intended, demonstrates the importance of catering to a variety of learning styles. Although it was not a primary outcome measure, it should be noted that the 3-D models were inexpensive to create. Models typically cost < $10 of material to build. There are several limitations associated with this study. First, the pool of learners was relatively small, and years of residency experience varied (PGY-2 through PGY-5). Because this study was performed in the trauma department, many different injuries with varying fracture complexity were included in the dataset. Even when considering these shortcomings, the results of this study show that 3-D printed models provided effective tools which may improve overall outcomes. In the future, we plan to continue this study to strengthen these preliminary results.

Significant/Clinical Relevance

The results of this study demonstrate the ease and utility of AM models of fracture for improving resident trainee comprehension and performance during surgery.

Acknowledgements

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Nitinol Staple Fixation of Clavicle Fractures Results in a More Flexible Construct than Plating

Elaine C. Schmidt, MS[1]
Chelsea J. Hendow, MD[2]
Liane M. Miller, MD[2]
Kayley A. Dear, MS[1]
Samir Mehta, MD[1,2]
Michael W. Hast, PhD[1]

[1]Biedermann Lab for Orthopaedic Research, University of Pennsylvania, Philadelphia, Pennsylvania

[2]Department of Orthopaedic Surgery, University of Pennsylvania, Philadelphia, Pennsylvania

Introduction

Midshaft clavicle fractures are often reconstructed with plates and screws, but these implants

cause poor cosmesis and irritation, which may result in a second surgery for hardware removal.[1] This has driven the need for innovation in clavicle fixation, including the use of smaller 2.7 mm plates.[2,3] However, these techniques have not definitively shown improvements in hardware related complication rates.[4] Thus, areas of possible improvement remain in the operative management of these fractures. Continuous compression implants (CCIs) fabricated with shape memory alloys, such as Nitinol, provide an attractive alternative to plate and screw fixation, due to their low profile and ability to provide compression at the fracture site. The use of CCIs gained traction in foot and ankle reconstructions[5], but the technology has not yet been tested in the milieu of clavicular fixation. We hypothesized that CCI-based reconstructions would decrease resistance to external loads compared to plate and screw fixation.

Methods

This study was performed with 36 synthetic and 12 matched pairs of fresh-frozen, osteopenia-confirmed cadaveric clavicles (8F, 4M, 80 ± 8 years old). The synthetic study consisted of four reconstruction techniques: a single superiorly-placed staple (SS; n = 6), a single anteroinferiorly-placed staple (AS; n = 6), a 3.5 mm reconstruction plate (PLT; n = 12), and two Nitinol staples placed orthogonally to each other (2S; n = 12) (Fig 1). The cadaveric study examined three reconstruction techniques: PLT (n = 8), 2S (n=8), and a new group with a 2.7 mm reconstruction plate placed combined with a Nitinol staple (PLT+SS; n = 8) (Fig 1). All specimens underwent non-destructive 4-point bending (loading in superior-inferior direction, 2 mm deflections) and axial torsion tests (+/−10°) for 10 cycles each. Half of each group was then subjected to either a 3-point cantilever bend to failure (0.5mm/s), or cyclic failure under increasing torsion (+0.1 Nm/cycle) until implant breakage or bending exceeding 30 mm. Groups were evaluated for normality and equal variance and compared using one-way ANOVAs ($p < 0.05$).

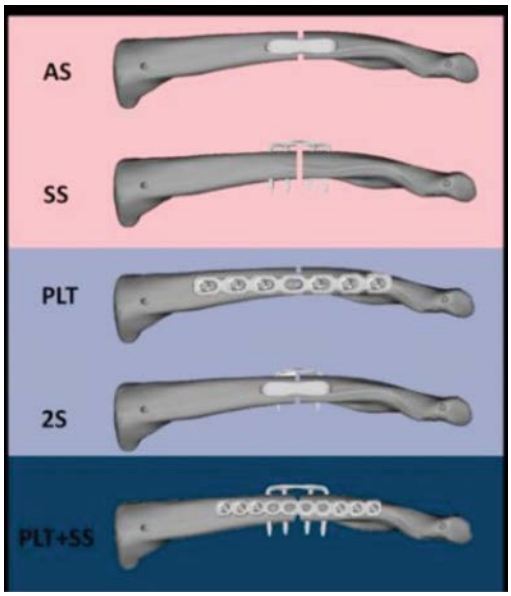


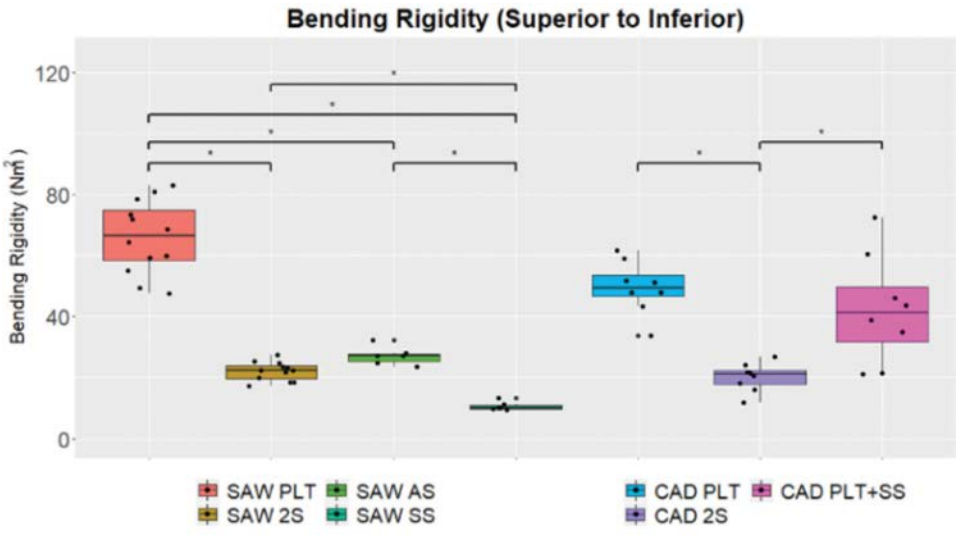
Figure 1. Clavicle fixation techniques examined in this study. Groups highlighted in pink were tested with synthetic bones, groups highlighted in blue were tested in cadaveric specimens. Purple represents overlap of synthetic and cadaveric test groups.

Results

In comparison to plated groups, the single-staple and double-staple groups demonstrated significantly decreased resistance to bending and torsion. For example, the synthetic and cadaveric PLT group exhibited significantly higher bending rigidity than all other groups in superior-inferior 4-pt bending ($p < 0.001$), except for the cadaveric PLT+SS group (Fig 2). In cantilever failure tests, the failure mode for PLT and AS groups was bending > 30mm, while all other groups exhibited catastrophic bone fractures primarily at the medial-most components of the implants. In destructive torsional testing, failure modes for cadaveric specimens were primarily due to implant tear-out (75%). (Fig 3A,C). Synthetic bone specimens primarily failed via implant breakage (67%) (Fig 3B, D).

Discussion

In accordance with our hypothesis, the use of Nitinol staples resulted in reconstructions that were significantly less stiff than those created with plates and screws. Single staples provided inadequate construct stiffness in non-destructive and destructive tests and are not currently indicated for stand-alone use in



p-values			
PLT vs 2S	<0.001	PLT vs 2S	<0.001
PLT vs AS	<0.001	PLT vs PLT+SS	0.241
PLT vs SS	<0.001	2S vs PLT+SS	0.002
2S vs AS	0.181		
2S vs SS	0.008		
AS vs SS	0.002		

Figure 2. Results from non-destructive 4pt bend tests on Sawbones (SAW) and cadaveric (CAD) specimens.

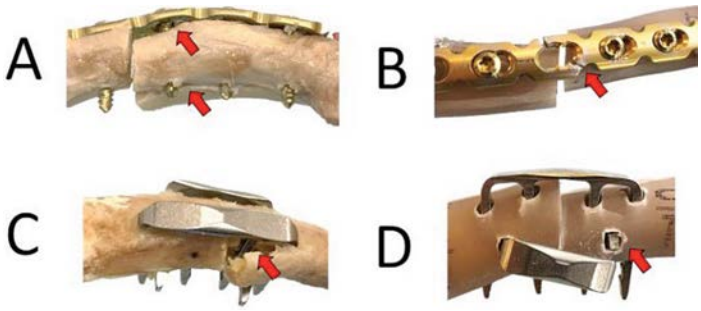


Figure 3. Differences in failure modes for cadaveric and synthetic specimens for the PLT and 2S groups.

the clavicle or in osteoporotic bone. However, the lack of permanent deformation of constructs during non-destructive cadaveric testing suggests that CCI fixation—particularly for configurations reinforced by an additional staple or plate—may provide adequate relative stability while the patients is in rehabilitation and protected from large ranges of motion and high external loads. Strikingly, the synthetic models produced failure mechanisms that were completely different from the cadaveric specimens, suggesting that plastic models are poor surrogates in these mechanical tests.

Significant/Clinical Relevance

Clavicle fracture fixation continues to be a challenging clinical problem, and improving fixation while minimizing cosmesis and irritation is a worthwhile clinical endeavor. This study also highlights the need for better synthetic bone analogs, especially for osteoporotic bone.

Acknowledgements

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U·P·O·J

Topical Administration of Raloxifene Does Not Significantly Improve Bone Toughness or Screw Pull-out Strength

Michael R. Eby, MD[1]
Danielle M. Cristino, PhD[2]
Matthew Counihan, MD[1]
Kendall M. Masada, MD[1]
Michael W. Hast, PhD[2]
Jaimo Ahn, MD, PhD[1]

[1]Department of Orthopaedic Surgery, University of Pennsylvania, Philadelphia, Pennsylvania

[2]Biedermann Lab for Orthopaedic Research, University of Pennsylvania, Philadelphia, Pennsylvania

Introduction

Upper extremity fractures account for one-third of all fractures in the elderly.[1-3] In addition, there is an increased risk of proximal humerus fractures in patients with osteoporosis.[1,4,5] Failure of fixation has been shown in some series to be greater than 40 percent[6] and is attributed to limited pullout strength of screws in poor quality of bone stock.[7] While considerable efforts have been made towards improving implant design, relatively little research has addressed localized treatment of the underlying changes in the mechanical properties of cancellous bone in the humeral head. Previous studies have shown that Raloxifene, a selective estrogen receptor modulator used to prevent and treat osteoporosis, can increase the toughness of bone in vitro.[8] To date, it is unknown if this improvement in mechanical toughness will translate into a clinically significant difference in screw pull-out strength. The purpose of this study was to make direct comparisons between osteoporotic bones treated topically with Raloxifene and untreated bone. It was hypothesized that toughness and implant fixation strength can be improved with this straightforward approach.

Methods

The first portion of this study involved four-point bending tests of bone beams to determine toughness. Cancellous bone specimens were carefully harvested from fetal bovine femora using a bone saw and sanded to a uniform size (25 × 4 × 1.5 mm). Digital calipers were used to ensure that specimen size fell within a ± 0.05 mm tolerance. Prior to mechanical testing, bone specimens were sonicated for thirty seconds, wrapped in gauze with phosphate-buffered saline (PBS) solution, and subjected to two freeze-thaw cycles at −20°C. Matched pairs of specimens were then submerged in solutions for one week at a temperature of 4°C with continuous stirring. Specimens were soaked in either a Raloxifene solution at a concentration of 20 μM (RAL) or a PBS solution as a control (CTL). All solutions had 1% penicillinstreptomycin. Specimens were thawed to room temperature prior to testing. The beams were positioned within a test fixture (Fig 1.) on a universal testing frame (Instron 5542; Norwood, MA) equipped with a 50 N load cell and quasi-statically loaded

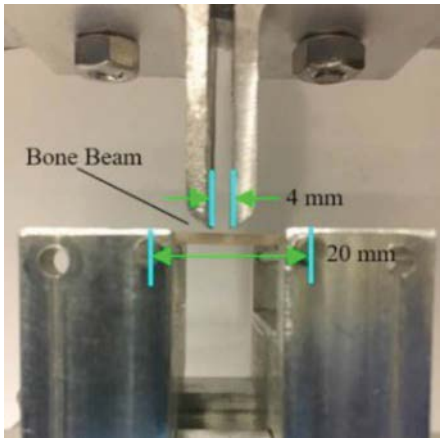

Figure 1. 4-point bending test setup.

to failure. The second portion of the experiment involved pull-out testing of 3.5 mm cancellous screws (DePuy Synthes, Warsaw, IN) from human cadaveric humeri that were confirmed to be osteoporotic by DEXA scans. The humeri were decorticated with the exception of the lateral wall. The screws were inserted unicortically to a depth of 30 mm in 5 standard trajectories based on a small fragment locking proximal humerus plate (DePuy Synthes, Warsaw, IN). Each sample came as a matched pair and one side was soaked in RAL solution and the contralateral side in control solution. Pull-out testing was conducted on a universal testing frame (TA Electro-Force 3550; Eden Prairie, Minnesota) equipped with a 1,110 N/14.1 N-m load/torque cell. The screws were pulled out at 0.03 mm/sec until failure and the load at failure was determined.

Results

The toughness in four-point bend testing was not significantly different between groups ($p = 0.876$) (Fig. 2). The toughness values were 0.151 ± 0.068 J/m3 and 0.155 ± 0.0439 J/m3 for the RAL and CTL groups, respectively. For the screw pull-out tests, the Raloxifene soaked samples trended towards a higher load at failure, however these results were not statistically significant (p-value = 0.099) (Fig. 3). Failure loads were 122 ± 74.3 N and 89.5 ± 63.8 N for the RAL and CTL groups, respectively.

Discussion

Research into biological therapies to address osteoporotic disease is scarce, despite the

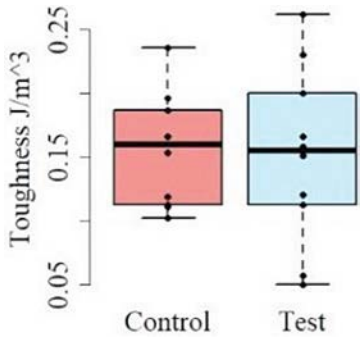

Figure 2. Toughness results.

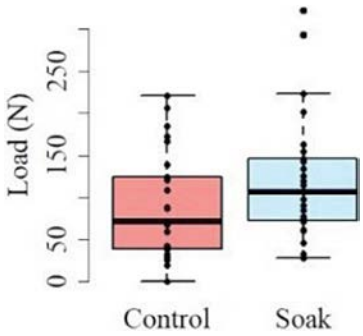

Figure 3. Screw pull-out results.

profound improvements to surgical outcomes that they may offer patients. While screw pull-out strength trended towards a higher failure load in the RAL group, the results were not statistically significant. Bone toughness was not increased by soaking the specimens in Raloxifene. This is in contrast to previously published data by Gallant et al., which found that topical administration of Raloxifene solution increased toughness, however these results are not directly comparable. The current study included fetal bovine and human cadaveric bone, whereas the study by Gallant et al. was performed on dog tibiae.[8] In addition, the current study used cancellous bone instead of cortical bone. This study included several limitations. The number of samples that could be harvested from each bone was limited by the size of the bone and the presence of arteries. In addition, cancellous bone introduced greater structural variability into the specimens. Future work on this project with larger sample sizes may demonstrate a statistically significant trend that could directly influence clinical practice. Rather than using individual screw pull-out testing as a proxy for failure, an entire locking plate-screw construct could be tested. While significantly more costly, testing a locking plate-screw construct would be more clinically relevant.

Significant/Clinical Relevance

This research shifts the focus of the discussion regarding osteoporotic fracture care from implant design to identifying biologic solutions that address the true underlying issue of bone quality. The results show that topical administration of Raloxifene does not significantly increase bone toughness or screw pull-out strength, which contradicts the results of previous work.

Acknowledgments

This study was funded by AO Trauma North America.

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U·P·O·J

Spine Tips & Tricks: Performing a Pedicle Subtraction Osteotomy (PSO)

Sachin Gupta, MD[1]

[1]Department of Orthopaedic Surgery
University of Pennsylvania

Introduction

First described by Thomasen et al., the pedicle subtraction osteotomy (PSO) is a useful technique in the treatment of adult spinal deformity (ASD).[1] The PSO involves a transpedicular wedge resection from the posterior elements through the vertebral body and can provide correction in the sagittal plane of up to 30 to 40 degrees without the need for a combined anterior and posterior approach in the setting of rigid curves[2]pedicles, and vertebral body through a posterior approach. In addition, this posterior-only osteotomy can provide significant correction without lengthening the anterior column, avoiding injury to the anterior abdominal structures.[2–5]pedicles, and vertebral body through a posterior approach

Despite its ability to provide such great sagittal correction, there is a high number of complications associated with the PSO, especially rod failures. Naturally performed with 2 rods, when correction is achieved following wedge closure this can create a large amount of stress at the apex of the osteotomy. Rod failure rates have been reported as high as 15.8%.[6] The technique described below has been shown to prevent these rod failures, utilizing a four-rod construct.[7] It allows for distribution of the stress along two smaller rods placed immediately above and below the osteotomy sites with 2 additional long rods that bridge across the osteotomy without being connected to the smaller rods, decreasing the vulnerability of the rods for rod fracture and reduces the rate of pseudarthrosis.

Technique

Indications for the PSO include fixed sagittal malalignment and prior anterior column fusion[8]. Decision-making regarding the PSO level depends on several factors. It is more commonly performed below the conus in the lumbar spine to reduce neurological complication from thecal sac manipulation and wedge closure. However, it can be performed at the thoracic or cervical level in certain cases such as post-traumatic kyphosis. In these cases, retraction of the thecal sac should be avoided.

The level of the PSO itself should depend on the location and the type of the pathology. If the patient has a focal fixed-angled sagittal deformity, the PSO should be performed at the level of the kyphosis. However, in the absence of such kyphosis, a lumbar PSO should be performed.

Careful planning beginning outside the operative room is paramount to achieving improved efficiency of the procedure itself and prevent complications.

Exposure

The surgeon should take great care in providing extensive, meticulous exposure with excellent hemostasis. One should preserve the interspinous and the supraspinous ligaments in the area of the upper instrumented vertebra, to prevent PJK.[9]with corresponding torques recorded. Data were collected after a series of 6 posterior procedures. Differences with P value < 0.01 were considered significant and those with P value < 0.05 marginally significant. RESULTS: Supratransverse process hook, supralaminar hook, pedicle screw placement, or pedicle screw removal done, bilaterally, produced similar, small (range, 2.09%-6.03% With careful attention to the anatomical variation in size, angulation, and rotation of the pedicles, screws are then placed above and below the planned level of the PSO at multiple levels, with two being the minimum.

Decompression

The posterior laminectomies and decompression are then performed. At the level of the PSO, a complete laminectomy extending through the bilateral pars interarticularis is performed in addition to bilateral facetectomies. However, superior and inferior to the level of the PSO, a partial laminectomy is performed through the bilateral pars interarticularis. Centrally, decompression is achieved with resection of the ligamentum flavum. In the case of revision laminectomies, one should take care removing the scar tissue above the thecal sac. Removing the scar allows the dura to have multiple buckles rather than one stiff area producing a single buckle which can cause cauda equina compression. At the level of the PSO, the bone surrounding the pedicle is completely removed, including the transverse process. This should provide exposure of the four nerve roots bilaterally (Figure 1). At the level of the pedicle, the cobb elevator is used to expose the vertebral body on both sides. If the segmental vessels are

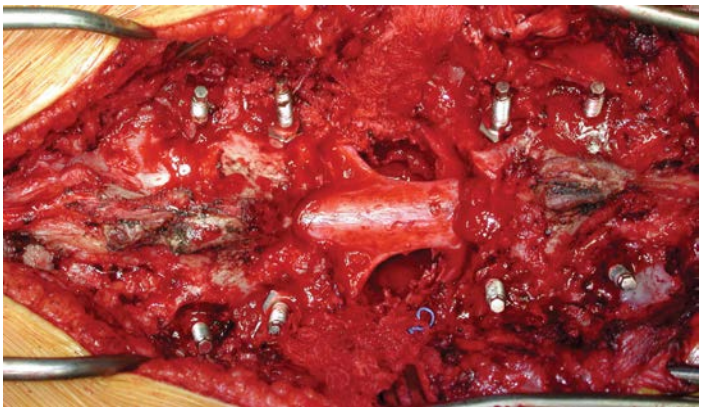

Figure 1. Exposure of the four nerve roots and six pedicles is essential prior to performing the pedicle subtraction osteotomy.

encountered, bipolar cautery is used to control the bleeding. The plane between the lateral aspect of the vertebral body and the adjacent soft tissue is then developed and maintained with the use of sponges or retractors. This allows for adequate visualization of the bony anatomy including the vertebral body. At this point, the posterior retractors are placed. Utilizing nerve root retractors to protect each individual nerve root, the pedicle is decancellated and the vertebral body is hollowed out using a curette. The wall of the pedicle is then resected using a rongeur.

Wedge Osteotomy

Using an osteotome, a pre-planned wedge is made with wider resection posteriorly, allowing for creation of the proper wedge. If necessary, fluoroscopic guidance can be utilized to maintain orientation when creating such a wedge. If a wedge is not created, this will not improve the lordosis or sagittal alignment, but instead will result in shortening of the entire column. One must also take care to resect laterally from the walls of the vertebral body, to prevent impingement upon closure. The spoon retractors should be placed with care to separate the psoas from the vertebra body side walls and not left in place for a long time.

In this manner, the anterior cortex remains preserved, which allows for decreased risk of injury to the anterior vessels and viscera. During the osteotomy, one must take care to continuously protect the nerve roots and thecal sac with the appropriate nerve root retractors in addition to providing hemostasis control with the use of hemostatic agents and sponges. When performing an osteotomy on one side, a rod should be placed above and below the osteotomy site and the process should be repeated on the other side. When decancellating the vertebral body, one must take care to begin with creating a thin posterior cortical wall. Then a Woodson or a curved freer can be used to remove any dural adhesions to the posterior wall, to prevent injury to the anterior portion of the dura. Once the resection of the lateral walls is complete, a Woodson or a posterior body wall impactor can be used to fracture the posterior wall into the cavity created and these elements can be resected using a Leksell or pituitary rongeur. In addition, asymmetric PSOs can be performed in the cases of kyphoscoliotic deformities, allowing for correction in the coronal plane upon wedge closure.

Osteotomy Closure

Before obtaining closure of the osteotomy, care must be taken to remove any remaining bony fragments than might compress the exiting nerves, since the two adjacent exiting nerves will now share a newly created "super" foramen on each side. A table that may bend the torso in extension can be very useful in closing the osteotomy. This can be more useful then closing the osteotomy by compression across the screws above and below the osteotomy. During closure, with the help of neuromonitoring, the neural elements are carefully accounted for. If no neuromonitoring changes are recorded and the nerve roots are free of any impingement from bone or soft tissue, the surgeon can then place the final rods and perform final tightening.

In this manner, the wedge osteotomy can be successfully closed and the correction is maintained by the short rods connecting the immediate adjacent levels. (Figure 2). The long rods are then placed along the entire length of the

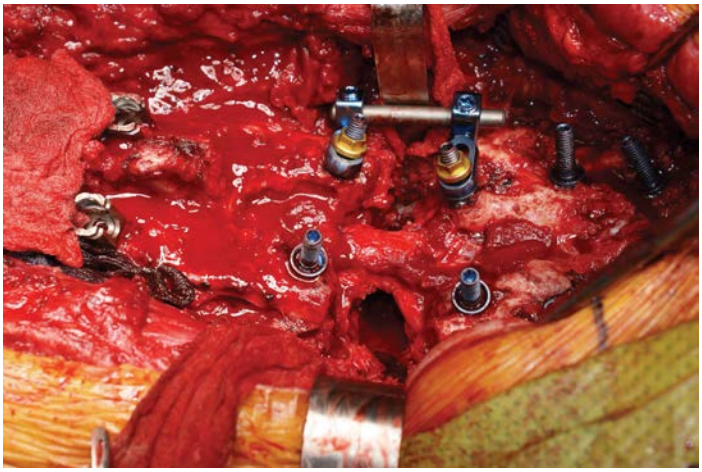

Figure 2. The short rods control the osteotomy closure as well as prevent translation while finishing the osteotomy.

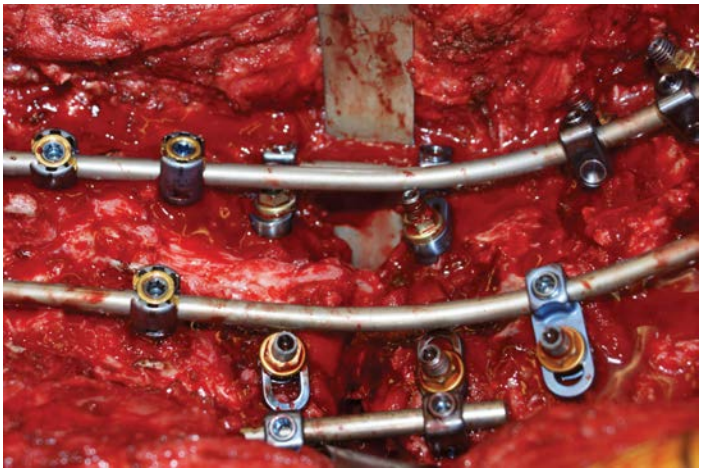

Figure 3. The short rods hold the osteotomy correction during placement of the long rods and are independent of the long rods.

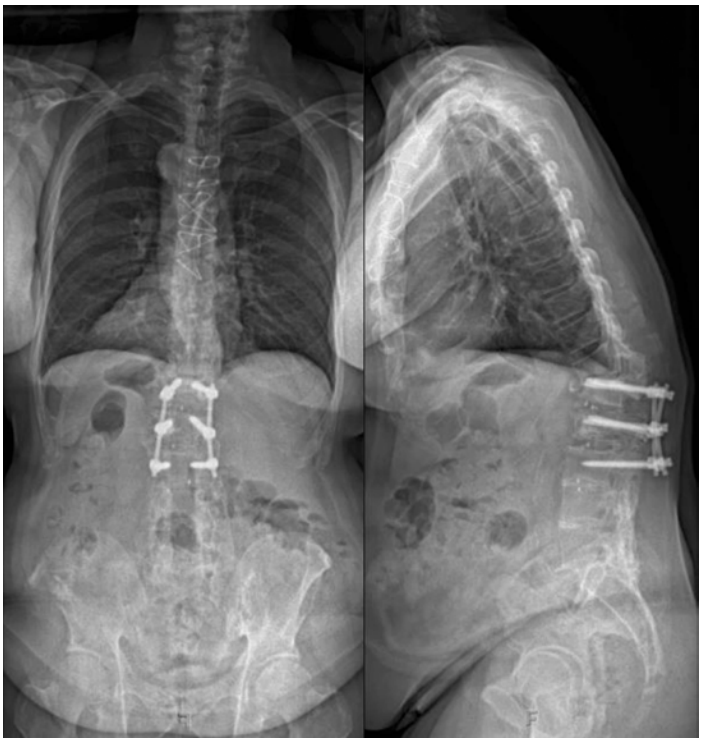

Figure 4. These are the pre-operative x-rays of a 65 year old male with 4 prior spine surgeries in 1998, 2008, 2015, and 2016. He had a fusion at L4-L5 and developed footdrop on the right side. The fusion was extended to L3 and then extended again to L1. The fusion was revised from L1 to L3 because of screw cut out. He presented in clinic with junctional failure above L1.

instrumented fusion and are not connected to the screws attached to the short rods (Figure 3). This avoids the need for severe angular bending of the long rods, which can weaken the rods, make them vulnerable to rod fractures, and predispose the patient to pseudarthrosis. If there is any concerning change in the neurophysiological monitoring, the closure should be stopped and reversed to protect the neural elements and further decompression and resection of the bony elements may be necessary.

Finishing Steps

The procedure is then completed with decortication with a high-speed drill followed by placement of harvested bone graft or the off-label use of rh-BMP2, bone morphogenetic protein. Drains are then placed and closure of the wound is then performed. A case example is presented in Figures 4-6.

Conclusions

Pedicle subtraction osteotomies are an outstanding tool in the treatment of adult spinal deformity. They are useful in revision surgery as well as in the treatment of severe, rigid curves. However, surgeons must be aware of the higher complication rates associated with osteotomies and should carefully review the lessons and newly-derived technique modifications illustrated in the recent literature.

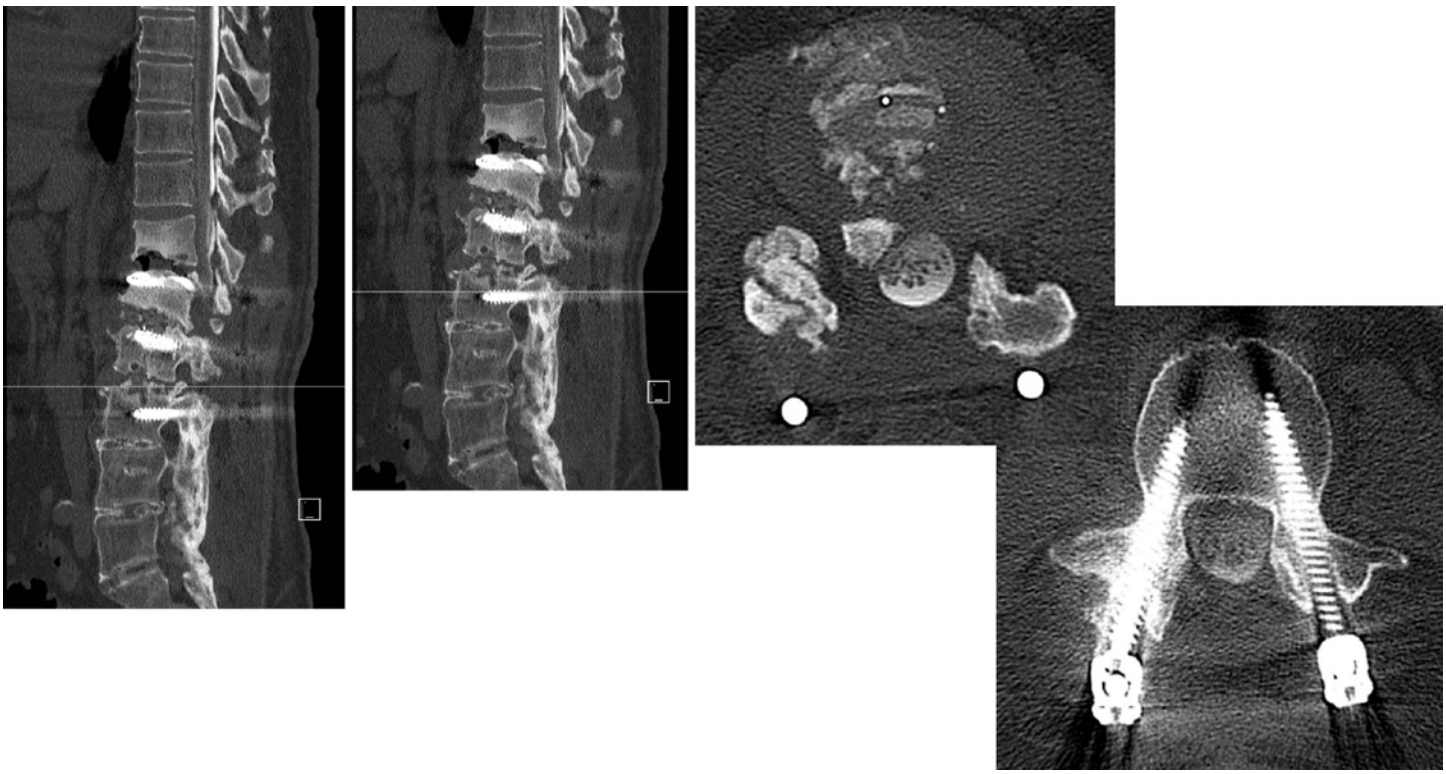

Figure 5. The CT scan shows bone fragments in the canal as well as pseudarthroses at multiple levels.

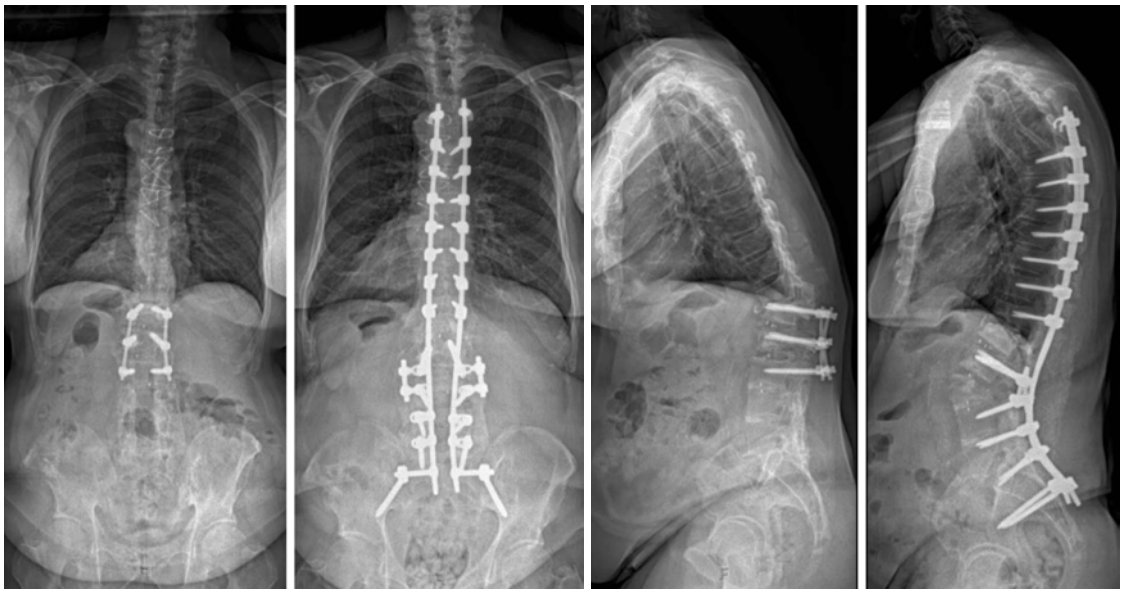

Figure 6. Pre-operative and Post-operative x-rays demonstrating the amount of correction achieved with the four-rod technique. PSO allows for correction of the flatback as well as extension of the fusion into the thoracic spine.

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Engineered Total Disc Replacements in a Large Animal Model Recapitulate Native Disc Structure and Function

Sarah E. Gullbrand[1,2]
Beth G. Ashinsky[1,2,3]
Dong Hwa Kim[1,2]
Lachlan J. Smith[1,2]
Dawn M. Elliott[4]
Thomas P. Schaer[1]
Robert L. Mauck[1,2]
Harvey E. Smith[1,2]

[1]University of Pennsylvania, Philadelphia, PA

[2]Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA

[3]Drexel University, Philadelphia, PA

[4]University of Delaware, Newark, DE

Introduction

Intervertebral disc degeneration is commonly associated with back and neck pain, and current surgical treatments for end-stage degeneration, including spinal fusion, do not restore spine function. Replacement of the degenerative intervertebral disc with a living, tissue engineered construct has the potential to restore normal structure and function to the spine.[1] Towards this end, we developed endplate-modified disc-like angle ply structures (eDAPS) that recapitulate the structure and function of the native disc. These implants combine a cell-seeded hydrogel nucleus pulposus (NP) and an electrospun poly(ε-caprolactone) (PCL) annulus fibrosus (AF) with acellular PCL foam endplates.[2,3] We previously showed in a rat tail disc replacement model that eDAPS functionally mature *in vivo*, recapitulating many of the characteristics of the native disc and that eDAPS could be fabricated at human length scales for evaluation in a large animal model.[4] Here, we compare eDAPS structure and mechanical function following *in vivo* implantation to healthy and degenerative (discectomy) goat cervical discs at 8 weeks.

Methods

eDAPS sized for the goat and human cervical disc space (9 mm height, 16 mm diameter) were fabricated as previously described[4] and seeded with allogeneic goat bone-marrow derived mesenchymal stem cells. eDAPS were cultured for 13-17 weeks in a chemically defined media with TGF-β3 prior to implantation. With IACUC approval, 5 male large frame goats underwent a surgical procedure to implant the eDAPS at the C2-C3 level of the cervical spine. Implanted motion segments were immobilized with an anterior cervical plate to ensure construct retention. The C3-C4 discs adjacent to the eDAPS implants were utilized as healthy controls. 3 additional goats underwent a surgical procedure to induce degeneration of the C2-C3 disc via sub-total discectomy. Animals in both cohorts were euthanized at 8 weeks for analyses. Cervical spines were subjected to MRI at 3T to obtain both a T2-weighted image, and an image series for quantitative T2 mapping. Following MRI, cervical motion segments from each experimental group (healthy, degenerative, and eDAPS implanted) were isolated and subjected to 20 cycles of compression, where the applied compressive stress was equivalent to that of the human cervical disc, due to the weight of the head (0 to −25 N, 0.084 MPa). Mechanical properties were quantified via a bilinear fit of the toe and linear regions of the stress-strain curve. Motion segments in each group were then fixed, decalcified and processed through paraffin for histology. Sections were stained with alcian blue (proteoglycans) and picrosirius red (collagens). Significant differences ($p < 0.05$) in quantitative outcomes were assessed via a Kruskal-Wallis with Dunn's multiple comparison test.

Results

eDAPS implants generally recapitulated the structure and composition of the healthy disc after 8 weeks *in vivo* (Figure 1A), with a proteoglycan rich nucleus pulposus and a lamellar and collagen rich annulus fibrosus. Furthermore, histology demonstrated robust integration of the PCL endplates with the adjacent vertebral bodies. In contrast, discectomy resulted in substantial degeneration of the motion segment, including severe annular disorganization, boney endplate remodeling, NP fibrosis, and loss of disc height. T2 weighted MRIs (Figure 1B) demonstrated high signal intensity within the eDAPS, similar to the control disc, compared to a loss of NP signal intensity in the discectomy group. T2 relaxation time in the NP (Figure 1C) was significantly reduced in degenerative discs compared to controls. There was no detectable difference in NP T2 between eDAPS implants and healthy or degenerative discs. Degeneration induced via discectomy also compromised disc mechanical function, with significant increases in compressive strain and reductions in toe and linear moduli, compared to eDAPS implants (Figure 2). Although the moduli of eDAPS implanted motion segments trended higher than controls, transition and maximum strains were within the range of controls.

Discussion

Our results demonstrate that surgically induced disc degeneration significantly alters the structure, composition and mechanical function of the healthy disc, while eDAPS implantation improved motion segment structure and function toward healthy levels.

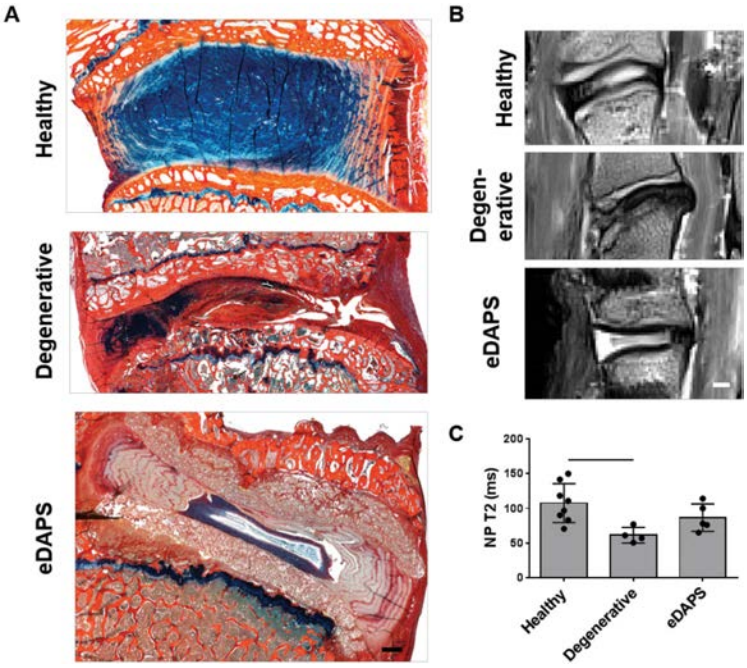

Figure 1. (A) Alcian blue and picrosirius red stained histology of eDAPS 8 weeks post-implantation compared to healthy and degenerative goat cervical discs, scale = 1 mm; **(B)** T2 weighted MRI of eDAPS after 8 weeks of implantation, compared with healthy and degenerative goat cervical discs, scale = 4 mm; **(C)** NP T2 relaxation times for all groups (bars denote $p < 0.05$).

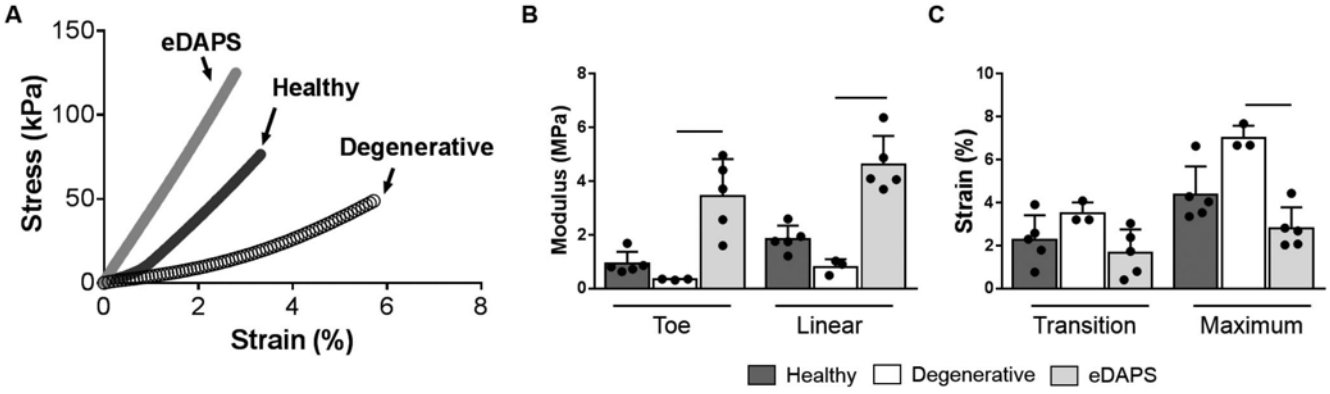

Figure 2. (A) Representative compressive stress-strain curves for each experimental group, from which **(B)** toe and linear region moduli and **(C)** transition and maximum strains were calculated. Bars denote $p < 0.05$.

After two months *in vivo*, eDAPS integrated with the native tissue, and their structure and function recapitulated many features of the native, healthy disc. However, quantitative MRI revealed that the NP T2 of the eDAPS spanned the range of NP T2 relaxation times for both healthy and degenerative discs, and corresponded with low GAG staining and matrix content in the central NP on histology. This is likely due to low cell viability and matrix accumulation in this region during *in vitro* culture[5]. Future work will focus on strategies to enhance cell viability and improve matrix homogeneity within these large human-scale engineered constructs. Ongoing work is also focused on exploring the effects of plate removal to restore anabolic, physiologic loading to the eDAPS *in vivo*, post implantation and integration.

Conclusion

Results from this study demonstrate that a tissue engineered disc replacement can restore native-like structure and function to the disc, compared with degenerative discs. Development and translation of tissue engineered total disc replacements has the potential to significantly expand treatment options for patients with symptomatic advanced disc degeneration, restoring disc structure and function via a living implant.

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Inflammatory Cytokine and Catabolic Enzyme Expression in a Goat Model of Intervertebral Disc Degeneration

Chenghao Zhang[1,2]
Thomas P. Schaer[1]
Sarah E. Gullbrand[1,2]
Zhirui Jiang[1,2]
Yian Khai Lau[1,2]
Dawn M. Elliott[3]
George R. Dodge[1,2]
Robert L. Mauck[1,2]
Neil R. Malhotra[1]
Lachlan J. Smith[1,2]

[1]University of Pennsylvania, hiladelphia, PA

[2]Corporal Michael J. Crescenz Philadelphia VA Medical Center, Philadelphia, PA

[3]University of Delaware, Newark, DE

Introduction:

Intervertebral disc degeneration is implicated as a leading cause of low back pain. Persistent, localized inflammation within the disc nucleus pulposus (NP) and annulus fibrosus (AF) is considered to be a key mediator of disc degeneration, and is associated with downstream catabolic enzyme activity and extracellular matrix destruction. Disc inflammation is characterized by expression of cytokines including IL-1β, IL-6 and TNF-α, amongst others, with expression levels positively correlating with severity of degeneration[1]. There is currently a lack of validated preclinical animal models of disc degeneration that recapitulate clinically-relevant, persistent local disc inflammation. We recently described a goat model of disc degeneration in which increasing doses of chondroitinase ABC (ChABC) were used to reproducibly induce a spectrum of structural, biomechanical and histological degenerative changes.[2] The objective of this study was to evaluate and extend the clinical-relevance of this model by establishing whether these degenerative changes are associated with tissue-level expression of inflammatory cytokines and downstream catabolic enzymes.

Methods

With IACUC approval, 9 adult male goats underwent surgery to induce degeneration of the lumbar intervertebral discs. Using an open, lateral, retroperitoneal transpsoatic approach, L1-2, L2-3 and L3-4 lumbar discs were randomized to receive either subtotal mechanical nucleotomy (n = 4) or injection of 200μL of 0.1U, 1U or 5U ChABC via a 22G spinal needle (n = 4 per dose). The L4-L5 disc (n = 4) received a sham saline injection, and the T13-L1 and L5-L6 discs served as intact controls. Animals were euthanized 12 weeks after surgery, and lumbar spines harvested. Discs were imaged using a 3T MRI scanner, and NP T2 and T1ρ relaxation times were determined.[2] Discs (with bony endplates intact) were then isolated, fixed in formalin, decalcified, and processed for paraffin histology. Mid-sagittal sections were double stained with either Alcian blue (glycosaminoglycans) and picrosirius red (collagen), or hematoxylin and eosin. Severity of degeneration was established via semi-quantitative histological grading.[2] Immunohistochemistry was performed to investigate expression of inflammatory cytokines (IL-1β, IL-6, TNF-α) and catabolic enzymes (MMP-1, MMP-13 and ADAMTS4) in the NP and AF. Sections were counterstained with hematoxylin and imaged using bright field microscopy. Expression levels were quantified by determining the percentage of positive vs. total cells in the NP and AF. Differences in expression between groups were established using Kruskal-Wallis tests with post-hoc Dunn's tests ($p < 0.05$). Spearman rank correlations between degenerative condition (histology and MRI scores) and expression levels of cytokines and enzymes were determined.

Results

Positive cytokine and enzyme staining was found to various degrees in the NP and AF of most discs (examples, Fig 1). Multiple comparisons tests revealed significant effects of intervention type on expression levels of inflammatory cytokines and catabolic enzymes in both the NP (Fig 2) and AF (not shown). For cytokines, TNF-α expression was significantly elevated in 1U ChABC discs compared to controls, while IL-1β and IL-6 expression were significantly elevated in both the NP and AF of 5U ChABC discs. For enzymes, MMP-13 was significantly elevated in the NPs of 0.1U ChABC discs, while ADAMTS-4 was significantly elevated in the NP and AF of both 0.1 and 5U ChABC discs compared to controls. In general, both cytokine and enzyme expression levels were positively correlated with histological grade, and negatively correlated with MRI T2 (Fig 3) and T1ρ times.

Discussion

Localized inflammation is a defining feature of human disc degeneration and is a key mediator of tissue breakdown and painful innervation. Anti-inflammatory therapies such as catabolic cytokine inhibitors[3,4]a condition strongly implicated as a cause of lower back pain. The objective of this study was to investigate the therapeutic potential of poly(lactic-co-glycolic acid have the potential to slow the degenerative cascade and provide a microenvironment more conducive to stem cell-based disc regeneration; however, the absence of a preclinical animal model that effectively recapitulates inflammation

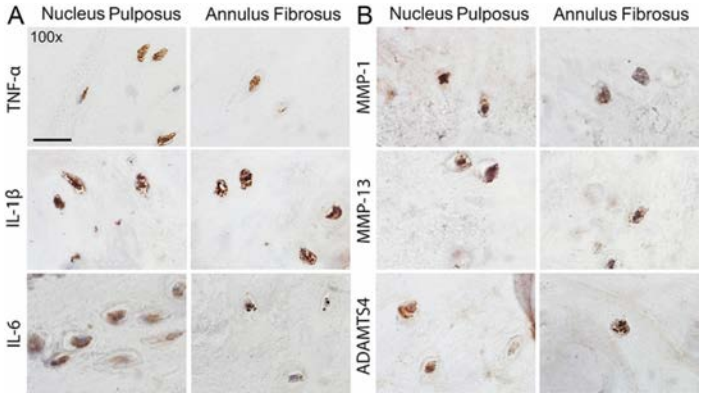

Figure 1. Immunostaining of **A.** Cytokines and **B.** Enzymes in the NP and AF of degenerate (1U ChABC-treated) goat discs. Scale = 20μm.

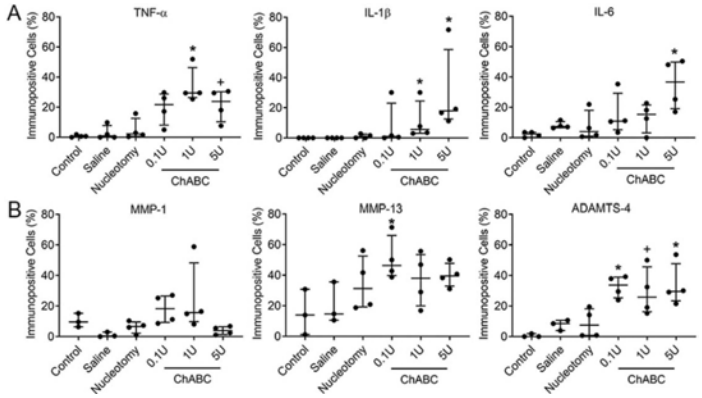

Figure 2. Effects of different surgical interventions on expression levels of **A.** Cytokines and **B.** Enzymes in the NP. N = 4; *p < 0.05 and +p < 0.1 vs. control.

represents an impediment to effective translation of such therapies. In this study, we provide evidence that an established goat model of disc degeneration is characterized by elevated expression of clinically-relevant inflammatory cytokines and downstream catabolic enzymes. This model exhibits significantly elevated expression in moderately to severely degenerate discs treated with ChABC, suggesting that these discs may provide the most suitable models for evaluating anti-inflammatory therapies. We also show that non-invasive, quantitative MRI is a reliable predictor of the inflammatory state of the disc. We are currently applying this model towards our goal of evaluating anti-inflammatory and cell-based therapies for disc regeneration.

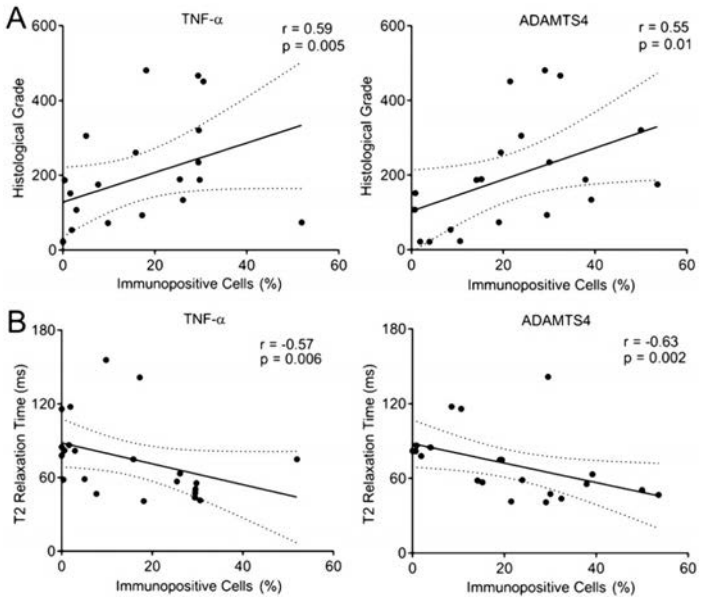

Figure 3. Correlations between NP cytokine and enzyme expression levels and **A.** Overall histological grade; and **B.** NP MRI T2 times.

Conclusion

Anti-inflammatory and cell-based therapies represent promising treatment strategies for painful disc degeneration. The animal model described here provides a platform for preclinical evaluation of such therapies and progressing them towards clinical use.

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Sports Tips & Tricks: Distal Triceps Tendon Knotless Anatomic Footprint Repair

Eric M Pridgen, MD, PhD[1]
Daniel Gittings, MD[1]
John D Kelly IV, MD[1]

[1]Department of Orthopaedic Surgery, University of Pennsylvania

Background

Distal triceps tendon tears are a rare injury accounting for only 0.8% of reported tendon injuries[1]. The injury is most commonly seen in men (2:1 ratio) ages 30-50 and occurs most frequently due to bodybuilding, competitive weightlifting, and football. The greatest risk factors are anabolic steroid use and weight lifting[2]. Other risk factors include local corticosteroid injections, olecranon bursitis, metabolic bone disease (hyperparathyroidism, renal disease), rheumatoid arthritis, type 1 diabetes, and Marfan syndrome[3,4].

The mechanism of injury is most commonly a sudden eccentric load applied to a contracting triceps muscle, such as during weight lifting or a fall on an outstretched hand. Other less common mechanisms include laceration, direct blow to the posterior elbow, and open fracture[5]. Tendon tears typically occurs at the tendon insertion into the olecranon[6], although there are reports of tears at the myotendinous junction or within the muscle belly itself[7].

Management of distal triceps tendon tears is based on the degree of tendon tear and elbow extension loss of function. Partial tears are repaired based on the functional needs of the patient taking into account medical comorbidities. In general, patients with <50% tendon tear can be treated conservatively with acceptable outcomes, as well as patients with >50% tears that are sedentary[8]. Active patients or those with complete tears are treated surgically. Ideally, tendon repair would occur within 2 weeks of the injury.

Conservative management consists of initial splint immobilization at 30 degrees of flexion, followed by progression to passive then active range of motion and strength training. Most properly selected patients treated conservatively will return to their pre-injury level of activity[9].

Surgical management involves primary repair of the distal triceps tendon to the olecranon. The tradition approach for repair has been the transosseous tunnel technique where nonabsorbable sutures are placed in the distal tendon using a Krackow or similar locking stitch, followed by passing the sutures through transosseous tunnels drilled in the olecranon, then tying the sutures over a bone bridge[5]. However, cadaveric studies have shown that the triceps insertion on the olecranon is rather expansive and traverses a wide footprint on the olecranon[10]. The footprint commences 12 mm distal to the tip of the olecranon and blends with the posterior capsule. Biomechanical studies showed that the transosseous tunnel repair technique only covered 31% of the anatomic footprint of the tendon. Therefore, alternative techniques were developed to create a more anatomic repair of the tendon.

Alternative techniques included a double row suture anchor technique similar to rotator cuff tendon repairs[10] and a knotless anatomic footprint repair that uses bone tunnels and creates a "box-and-x" suture configuration to compress the tendon over the tendon footprint on the olecranon[11]. Initial biomechanical studies comparing the transosseous tunnel technique to the knotless anatomic footprint repair technique showed that the knotless anatomic repair technique increased the footprint coverage to 74%[12]. In addition, the knotless anatomic technique resulted in less displacement after cyclic loading, higher peak load, and higher load at yield than the transosseous tunnel technique. However, functional outcome studies comparing the two techniques showed no clinically significant difference between the two techniques[13]. A more recent biomechanical study pointed out the fact that prior studies comparing the two techniques used different numbers of sutures in the triceps tendon. When those studies were repeated using the same number of sutures for the two techniques, no significant difference was found in cyclic load displacement[14].

Case Report

A 15 year old right-handed male that presented with an injury to the left arm after being tackled while playing football 1 week ago. His exam was notable for 3/5 elbow extension strength and a palpable gap in the triceps tendon insertion. Although not specifically noted for this patient, other common physical exam findings for a distal triceps tendon tear include elbow pain, swelling, and ecchymosis. Inability to extend the elbow actively is a sign of complete tear, although some patients with a complete tear of the distal triceps tendon are still afforded some extension due to an intact lateral triceps expansion. In fact, 50% of

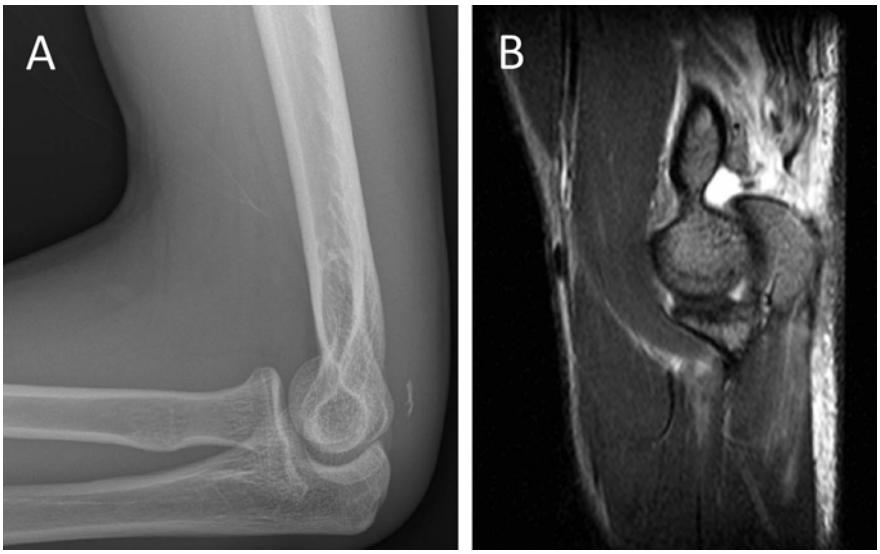

Figure 1. Imaging of left elbow. **(A)** Radiograph of the lateral elbow showing a flake of bone avulsed from the olecranon indicating a triceps tendon tear. **(B)** STIR MRI of the left elbow showing a fluid gap between the olecranon and distal triceps tendon consistent with a triceps tendon tear.

acute triceps tendon tears are misdiagnosed because of active elbow extension due to the lateral triceps expansion[6]. There is also a modified Thompson squeeze test for triceps tears that is analogous to the test for Achilles tendon tears that can aid in the diagnosis[5]. For higher energy injuries, it is important to do an ulnar nerve exam and check all arm compartments as well[15].

Imaging for the patient is shown in Figure 1. On the lateral X-ray of the elbow in Figure 1A, there was a positive 'flake sign' that indicates avulsion of bone from the olecranon. This is almost always pathognomonic for a distal triceps tendon tear. The MRI image in Figure 1B confirmed the distal triceps tendon avulsion. Ultrasound can also be used to evaluate the integrity of the triceps tendon and determine if the tear is partial or complete. Since the patient was young and active with a loss of elbow extension strength and a confirmed distal triceps tear on MRI, surgical repair of the tendon was indicated and the knotless anatomic footprint repair technique described below was used.

For the procedure, the patient is positioned in the lateral decubitus position using a bean bag with the left arm draped over an arm bolster. A posterior approach to the elbow is used with a midline incision that curves slightly radial to the olecranon to prevent scar formation directly over the tip of the olecranon. Full thickness skin flaps are raised radially and ulnarly. The distal end of the torn triceps tendon is identified and debrided. The tendon footprint on the olecranon is then identified and debrided down to bleeding bone to aid in healing.

The triceps tendon is freed of any adhesions to aid in mobilizing the tendon. Two No. 2 FiberWire (Arthrex, Naples, Fla.) sutures, one medial and one lateral, are passed through the tendon using a locking Krackow stitch both starting and ending at the proximal aspect of the tendon footprint on the deep aspect of the tendon (Figure 2A). In addition, two FiberLink (Arthrex, Naples, Fla.) sutures are placed medial and lateral at the proximal aspect of the tendon footprint. The looped ends of the FiberLink sutures are on the superficial side of the tendon.

Two parallel tunnels are drilled through the olecranon using a 2.4 mm drill bit. The tunnels start at the proximal footprint of the tendon on the olecranon aiming distally towards the posterior ulna. The distance between the two tunnels is wide enough to place a 4.75 mm SwiveLock (Arthrex, Napes, Fla.) suture anchor. Once the tunnels are drilled, the ulna is drilled and tapped just distal to the exit point of the tunnels for the suture anchor with the trajectory directed away from the joint.

Once the bone tunnels are drilled, the sutures are passed using a Hewson suture passer. The three medial sutures (two FiberWire and one FiberLink nonlooped end) are passed through the medial tunnel, and the three lateral sutures are passed through the lateral tunnel (Figure 2B). One of the medial FiberWire tails is then placed through the lateral FiberLink looped end and passed through the lateral bone tunnel. The same is done for one of the lateral FiberWire tails to pass through the medial bone tunnel (Figure 2C). This creates a "box-and-x" configuration to compress the tendon over the footprint (Figure 2D). The FiberWire sutures (2 medial, 2 lateral) are then tensioned and passed through the eyelet of the 4.75 mm SwiveLock suture anchor and the anchor is placed in the prepared hole in the olecranon (Figure 2E). Final tensioning is done before screwing the anchor into the olecranon until it is flush with the bone. The incision is then closed and the patient is placed in a posterior splint.

Post-operatively, the patient remains in a splint for 2 weeks and then the sutures are removed. The patient is transitioned to an elbow brace and allowed to perform passive range of motion exercises starting at 0 to 45 degrees and increasing flexion by 10 degrees each week. The goal is to reach full range of motion by 6-8 weeks post-operatively, at which point the elbow brace can be discontinued. At that point, the patient can begin strength training. Return to work or sports is not recommended until patient has full range of motion of the elbow and 85% of the strength of the contralateral side.

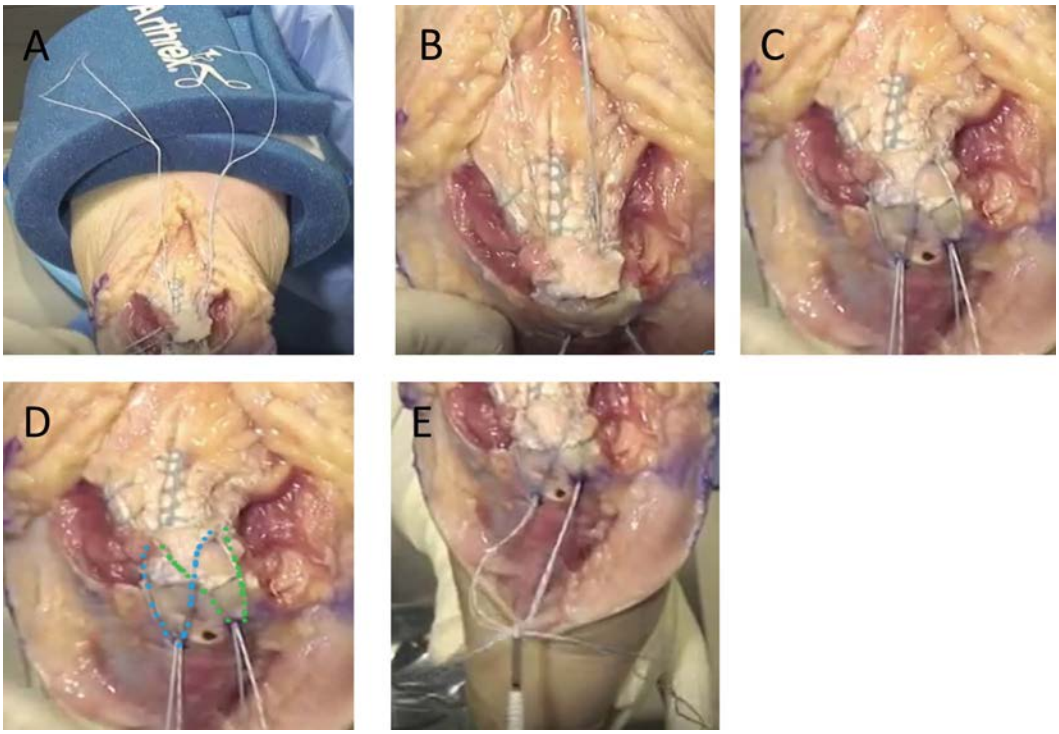

Figure 2. Suture passing technique demonstrated on a cadaver[16]. **(A)** Two FiberWire sutures, one medial and one lateral, are passed through the tendon using a locking Krackow stitch. Two FiberLink sutures are placed medial and lateral with the looped ends of the FiberLink sutures are on the superficial side of the tendon. **(B)** FiberWire sutures are passed through the parallel bone tunnels using a suture passer. **(C)** One FiberWire suture on each side is placed through the opposite side FiberLink loop and passed through the opposite tunnel. **(D)** Illustration of how one of the FiberWire sutures is passed through the opposite bone tunnel to create the "box-and-x" configuration over the tendon footprint. **(E)** FiberWire sutures are tensioned and passed through the eyelet of the SwiveLock suture anchor before being placed in the prepared suture anchor hole.

Discussion

Distal triceps tendon tears are relatively rare tendon injury seen most commonly in middle aged men and associated with weight lifting and playing football, although other mechanisms include lacerations, open fractures, and direct blows to the posterior elbow. The injury can be treated conservatively or surgically depending on whether the tear is partial or complete, the degree of functional loss, and the demands of the patient. Surgical techniques include transosseous tunnels and the knotless anatomic footprint repair. Biomechanical studies have shown that the anatomic footprint repair results in a greater coverage of the tendon footprint on the olecranon, but cyclic load displacement is similar between the techniques when the same number of sutures is used. Functional outcomes are similar between the two techniques with the knotless technique perhaps more facile as transosseous tunnels are avoided.

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State of the Field: The Utility of Ultrasound in the Diagnosis of Rotator Cuff Tears

Alexander Lee, BS[1*]
Ali S. Farooqi, BA[1*]
Robert L. Parisien, MD[2]
Viviane Khoury, MD[1]
John D. Kelly IV, MD[2]

[1]Perelman School of Medicine
University of Pennsylvania

[2]Department of Orthopaedic Surgery
University of Pennsylvania

[*]Co-First Authors

Introduction

The rotator cuff is a dynamic stabilizer and is a chief contributor to both glenohumeral joint stability and movement.[1, 2] Tears of the rotator cuff can occur as the result of an acute eccentric load, glenohumeral joint dislocation, or via chronic, age-related tendon degeneration.[3] Injuries can vary in severity from partial-thickness to full-thickness tears and may cause significant pain, decreased shoulder mobility, and irreparable damage to the rotator cuff or glenohumeral joint.[4] Rotator cuff disorders are highly prevalent and are the most common cause of shoulder disability in the United States. Specifically, rotator cuff disorders are responsible for approximately 30-70% of pain-related shoulder conditions and 70% of shoulder-related physician visits, accounting for over 4.5 million annual visits in the US.[5-7] Cadaveric evaluation has indicated the prevalence of partial and full-thickness rotator cuff tears to range from 5-40%. Additional population-based studies of both symptomatic and asymptomatic individuals have found a 21% prevalence of rotator cuff tears.[8, 9]

With over 270,000 rotator cuff surgeries performed annually, the diagnosis and management of rotator cuff injuries has become a significant healthcare burden.[10] Recent analyses have estimated that the diagnosis and repair of rotator cuff injuries account for over $3 billion in total associated healthcare costs.[11, 12] Given the high prevalence and large economic burden of rotator cuff injury, accurate and cost-effective diagnostic modalities are critically important for evaluating patients. Historically, Magnetic Resonance Imaging (MRI) without contrast was the preferred imaging modality for assessment of rotator cuff pathology. Subsequently, direct and indirect MRI with contrast, known as Magnetic Resonance Arthrography (MRA), was developed to provide improved intra-articular enhancement in joints and overall visualization.[13, 14] Although a recent study by Lee et al[15] demonstrated increased specificity and sensitivity for the diagnoses of rotator cuff tears with utilization of MRA, non-contrast MRI remains the preferred diagnostic modality among both sports and shoulder-trained surgeons.

In addition to MRI and MRA, ultrasound has also emerged as an important diagnostic modality throughout the field of orthopaedic surgery. Initially described in 1984, ultrasound evaluation of shoulder pathology started gaining acceptance among orthopaedic surgeons in the 1990s due to improvements in transducer strength, resolution, and operator training.[16, 17] In the early 2000s, ultrasound became more commonly used in the diagnosis of both partial and full-thickness rotator cuff tears, partly as a result of increased musculoskeletal ultrasound training for radiologists.[18, 19] Recent meta-analyses have found the specificity and sensitivity of ultrasound (US) to be similar to that of MRI and MRA for the diagnosis of rotator cuff tears.[20-22] A recent meta-analysis from 2015 identified comparable sensitivity (0.90–0.91) and specificity (0.93–0.95) for ultrasound as compared to both MRI, and MRA in the diagnosis of full-thickness rotator cuff tears. These results were consistent for trained clinicians across multiple sub-specialties including radiologists, orthopaedic surgeons and sonographers.[20] Similar to MRI and MRA, ultrasound appears to be more accurate in the diagnosis of full-thickness rotator cuff tears as compared to partial-thickness tears.[20,23]

Clinicians have traditionally considered diagnostic accuracy to be the most important factor when selecting between diagnostic imaging modalities. With the comparable diagnostic capabilities of US, MRI, and MRA, there are several other factors that make US an appealing option. Ultrasound has essentially no contraindications because it does not utilize rotating magnetic fields or contrast agents. MRI and MRA are contraindicated for patients with implanted devices with ferromagnetic or electrically conductive materials, such as left ventricular assist devices (LVADs), electrically conductive pulmonary artery monitoring catheters, and cochlear implants. Additionally, patients with ferromagnetic foreign bodies, common with metal workers and veterans, may be not be able to obtain a MR evaluation.[24-26] MRA is also contraindicated for patients with renal disease as prolonged exposure to Gadolinium may cause Nephrogenic Systemic Fibrosis.[27] Additionally, MRI and MRA are relatively contraindicated for the 1% of individuals who experience claustrophobic events during MRI.[28]

The recent focus on healthcare cost and expenditure has led to an increased interest

in developing cost-effective and responsible practices and metrics. Specifically, cost-effective imaging modalities are needed as healthcare continues to move from a fee-for-service model towards a value-based model where physicians and other health-care professionals are evaluated based on patient outcomes. Given these important considerations, ultrasound has been shown to be more cost-effective than MRI.[29] Medicare reimbursement for a hospital-based shoulder MRI (CPT:73221) ranges from $303.51 to $387.01, while reimbursement for a hospital-based shoulder ultrasound (CPT:76881) ranges from $144 to $189.37.[30] Studies suggest that this difference may be even greater within private insurance, where the average MRI reimbursement is $999.67 per patient.[31] Furthermore, increased efficiency within healthcare is vital as it allows for greater access to care, providing increased value and improved outcomes while simultaneously limiting cost. Unlike MRI, ultrasound can be performed in the office and, as such, is a more efficient and convenient diagnostic modality. At our institution, shoulder US requires roughly 10 minutes to perform while shoulder MRI requires around 40 minutes. When offered the choice, patients who have undergone both procedures report less discomfort during the ultrasound exam, greater satisfaction following the procedure, and an overall preference for US over MRI of the shoulder.[32] Ultrasound also allows for a dynamic evaluation of the shoulder with identification of pathologies not detectable by MRI or MRA, which are static examinations.[33]

Despite these relative advantages of US over MRI and MRA, integration of ultrasound into clinical practice has been slow. A recent survey of members of the American Shoulder and Elbow Surgeons group (ASES) found that only 55% of respondents used ultrasound in their practice and only 10% felt comfortable using it as their sole imaging modality preoperatively.[34] One reason for this may be that shoulder surgeons are not comfortable conducting or interpreting shoulder ultrasound evaluations and are therefore reluctant to rely solely on the ultrasound report and images captured by the radiologist. These concerns may be valid as US accuracy has been shown to be operator-dependent with considerable training required to reach proficiency. Literature demonstrates that orthopaedic surgeons must scan between 50 to 100 unique shoulders before they achieving diagnostic proficiency comparable to their ability to read MRI.[35, 36] Despite the diagnostic abilities of ultrasound, as demonstrated in the radiology literature, some respondents to the ASES survey also stated that they were not confident that US could determine whether a tear is reparable.[34]

With regards to the development of diagnostic proficiency, ultrasound certifications are readily available via the musculoskeletal sonography certification (RMSK) accredited by The American Registry for Diagnostic Medical Ultrasonography (ARDMS) and the American National Standards Institute (ANSI). Additionally, there are several musculoskeletal ultrasound conferences that provide updates on the current state of ultrasound imaging, which include, but are not limited to, the Musculoskeletal Ultrasound Society and the American Institute of Ultrasound in Medicine. This demonstrates the availability and accessibility of valuable resources to orthopedic surgeons interested in developing diagnostic ultrasound proficiency and accreditation. In addition, further clinical analysis comparing inter- and intra-operator reliability, as well as diagnostic accuracy for partial thickness tears, are needed to establish shoulder ultrasound as an ubiquitous diagnostic modality within the field of orthopaedic surgery.

Penn Insights

Andrew F. Kuntz, MD
Assistant Professor of Orthopaedic Surgery
Hospital of the University of Pennsylvania

Despite the relative advantages of ultrasound over MRI for rotator cuff tear diagnosis, MRI is still the default study for most orthopedic shoulder surgeons. One of the main reasons for the under-utilization of shoulder ultrasound is that many orthopedic surgeons cannot independently perform or interpret images from a shoulder ultrasound. As a result, these surgeons are completely dependent on the radiology report. Moreover, the diagnostic accuracy of ultrasound is operator dependent and surgeons must establish a high level of trust in the radiologist performing the ultrasound before they feel comfortable acting solely upon the radiologist's ultrasound results. By contrast, most orthopedic surgeons independently assess MRI images in addition to reviewing the radiology report. In addition, MRI allows for complete evaluation of the bony anatomy and soft-tissues about the shoulder whereas there are some limitations to ultrasound. Specifically, ultrasound cannot be used to assess subscapularis muscle atrophy or the glenoid labrum in detail.

The above notwithstanding, ultrasound is very appealing because of its efficiency, decreased cost, and the dynamic nature of the exam as opposed to the static images obtained with MRI. In my own practice, I order shoulder ultrasounds when there is a contraindication for MRI, in some situations when there is pain that cannot be explained by MRI results, or when dynamic pathology with respect to movement needs to be evaluated. I also routinely order an ultrasound for image-guide lavage of calcific tendinitis. As ultrasound becomes more commonly taught in medical student education and orthopaedic surgery residency / fellowship, I believe ultrasound will be more commonly utilized by practicing orthopaedic surgeons.

Miltiadis H. Zgonis, MD
Assistant Professor of Clinical Orthopaedic Surgery
Penn Sports Medicine Weightman Hall

While ultrasound is an interesting imaging modality due to its cost-effectiveness and efficiency, MRI is still the more reliable imaging modality for the diagnosis of rotator cuff tears and shoulder pathology. One of the main barriers to the use of shoulder ultrasound is that most orthopaedic surgeons cannot read ultrasound scans. As a result, the surgeon cannot independently evaluate and verify the scans and must make a clinical decision solely based upon the radiology

report. Making a clinical decision without independent verification requires a certain degree of trust which is hard to establish with shoulder ultrasound given the variability in operator experience and quality of scans received. MRI allows orthopaedic surgeons to independently evaluate and verify scans which helps to prevent unnecessary operations and pick up pathology that warrants surgical intervention. Moreover, MRI is standardized across institutions which makes it a very reliable and trustworthy imaging modality. In my own practice, I have used shoulder ultrasound when patients are contraindicated for MRI, but I will still supplement the ultrasound scans with a CT arthrogram to completely evaluate shoulder pathology.

Shoulder ultrasound has a use in orthopaedics when a general evaluation of rotator cuff integrity is necessary. For example, ultrasound may be indicated when checking whether a patient's rotator cuff is intact prior to arthroplasty for arthritis, helping to decide if total or reverse arthroplasty is warranted. However, ultrasound for more detailed evaluation of shoulder pathology is not adequate and not a replacement for MRI due to the increased operator variability and inability to pick up specific pathology such as chondral defects.

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U·P·O·J

Bankart Repair versus Bankart Repair with Remplissage: Meta-analysis and Comparison of the Shoulder Re-Dislocation Rate

Gabrielle Leavitt[1]
John D. Kelly IV, MD[2]
Leslie Barnes, MD[3]

[1]Department of Bioengineering
University of Pennsylvania

[2]Department of Orthopaedic Surgery
University of Pennsylvania

[3]Department of Orthopaedic Surgery
Temple University

Abstract

Bankart repair (B) and bankart repair with remplissage (BR) are two popular arthroscopic methods to surgically address shoulder instability. A meta-analysis was conducted to assess these two arthroscopic treatment options. This study tested the hypothesis that the re-dislocation rate is statistically lower after arthroscopic BR compared with arthroscopic B alone. The weighted re-dislocation rate from all included studies was found to be 5.300% after arthroscopic BR, while the weighted re-dislocation rate from all included studies was found to be 14.800% after arthroscopic B alone. The addition of remplissage results in a statistically significant reduction in recurrence of anterior shoulder instability.

Introduction

Recurrent shoulder instability affects approximately 1.7% of the world's population. The most common type of shoulder instability is an anterior dislocation, accounting for over 90% of all shoulder dislocations. Rates are increased in men, contact athletes, and military personnel.[1] Multiple factors must be considered prior to surgical treatment. These include patient age, vocation, and desired level of activity. Surgical management should be considered in patients with recurrent unidirectional shoulder instability and in young active people, particularly those that engage in high demand and contact sports1. Consequences of recurrent shoulder instability include labral tearing, bone loss, cartilage damage, glenohumeral arthritis, persistent pain and disability.

There are currently two popular arthroscopic methods used to surgically address anterior shoulder instability in the presence of anteroinferior labral pathology: bankart repair (B) and bankart repair with remplissage (BR). The aim of this meta-analysis is to assess these two arthroscopic treatment options on the basis of post-operative re-dislocation rates. This study tested the hypothesis that the post-operative re-dislocation rate is statistically lower after arthroscopic BR compared with isolated arthroscopic B by performing a systematic review and meta-analysis of the current literature.

Materials and Methods

This meta-analysis followed guidelines published by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[2]

Search Strategy and Eligibility Criteria

A search was performed of the PubMed,Web of Science, Embase, and Clinicaltrials.gov databases on June 19, 2018 for studies evaluating the shoulder re-dislocation rate after arthroscopic B versus after arthroscopic BR procedure. The search syntax is provided in Table 1. After deleting all duplicates and screening through the title and abstract of all identified records, articles were assessed based on full text. The inclusion criteria were clinical studies or trials; arthroscopic B and/or arthroscopic BR treatment groups; sample sizes of five or greater;

Table 1. Search terms and findings from every database including within this meta-analysis.

Search Terms	Database
("Bankart Lesions" [Mesh] OR shoulder instabilit*[tiab] OR anterior shoulder instabilit*[tiab] OR shoulder redislocat*[tiab]) AND bankart repair*[tiab] AND remplissage*[tiab]	PubMed (NLM-search platform): 39 Results
TS=(("Bankart Lesions" OR shoulder instabilit* OR anterior shoulder instabilit* OR shoulder redislocat*) AND (bankart repair* AND remplissage*))	Web of Science (Clarivate Analutics-serarch platform): 100 Results
('bankart lesion'/exp OR 'recurrent shoulder dislocation'/exp OR 'shoulder instabilit*':ti,ab OR 'anterior shoulder instabilit*':ti,ab) AND ('bankart repair'/exp OR 'bankart repair*':ti,ab) AND remplissage*:ti,ab	Embase (Elsevier-search platform): 45 Results
Bankart repair AND remplissage	Clinicaltrials.gov: 2 Results

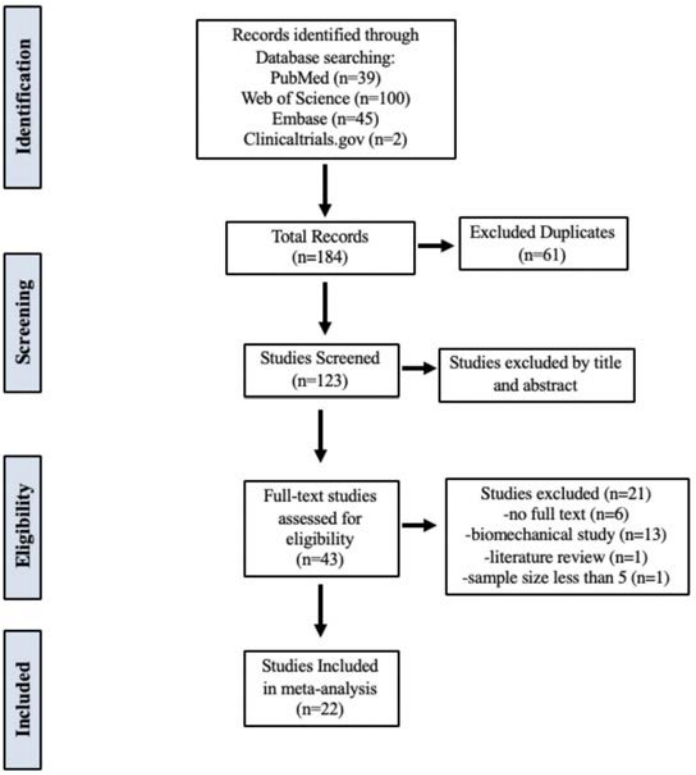


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram representing the search and screen process of evaluating studies examining the results of arthroscopic bankart repair and arthroscopic bankart repair with remplissage

reporting of the re-dislocation rate in the study and publication in 2000 or later. The meta-analysis excluded all studies not reporting the re-dislocation rate; biomechanical studies and literature reviews; studies prior to 2000; no availability of full text; and all articles not written in English. References were organized via RefWorks citation builder (ProQuest, Ann Arbor, MI). Figure 1 shows the PRISMA flowchart of the literature search conducted.

Data Extraction

The following data was extracted from each article: title, author, publication date, methodology of the study, treatment groups, characteristics of the sample, percent of glenoid bone loss when recorded, and post-operative re-dislocation rate.

Outcome Measures

The shoulder re-dislocation rate within a treatment group was observed and recorded for each treatment group (Table 2). This was given as a percentage of patients that experienced a dislocation recurrence after the operation divided by the total sample size of that treatment group. In addition, the percent of both humeral and glenoid bone loss reported was recorded in order to determine if a correlation existed between percentage of glenoid bone loss present at the index operation and post-operative recurrence of shoulder instability.

Statistical Analysis

Comprehensive Meta-Analysis software version 3 (Biostat, Englewood, NJ) was used to pool the data and run the statistical tests. On the studies that collected the shoulder re-dislocation rate of both treatment groups, the odds ratio and 95% confidence intervals were calculated using this software. In addition, the re-dislocation data was pooled from all studies having one or two of the treatment groups, to get a single weighted re-dislocation rate for each treatment group. The variance ratio test showed that a two-sample t-test with unequal variances was required to determine statistical significance (Figure 2). A two-sample t-test with equal variances would

Table 2. Re-dislocation rates from the 22 included articles.

Study Number	Re-dislocation Rate group 1: remplissage and bankart repair	Re-dislocation Rate group 2: bankart repair
1	0	20
2	Not included	22
3	15	Not included
4	Not included	6
5	11.8	Not included
6	Not included	16.6
7	14.7	Not included
8	9	Not included
9	2.04	Not included
10	0	Not included
11	4.4	Not included
12	1.6	Not included
13	6.7	Not included
14	6.3	Not included
15	5.4	25.7
16	4.5	33
17	0	9
18	2	Not included
19	0	5.9
20	0	0
21	3.9	Not included
22	9.1	Not included

Treatment Group	Observations (number of groups)	Mean (% re-dislocation rate)	Standard Error	Standard Deviation	95% Confidence Interval
group 1: remplissage and bankart repair	19	0.052	0.010	0.045	0.034 – 0.074
Group 2: bankart repair	9	0.148	0.032	0.095	0.076 – 0.221
Combined: groups 1 and 2	28	0.083	0.015	0.078	0.053 - 0.114
Ratio = sd(x)/sd(y)		H_0 : ratio = 1	F = 0.226	Degrees of freedom = 18 , 8	
H_a : Ratio < 1		H_a : Ratio = 1		H_a : Ratio > 1	
Pr (F < f) = 0.004		2 * Pr (F < f) = 0.008		Pr (F > f) = 0.996	

Figure 2. Variance ratio test which determines which type of two sample t-test to perform.

not be statistically valid as the two treatment groups had different total sample sizes. The main quantitative assessment of significance was the "t-value". When the t-value was less than or equal to 0.050, the re-dislocation rate was considered to be statistically different between the two groups.

Results

22 studies met the inclusion criteria. There were 6 case series[3-8], 15 retrospective studies[9-24], and 1 prospective study[25]. The 22 studies provided 1039 patients for meta-analysis: 380 treated with arthroscopic bankart repair and 659 with arthroscopic bankart repair in combination with remplissage. The mean patient age was 28 years and 54% of the patients were male. Follow up ranged from 1 to 6 years. There were 6 studies with both treatment groups[9,18,19,20,22,23]. However, one of these studies could not be used for the paired statistical testing due to the fact that no recurrent dislocations were observed in that study for either treatment group. Therefore, only five studies are shown in Figure 3A. A subsequent paired statistical test was conducted modifying this study to have the same lowest nonzero dislocation rates to determine if this study would impact the pooled result. This test is shown in Figure 3B.

The weighted re-dislocation rate from all included studies was found to be 5.300% after arthroscopic BR, and the weighted re-dislocation rate from all included studies was found to be 14.8% after arthroscopic B alone. This was found to be a statistically significant difference as calculated by the result of the two-sample t test with unequal variances; the results of this statistical analysis show the difference between the two groups to be statistically significant with a p-value of 0.017 (Figure 4).

Figure 3 shows the results of the Meta-Analysis. The pooled odds ratio and 95% confidence interval (CI) were calculated, and because the 95% CI of both Figure 3A and Figure 3B of the paired studies does not cross over 1.0, the odds ratio test shows the difference in re-dislocation rates observed between the two treatment groups to be statistically significant, regardless of whether study 20 was included or not.

Regarding glenoid bone loss, none of the studies identified in this review included data on the glenoid bone loss of individual patients, they only reported the range of bone loss in each sample. The reported bone loss ranged from 0-40% in the different studies. For example, in a study which reported a 25% bone loss or less, there may be some patients in that study with 10% bone loss and some patients with 20% bone loss. This would skew the results when comparing data to another study with inclusion criteria of 10% bone loss or less. Therefore, no valid statistical conclusions on glenoid bone loss as it related to post-operative re-dislocation could be drawn due to the overlap of the sample groups.

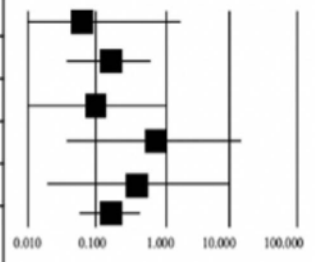
Discussion

The re-dislocation rate for arthroscopic BR in this review was significantly lower than the re-dislocation rate for arthroscopic B alone. This applies to the analysis performed on the paired studies containing both groups as well as the analysis executed with the weighted recurrence rate from all the studies pooled together.

This meta-analysis supports the growing consensus of literature in the field that arthroscopic BR significantly decreases the re-dislocation rate. The consistent result of BR resulting in a lower recurrence rate compared to arthroscopic B alone may prompt more surgeons to consider adding remplissage to their arthroscopic bankart repairs. The addition of remplissage has been shown to help avert a second surgery for a large number of patients with anterior shoulder instability who undergo arthroscopic treatment. Further studies are needed to determine which patients would benefit most from the addition of the remplissage procedure.

A

Study Name	Odds Ratio	Upper Limit	Lower Limit	Z-value	P-value	Odds Ratio and 95% CI
9	0.073	0.004	1.400	-1.736	0.082	
18	0.165	0.033	0.829	-2.187	0.029	
19	0.096	0.010	0.901	-2.051	0.040	
20	0.606	0.029	12.481	-0.325	0.746	
22	0.354	0.013	9.351	-0.622	0.534	
Total	0.167	0.058	0.480	-3.326	0.001	



B

Study Name	Odds Ratio	Upper Limit	Lower Limit	Z-value	P-value	Odds Ratio and 95% CI
9	0.073	0.004	1.400	-1.736	0.082	
18	0.165	0.033	0.829	-2.187	0.029	
19	0.096	0.010	0.901	-2.051	0.040	
20	0.606	0.029	12.481	-0.325	0.746	
22	0.354	0.013	9.351	-0.622	0.534	
23	1.000	0.058	17.325	0.000	1.000	
Total	0.207	0.077	0.557	-3.119	0.002	

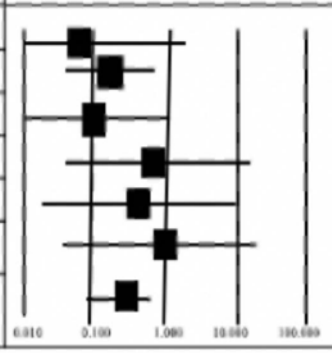


Figure 3. Results of statistical analysis performed by Comprehensive Meta-Analysis Software for Paired studies. **(A)** Statistical Meta-Analysis on Paired Studies excluding study 23. Dislocation rates were 0% for both treatment groups and because one cannot divide by zero (calculation required for odds ratio), that study was excluded from this particular paired statistical test. **(B)** Statistical Meta-Analysis on Paired Studies including modified study 23. Dislocation rate for both treatment groups in study 23 were altered from 0/18 to 1/18 (5.56%) to determine the effect on the pooled odds ratio of the study.

Treatment Group	Observations (number of groups)	Mean (% re-dislocation rate)	Standard Error	Standard Deviation	95% Confidence Interval
group 1: remplissage and bankart repair	19	0.052	0.010	0.045	0.034 – 0.074
Group 2: bankart repair	9	0.148	0.032	0.095	0.076 – 0.221
Combined: groups 1 and 2	28	0.083	0.015	0.078	0.053 - 0.114
Diff = mean (group 1) – mean (group 2) =		H_0 : diff = 0	t = -2.883	Satterthwaite's Degrees of freedom = 9.751	
H_a : Ratio < 0		H_a : Ratio != 0		H_a : Ratio > 0	
Pr (T < t) = 0.008		Pr (| T | > | t |) = 0.017		Pr (T > t) = 0.992	

Figure 4. Two sample t test with unequal variances showing the weighted average recurrence rate for all studies in either treatment group to be statistically different from one another.

The results of this systematic review must be interpreted in light of several limitations. The 22 studies identified each had different lengths of follow-up. This may have impacted the recurrence rate because groups with a longer follow up period clearly had more opportunity for re-dislocation to occur, which would negatively impact the results for either procedure. There were other limitations in some of the individual studies identified including industry funding and small sample sizes.

Recurrence of shoulder instability may be linked to the percent of both humeral and glenoid bone loss, but due to the ambiguity of bone loss measurement in the studies currently published, a correlation was unable to be derived here. In addition, insufficient data was present in the studies to comment on the presence of 'on track' vs 'off track' humeral head lesions.[27] However, future reviews or studies should explore this connection and help determine a possible specific threshold of bone loss where the addition of the remplissage procedure to the arthroscopic bankart repair becomes necessary. Similarly, the threshold percent of excessive humeral and glenoid bone loss for which even the addition of arthroscopic remplissage may be rendered inadequate, must be calculated.

For patients with only modest glenoid bone loss, the addition of remplissage to arthroscopic bankart repair can significantly reduce the re-dislocation rate.The added benefits of reducing the re-dislocation rate must be weighed against the reported (albeit inconsistent) risk of possible stiffness[26] and the burden of additional surgery. However, the results of this meta-analysis support the addition of remplissage to the treatment algorithm of arthroscopic shoulder stabilization.

Conclusion

The current available literature supports that the addition of remplissage to arthroscopic bankart repair results in a statistically significant reduction in recurrence of anterior glenohumeral instability and may be a useful adjunct in select cases.

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Hand Tips & Tricks: Tendon Transfers for Posterior Interosseus Nerve Palsy: Principles and Technique

C. Lucas Myerson, MD[1]
Martin Griffis, MD[1]
Ketan Sharma, MD[1]
Benjamin L. Gray, MD MSCE[1]

[1]Department of Orthopaedic Surgery
University of Pennsylvania

Introduction

Tendon transfer relies on the redistribution of functional parts, which is a fundamental principle of reconstructive surgery. Damage to one of the three major nerves of the hand can cause significant disability in motor and sensory function. The decision to perform a tendon transfer relies on first ruling out the possibility of nerve recovery or nerve repair, as this may restore both motor and sensory function.Tendon transfers restore motor function, but they are unable to restore sensation. They involve the detachment of a donor tendon from its insertion and rerouting it to a new insertion distally.

Prior to pursuing tendon transfer for a patient, the surgeon should consider the principles of the technique. Adherence to these principles will not only ensure that preoperative planning has been performed properly, but it will also allow for more predictable outcomes. Below we will discuss the principles of the technique. This will be followed by the surgical options and technique for a posterior interosseous nerve (PIN) palsy.

Principles

Correction of Contracture

Nerve injury is often complicated by joint contracture, especially when the presentation is delayed. The utility of tendon transfer depreciates in the presence of joint stiffness, and one may not achieve a postoperative active range of motion that exceeds the preoperative passive range of motion. To that end, patient selection should be dictated by the presence of contracture, scarring and stiffness around a joint over which a tendon transfer is planned. Postoperatively, a protocol should be employed to keep the joint supple and prevent scarring that would portend contracture.

Tissue Equilibrium

Tendon transfers should not be done until the local tissue environment has been optimized to receive a tendon transfer. Factors that might be hostile to a successful tendon transfer such as soft tissue swelling, thickened scars, stiff joints and immature wounds, should be addressed ahead of time. Open wounds are a contraindication to tendon transfer, as they carry with them a risk of infection. In the event that soft tissue coverage with a flap or graft is required prior to tendon transfer, it should be performed well in advance so as not to jeopardize the viability of the soft tissue coverage with the tendon transfer.

Adequate Strength

The muscle selected to be transferred must have sufficient strength to perform its new role. The power of the muscle correlates with the cross-sectional area of the muscle. After transferring the muscle, the muscle typically loses one grade of strength on the Medical Research Council (MRC) grading system. Therefore, muscles should only be selected for transfer if they have similar, or preferably greater, power than the muscle they have been selected to replace.

Adequate Excursion

There exists variation in the distance traveled by tendons with movement.This distance traveled is known as excursion, and it is directly related to the amount of joint rotation. It is essential that the tendon harvested has sufficient excursion to replace that which is deficient. As a rule, there is 3 cm of excursion with wrist extensors and flexors, 5 cm of excursion with finger extensors, EPL and FPL, and 7 cm of excursion with finger flexors.A tendon with 5 cm of excursion cannot be expected to replace a tendon with 3 cm of excursion. The result of such an attempt would be a floppy and ineffectual transfer.

Straight Line of Pull

When a tendon is transferred, it should ideally run in a straight line to its new insertion. By maintaining this straight line of pull, one minimizes the resistance of surrounding soft tissue present and the force needed to overcome that resistance. If the tendon must run through a pulley from its origin to its insertion, the less change in direction that occurs at the pulley will produce less friction and adhesion formation on the tendon. There should never be more than one change in direction for a tendon.

Synergism

Muscles that work simultaneously to perform a movement are described as synergistic. Whenever possible, the donor muscle tendon unit should be synergistic to the muscle tendon

unit it has been selected to replace. The wrist flexors and finger extensors are an example of synergistic muscles. According to the principle of synergism, a wrist flexor may be utilized to replace a deficient finger extensor as it would require minimal effort to retrain the brain to have the donor perform this new function.

Expendable Donor

Transfer of a tendon should never result in a critical loss of function. Ideal candidates for harvest are those that perform a function that is performed by another tendon. This allows for preservation of the tendon's original action following transfer. To that end, no two tendons that perform the same function should be transferred simultaneously.

When adhered to, these principles fill an important role as a template for selection when planning a tendon transfer. Below we now cover the use of the tendon transfer for a palsy of the posterior interosseous nerve (PIN).

Tendon Transfer for PIN Palsy

Preoperative Assessment

Before a treatment plan is developed, a comprehensive physical exam, which focuses on wrist, hand and finger range of motion, as well as motor and sensory function of the radial, ulnar, and median nerves must be evaluated to identify any functional deficits. On exam patients may present with forearm extensor compartment atrophy in chronic cases. Weakness will be observed with extension of the thumb and fingers. Radiographs or advanced imaging may be obtained to evaluate possible etiologies such as fractures or tumors.

In regards to radial nerve deficits, one must distinguish a high radial nerve palsy from a low radial nerve palsy. Injuries proximal to the elbow result in a high radial nerve palsy, with loss of function of all wrist, thumb, and finger extensors as well as loss of sensation in the radial nerve distribution over the dorsal thumb and index finger. Injuries distal to the elbow result in a low radial nerve palsy, typically the posterior interosseous nerve. With an injury to the posterior interosseous nerve, patients will exhibit deficits in radial abduction and extension of the thumb as well as inability to extend the metacarpophalangeal (MCP) joints of the fingers. The function of the radial-sided wrist extensors is intact, so patients will maintain wrist extension with radial deviation as the extensor carpus ulnaris is no longer functioning to provide counterbalance. Sensation is usually maintained in low radial nerve palsy.

PIN Palsy Tendon Transfers

In low radial nerve injuries, as wrist extension is maintained with extensor carpi radialis longus (ECRL) and extensor carpi radialis brevis (ECRB), the goal is to restore finger extension at the metacarpophalangeal joints and thumb extension.

Finger Extension

Many tendon transfers exist for finger extension. Common transfers include flexor carpi radialis (FCR) to extensor digitorum communis (EDC), flexor carpi ulnaris (FCU) to EDC, or flexor digitorum superficialis of the long or ring finger (FDS III or IV) to EDC. Some authors advocate against the use of FCU as it is more difficult to harvest than FCR, is too strong with excursion too short, and results in loss of coupled wrist flexion and ulnar deviation, causing both weakness in grip strength and decreased function in tasks such as hammering. In transferring the FDS, the surgeon has the option of excising a large opening in the interosseous (IO) membrane to pass the tendons or routing the tendons around the radius and ulna. In passing through the IO membrane, there is the risk of adhesions and limited function of the transfer.

Thumb Extension

For thumb extension, the most common transfer is palmaris longus (PL) to extensor pollicis longus (EPL). In patients with an absent PL, FDS III or IV can be transferred to the EPL. The brachioradialis is another option but has limited excursion, and it can be difficult to reeducate the patient during rehabilitation.

Tensioning the tendon transfer is a subject of debate. Some authors propose tensioning the tendons until wrist flexion of 30° produces appropriate thumb and finger extension through the tenodesis effect. Other authors suggest that for the FCR to EDC transfer, the wrist be placed in neutral with the MCP joints in full extension and to tension the FCR to around 75% of its maximal tension. Optimally, tension must be tight enough to allow for full extension of thumb and fingers while allowing full flexion of the wrist and fingers. It is better to err being too tight rather than too loose as tendons tend to stretch over time and additional excursion can be regained with therapy. If it is too loose from the start, then the transfer will not function.

Author's Preferred Technique: FCR to EDC, PL to EPL

This operative technique is useful in the setting of a chronic posterior interosseous nerve palsy. Care must be taken to ensure that sufficient wrist extension is intact as an additional tendon transfer would be needed in this case.

Procedure

The patient is positioned supine on a regular operating table with the operative extremity placed on a hand table. A non-sterile, well-padded brachial tourniquet is placed and set to 250mmHg. The operative extremity is prepped and draped in the usual sterile fashion. The limb is then exsanguinated with a sterile esmarch and tourniquet inflated to 250mmHg.

The first incision is made volarly over the FCR tendon. The tendon is identified and the subsheath is released the length of the tendon to accommodate further excursion and allow a more direct line of pull. Without this release, the tendon often makes more of a right angle turn to be transferred dorsally. The wrist is then flexed and the FCR tendon is cut at the level of the trapezium.

Attention is then turned to dissection of the palmaris longus tendon, which will be found just ulnar to the FCR tendon. One

must be vigilant preoperatively to make sure the patient has a palmaris longus tendon, as there have been cases where the median nerve was mistakenly harvested. We typically mark the exact location of the tendon at the wrist crease in the preoperative holding area with the patient actively flexing the PL. Once the PL has been identified, the median nerve is then visualized and protected. The palmaris longus is freed from its surrounding sheath using tenotomy scissors and cut at its insertion into the palmar fascia. Typically, there is abundant length of tendon for this transfer and dissection into the palmar fascia is not necessary.

Dorsally, an incision is made just ulnar to Lister's tubercle to expose the recipient tendons. Dissection is taken down to the level of the fascia with subsequent release of the extensor retinaculum.The EPL tendon is transposed from its sheath and cut proximally at its musculotendinous junction.

Next, the EDC tendons are identified just ulnar to the EPL tendon in the 4th extensor compartment. The extensor retinaculum is released as there is no risk of bowstringing after tendon transfer given the volar pull of the FCR. Prior to cutting the tendons, the wrist is placed in neutral and all fingers are placed in full extension to set the tension of the 2^{nd}-5^{th} extensor tendons. In cases where there is not an EDC to the small finger, one can elect to use the extensor digiti minimi (EDM). Once the tension is set, all four slips are sutured together with 3-0 Ticron suture.The tendons are then cut just proximal to the suture.

After the donor and recipient tendons are exposed, a plane is developed to pass the tendons superficial to the radial artery and deep to the superficial branch of the radial nerve, making sure the tendon transfer does not compress the nerve.

FCR to EDC (Finger Extension)

The FCR tendon is passed from the volar wound to the dorsal wound.At this point, the wrist is placed in neutral and all digits are extended by placing towels beneath them and having an assistant ensure that they remain extended. Once positioned, the tendon transfer is initiated. Using a sharp Pulvertaft weaver, the FCR is passed through each of the four EDC tendons.After the first pass, one must check to make sure tension is adequate. If satisfied, 2 more passes through the tendon are performed and sutured into place with 3-0 Ticron (Figure 1).

PL to EPL (Thumb Extension)

The EPL is then passed from the dorsal wound to the volar wound. Again, the thumb is positioned in full extension with the wrist in neutral. A pulvertaft weave between EPL and PL is performed with tension checked after the first pass. Two additional passes are performed and the ends of each tendon are split and sutured so that they are flush on the sides of the other tendon. (Figure 2).

At this point, tension is checked by testing the tenodesis.The wrist is flexed and extended to ensure adequate excursion and full extension of the thumb and digits. If the transfer appears loose, it is better to revise now than a later date. Once this is satisfied, the tourniquet is released and hemostasis achieved.

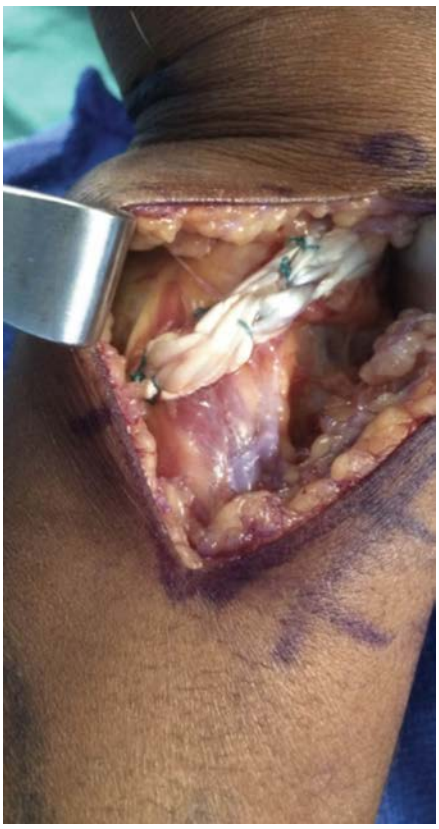

Figure 1. FCR to EDC transfer. With a pulvertaft weave, FCR is passed through each of the four EDC tendons and sutured into place with 3-0 Ticron using the dorsal wound.

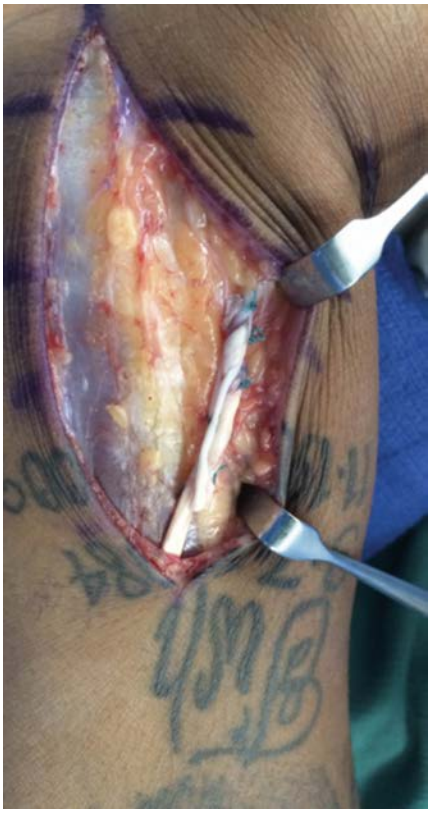

Figure 2. PL to EPL transfer. Picture of the volar wound demonstrating the Pulvertaft weave of the PL to EPL.

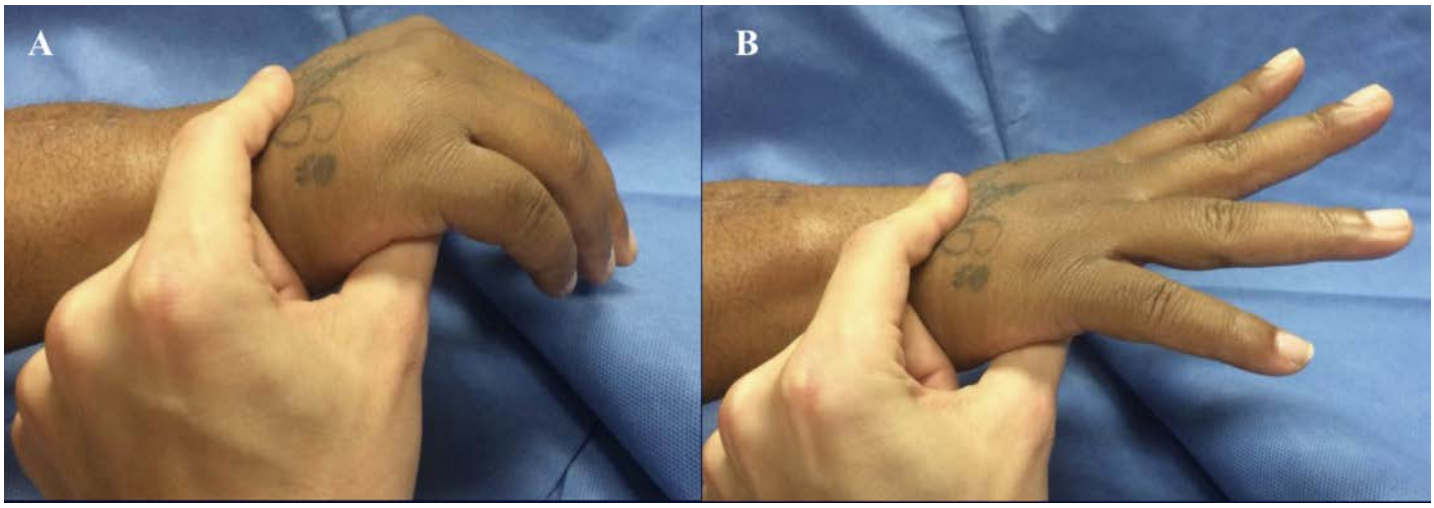

Figure 3. FCR to EDC transfer at the two month postoperative visit. **(A)** MCP joints resting in flexion. **(B)** The patient is able to achieve extension of the MCP joints while the wrist is held in slight extension.

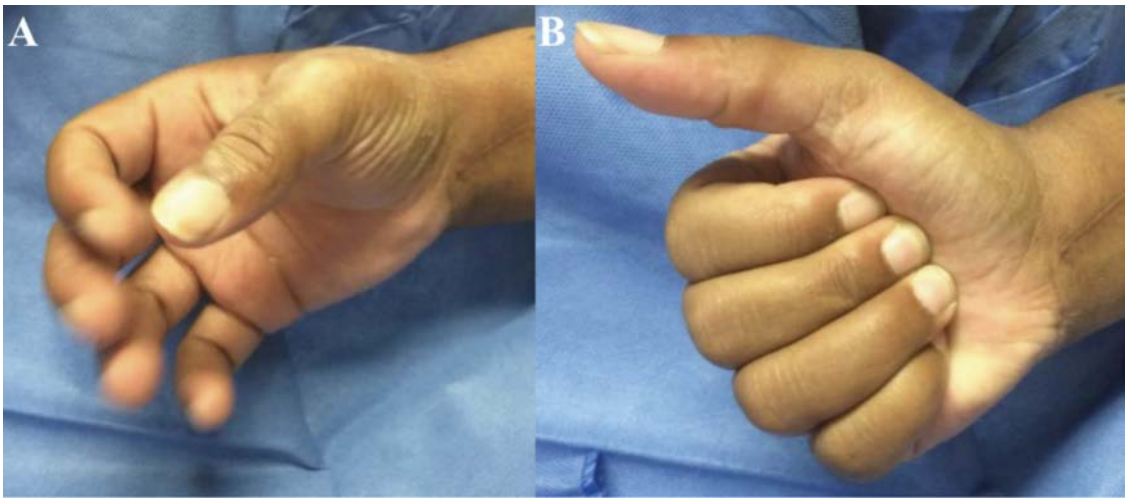

Figure 4. PL to EPL transfer at the two month postoperative visit. **(A)** Thumb IP joint resting in flexion. **(B)** Extension of thumb IP joint achieved through the PL to EPL transfer while the wrist is held in neutral.

The incision is closed in a layered fashion and a dry sterile dressing is placed. The operative extremity is splinted with the wrist in neutral to slight extension and the thumb and fingers extended so as to not place tension on the repair.

Postoperative Protocol

One to two weeks postoperatively the splint is taken down and the wound is examined. A short arm cast is applied with the wrist and thumb extended while the MCP joints are placed in slight flexion. Care is taken to pad all bony prominences. At six weeks, patients are fitted for a custom removable splint, and therapy is initiated. The splint is molded such that the fingers, thumb and wrist are placed in extension. The patient is instructed that they may flex the MCP joints while the interphalangeal (IP) joints are in extension. Similarly, they can flex the IP joints while the MP joints are in extension. At ten weeks postoperatively patients may be advanced to strengthening. (Figures 3 and 4)

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Engineered Anatomic Implants Restore Geometry and Load Transfer in the Porcine Accessory Carpal Joint

Brendan D Stoeckl, MSE[1,2]
George W Fryhofer, MD, MTR[1,2]
Megan J Farrell, PhD[1]
Hannah M Zlotnick, BS[1,2,4]
Michael W Hast, PhD[1]
Thomas P Schaer, VMD[3]
David R Steinberg, MD[1,2]
Robert L Mauck, PhD[1,2,4]

[1]Department of Orthopaedic Surgery
University of Pennsylvania
Philadelphia, PA

[2]Translational Musculoskeletal Research Center
Corporal Michael J. Crescenz VAMC
Philadelphia, PA

[3]Comparative Orthopaedic Research Laboratory
School of Veterinary Medicine
Kennett Square, PA

[4]Department of Bioengineering
University of Pennsylvania
Philadelphia, PA

Introduction

Trapeziometacarpal (TMC) osteoarthritis (OA) is one of the most common conditions affecting middle and older aged adults.[1] Many patients will eventually require destructive surgical intervention, involving removal of all or part of the trapezium, and replacement with tendon, fascia, or an artificial implant.[2] While effective at reducing pain, these procedures compromise grip strength and, in some cases, result in subsidence and disfigurement of the hand.[2] Efforts to replace articular cartilage (and bone) with living, functional tissue have matured substantially over the last two decades,[3] as has technology for generating constructs that can match the anatomical complexity and geometry of native articulating surfaces.[3,4] For these technologies to progress towards translation, appropriate large animal models are required. In our previous work, we identified the porcine accessory carpal (AC) as a potential model for TMC OA, given its multiple similarities.[5] We designed a tissue engineered implant for the articulating surface of the AC (consisting of a PCL foam bone integrating portion, and a hydrogel cartilage articulating surface) and demonstrated the feasibility of its implantation in a living animal.[6] Here, we standardized our design and fabrication protocol to build patient-specific implants and evaluated our ability to recreate the geometry and load transfer across the native AC.

Methods

Construct design and fabrication

Clinical CT images of three forelimbs of skeletally mature Yucatan minipigs were obtained with a portable 8-slice CT scanner (CereTom, Neurologica). From these, the AC bones were segmented using ITK-SNAP[7]. For each, a surface mesh was exported and opened in MeshLab (ISTI), where the mesh was smoothed and simplified. This mesh was imported into Solidworks (Dassault Systèmes) and a 3D object was created. The articulating surface was translated normally 500 μm and the resulting shell became the "cartilage" of the implant. Next, a plane was defined parallel to and ~3mm deep from the top of the bone; this plane was used to remove the bottom portion. Finally, a 2mm wide by 5mm deep "keel" was added to the bottom of the bone to enable subsequent fixation. A positive mold of both the bone only and composite implant was then designed and 3D printed. To fabricate elastomeric negative molds, Sylgard 184 (polydimethylsiloxane, PDMS) was prepared at a 10 parts monomer to 1 part curing agent ratio, poured over the 3D printed designs, degassed, and allowed to cure at 40°C overnight. Poly(ε-caprolactone) (PCL) was dissolved in chloroform at 20% wt/vol and mixed with NaCl crystals sieved to ~106 μm with inclusion of Zirconium nanoparticles for radio-opacity. The slurry was poured into the mold and the solvent was evaporated. The units were demolded and the salt was leached. A 30% solution of poly(ethylene glycol) diacrylate (PEGDA) containing 0.05% Lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) photoinitiator was added to the bone and cartilage composite mold, the PCL "bone" portion was added, and the hydrogel was polymerized using UV light at 380nm for 10 minutes to form a 'cartilage' cap on the implant.

Geometry measurement

The thickness of the designed cartilage surface of each implant was measured in Solidworks on a grid spacing of 1.25 mm and compared with previously generated thickness maps based on native AC cartilage. Each of the three animal-specific implants was scanned via μCT (μCT50, Scanco medical), and the results were segmented, cleaned, and imported into Solidworks and compared to the original designs.

Joint biomechanics

In each of the three forelimbs, an incision was made and a TekScan iScan 6900 pressure sensor was inserted into the joint space between the AC and the ulnar carpal. The carpus was extended through a range of angles from 90 degrees to 0° while contact forces were measured. Next, composite AC constructs were implanted. A reciprocating saw was used to remove the surface of the AC and a 2mm burr to create a slot in the remaining bone matching the keel on the construct. After implantation, TekScan measurements were repeated. T-tests at 0° compared force and contact area pre- and post-op, with $p < 0.05$ indicating significance.

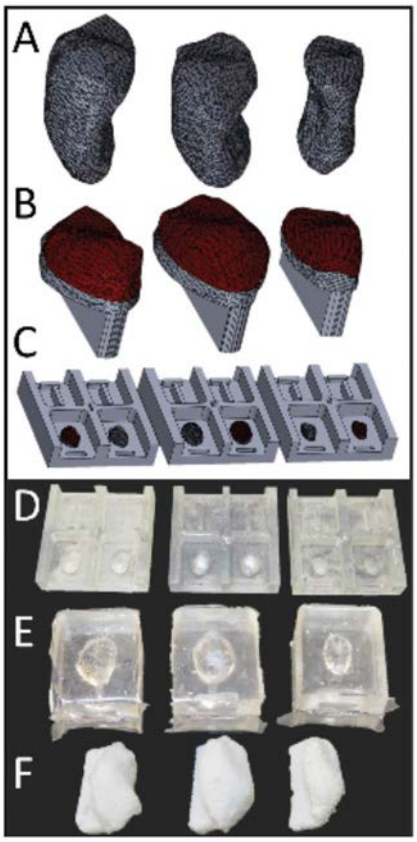

Figure 1. (A) Renderings of 3 AC bones from CT data. **(B)** Designed AC implants with cartilage in red. **(C)** Design of positive molds of the three implants. **(D)** 3D printed positive and **(E)** cast PDMS negative molds. **(F)** Resulting PCL foam constructs.

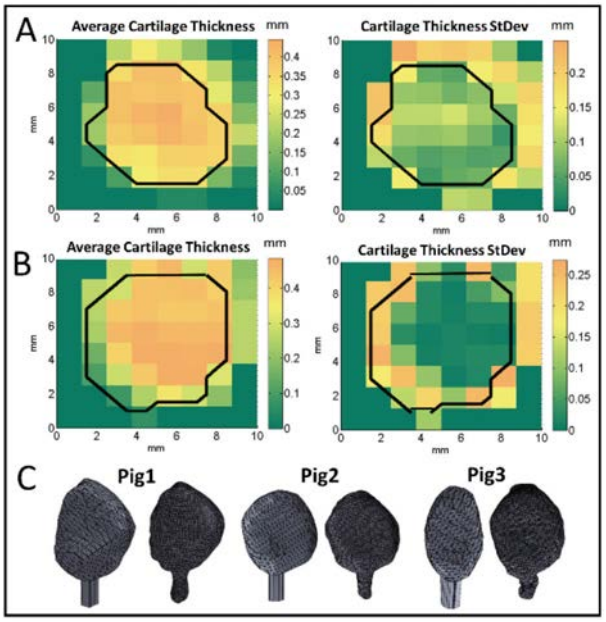

Figure 2. (A) Average (left) and standard deviation (right) of cartilage thickness of 8 native porcine ACs. The black line represents the average cartilage profile. **(B)** The same thickness maps as in **(A)** but for the designed implants for 3 individuals. **(C)** The design (left) and fabricated PCL implant as determined from μCT imaging (right) of each of the three individuals

Results

Starting from clinical CT, we designed animal-specific implants to replace the surface of the AC and molds with which to fabricate them (Fig. 1). Our design technique resulted in a cartilage thickness of ~400-500 μm throughout, much like the native tissue (Fig. 2A-B). Scanning the fabricated constructs by μCT showed that they faithfully reproduced the designs. In the joint loading experiments (Fig. 3), in all preoperative trials, as the limb was extended from 90° to full extension, force and contact area remained close to 0N until the joint approached 0° at which point the average force rose to 21.6N and the average contact area rose to 74.2mm^2. Post-implantation, a similar loading pattern was observed, with force averaging 21.5N and contact area averaging 72.0mm^2.

Discussion

In this study, we expanded on our previous work[5,6] by creating a robust protocol for fabricating biphasic constructs for replacing the osteo-articular surface of the porcine AC bone matched to the geometry of a specific animal's joint. The hydrogel portion of said constructs faithfully recreated the cartilage thickness profile of the native AC and the PCL foam portion restored the original geometry of the bone. Importantly, there was more variation in the size and shape of individual ACs than in the thickness of the cartilage, and

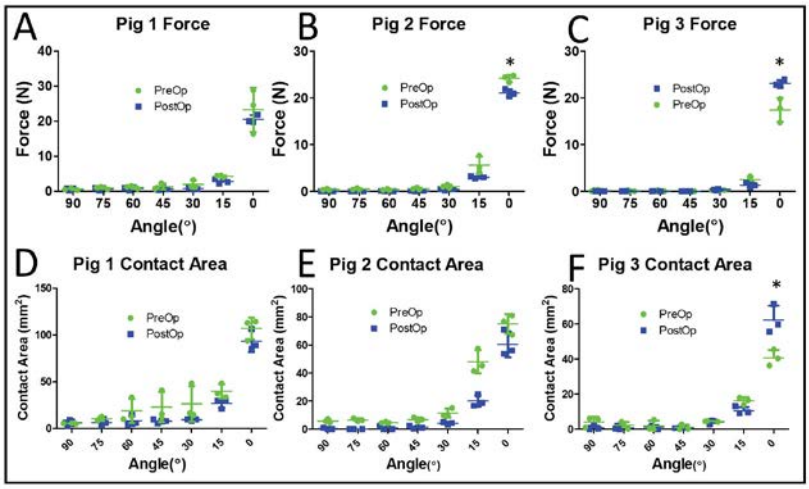

Figure 3. (A-C), Force measurements across flexion angles for each of 3 pigs before and after implantation of composite implant; **(D-F)**, contact area of same.

so knowing the shape of the bone from clinical CT enables us to reasonably approximate the cartilage without the need for contrast agents. When animal-specific constructs were implanted into the forelimb *ex-vivo*, they restored the loading patterns of the joint. Future steps are to evaluate the long-term function of cell seeded osteochondral implants (with a stem cell-laden hydrogel cap to form a cartilage layer) as well as implantation of patient-specific constructs in a living animal to evaluate their long-term efficacy *in vivo*.

Significance

This study refines an approach to design and fabricate of patient-specific implants, furthering the goal of total biologic resurfacing for the treatment of TMC OA in humans.

Acknowledgments

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U·P·O·J

Pediatrics Tips & Tricks: Pros and Cons of Waterproof Cast Liners in Pediatric Injuries

Brandon Haghverdian, MD[1]

[1]Department of Orthopaedic Surgery
University of Pennsylvania

Introduction

Cast immobilization is a commonly used method to protect pediatric injuries of the upper and lower extremities, both following closed reduction as well as surgical fixation. Introduced in 1852, Plaster of Paris-impregnated bandages rapidly became the standard casting material until the emergence of fiberglass casting tape in the 1970's.[1] Fiberglass is waterproof and offers several novel advantages over plaster, including its greater radiolucency, lower setting temperature (reducing the associated risk of cast burns), availability in multiple colors, as well as its lightweight nature without compromise of strength or yield.[1,2] In recent decades, the development of waterproof cast liners have allowed patients the added comforts of hand washing, bathing, showering, and swimming. Despite these benefits, many practitioners have been reluctant to adopt waterproof liners in the acute and follow-up treatment of pediatric injuries. Here, we synthesize the recently-available literature and studies comparing the efficacy and safety of waterproof liners to standard cast liners.

History

The first widely-adopted waterproof liner was introduced in 1990 utilizing Gore-Tex® fabric as cast padding (W. L. Gore & Associated, Inc, Flagstaff, Arizona). Composed of stretched polytetrafluoroethylene (PTFE), this material was found to protect fracture alignment and allow improvements in patient satisfaction and hygiene while also protecting against the attendant risks of prolonged immobilization.[3-5] Since then, numerous brands of water-resistant undercast padding have become available, including Delta Dry®, AquaCast® (Figure 1), Wet or Dry®, Procel®, Water Pruf®, Infina Under-Cast®, and Nemoa® Cast.[6] These materials have evolved to become durable, stretchy, mesh-like, wrinkle-free, and lightweight. To date, relatively few studies have been performed to compare different waterproof liners. Stevenson and colleagues were the first to compare Wet or Dry® with Delta Dry® liners, and found that the Wet or Dry® demonstrated significantly better performance with odor and water resistance, whereas Delta Dry® was found to provide greater ease of application, moldability, durability, and padding level.[6]

Advantages

There are numerous proposed benefits supporting the use of waterproof liners over cotton or synthetic liners in pediatric patients. First, synthetic and cotton liners often retain moisture after application of the fiberglass, increasing the risk of dermal and integumentary complications including maceration, infection, itch, burns, and contact dermatitis.[7] Furthermore, waterproof liners allow patients the opportunity to rinse casts daily, shower and bathe, and swim without restriction. Numerous studies have confirmed the finding that waterproof liners engender greater patient satisfaction, less skin problems, and fewer unscheduled cast changes due to water exposure.[3,8,9] Guillen *et al.* were the first to directly compare patient outcomes amongst two groups of pediatric patients with upper extremity injuries utilizing cotton versus water-resistant cast padding.[10] Patients found that waterproof liners resulted in less odor and sweat scores, preferring them 75% of the time compared to cotton liners. Moreover, waterproof

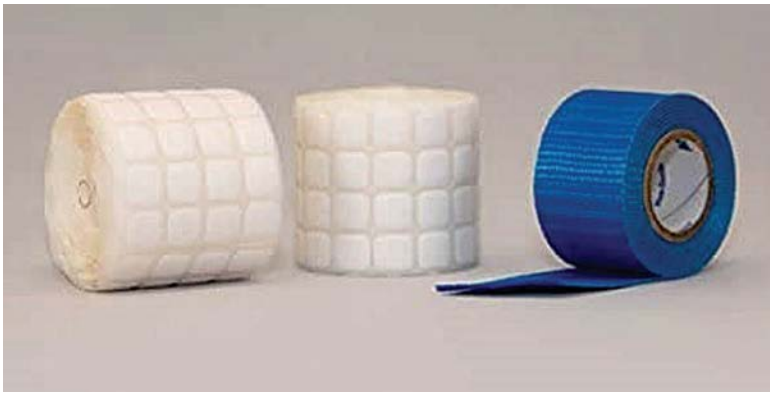

Figure 1. AquaCast® Liner with Saw Stop Protective Strip. Available at: http://www.aquacastliner.com/

liners resulted in better skin conditions as rated by a blinded physician.

Several complications exist related to the application and utilization of casts in pediatric injuries; chief among them is the occurrence of unplanned cast changes. DiPaola *et al.* performed a prospective study of 1135 casts applied at a single institution, evaluating the incidence, etiology, and complications related to unplanned cast changes.[11] The authors found that, of the sixty casts requiring an unplanned change, 47% were changed for wetness. Sawyer and colleagues similarly reported a total of 168 pediatric emergency room visits for cast-related problems over a 5-year study period at their institution.[12] The most common reason for visit was because of a wet cast. Taken together, these results suggest a high cost and economic burden related to wet cast complications, which could be ameliorated with more widespread adoption of waterproof lining in cast application. Indeed, Wolff and James demonstrated a decrease in the incidence of unscheduled cast changes from 14% to 2.9% with use of waterproof casts.[5] Similar results were found by Haley *et al.* (33% of unscheduled cast changes with cotton casts versus 10% with Gore-Tex® casts).[7]

Waterproof-lined casts have demonstrated an ability to maintain fracture alignment that is comparable to traditional cotton-lined casts. In a review of 59 pediatric patients with unstable, 100% displaced distal radius fractures, Gore-Tex® and cotton casts were equally effective in their ability to maintain long-term reduction after closed reduction.[15] Another study demonstrated that waterproof casts may be effectively used to immobilize sprains, stable fractures, and unstable fractures more than 2 weeks post-reduction.[3] Similar findings have been noted in the setting of pediatric forearm fractures.[6]

The application and use of waterproof cast liners is similar to that of traditional cast liners, with few notable exceptions: patients should allow gravity to drain the wet cast for at least 15 minutes, swimming in untreated water (oceans and lakes) is not recommended, and patients should avoid getting the cast wet before removal.[13] Patients and their families should be appropriately educated regarding these special precautions, in addition to other standard cast restrictions. Because of the similarities in cast application, minimal additional training is needed for practitioners and technicians seeking to adopt waterproof liners. Notably, a stockinette is not used during application of a waterproof cast.

Disadvantages

There are several proposed disadvantages of waterproof casting reported by some practitioners. Chief among them is the additional cost incurred with waterproof liners as compared to traditional liners. Gore-Tex® cast liners, for instance, are reported to cost $30 to 50 more per cast.[3] The average cost of Procel® liners is also 3.5-4.5 times more expensive than cotton liners for short-arm, long-arm, and short-leg casts.[3] To our knowledge, a high-powered, formal cost analysis has not been performed to evaluate the cost efficiency of utilizing waterproof casts. In principle, however, the reduced frequency of unscheduled cast changes, as well as unexpected emergency room and office visits, far outweigh the additional expenditures related to waterproof liners. A standardized practice of waterproof casting could thereby significantly reduce the economic and time burden on the health care system incurred by unexpected cast damage.

Use of a waterproof cast liner is not without some risk. Shannon *et al.* reported a 10.7% rate of minor skin problems in their series of 112 patients with waterproof-lined casts, as compared to 26.6% of patients with standard casts.[3] These included complications such as blistering, erythema, and contact dermatitis; all problems resolved with no additional intervention, and no significant cutaneous problems were observed. In addition, one study reported significantly higher cast pressures when a pediatric blood pressure cuff bladder was inflated within waterproof-lined casts as compared to cotton-lined casts.[14] The authors concluded that consideration should be given for using cotton cast padding in the acute fracture setting to better accommodate soft tissue swelling. However, other studies have supported the safe and effective application of waterproof casts immediately after closed fracture reduction.[15] Waterproof casting is therefore widely considered to be safe with appropriate cast application and parental monitoring, both in the immediate and follow-up treatment of pediatric fractures.

Conclusion

Waterproof casting represents a safe and effective alternative to traditional cotton or synthetically-lined casts in the treatment of upper or lower extremity pediatric injuries. There are several benefits of waterproof lining, including improvements in patient hygiene, greater patient satisfaction, ability to maintain fracture reduction, and reduced frequency of unexpected cast changes. While waterproof liners are more expensive, the added cost is likely offset by the reduction in cast changes as well as emergency room and office visits. We therefore support a more widespread adoption of waterproof liners in appropriate pediatric patients with extremity injuries.

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Pediatric Ramp Lesions: Incidence, MRI Sensitivity, and Associated Risk Factors

Joshua T. Bram, BS[1]
Jie C. Nguyen MD, MS[1]
Margaret L. Wright, MD[1]
Tomasina M. Leska, BS[1]
Julien T. Aoyama, BA[1]
Theodore J. Ganley, MD[1]

[1]Department of Orthopaedic Surgery
The Children's Hospital of Philadelphia,
Philadelphia, PA

Introduction

The incidence of anterior cruciate ligament (ACL) injuries in children is steadily increasing and over half of cases are associated with meniscal tears.[1,2] One type of meniscal pathology is known as a "ramp" lesion, which describes injury to the meniscocapsular junction, located between the posterior horn of the medial meniscus (PHMM) and the joint capsule. They have been historically underdiagnosed in ACL deficient patients, likely due to their location in a "blind spot" using traditional anterior arthroscopic approaches and the absence of validated MRI criteria.[3-5] However, it is well understood that the PHMM is an important anatomic restraint to anterior tibial translation, particularly in the setting of ACL injury.[6]

Recent studies show that ramp lesions occur in 9-30% of adults with ACL injuries, with repair significantly improving post-operative functional scores.[7-9] While there has been increasing interest in identifying and treating ramp lesions in the adult orthopedic literature, little is known about ramp lesions in pediatric patients.[10] The purpose of this study was to: 1) determine the incidence of ramp lesions in pediatric patients with ACL tears, 2) identify associated risk factors for the occurrence of a ramp lesion, and 3) determine the sensitivity of magnetic resonance imaging (MRI) for identifying ramp lesions.

Methods

This was a retrospective cohort study of 144 patients ≤ 21 years old who underwent ACL reconstruction at a single institution from 2/2019 to 1/2020. Preoperative characteristics, including injury mechanism and exam findings, were recorded from the medical record. Preoperative MRIs, when available, were blinded and reviewed by an experienced musculoskeletal radiologist to determine the presence of a ramp lesion and/or a posteromedial tibial bone bruise. Intraoperative records were also searched for ramp tears and other associated injuries.

Patients were separated into cohorts based on the presence or absence of an arthroscopically-identified ramp lesion. Descriptive statistics for injury risk factors were reported, with Chi-squared and Fisher's exact tests used to analyze categorical variables. Independent T and Mann-Whitney U tests were used to compare continuous variables after evaluation of normality using Kolmogorov-Smirnov tests. Binary logistic regressions were used to calculate odds ratios and 95% confidence intervals (CI) for significant predictors of arthroscopic ramp lesion identification. Using an α of 0.05 for significance, all tests were performed utilizing IBM SPSS Statistics for Macintosh (Version 24.0. Armonk, NY).

Results

One hundred forty-four patients were included in the study: 19 with intra-operatively identified ramp lesions (13.2%) and 125 (86.8%) without. There were no significant differences between groups based on sex, time between injury and surgery, laterality, or prior contralateral ACL injury history (Table 1). Patients with ramp lesions were significantly older (16.7 ± 2.2 vs 15.5 ± 2.3 years, $p = 0.037$) and were more likely to be undergoing a revision ACL reconstruction (15.8% vs 3.2%, $p = 0.049$). There were no differences in preoperative exam characteristics, mechanism of injury, or the proportion of sports-related injuries. Intraoperatively, patients with ramp tears did not have an increased incidence of concomitant ligamentous or lateral meniscus tears. A revision ACL procedure (OR 5.67, 95% CI 1.16-27.68, $p = 0.032$) and older age (OR 1.25, CI 1.01-1.54, $p = 0.040$) increased the odds of having a ramp lesion, though neither variable achieved significance in multivariate analysis. MRIs were available and reviewed retrospectively for 18 patients with and 120 patients without ramp tears (Table 2). MRI more frequently revealed a complete ramp lesion (33.3% vs 10.8%, $p = 0.010$) or posteromedial tibial bone bruise (88.9% vs 56.7%, $p = 0.009$) for patients with arthroscopically identified ramp tears. The sensitivity of MRI for ramp lesion (full or partial) detection was 50.0% (95% CI 26.0%-74.0%) with a specificity of 72.5% (95% CI 63.6%-80.3%). The overall accuracy was 69.6% (95% CI 61.2%-77.1%).

Discussion

This is the largest known study describing ramp lesion incidence in a pediatric population, occurring in 13% of our patients. The only significant predictors of a ramp lesion were revision ACL procedure and older age at

Table 1. Baseline Demographics and Injury Characteristics.

Variable	No Ramp Lesion (N = 125)	Ramp Lesion N = 19	*P*-value
Demographics			
Age at Surgery (yrs)	15.5 ± 2.3	16.7 ± 2.2	**0.037**
Female Sex	62 (49.6%)	11 (57.9%)	0.500
BMI	23.8 ± 5.2	23.0 ± 3.4	0.758
Left Knee	62 (49.6%)	10 (52.6%)	0.806
Injury Characteristics			
Time from Injury to Surgery (days)	87.7 ± 128.3	56.3 ± 21.4	0.422
Revision ACL	4 (3.2%)	3 (15.8%)	**0.049**
Prior contralateral ACL injury	7 (5.6%)	1 (5.3%)	1.000
Sports-Related	113 (90.4%)	18 (94.7%)	1.000
Injury Mechanism			
Contact	38 (30.4%)	3 (15.8%)	0.462
Non-Contact	84 (67.2%)	16 (84.2%)	
Unknown	3 (2.4%)	0 (0%)	
Concomitant Injury			
ALL sprain/tear	9 (7.2%)	4 (21.1%)	0.072
LCL sprain/tear	2 (1.6%)	0 (0%)	1.000
MCL sprain/tear	5 (4.0%)	0 (0%)	1.000
Lateral Meniscus Tear	84 (67.2%)	13 (68.4%)	0.916
Exam Findings			
Effusion			
None	25 (20.0%)	3 (15.8%)	0.594
Mild (fluid wave, < 25mL)	64 (51.2%)	8 (42.1%)	
Moderate (easily ballotable, 25-60mL)	34 (27.2%)	8 (42.1%)	
Severe (tense, > 60mL)	2 (1.6%)	0 (0%)	
Lachman Grade‡			
Normal (< 6mm)	12 (10.3%)	0 (0%)	0.349
Abnormal (6-10mm)	87 (74.4%)	17 (89.5%)	
Severely abnormal (> 10mm)	18 (15.4%)	2 (10.5%)	
Positive McMurray's	47 (37.6%)	8 (42.1%)	0.707
Total Beighton score	1.8 ± 2.2	2.2 ± 2.7	0.780

‡Only 136 patient's with recorded Lachman findings

surgery. There were no other significant demographic, injury, or exam differences between patients with and without intraoperatively confirmed tears.

Our findings corroborate past work in adults that has shown revision ACL reconstruction to be predictive of identifying a ramp lesion, though it is unclear if these tears were not seen at initial reconstruction or if they occur more common in repeat injuries.[11] While it is possible that index injuries were missed, the excellent blood supply to the periphery of the meniscus should allow these lesions to heal after ACL reconstruction regardless of lesion management, unless the initial lesion was very large.[12] Therefore, it is possible that there is another biomechanical reason that they occur more commonly during graft tears, given the role of the medial meniscus as a secondary restraint to anterior tibial translation.[6]

Interestingly, younger age has actually been associated with a higher incidence of ramp lesions in adult-based studies, making it likely that there is a peak injury incidence in athletic young adults.[11, 13] Other previously reported risk factors for ramp tear in adults are an increased time from injury to surgery, male sex, and a contact injury mechanism.[11, 13-15] However, none of these factors were different between the groups in our study.

MRI showed high specificity (72.5%), but low sensitivity (50%) for diagnosing ramp lesions. These values are on the lower end of what has been reported in adults (48-86% sensitivity, 79-99% specificity), which reflects the need for validated imaging criteria.[4, 5, 16] This may be the result of a higher prevalence of peripheral meniscus signal irregularities in children, which lead to a limited ability to preoperatively identify ramp lesions in pediatric patients.[17] Posteromedial tibial edema (or bone bruising), as shown in our study, has also been shown to increase the odds of ramp tear over a meniscal body tear, perhaps related to the higher rate of contact injuries

Table 2. Preoperative MRI Findings.

Variables	No Ramp Lesion	Ramp Lesion	*P*-value
N	120	18	-
Delay from Injury to MRI (days)	30.3 ± 112.2	6.9 ± 4.6	0.105
Delay from MRI to Surgery (days)	57.9 ± 43.7	48.7 ± 21.5	0.824
Location of MRI			
Our Institution	46 (38.3)	7 (38.9)	0.964
Outside Hospital	74 (61.7)	11 (61.1)	
Sequences available for diagnosis			
T2-Weighted	91 (75.8)	13 (72.2)	0.740
Proton-Density Weighted (PD)	44 (36.7)	8 (44.4)	0.525
Other	2 (1.7)	0 (0)	1.000
Ramp Lesion on MRI			
Full	13 (10.8)	6 (33.3)	**0.010**
Partial	20 (16.7)	3 (16.7)	1.000
Total	33 (27.5)	9 (50.0)	0.096
Posteromedial tibial bone bruise	68 (56.7)	16 (88.9)	**0.009**

that are associated with both tibial bone bruising and ramp lesions.[14, 15, 18]

Conclusions

Revision ACL surgery and older age predicted a higher occurrence of ramp lesions in our pediatric and adolescent population. The observed low MRI sensitivity is overall consistent with findings in the adult literature, and emphasizes the need for validated imaging criteria and thorough intraoperative exam in order to consistently identify ramp lesions.

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Pediatric Jones Fractures

Nicolas Pascual-Leone, BA[1]
Nishank Mehta, BA[2]
Joshua Bram, BS[1,2]
Theodore Ganley, MD[1,2]

[1]Perelman School of Medicine
University of Pennsylvania

[2]Department of Orthopaedic Surgery
The Children's Hospital of Philadelphia,
Philadelphia, PA

Introduction

Fifth metatarsal fractures are common injuries across all age groups. Jones fractures are a specific type of 5th metatarsal injury, originally defined as a fracture ¾ inches from the base of the fifth metatarsal.[1] However, many definitions have been used in the literature, including a fracture within 1.5 cm of the 5th metatarsal tuberosity, fractures within 1.5 to 3 cm from the base of the 5th metatarsal, and any fracture just distal to the 4th and 5th intermetatarsal articulation.[2] Regardless of definition, these fractures often result from sports such as basketball or soccer after a twisting or inversion injury, leading to acute pain and swelling.[3,4]

In non-athletes, Jones fractures are typically managed non-operatively with an initial non-weightbearing period to ensure union.[5] However, past work predominantly in adult male athletes has suggested that operative management decreases non-union rates and results in a quicker return to sports.[6,7,8] Therefore, the goal of our study was to describe injury and treatment characteristics of pediatric patients with Jones fractures to provide physicians with information on management options and outcomes.

Methods

This was a retrospective case-control study of pediatric patients who were treated for a fracture of the fifth metatarsal at a high-volume tertiary care center between 1/2014 and 12/2019. Patient records were reviewed to collect basic demographic information as well as details on fracture characteristics, management, and outcomes. To separate from other fracture types, Jones fractures were defined as those occurring between 1.5 and 3 cm from the base of the fifth metatarsal. A control cohort of patients with avulsion fractures of the fifth metatarsal was matched by sex and age (within 2.5 years) to patients with Jones fractures. Analyses were performed using IBM SPSS Statistics, Version 26.0 (Armonk, NY). Descriptive statistics were reported for baseline variables, while case and control groups were compared using Chi-Squared and Fisher's exact tests for categorical variables and Independent t-tests for continuous variables using an alpha of 0.05 for all tests.

Results

Of 958 patients seen at our institution for fifth metatarsal fractures, 24 sustained a Jones fracture and 193 sustained an avulsion fracture. Twenty-three of the patients with Jones fracture (mean age 14.7 years, 43.4% female, Table 1) were then matched 1:1 to the control group of avulsion fracture patients (mean age 14.4 years, $p = 0.754$). The most common sports at the time of injury for Jones fracture patients were football (4 patients), and basketball, running, or dance (3 patients each), while most avulsion fracture patients did not specify a sport ($p > 0.05$ for all sports). There was no difference in body mass index at injury for Jones fracture patients (27.6 vs 24.2, $p = 0.072$) versus patients with avulsion fractures. Inversion injuries were the most common mechanism of injury for both groups and accounted for 33.3% and 45.8% of Jones and avulsion fractures, respectively ($p > 0.05$ for all mechanism comparisons). Two Jones fracture patients were treated operatively with cannulated screw fixation, whereas all other Jones and avulsion fractures were treated conservatively with a CAM walking boot or casting. 14 patients with Jones fractures and 7 patients with avulsion fractures had adequate follow-up imaging to assess healing and return to activity. For patients with Jones fractures, the average healing time was 14.4 weeks and return to sport took 15.8 weeks versus 11.0 weeks to union ($p = 0.140$) and 12.2 weeks to return to sport ($p = 0.061$) for avulsion patients.

Discussion

This study serves as one of the first to analyze demographics, management, and outcomes for pediatric patients with Jones fractures. Compared to patients with 5th metatarsal avulsion fractures, there were no significant differences in baseline demographics, gender, or injury mechanism. There were no differences in body mass index between groups, suggesting that heavier patients may not be at higher risk of suffering a Jones fracture. Despite non-operative management in nearly all Jones fracture cases, time to fracture union and return to sport were in line with previously reported rates.[3]

The management of Jones fractures is highly debated, particularly due to varying definitions in the literature. Previous studies

Table 1. Comparison of Patients with Jones Fractures and Avulsion Fractures

Variables	Jones Fracture (n = 23)	Avulsion Fracture (n = 23)	P-value
Age	14.7 ± 3.6 years	14.4 ± 2.8 years	0.754
Female	10 (43.4)	10 (43.4)	1.000
BMI	27.6 ± 7.4	24.2 ± 4.4	0.072
Mechanism of Injury	5 (20.8)	1 (4.3)	0.141
Contact	6 (25.0)	10 (43.5)	0.187
Fall	8 (33.3)	11 (45.8)	0.216
Inversion/Twist	2 (8.3)	0 (0)	0.369
Jumping	3 (12.5)	1 (4.3)	0.489
Other/ Unspecified			0.608
Sport			0.938
Basketball	3 (12.5)	2 (8.7)	1.000
Dance	3 (12.5)	0 (0)	0.233
Football	4 (16.7)	1 (4.3)	0.346
Running	3 (12.5)	1 (4.3)	0.608
Soccer	2 (8.3)	0 (0)	0.489
Volleyball	1 (4.2)	0 (0)	1.000
Time to Union (weeks)	14.4 ± 5.5	11.0 ± 2.8	0.140
Return to Sport (weeks)	15.8 ± 4.2	12.2 ± 4.9	0.061

have suggested that due to their watershed location, patients should be considered for surgical intervention to limit the risk of re-fracture and decreased healing resulting from poor perfusion.[9-11] Two large meta-analyses of Jones fractures in mostly high-level male athletes have favored operative over non-operative management, reporting significantly faster time to fracture union and time to full activities.[3,4] Kerkhoffs et al further found that non-operative management of 5th metatarsal avulsion fractures led to rapid time to healing (7.1 weeks) and return to sport (7.5 weeks). While the majority of studies on Jones fractures have been in adult athletes, Herrera-Soto et al studied fifth metatarsal fractures, including Jones fractures, in pediatric patients and recommended that younger patients can be treated conservatively with initial non-weight bearing followed by progressive return to activity, while older patients should be considered for surgical intervention to limit delayed healing.[12] In our study, there were no differences in healing or return to sport times between patients with Jones versus avulsion fractures, perhaps indicating that conservative management in children can be as effective in certain cases.

This study is limited due to its relatively small sample size as we adhered to the precise, technical definition of Jones fractures to only include fractures between 1.5-3 cm from the 5th metatarsal base. Future studies in pediatric patients would be aided by a consensus definition of a Jones fracture, which would allow for the inclusion of more patients to increase statistical power. Moreover, a significant proportion of our patients were lost to follow-up after conservative management, limiting our ability to understand the natural history of this fracture and optimal treatment.

Conclusions

Overall, we did not identify baseline demographic risk factors for the occurrence of a Jones fracture in the pediatric population. Further, there were no differences in healing times or return to sport when compared to patients with 5th metatarsal avulsion fractures.

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Shoulder Tips & Tricks: The Essentials of Physical Examination

Lauren M. Boden, MD[1]
Stephanie A. Boden, MD[2]
Allison L. Boden, MD[3]

[1]Department of Orthopedic Surgery
University of Pennsylvania

[2]Department of Orthopedic Surgery
University of Pittsburgh

[3]Department of Orthopedic Surgery
Jackson Memorial Hospital,
University of Miami

Introduction

Shoulder pain is a common complaint in the outpatient orthopedic setting. A thorough physical examination is key in delineating the underlying diagnosis in patients with shoulder complaints. Although the shoulder physical examination is crucial for diagnosis and management, it often remains elusive to residents. The examination can be simplified by dividing it into the following: inspection, palpation, range of motion (ROM), neurovascular and cervical spine exam, and special testing.

Inspection

The physical examination of the shoulder should begin with thorough inspection. This includes full visualization of both the front and back of the patient. It is best to begin the exam from behind, as this is the area that is most forgotten. The patient should be wearing a gown open in the back. The goal with inspection is to identify any abnormalities in muscle bulk, signs of muscular atrophy, or any bony or soft tissue asymmetries. It is important to visualize the scapula bilaterally and observe for any asymmetry. Atrophy of a muscle or group of muscles can be a key indicator for underlying nerve damage or chronic rotator cuff tear. Protraction of the scapula in the resting position is a sign of scapular dyskinesis.

Palpation

Palpation of relevant anatomic structures should be systematic and consistent. Palpation is important to identify tender and nontender areas as well as areas of crepitation. Position yourself behind the patient. Palpation should include the coracoid process, acromioclavicular joint, anterior process of the acromion, greater tuberosity of the humerus, bicipital groove, and lesser tuberosity of the humerus (Figure 1).

Range of Motion

Range of motion can be an important indicator of underlying shoulder pathology. Shoulder range of motion consists of forward flexion, abduction, adduction, extension, internal and external rotation. Normal values for ROM are listed in Table 1. While active range of motion can be limited by pain or weakness, not many conditions cause diffuse reduction in passive range of motion, making it an important aspect

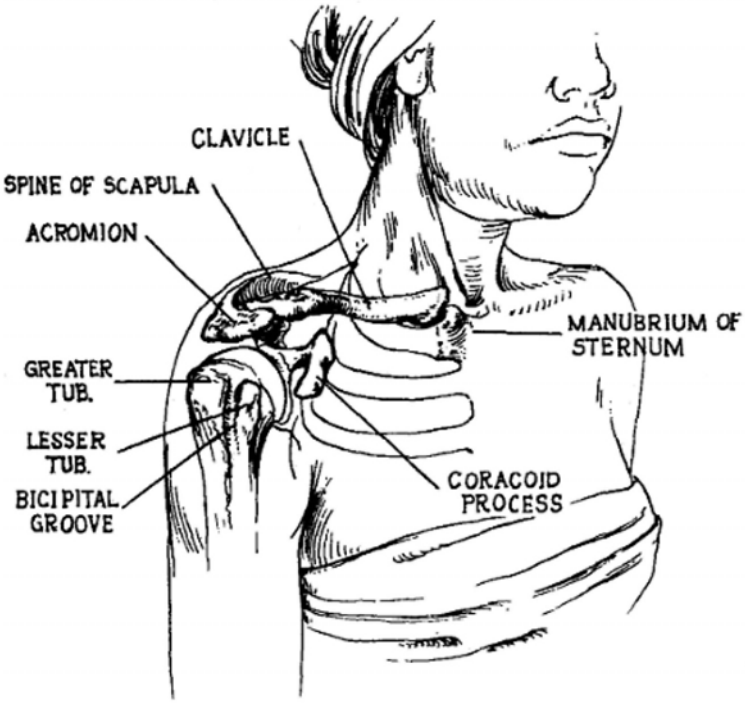

Figure 1. Bony landmarks of the shoulder as published in Hoppenfeld.[1]

Table 1. Normal Values for Shoulder Range of Motion

	Degrees
Forward flexion	0-180
Abduction	0-90
Adduction	0-50
External rotation at 0/90	0-70 / 0-100
Internal rotation at 0/90	T7 / 0-70
Extension	0-45°

of the physical exam. There are two main causes of significantly decreased passive range of motion; severe arthritis and frozen shoulder. Isolated decrease in passive internal rotation of the dominant arm in an overhead throwing athlete likely represents glenohumeral internal rotation deficit (GIRD), placing the athlete at greater risk of impingement and labral injury.

The exam begins with the patient sitting upright. Forward flexion and abduction are tested, followed by internal and external rotation at neutral. Then the patient is instructed to lie supine at the edge of the table for testing of internal rotation and external rotation at 90 degrees, also known as the ABER position. The examination table provides stabilization of the scapula to isolate glenohumeral motion.

Lastly, scapular motion must be tested. This may be done during the inspection aspect of the exam or range of motion portion of the exam. In addition to the resting position of the scapula, the examiner must evaluate the position of the scapula during movement. Medial winging of the scapula is an indicator of serratus or long thoracic nerve dysfunction. Lateral winging is less common and typically results from nerve injury to the spinal accessory nerve.

Neurovascular Exam and Cervical Spine Exam

In the majority of patients distal sensory, motor, and vascular examination will be normal. However, these tests must not be overlooked as they may steer the clinician towards the proper diagnosis outside of the shoulder. Weakness in major muscle groups may be caused by injury to the muscle itself or from a nerve palsy. Knowing the anatomy will help direct further diagnosis and workup. Similarly, the neck may be the cause of the patient's symptoms rather than the shoulder.

Always check the cervical spine. The Spurling maneuver is usually performed with the patient in the seated position and is used to assess for radicular pain. The examiner turns the patient's head so that the patient is facing the affected side. The patient's head is then extended, and a downward pressure is applied to the top of the patient's head.

Special Testing

In addition to the standard physical exam, a myriad of special tests can be performed to home in on a diagnosis. Scapular dyskinesis, previously described, may be the cause of shoulder impingement. Other tests may identify rotator cuff pathology, labral pathology, or shoulder instability. It is important to stabilize the scapula to isolate glenohumeral joint motion. Often these tests will have some overlap, but when used in combination with history can be quite useful.

Impingement tests

Neer's test—The patient's arm should start in a resting position, relaxed at the side of the patient's body. The examiner internally rotates the arm and then passively moves the arm through the full range of forward flexion or until the patient reports pain. The test is considered positive if the patient feels pain in the antero-lateral aspect of the shoulder.

Hawkin's test—Passively forward flex the shoulder to 90 degrees and internally rotate the arm. Pain indicates subacromial impingement or rotator cuff pathology.

Adduction test—The patient's arm is flexed to 90 degrees with maximum adduction across the body. A positive test will cause pain at the AC joint.

Biceps tendinopathy tests

Speed's test—The arm is forward flexed to 90 degrees with the forearm in supination and the elbow fully extended. The patient then resists a downward force. This test is positive if the patient feels pain in the bicipital groove and is indicative of biceps tendonitis or instability.

Yergason's test—The patient's arm is adducted and examiner the elbow is flexed to 90 degrees with the forearm in neutral or pronation. The examiner places one hand on the bicipital groove and attempts to hold the arm in pronation while the patient attempts to supinate. The test is positive if there is pain in the area of the bicipital groove and often indicates bicipital tendonitis. If you feel a snapping of the bicipital tendon, there is likely transverse ligament pathology.

Labrum tests

O'Brian's test—With the arm in 90 degrees of forward flexion and 10 degrees of adduction, the patient should extend and internally rotate/pronate their arm, with their thumb pointed at the ground. The examiner provides a downward force distally on the wrist while the patient forcefully resists. This maneuver should be done both with the forearm in the neutral position and with the forearm pronated. The test is very similar to the Empty Can test, but the patient's arm is in an adducted position. The test is positive if the patient has pain and/or clicking when the forearm is pronated but has no pain with the forearm in a neutral position and indicates a SLAP lesion.

Crank test—The examiner should flex the patient's elbow to 90 degrees and forward flex the shoulder in the scapular plane to roughly 160 degrees. A gentle compressive force is then applied along the axis of the humerus while the shoulder is internally and externally rotated. If the patient's pain is reproduced with this test, or there is an audible or palpable click associated with the maneuver, there should be concern for a labral tear.

Kim test—The examiner should place the arm with the shoulder abducted to 90 degrees and forward flexed to 45 degrees. A posteriorly and inferiorly directed force is then applied to the humerus. The test is positive if the patient experiences pain and is highly indicative of a posteroinferior labral tear.

Rotator cuff tear tests

Jobe's/ Empty can test—Place the patient's arm with the shoulder at 90 degrees of forward flexion and roughly 30 degrees of abduction with the thumbs pointing downwards as if they are emptying a can. The patient should then attempt elevation of the arm against the examiner's resistance. Pain indicates a supraspinatus tear.

External rotation test—With the patient's elbow flexed to 90 degrees and the shoulder in neutral, the patient should attempt external rotation against resistance provided by the examiner. A test is positive if there is pain with resisted external rotation and is indicative of infraspinatus and/or teres minor pathology.

Internal rotation lag sign—The patient's arm is placed at the maximal internal rotation position, with the dorsum of their hand resting on their back. The examiner should grasp the forearm and lift the dorsum of the hand away from the spine. The patient is instructed to keep their hand off of their back. A positive test occurs when the patient is unable to maintain the position off of the back and is indicative of subscapularis tendon pathology.

Lift off test—Place the patient's arm internally rotated behind the back with the dorsum of the hand placed on the back. Ask the patient to lift the arm off of their back. A positive test is when the patient is unable to elevate their hand from their back and indicates subscapularis tendon pathology.

Belly press test—Place the patient's hand on their stomach and ask them to push their hand into their stomach as hard as they can. The patient should then attempt to bring the elbow forward in the scapular plane. The test is positive if the patient is unable to maintain the pressure on the stomach as they move their elbow forward or if the patient extends the shoulder and is indicative of a subscapularis lesion.

Shoulder instability tests

Apprehension / relocation test—For this test, the patient needs to be positioned supine on a table. The patient's shoulder is abducted to 90 degrees and passively externally rotated. If the patient has apprehension with external rotation of the humeral head, the apprehension test is positive which indicates anterior instability of the shoulder. The patient commonly reports that this sensation is similar to what they felt in prior subluxation or dislocation events. After the shoulder is externally rotated, the examiner places a hand over the humeral head and applies a posterior force. Relief of apprehension with this maneuver also indicates anterior instability of the shoulder.

Sulcus sign—With the patient's arm at their side, the examiner should place one hand on the patient's wrist and apply an inferior force as if to pull the patient's arm into the ground. An increased acromiohumeral interval reflects inferior laxity of the humeral head or instability.

Jerk test—With the patient seated, the examiner forward flexes the patient's arm to 90 degrees and internally rotates the arm while applying a compressive force along the humerus. While maintaining the axial compressive force, the arm is adducted across the patient's body. The test is positive if there is a sudden jerk, palpable clunk, or apprehension and this is indicative of posterior subluxation and instability. This test is highly sensitive and specific for a posterior labral tear.

Conclusion

The physical examination of the shoulder provides a wealth of information in patient diagnosis. Using the history and physical examination alone will often provide the diagnosis. At the very least it will direct the clinician towards proper imaging and can also assist in surgical planning.

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Long-Term Nicotine Exposure Alters Rat Supraspinatus Tendon and Bone Properties

Julianne Huegel, PhD
Courtney A. Nuss
Peter Chan
Adnan N. Cheema, MD
Andrew F. Kuntz, MD
Louis J. Soslowsky, PhD

McKay Orthopaedic Research Laboratory, University of Pennsylvania, Philadelphia, PA

Introduction

Nicotine is a well-established risk factor for rotator cuff injuries.[1] Several laboratory studies showed that nicotine negatively impacts tendon healing after injury, in both the rat rotator cuff[2] and Achilles.[3] Surprisingly, after twelve weeks of nicotine exposure, material properties of the uninjured rat supraspinatus tendon had increased maximum stress and elastic modulus compared to controls.[4] Conversely, nicotine decreased bone mass due to imbalanced bone turnover.[5] However, an understanding of nicotine effects on rotator cuff tendon-to-bone properties after long term exposure is lacking. Therefore, the objective of this study is to investigate the effects of eighteen weeks of nicotine exposure on tendon-to-bone properties in a rat model via mechanical, μCT, and histological analyses. We hypothesized that long term nicotine exposure would lead to decreased tendon mechanical properties, decreased subchondral bone insertion properties, and decreased trabecular bone properties in the humeral head, as well as altered tendon cell morphology.

Methods

24 adult male Sprague-Dawley rats (350-400g) were used (IACUC approved). Animals were randomized to receive either 0.9% sterile saline (n = 12) or 61 mg/ml nicotine (n = 12) through subcutaneously implanted osmotic pumps, which correlated with appropriate levels of cotinine measured in the blood serum (400-700 ng/ml).[3] Rats were sacrificed after 18 weeks of exposure. Animals were stored at -20°C until supraspinatus tendon-humerus complexes were dissected out and processed for histological analysis (n=5, right limbs) or cross-sectional area measurement and quasistatic mechanical testing (n=12, left limbs). Testing consisted of pre-conditioning, stress relaxation at 5% strain, and a quasi-static ramp to failure at 0.3%/s. Post-test, humeri were μCT scanned at 6μm resolution to assess trabecular properties of the epiphysis proximal to the humeral growth plate, representing the region of rotator cuff attachment on the greater tuberosity. Additionally, the mineralization gradient was calculated (Amira 6.7) across the subchondral plate, defined as the mineralized fibrocartilage of the supraspinatus tendon enthesis and subchondral bone. Briefly, a 100x120x230 voxel volume was identified in the greater tuberosity at the supraspinatus tendon insertion site. After thresholding, the innermost layer of the subchondral bone was defined. Individual layers were then defined outwards towards the mineralized fibrocartilage boundary. Layer intensity values were averaged to construct a mineralization gradient, normalized to the total subchondral plate thickness. Intensity was compared at normalized thickness of 0, 0.5, and 1.0, marking the boundaries between trabecular bone, subchondral bone, mineralized fibrocartilage, and tendon. Statistical comparisons were made between the saline and nicotine groups. Comparisons for mechanics and μCT metrics were made using Student's t-tests. Mineralization intensity was also compared with two-way ANOVA across subchondral thickness. Histological comparisons were made using Mann-Whitney tests. Significance was set at $p < 0.05$ (solid bars), and trends at $p < 0.1$ (dashed bars).

Results

Mechanical properties

Tendons in the nicotine group had a smaller cross-sectional area than the saline group (Fig 1A). There were no differences in stress relaxation (not shown) or tissue modulus measured through the length of the tendon (Fig 1B). However, the nicotine group showed a trend toward decreased modulus at the insertion (first 2 mm proximal to the insertion, Fig 1C), as well as significantly decreased tendon stiffness (Fig 1D).

Histological measures

No differences were seen at the tendon insertion in cellularity or cell shape (Fig 2A,B). However, cell density in the midsubstance was decreased with nicotine exposure (Fig 2C); cell shape was not different (Fig 2D). Representative images of each region are shown in Figure 2E.

μCT parameters

Although no differences were identified in bone volume fraction or trabecular thickness (Fig 3A,B), there was a trend toward increased trabecular number and decreased separation (Fig 3C, D). Additionally, mineralization intensity was significantly different across the subchondral

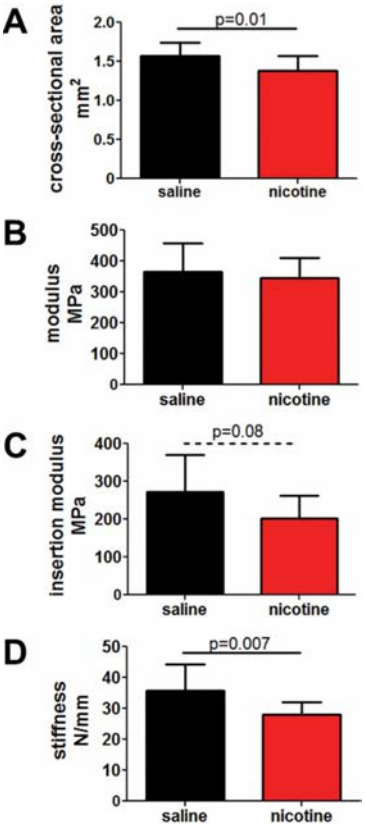

Figure 1. Mechanical Properties. Tendons exposed nicotine had **(A)** decreased tendon area, **(B)** no difference in modulus, **(C)** decreased modulus at the tendon insertion, and **(D)** decreased stiffness. Data shown as mean±SD.

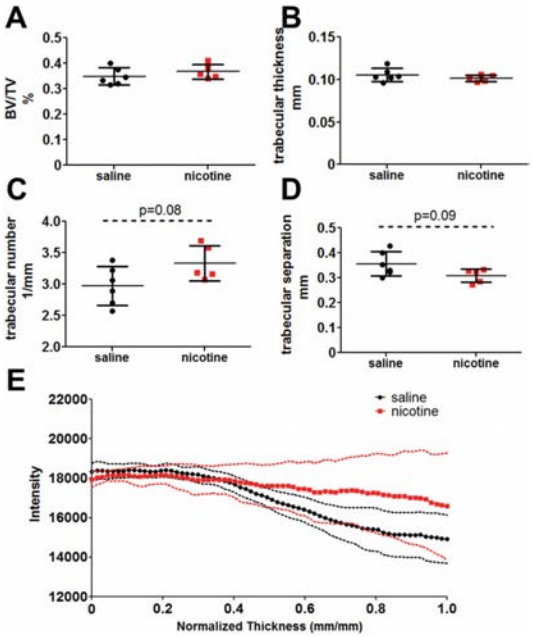

Figure 3. µCT Properties. Nicotine did not have an effect on **(A)** trabecular bone fraction or **(B)** trabecular thickness in the humeral epiphysis. **(C)** Trabecular number was increased and **(D)** trabecular separation was decreased in nicotine treated rats. **(E)** Bone mineralization (intensity) across the subchondral plate from the trabecular boundary (0) to the tendon boundary (1.0) was different between groups ($p < 0.04$). Data shown as mean±SD.

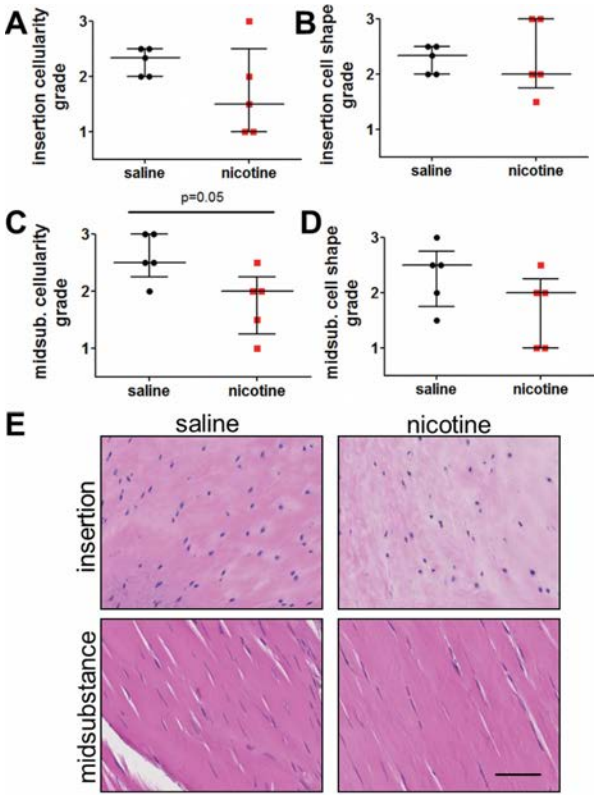

Figure 2. Histological Properties. No differences were found between groups for **(A)** insertion cellularity or **(B)** insertion cell shape. Nicotine tendons had **(C)** decreased cellularity in the midsubstance, but **(D)** cell shape was not changed. **(E)** Representative regions of interest at 200x magnification. Data shown as median±IQR. Scale bar: 100µm.

plate between treatment groups, although not when specific comparisons were made at locations of interest (0, 0.5, and 1.0 thicknesses; Fig 3E).

Discussion

This study measured the effects of long-term nicotine exposure on uninjured supraspinatus tendon and underlying humeral bone properties. Previous work found that nicotine caused decreased Achilles tendon cross-sectional area after injury;[3] similarly, nicotine-exposed animals had smaller uninjured supraspinatus tendons, suggesting a potential decrease in metabolic activity, consistent with decreased cell density in the current study. Contrary to previous reports,[4] this study demonstrated decreased tendon mechanical properties, supporting clinical findings and highlighting the importance of time course studies. Surprisingly, trabecular bone properties were slightly improved with nicotine exposure, suggesting that bone metabolism is also affected, though potentially not as hypothesized. Future studies will investigate additional time points as well as kinetic bone histomorphometry. Although data was variable, increased bone mineralization intensity at the tendon insertion could increase stress concentrations across the tendon-bone interface, increasing risk of tendon rupture.[6] Physical activity such as exercise or overuse may produce more dramatic changes to the tendon structure and composition.

Significance

This study demonstrates that nicotine leads to decreased mechanical properties in uninjured supraspinatus tendons as well as alterations in bone structure. Patients should be

counseled that use of nicotine increases their risk of tendon degeneration and may predispose them to tendon injury.

Acknowledgements

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Mechanisms of Action of Pulsed Electromagnetic Field Therapy on a Rat Model of Rotator Cuff Injury and Repair

Julianne Huegel, PhD[1]
Stephanie N. Weiss, BS[1]
Courtney A. Nuss[1]
Harina Raja, MS[1]
Waldorff EI[2]
Zhang N[2]
Ryaby JT[2]
Louis J. Soslowsky, PhD[1]
Andrew F. Kuntz, MD[1]

[1]McKay Orthopaedic Research Laboratory, University of Pennsylvania, Philadelphia, PA

[2]Orthofix Inc., Lewisville, TX

Introduction

Rotator cuff tears affect millions of individuals each year, often requiring surgical intervention. Although advancements in surgical and rehabilitation protocols have improved clinical results, rotator cuff repair failure is common.[1] To improve surgical outcomes, non-invasive therapies have been utilized post-operatively.[2] We have previously shown that pulsed electromagnetic field (PEMF) therapy improved tendon-to-bone mechanical properties in a rat model of rotator cuff injury and repair,[3,4] consistent with increased type I collagen and fibronectin protein expression and increased collagen alignment,[4] potentially providing an explanation for the improved mechanical properties. However, these alterations in composition and tissue structure could be downstream of specific physiological responses to PEMF treatment, including changes in inflammation, cell signaling, cell metabolism, increased production of matrix components, and/or changes in matrix degradation and remodeling.[5] Therefore, the objective of this study was to determine the influence of PEMF treatment on tendon gene expression and cell composition during early stages of healing. We hypothesized that PEMF treatment would amplify tendon-healing related signaling pathways such as TGF-β while mitigating inflammation.

Methods

106 adult male Sprague-Dawley rats (400-450g) were used (IACUC approved). Animals underwent acute supraspinatus injury and repair[3] followed by systemic exposure to Physio-Stim® PEMF (Orthofix, Inc.) for 1 hour daily. Control animals did not receive PEMF therapy (non-PEMF). Animals were euthanized at 3, 7, 14, 21, or 28 days post-op (n = 10/group/time point). From half of the animals, right supraspinatus tendons were dissected out and divided into insertion and midsubstance portions for RNA isolation, cDNA synthesis, specific target amplification, and Fluidigm qPCR for 40 target genes and 2 housekeeping genes (n = 5/group/time point). Expression was normalized to the housekeeping genes and then to non-PEMF at each time point. From the other half of the animals, right shoulders were dissected and processed for histological analysis. H&E stained sections were semi-quantitatively graded for cell density (cellularity) and cell shape[3,4] (n = 5/group/time point), and CD68 and CD163 immunohistochemical staining was performed for M1 and M2 macrophages, respectively (n = 4/group at 14 and 28 days). Statistical comparisons were made between PEMF and non-PEMF groups over time and at each time point, using two-way ANOVAs with Bonferroni post-hoc tests. Immunohistochemical staining was qualitatively assessed in a blinded manner.

Results

Gene expression

Expression of the BMP2 signaling molecule was increased with PEMF treatment in the tendon insertion across time (Fig 1A); downstream targets collagen type 1a (Fig 1B), alkaline phosphatase (Fig 1C), and osteocalcin (Fig 1D) were also upregulated with PEMF. Although transforming growth factor (TGF) β1 and 2 were unchanged (data not shown), expression of TGFβ3 was downregulated with PEMF treatment in the tendon insertion (Fig 1E). Matrix metalloproteinase (MMP) 9 and connective tissue growth factor (CTGF) were upregulated early and downregulated late (Fig 1F,G), and MMP13 was downregulated across time (not shown). Fibronectin expression increased in PEMF treated tendons (Fig 1H). Similar expression patterns of TGFβ3, MMP9, and fibronectin were seen in the tendon midsubstance (not shown). Expression of inflammatory markers was also altered with PEMF, including increased interleukin-10 and tachykinin (Fig 2A,B), and decreased interleukin-1β and tumor necrosis factor α (Fig 2C,D).

Immunohistochemistry

At 14 days, CD68+ (M1) macrophages were increased in the midsubstance of non-PEMF tendons (Fig. 2E, top panel). No differences were seen at 28 days, or in the insertion (not shown). CD163+ (M2) macrophages were increased in the insertion of PEMF tendons at 14 days (Fig 2E, bottom) with no differences seen at 28 days or in the midsubstance (not shown).

Histology

There were no differences in cell density or cell shape in either the tendon insertion or

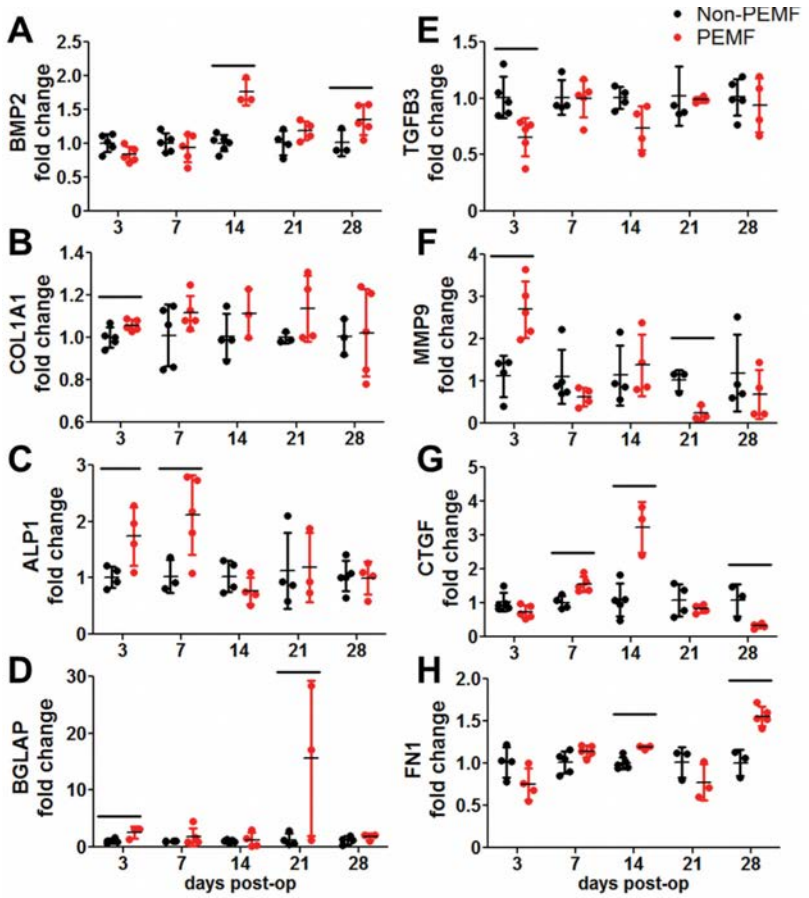

Figure 1. BMP2 & TGFβ Related Gene Expression. At the tendon insertion, PEMF treatment **(A)** increased *Bmp2*, **(B)** increased *Col1a1*, **(C)** increased *Alp1*, **(D)** increased *Bglap*, **(E)** decreased TGFβ3, **(F)** altered *Mmp9*, (G) increased *Ctgf*, and increased (F)*Fn1*. Data shown as mean±SD, normalized to housekeeping and then normalized to non-PEMF at each time point (n = 5/group/time point).

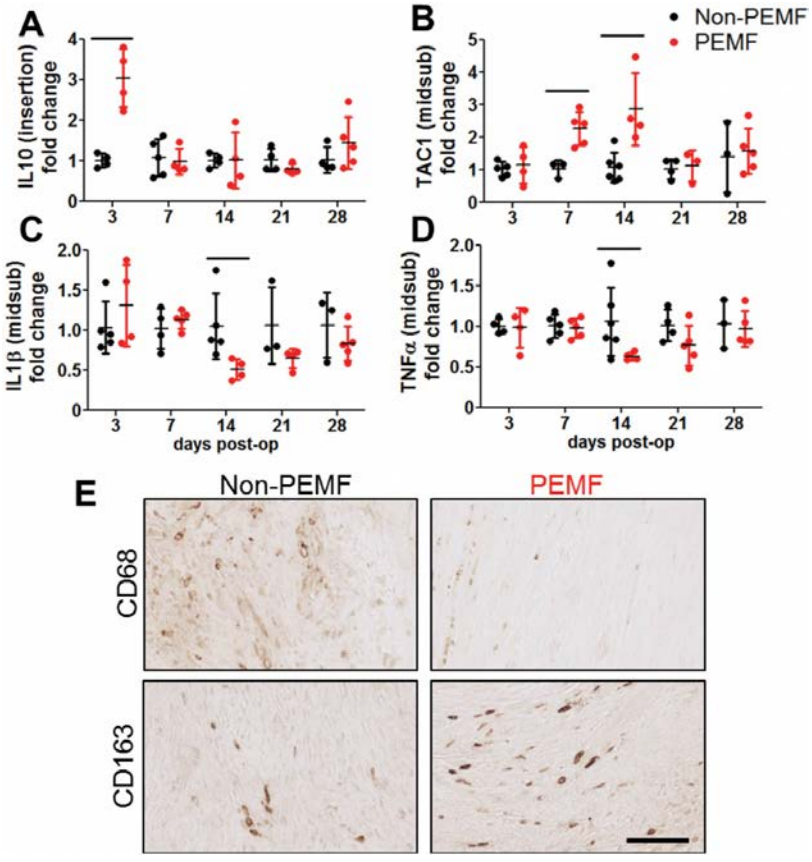

Figure 2. Inflammation. Gene expression of inflammatory markers were altered with PEMF treatment, including **(A)** increased *Il10*, **(B)** increased *Tac1*, **(C)** decreased *Il1*β, and **(D)** decreased *Tnf*α. Representative 200x images show **(E, top)** decreased CD68+ staining at the midsubstance and **(E, bottom)** increased CD163+ staining at the insertion at 14 days post-op in PEMF tendons. Scale bar: 100μm.

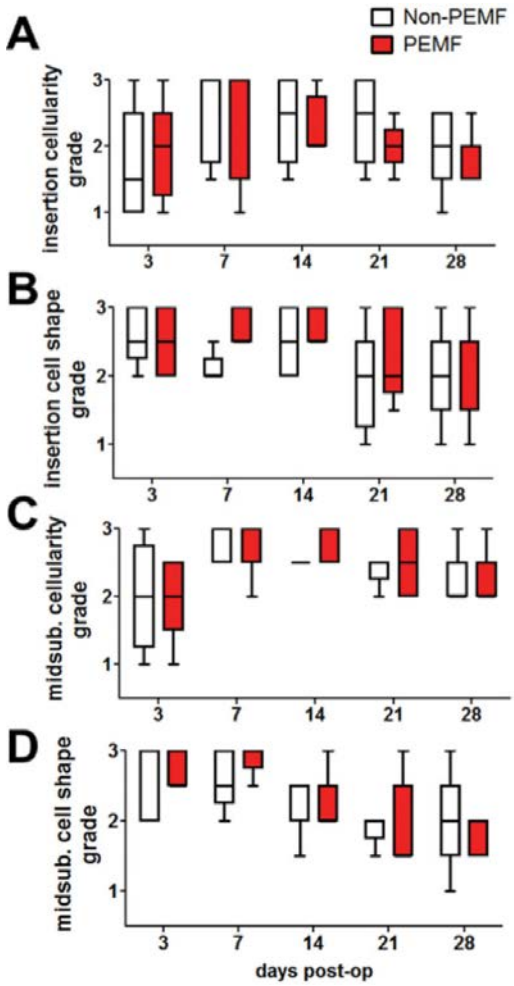

Figure 3. H&E Histological Properties. No differences were found between groups for **(A)** insertion cellularity, **(B)** midsubstance cellularity, **(C)** insertion cell shape, or (D) midsubstance cell shape. Midsubstance properties were altered over time. Data shown as median+IQR.

midsubstance with PEMF treatment compared to non-PEMF controls (Fig 3). Cell shape and cellularity varied over time in the midsubstance for both groups but did not significantly change in the insertion.

Discussion

This study demonstrated molecular and cellular changes within supraspinatus tendons after injury with PEMF treatment. Gene expression data suggests an upregulation in the BMP2 signaling pathway, including increased collagen production during early healing. Increases in pro-osteogenic genes at the insertion could support important processes to re-establish the tendon-bone interface. Future work will assess kinetic bone properties in the greater tuberosity. Decreased TGFβ3 and changes in MMP expression support a downregulation in the fibrotic response with PEMF, which coincides with a decreased tendon cross-sectional area at 4 weeks seen in previous studies.[4] Interestingly, PEMF had a consistent anti-inflammatory effect, upregulating *Il10* and *Tac1*, and downregulating IL1β and TNFα, as well as a decrease in CD68+ macrophages and increase in CD163+ macrophages at 14 days in PEMF- treated tendons. Similar mechanisms have been shown in intervertebral disc cells after PEMF treatment *in vitro* [5] and *in vivo*.[6] Although statistical comparisons were not made, regional differences in gene expression and cell morphology support the need to assess tendon responses regionally.

Significance

Previous work showing improved rotator cuff healing with PEMF supported the initiation of a PEMF clinical trial for this condition. This study provides important mechanistic insight into how PEMF affects cellular and molecular processes in the supraspinatus tendon after injury.

Acknowledgements

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Arthroplasty Tips & Tricks: Manual Fixed-Bearing Medial Unicompartmental Arthroplasty

Yehuda E. Kerbel, MD[1]
Rahul Singh, MBBS[2]
Pedro N. Giglio, MD[3]
Neil P. Sheth, MD[1]

[1]Department of Orthopaedic Surgery, The University of Pennsylvania

[2]Department of Orthopaedic Surgery, Wockhardt Hospital, Mumbai, India

[3]Department of Orthopaedic Surgery, University of Sao Paulo

Introduction

Patients presenting with isolated single compartment degenerative joint disease may be considered for unicompartmental arthroplasty (UKA) after having exhausted conservative treatment. UKA offers the advantages of less invasive surgical exposure, preservation of bone stock, retention of cruciate ligaments, and easier post-operative recovery.[1] Previous studies demonstrate improved patient satisfaction following UKA as compared to total knee arthroplasty (TKA), with better range of motion at discharge, shorter hospital stay, improved functional scores, and equivalent survivorship.[2,3]

As implant design and minimally invasive surgical techniques have improved over the last few decades, there has been increased interest in UKA and expansion of patient indications.[4] In addition, recent technological advances have introduced the robotic-assisted UKA, which has been shown to lead to improved component positioning and comparable short-term survivorship to manual UKA.[5-7]

Despite the early promise of robotic-assisted UKA, most institutions do not readily possess this technology. In addition, intra-operative technical difficulties with the robot will require the procedure to be performed manually. Thus, it is critical for arthroplasty surgeons to still have the ability to perform the procedure without robotic assistance. Relatively little has been published in the primary literature describing the technical steps of the procedure.[8] In this review, we present a systematic method for performing a manual fixed-bearing UKA in the appropriately selected patient with isolated medial compartment arthritis.

Indications

The current accepted indications for performing a UKA are[9]:

- Isolated single compartment arthritis
- Absence of inflammatory arthritis
- Varus or Valgus deformity $<$ 10 degrees (a correctable deformity)
- Pre-operative range of motion $>$ 90 degrees
- Flexion contracture of $<$ 10 degrees

Historically, patient-specific contraindications included weight over 180 pounds, age greater than 60 or anterior cruciate ligament incompetence.[9] However, more recent studies demonstrate that even patients that don't fit the "ideal" criteria may have favorable clinical outcomes following UKA.[10]

Surgical Technique

Positioning

The patient is placed in a supine position with a bump under the ipsilateral hip, a tourniquet around the ipsilateral thigh and an Alvarado knee positioner at the level of the medial malleolus. Standard TKA prepping and draping is then performed.The incision is marked out just medial to the patella, starting from the proximal pole of the patella to a point 5cm distal and lateral. The limb is exsanguinated, and the tourniquet inflated to 100 mmHg above the starting systolic blood pressure.

Exposure

Once the tourniquet is inflated, the incision is made with a 10-blade through the skin and dermis and a Weitlaner retractor is placed in position. Dissection scissors are then used to continue down to the level of the medial retinaculum and extensor mechanism. Two knee joint retractors are used to expose the vastus medial obliquus (VMO). A fresh 10-blade is used to perform a mini-midvastus arthrotomy, and a retractor is placed deep to the VMO after delineating the space between the VMO and deep synovium using scissors. Dissecting scissors are used to remove the synovium medially and a single prong retractor is placed around the medial femoral condyle (MFC).

The medial meniscus is next excised using a bovie, beginning at its tibial attachment and working radially to release the anterior horn. Once the release reaches the anteromedial corner of the tibia, a single prong retractor is placed medially around the tibial plateau and a small medial collateral ligament (MCL) release is performed around the medial plateau to the posteromedial corner about 3-5mm from the joint line. A double prong retractor should then slide around the posteromedial tibial plateau easily in place of the single prong retractor which is now moved to the lateral aspect of the MFC in the intercondylar notch.At this point, the surgeon should have a clear view of the medial tibial plateau and the MFC.A small portion of the

infrapatellar fat pad can be resected in order to visualize the lateral aspect of the medial femoral condyle, which will guide the sagittal tibial resection.

Tibial Cut

The tibial resection guide is placed, and all its articulations are unlocked. The resection depth is set first using an angel wing, typically just below the anteromedial tibial osteophyte. Otherwise, a stylus can be used to measure a 2-3mm resection depth. Next, the varus/valgus portion of the jig is adjusted, with the typical position set at 2-3 clicks medially to ensure a neutral cut with regards to the tibial mechanical axis. Lastly, the tibial slope is set based on the preoperative X-rays, with the goal of restoring the native slope. The guide has 5 degrees of slope built in, which must be taken into account.

All articulations are then locked, and a single pin is placed into the tibia to secure the position. The tibial plateau is cut with an oscillating saw and the pin and cutting jig are removed. A single-sided reciprocal saw is then used to perform the sagittal tibial cut (Figure 1). The lateral aspect of the MFC is used as a guide for the mediolateral position of the cut. The cut is performed with a slight amount of external rotation to ensure that it is adjacent to the anterior cruciate ligament (ACL) footprint on the tibia. It is imperative to push the blade posteriorly along the intercondylar notch and perform the cut with an even distribution of force, without rocking the blade anteriorly and posteriorly. This avoids creating a stress riser on the tibial plateau. A 1-inch osteotome and kocher clamp are used to remove the cut portion of the plateau (Figures 2 and 3); this part of the case can be performed in extension if the piece is difficult to remove.

Distal Femoral Cut

The leg is moved into extension and the 10 mm distal femur cutting guide is placed, followed by assembly of the alignment rod used to assess varus/valgus (Figure 4). The tibial resection surface should be parallel to the tibial mechanical axis to prevent valgus angulation. A slight varus tibial resection surface is acceptable. If the alignment is off at this point, the tibial resection should be fine-tuned as needed. If the alignment is appropriate, then the extra-medullary distal femoral cutting guide can be secured in place (Figure 5) and the distal femoral cut made (Figure 6) using a regular saw blade (Figure 7). This resection can be difficult as the cutting slot has minimal tolerance.

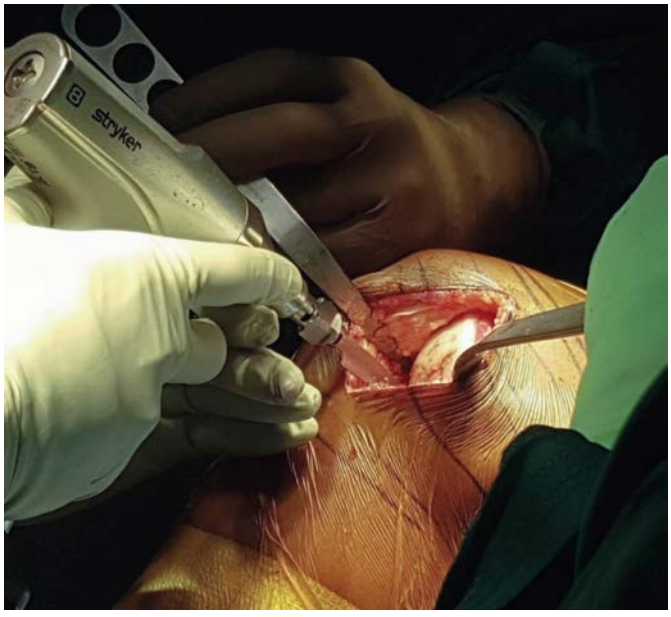

Figure 1. The second limb of the tibial cut.

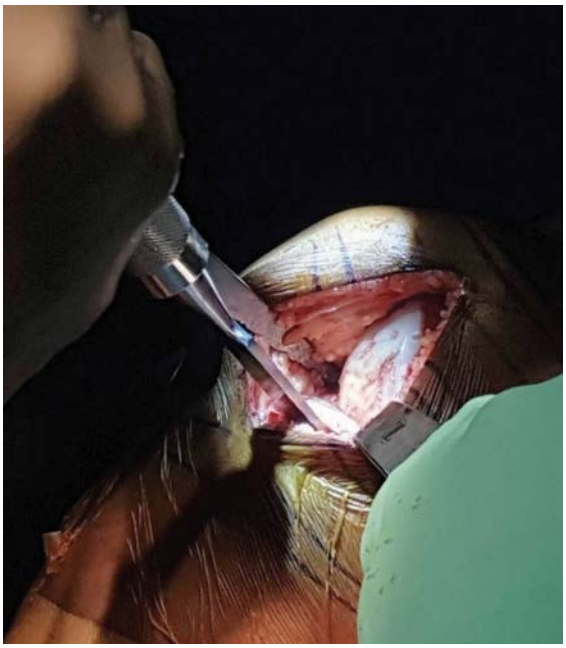

Figure 2. Removing the cut portion of the tibial plateau.

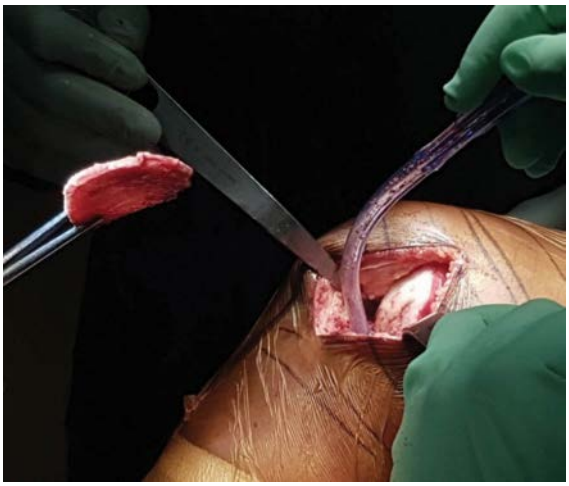

Figure 3. The removed portion of the tibial plateau.

Assessment of the Flexion and Extension Gaps

Once both resections have been performed, the thick side of the 8 mm and 10 mm spacer guides are used to assess the extension gap. The 8mm spacer should go in easily with approximately 2 mm of laxity with a valgus stress, and the 10mm spacer should go in with no valgus laxity while

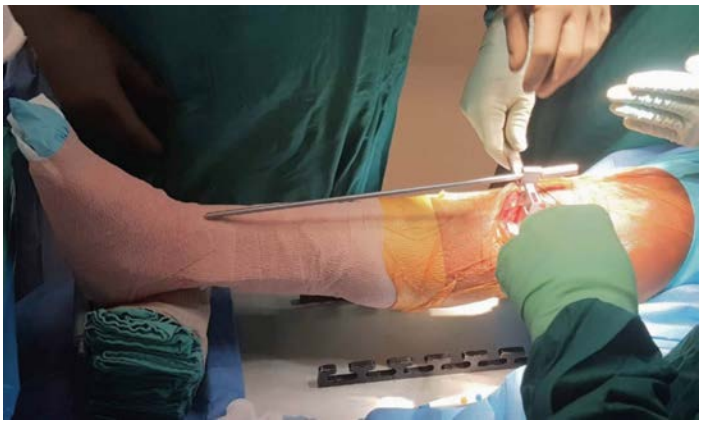

Figure 4. The alignment rod is used to asses varus/valgus.

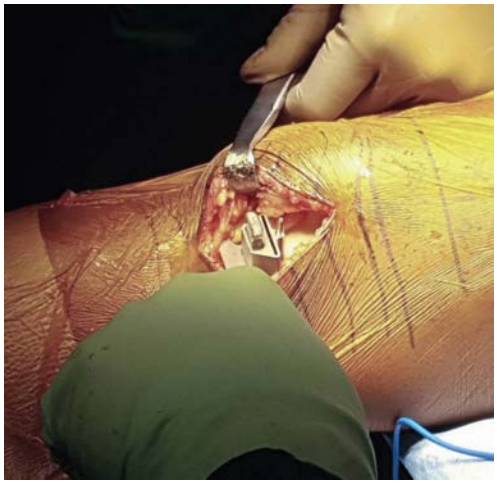

Figure 5. The femoral jig is pinned into place.

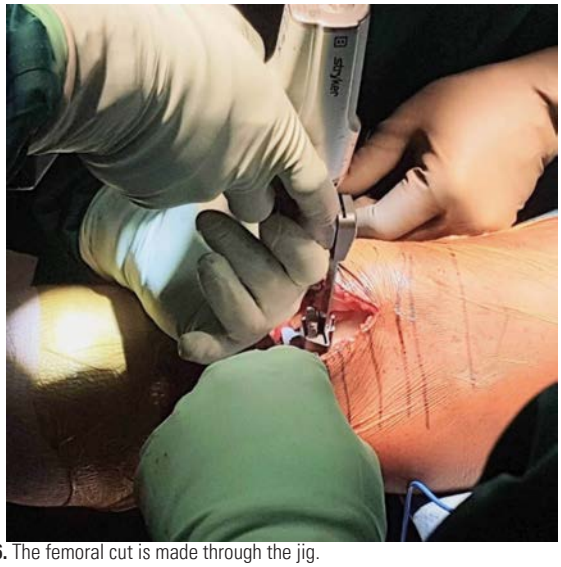

Figure 6. The femoral cut is made through the jig.

achieving full extension. The goal of the extension gap is to have 2 mm of laxity with an 8 mm polyethylene insert.

If the extension gap is adequate, the knee is then flexed, and the flexion gaps are similarly assessed with the thin portion of the 8 mm, 10 mm and 12 mm plastic spacer guides (Figure 8).

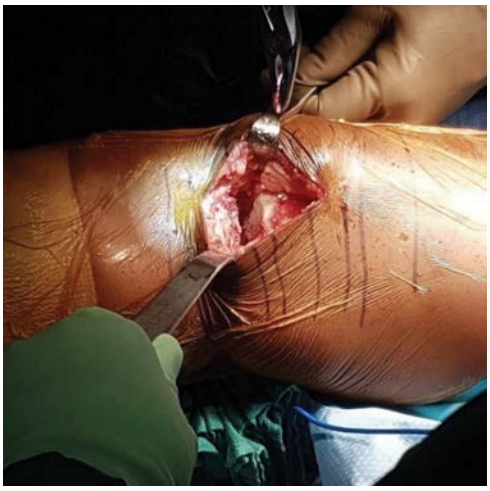

Figure 7. The knee after completing and removing the femoral bone cut.

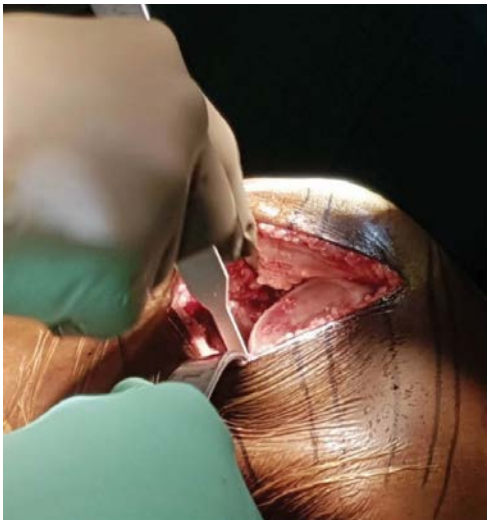

Figure 8. Assessing the flexion gap.

The 8 mm and 10 mm spacers should fit in easily and the 12mm spacer should not fit, signifying an approximate 11mm flexion space. The target should be 3 mm of laxity in flexion when placing an 8 mm polyethylene insert. If the knee is tight in flexion, a small free hand resection is made off the posterior condyle (Figure 9).

Femoral Sizing and Preparation

To determine the appropriate femoral size, the distal femoral tidemark is clearly identified anteriorly. The correct position of the anterior margin of the implant is at least 1mm posterior to the tidemark. The 2 mm end of the 2/3mm testing spacer ('popsicle stick') is placed under the femoral sizing block and the tibial resection is used as a guide for the degree of femoral component external rotation (Figure 10). The correct position is at least 1 mm under the tidemark. Once the correct femoral size has been selected, the cutting block is secured with one screw pin proximally and a second pin laterally towards the notch and two lug holes are drilled into the distal femur (Figure 11). The remaining femoral bone cuts are then made with a small oscillating saw (Figure 12), after

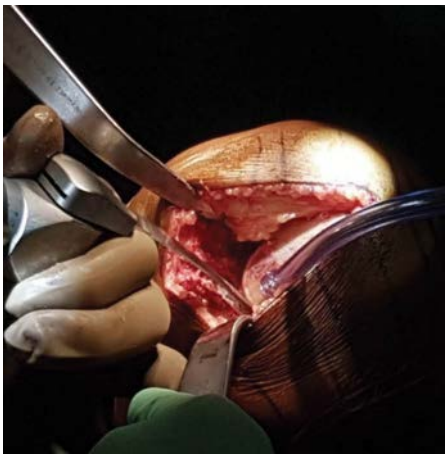

Figure 9. Making a free hand cut off the posterior condyle if tight in flexion.

Figure 10. Placing the femoral sizing block using the popsicle stick to help control rotation.

which the femoral cutting block and pins are removed; any incomplete resections are completed with a sagittal saw. All resections are removed with a ½ inch curved osteotome and kocher.

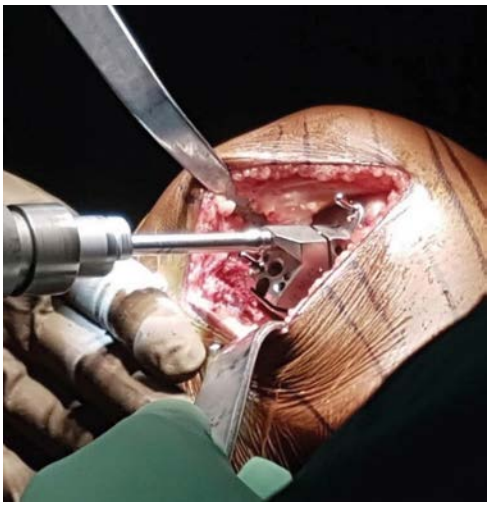

Figure 11. Punching the femoral sizing block with a drill.

Figure 12. Making the remaining femoral bone cuts through the cutting jig.

Medial Meniscus Removal

The leg is placed in extension with a towel bump placed under the proximal tibia. A rake is placed on the medial skin flap and a knee joint retractor is placed on the patella. The remainder of the meniscus is removed while bending the bovie tip and using a semi-circular motion along the length of the meniscus.

Tibial Sizing and Preparation

The leg is flexed with a posterior cruciate ligament (PCL) retractor placed medially and a single prong retractor in the intercondylar notch. The tibia is sized with paddles; first medial-lateral and then anterior-posterior with a hook (Figure 13). A sagittal saw is then used to make a groove into the lateral aspect of the tibial plateau slightly anteriorly (Figure 14), which will be used for the keel of the tibial implant. An offset impactor is used to move the trial tibial tray into position, using the groove and adjusting its posterior placement to ensure complete anteroposterior and mediolateral coverage of the tibia without overhang (Figure 15).

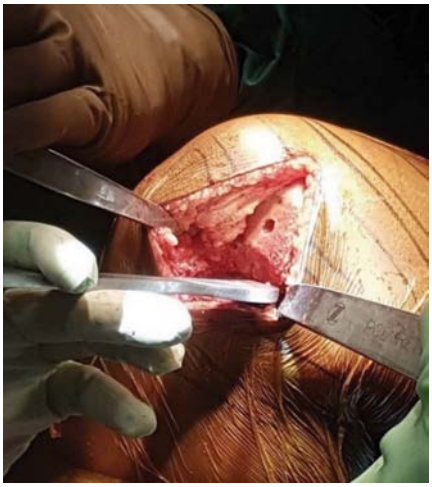

Figure 13. Sizing the tibia with a paddle.

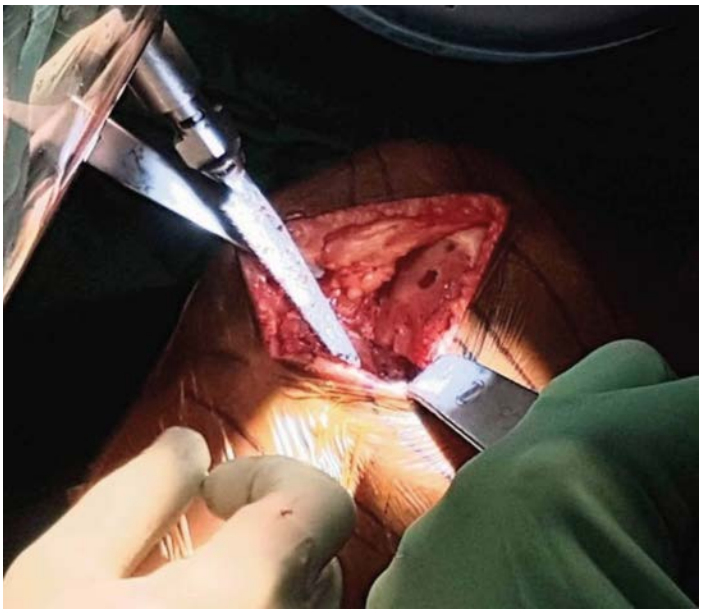

Figure 14. Making a groove in the anterior lateral aspect of the tibial plateau.

Final Gap Assessment, Rotation Adjustment and Tibial Preparation

The knee is then placed in flexion and valgus for placement of the femoral trial component (Figure 16). Next, the 8 mm plastic tibial trial polyethylene insert is placed between the components (Figure 17). The overall alignment is assessed as well as the flexion and extension gaps using the 2-3mm popsicle stick.The 2 mm and 3 mm edge of the stick should be able to fit into the knee while in flexion (Figure 18), and only the 2 mm edge should be able to be placed while the knee is extension (Figure 19). If the rotation of the femur needs to be adjusted at this stage of the procedure, a ¼ inch curved osteotome is used to move bone from the bottom femoral lug hole to change the rotation.The bone is moved from lateral to medial if more external rotation is desired, or from medial to lateral if more internal rotation is desired.

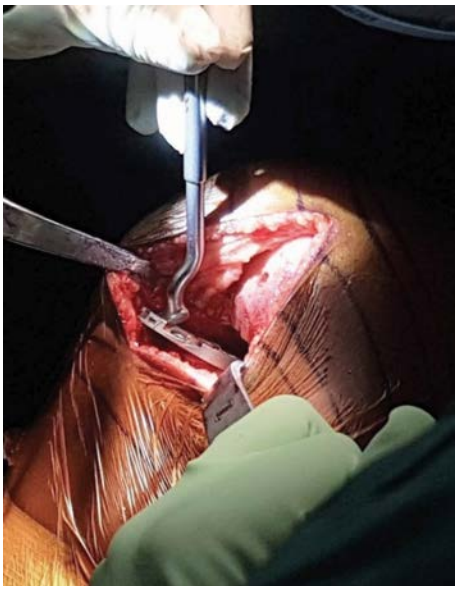

Figure 15. Placing the tibial trial sizing tray, avoiding overhang.

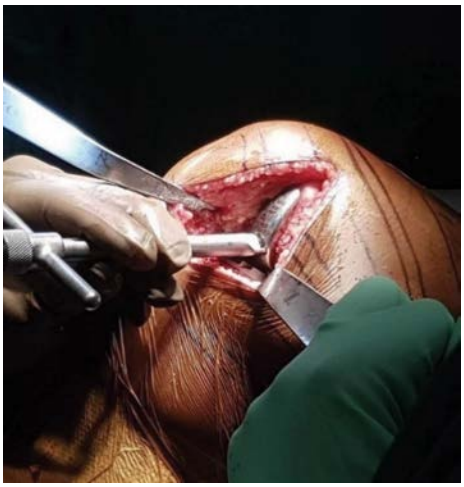

Figure 16. Impacting femoral trial component.

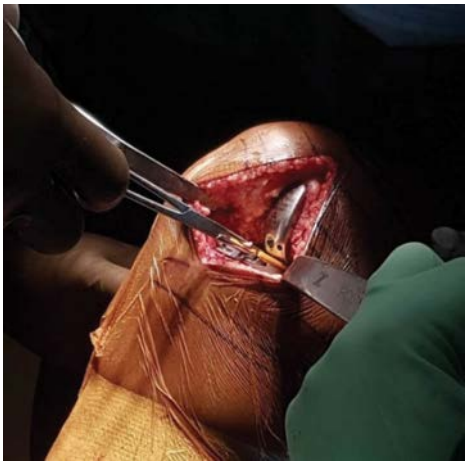

Figure 17. Placing the plastic trial tibial insert.

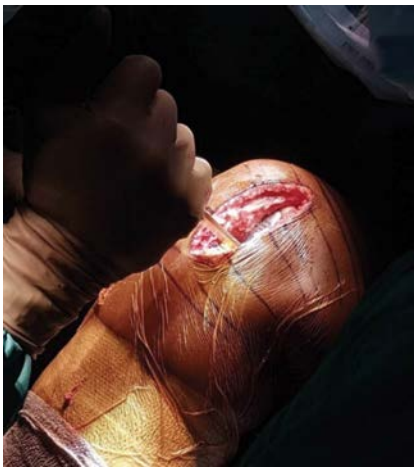

Figure 18. Trialing the 3mm popsicle stick in the knee while in flexion

Once rotation and alignment are adequate, the femoral trial and tibial plastic trial insert are removed, and a small drill bit is

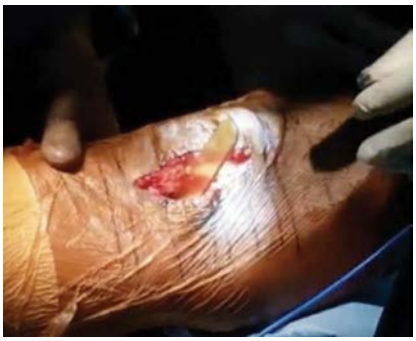

Figure 19. Trialing the 2mm popsicle stick in the knee while in extension and valgus.

used to hold the tibial tray in place (Figure 20). A drill is used to then punch two holes through the trial insert into the tibia (Figure 21) and the drill bit and trial tibial tray are removed.

Figure 20. A drill bit holds the trial tibial tray after the femoral component and plastic insert are removed.

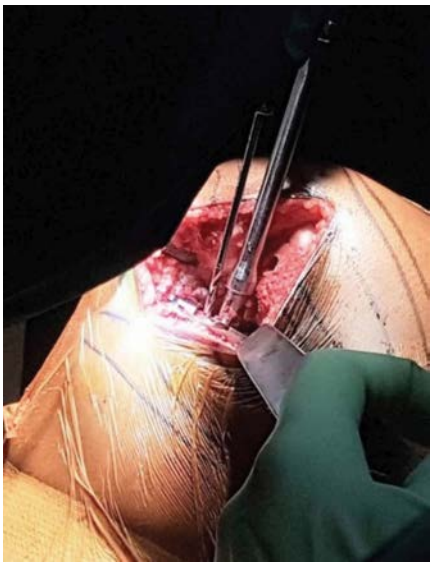

Figure 21. Punching two holes into the tibia through the trial tibial tray.

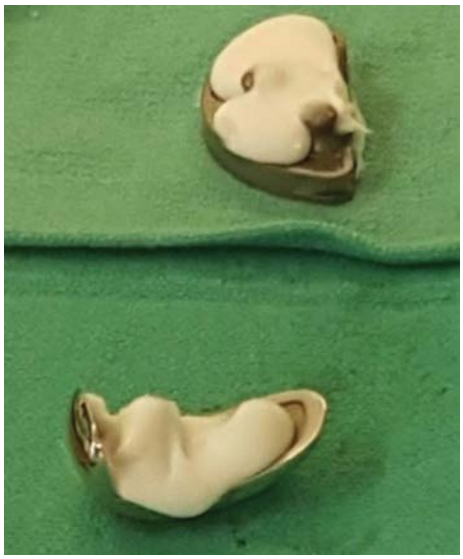

Figure 22. Cement is placed on the components prior to insertion.

Cementation, Final Implantation and Closure

While the cement is mixing, a 0.25% Marcaine solution is injected into the space between the capsule and the synovium, as well as into the medial femoral periosteum. The knee is then thoroughly irrigated. A 3.2 drill bit is then used to create holes in sclerotic surfaces and the bone surface is dried.

The entire surgical team then changes their gloves and cement is placed onto the femoral and tibial components prior to placing them on the bone (Figure 22), with the posterior aspect of the tibial implant having slightly less cement than the anterior aspect. A generous amount of cement should then be placed onto the tibia and a ¾ inch osteotome is used to pressurize the cement from posterior to anterior to get good cement inter-digitation. The offset impactor is then used to place the tibial tray on the bone and the ¾ inch osteotome is again used to further pressurize the cement, directing force from posterior to anterior, after which the tibial tray is impacted gently into place.

All extruded cement is meticulously removed while the knee is placed in flexion and valgus, which allows for good exposure of both the tibia and femur. Excess cement should be removed in a systematic fashion, utilizing the following steps:

- Remove cement from junction of tibial tray and bone ridge medially
- Remove cement from lateral wall above the tibial component from posterior to anterior
- Remove cement from posterolaterally towards the notch using the golf club tool
- Finally, make several sweeps with the golf club tool, moving posteromedially to anteromedially to ensure all remaining cement has been removed.

The femoral component is then impacted into place and excess cement is once again removed. Make sure to move the incision window medially and then laterally in order to maximize exposure and facilitate cement removal. The

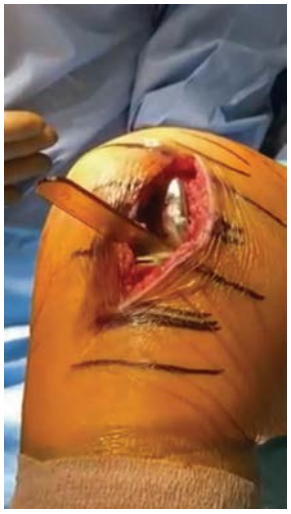

Figure 23. Final components in place with popsicle stick inserted during cement curing.

polyethylene insert is then placed on the tibial tray, making sure that the hand is not inadvertently raised during this maneuver, so as to avoid lifting off the tibial tray during insertion. A bump is placed under the tibia (the knee is now in 30° of flexion) and the 2 mm side of the popsicle stick is inserted between the polyethylene and femoral component while allowing the cement to cure (Figure 23).

The knee is then closed in a layered fashion, with 1-0 vicryl figure-of-eight sutures or a running quill suture for the arthrotomy, followed by 2-0 vicryl for the subcutaneous layer and a running 3-0 monocryl subcuticular closure, followed by skin glue. A hydrofiber dressing is used to cover the incision and the entire leg is wrapped in a large ACE bandage from the foot to the groin.

Post-operative Protocol

Post-operatively, the patient is given 6 weeks of 81mg of aspirin twice daily to prevent thromboembolism. Rapid recovery (23-hour admission) patients are given two doses of intravenous antibiotics post-operatively. Outpatients are only administered a single dose pre-operatively. Patients are made weightbearing as tolerated immediately with no range of motion restrictions and should begin physical therapy as an outpatient on post-operative day #1 or 2. The first follow-up visit is 2 weeks after surgery, at which time the surgical dressing is removed.

Case Report and Discussion

A 67-year-old male retired DEA officer initially presented to our clinic complaining of isolated medial-sided knee pain for the past 4 years. He had failed conservative treatment including anti-inflammatory medications, bracing, physical therapy and cortisone injections. On physical examination, the patient had range of motion of 0 degrees to 130 degrees; there was no pain with patellar provocative maneuvers and a negative Lachman test. The knee corrected to neutral with a valgus stress.

Pre-operative radiographs (Figure 24), demonstrated isolated medial compartment arthritis with well-preserved lateral and patellofemoral compartments. After a discussion of the risks, alternatives and benefits of the procedure, he elected to undergo UKA.

At latest follow-up at 2 years, his medial pain was completely resolved, and he had returned to his previous level of function. The post-operative radiographs (Figure 25), demonstrate well placed implants without any evidence of component migration, subsidence or loosening. Overall, the patient was so satisfied with his outcome that he elected to have the same procedure performed on his contralateral side.

Unicompartmental knee arthroplasty is effective for the treatment of isolated single compartment knee osteoarthritis, with survival rates greater than 90% at 10 years.[11] For the appropriately indicated patient who wishes to undergo a less invasive procedure with easier recovery, a properly performed UKA is an excellent surgical option.

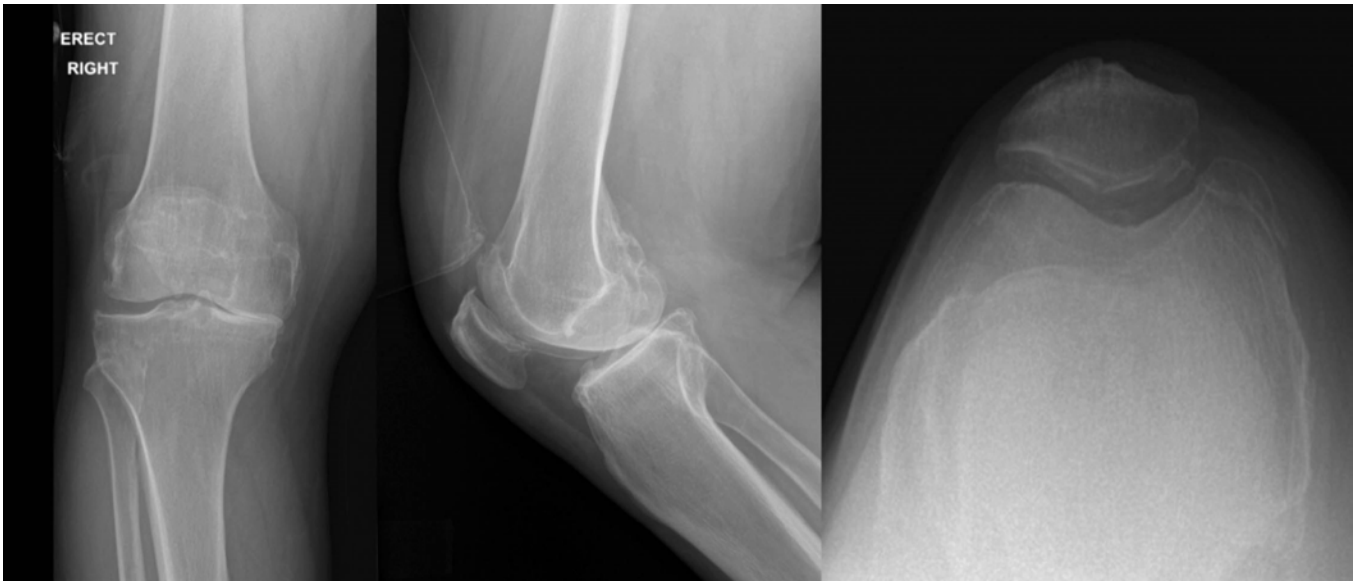

Figure 24. Pre-operative AP, lateral and merchant view radiographs of a patient with isolated medial compartment arthritis.

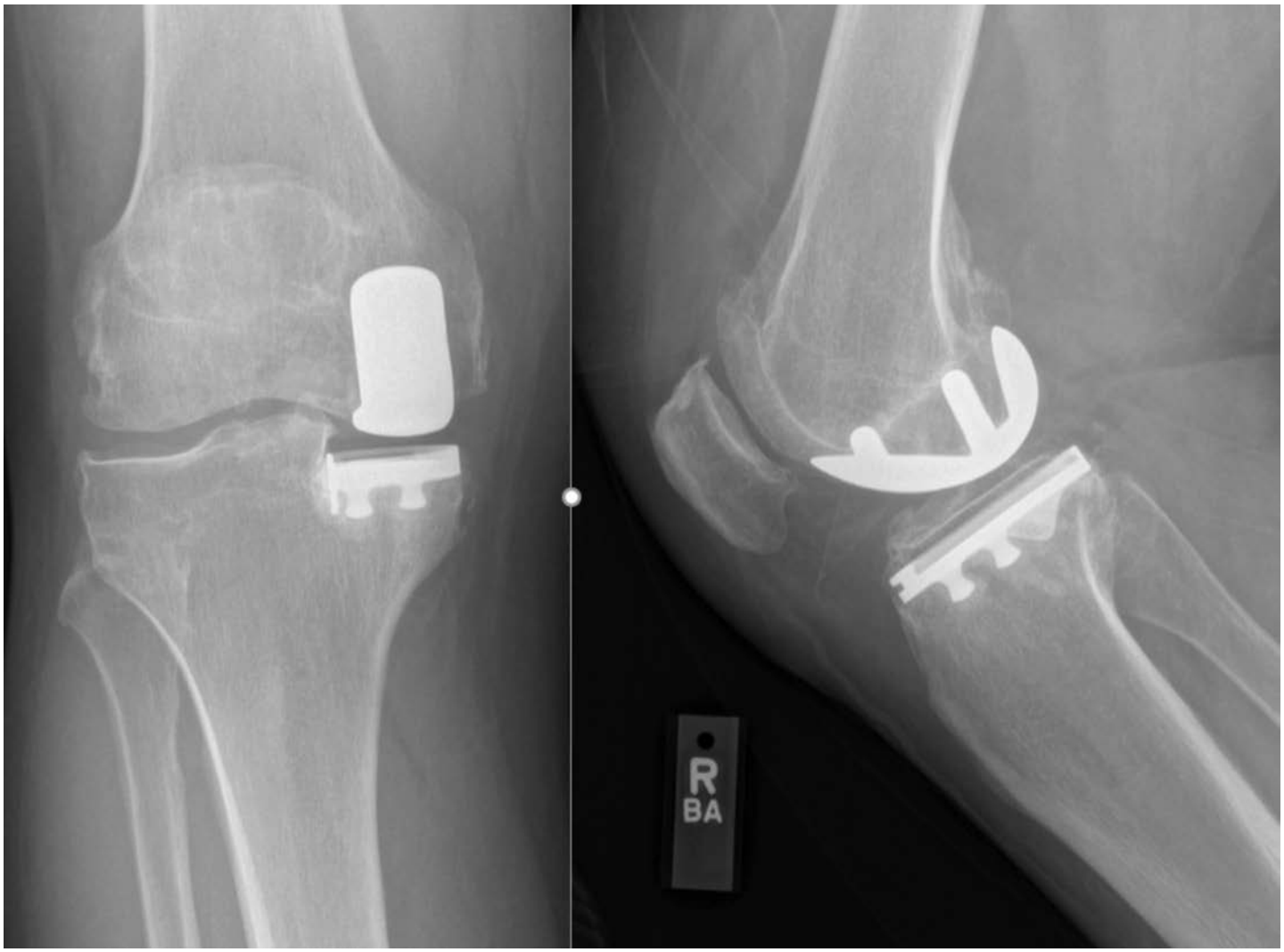

Figure 25. Post-operative AP and lateral view radiographs of the patient shown in Figure 24, after medial UKA.

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Comparison of Perioperative Adverse Outcomes Following Total Hip Arthroplasty In Patients with Diabetes: Insulin Dependence Makes a Difference

Matthew L Webb, MD[1]
Marissa A Justen, BS[2]
Andrew Konopitski, MD[3]
Yehuda E Kerbel, MD[1]
Christopher M Scanlon, MD[1]
Charles L Nelson, MD[1]
Jonathan N Grauer, MD[2]

[1]Hospital of the University of Pennsylvania, Philadelphia, PA

[2]Yale School of Medicine, New Haven, CT

[3]St. Luke's University Hospital, Bethlehem, PA

Introduction

Diabetes mellitus (DM) is among the most common health conditions in the United States. It affects an estimated 34.1 million adults in the United States, with 1.5 million people diagnosed in 2015 alone.[1] Meanwhile, record numbers of patients are undergoing total hip arthroplasty (THA), and the number of patients undergoing THA is projected to continue to increase.[2] DM is also a known risk factor for osteoarthritis,[3] and some authors have suggested that all patients should be screened for DM prior to total joint arthroplasty.[4]

Previous studies have found that patients with DM are at increased risk for postoperative complications including mortality, stroke, urinary tract infections, pneumonia, nerve injury, surgical site infections, and revision surgery.[5-9] However, these studies do not distinguish between patients with Insulin Dependent Diabetes Mellitus (IDDM) and those with Non-Insulin Dependent DM (NIDDM). The aim of the current study was to use a large national, multi-institutional database to assess the correlation between insulin-dependent status and perioperative adverse outcomes after THA. Findings of these analyses have potential implications for preoperative risk stratification and quality improvement initiatives for these patient populations.

Methods

The 2005-2017 NSQIP database collected demographic information, intraoperative variables, and 30-day postoperative complications, and it followed patients after hospital discharge. Our institutional review board has granted exemption to studies using this database because all patient information in the NSQIP database is deidentified. Patients who underwent primary THA were identified using the Current Procedural Terminology (CPT) Code and International Classification of Disease (ICD) code. Comorbidity burden was summarized with a modified version of the Charleston Comorbidity Index (CCI) that has been adapted to the NSQIP database.[14,15]

In the NSQIP database, diabetes status is defined as one of three states. Patients have IDDM if they require daily insulin therapy, they have NIDDM if they use only non-insulin anti-diabetic agents, or patients are classified as not having diabetes if they either have no diabetes diagnosis or if their diabetes is controlled by diet alone. Patients who underwent THA were therefore divided into three groups based on diabetes status: No Diabetes, IDDM, or NIDDM.

All statistical analysis was completed using STATA 13 (StataCorp LP, College Station, TX). Chi-squared test was used to compare pre-operative demographics and comorbidities between the 3 groups (Table 1). Multivariate Poisson regression with robust error variance was then used to compare the relative risk of 30-day adverse outcomes. Multivariate regressions controlled for pre-operative characteristics that were found to be significantly different between groups. Because 17 outcomes were examined, Bonferroni's correction for multiple hypotheses was used. The corrected p-value was $P = 0.003$, and likewise 99.7% confidence intervals are reported.

Results

Based on inclusion and exclusion criteria, 151,027 patients were identified for the study. Of those who were identified, 4,501 had missing data and were excluded. This was less than 3% of the cohort. The final sample size was 146,526 patients. Of the total study population, 128,928 (88%) did not have diabetes, 13,647 (9%) had NIDDM, and 3,951 (3%) had IDDM. Table 1 presents the differences in demographics of these groups.

The relative risk of adverse events within 30 days of THA in patients with NIDDM compared to those without diabetes are shown in Table 2 and Figure 1. Based on multivariate analyses controlling for the variables in Table 1, patients with NIDDM were at significantly greater risk for 4 of the 17 adverse events reported in the database relative to patients without DM. The relative risk of adverse events within 30 days of THA in patients with IDDM compared to those with no diabetes are shown in Table 2 and Figure 2. In contrast to NIDDM, patients with IDDM were at greater risk of 12 of the 17 adverse events studied based similar multivariate analyses.

Overall, IDDM was associated with three times as many perioperative adverse events after THA

Table 1. Demographics of 146,526 patients who underwent Total Hip Arthroplasty, 2005-2017

	Without DM		NIDDM		IDDM		
Total	**128,928**		**13,647**		**3,951**		**p-value***
Age	Average: 65.3		Average : 67.5		Average: 66.9		<0.001
18-54	20,639	16.0%	1,232	9.0%	3,951	10 .6%	
55-64	39,389	30.6%	3,898	28.6%	1,147	29.0%	
65-74	41,704	32.4%	5,137	37.6%	1,500	38.0%	
75+	27,196	21.0%	3,380	24.8%	886	22.4%	
Sex							<.001
Female	72,224	56.1%	6,755	49.5%	1,857	47.0%	
Male	56,704	43.9%	6,892	50.5%	2,094	53.0%	
BMI	Average: 30.0		Average: 33.4		Average: 34.2		<.001
18-25	26,640	20.7%	1,052	7.7%	237	6.0%	
25-30	45,152	35.0%	3,382	24.8%	901	22.8%	
30-35	33,077	25.6%	4,186	30.7%	1,150	29.1%	
>35	24,059	18.7%	5,027	36.8%	1,663	42.1%	
CCI	Average: 3.14		Average: 3.37		Average: 3.35		<.001
0-2	37,642	29.2%	2,658	19.5%	831	21.0%	
3	43,864	34.1%	4,928	36.1%	1,426	36.1%	
>4	47,422	36.7%	6,061	44.4%	1,694	42.9%	
Functional Status Prior to Surgery							<.001
Independent	126,783	98.3%	13,330	97.7%	3,812	96.5%	
Dependent	2,145	1.7%	317	2.3%	139	3.5%	
Smoker							<.001
Yes	14,447	12.0%	1,562	11.5%	455	11.5%	
No	113,451	88.0%	12,085	88.5%	3,496	88.5%	

DM – Diabetes Mellitus, NIDDM – Non-Insulin Dependent Diabetes Mellitus, IDDM – Insulin Dependent Diabetes Mellitus, BMI – Body Mass Index, CCI – Charlson Comorbidity Index;

* Chi-squared tests were used to compare these variables (significance at $p < 0.05$), **Bolding** indicates statistical significance.

than NIDDM. Additionally, patients with IDDM had greater relative risks of adverse events than patients with NIDDM (sepsis or septic shock: RR = 2.35 versus 1.57, respectively, renal insufficiency: RR = 4.34 vs. 2.25, readmission: RR = 1.70 vs. 1.24, and extended LOS: RR = 1.87 vs. 1.29).

Discussion

As the prevalence of DM continues to increase, so does the importance of assessing its role in surgical outcomes and perioperative adverse events. Although previous studies have demonstrated that DM is associated with an increased rate of adverse events after THA, these studies did not distinguish between clinically identifiable subpopulations of patients with DM based on use of insulin in their treatment regimen.[16,17] Comparing the risks of adverse events after THA in these subpopulations could assist patients and providers in pre-operative patient preparation and optimization and post-operative planning and management.

The current study of a large cohort of patients with DM who underwent THA found that the need for insulin in the management of DM is a risk factor for greater relative risk and more perioperative adverse events than those not requiring insulin, independent of demographic characteristics and comorbidity burden. The results of this study are consistent with recent literature that shows that patients with IDDM are at a greater risk for many more adverse events than patients with NIDDM following total knee arthroplasty.[18]

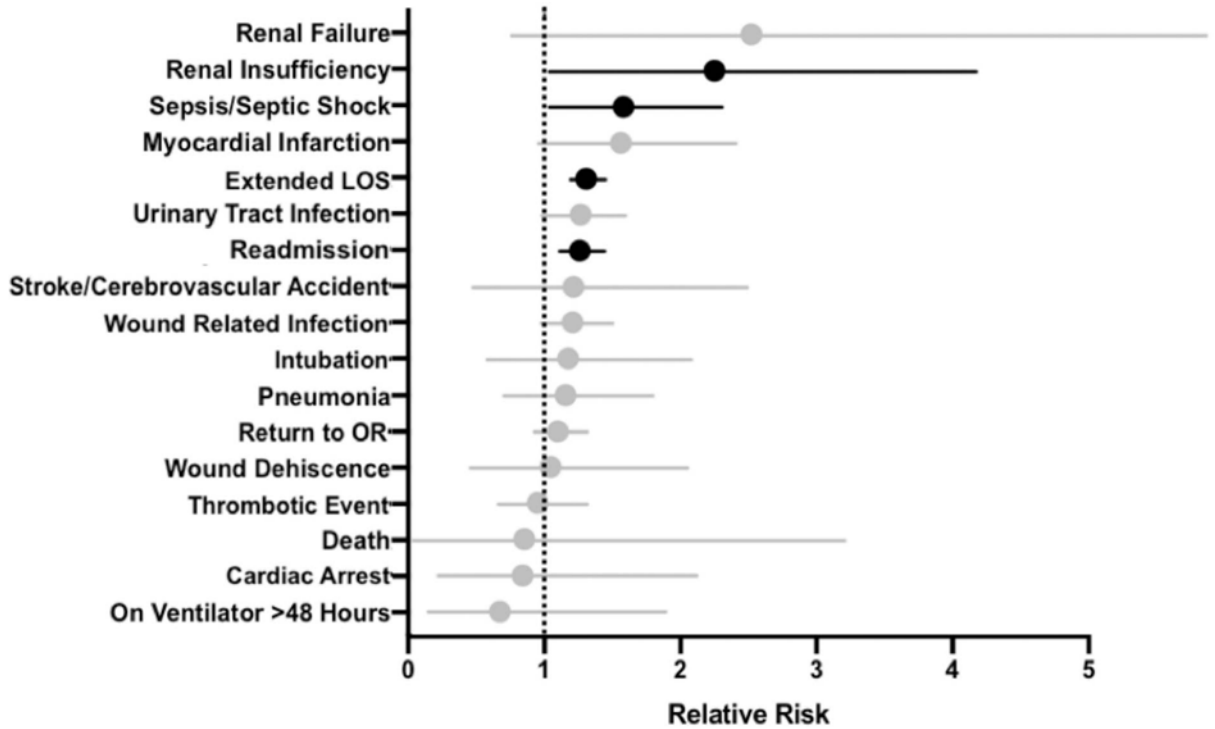
Compared to patients without diabetes, those with NIDDM were at increased perioperative risks of renal insufficiency, sepsis or septic shock, extended length of stay, or readmission with 30 days. Patients were IDDM were also at increased risk for these complications, but patients with IDDM were also at increased risk for renal failure, myocardial infarction, stroke or cerebrovascular accident, pneumonia, re-intubation, urinary tract infection, wound-related infection, or return to the operating room. Although both groups of diabetic patients were at increased risk for 4 of these 12 adverse events studied, compared to patients with NIDDM, the patients with IDDM were at greater relative risk for all 4 of these.

There were several limitations to the current study. One limitation relates to the method by which NSQIP defines patient populations with DM. DM was not classified as Type I or Type II, and measures of glycemic control such as hemoglobin A1c were not available. Additionally, THA specific outcomes and patient reported outcomes were not available for analysis, and the NSQIP database only followed patients for 30 days postoperatively. Finally, the mechanism of the association between the different DM categories and adverse events is not well defined or investigated using the available data.

Table 2. Relative Risk of adverse events within 30 days of THA in patients with NIDDM and IDDM vs those without DM

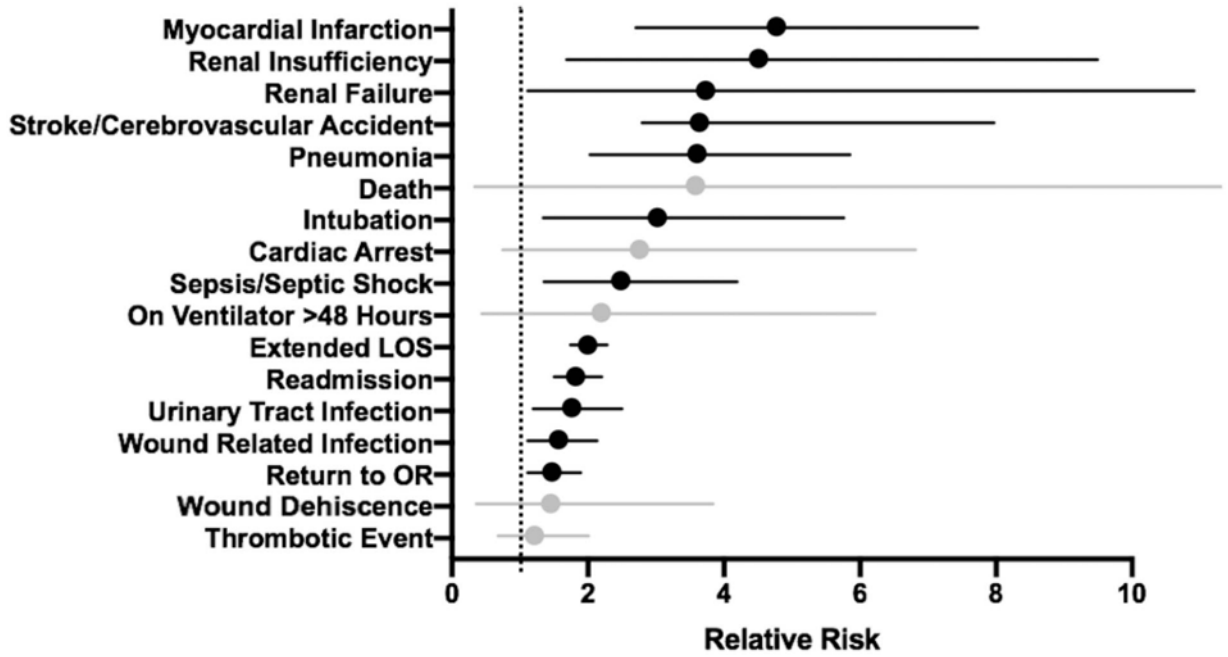
	Without DM	NIDDM				IDDM			
Total	**Percent**	**Percent**	**RR**	**CI**	**p-value**	**Percent**	**RR**	**CI**	**p-value**
	128,928		**13,647**				**3,951**		
Myocardial Infarction	0.19	0.36	1.55	0.93-2.40	0.005	0.99	4.59	2.56-7.48	< **0.001**
Renal Insufficiency	0.06	0.21	2.25	1.01-4.19	< **0.001**	0.43	4.34	1.56-9.21	< **0.001**
Renal Failure	0.03	0.11	2.52	0.73-5.91	0.004	0.18	3.57	1.00-10.6	**0.003**
Stroke/Cerebrovascular Accident	0.08	0.12	1.20	0.44-2.49	0.509	0.33	3.48	2.65-7.72	< **0.001**
Pneumonia	0.26	0.35	1.14	0.67-1.78	0.405	1.01	3.45	1.89-5.64	< **0.001**
Death	0.03	0.03	0.83	0.00-3.21	0.725	0.13	3.42	0.23-11.8	0.012
Intubation	0.13	0.20	1.16	0.55-2.07	0.495	0.51	2.87	1.22-5.55	< **0.001**
Cardiac Arrest	0.07	0.07	0.82	0.18-2.11	0.577	0.23	2.62	0.64-6.58	0.006
Sepsis/Septic Shock	0.25	0.51	1.57	1.01-2.30	**0.001**	0.81	2.35	1.23-4.01	< **0.001**
On Ventilator> 48 Hours	0.05	0.05	0.65	0.11-1.88	0.298	0.18	2.07	0.33-6.00	0.079
Extended Length of Stay (>3 days)	5.23	7.69	1.29	1.17-1.43	< **0.001**	11.1	1.87	1.61-2.14	< **0.001**
Readmission	2.94	4.30	1.24	1.09-1.42	< **0.001**	5.97	1.70	1.38-2.06	< **0.001**
Urinary Tract Infection	0.87	1.26	1.25	0.96-1.58	0.008	1.65	1.64	1.08-2.35	< **0.001**
Wound-Related Infection	0.98	1.58	1.19	0.95-1.48	0.018	2.02	1.45	1.00-1.99	**0.001**
Return to Operating Room	1.76	2.26	1.08	0.90-1.29	0.220	2.94	1.35	1.00-1.76	**0.002**
Wound Dehiscence	0.09	0.13	1.03	0.42-2.04	0.893	0.18	1.34	0.25-3.67	0.461
Thrombotic Event	0.54	0.59	0.93	0.63-1.29	0.562	0.71	1.10	0.57-1.87	0.628

THA – Total Hip Arthroplasty, NIDDM – Non-Insulin Dependent Diabetes Mellitus, IDDM – Insulin Dependent Diabetes Mellitus, DM – Diabetes Mellitus, RR – Relative Risk, CI – Confidence interval (95%), Poisson regression with robust error variance;
Bolding indicates statistical significance (significant at $p < 0.003$ after Bonferroni correction for multiple hypotheses)



THA – Total Hip Arthroplasty, DM – Diabetes Mellitus, LOS – Length of Stay, OR – Operating Room;
Error bars represent 95% confidence intervals and 2-sided alpha $p = 0.05$;
Bolding indicates statistical significance after correction for multiple adverse events ($p < 0.003$)

Figure 1. Relative risks of adverse events after THA in patients with non-insulin dependent diabetes mellitus vs patients without DM.



THA – Total Hip Arthroplasty, DM – Diabetes Mellitus, LOS – Length of Stay, OR – Operating Room;
Error bars represent 95% confidence intervals and 2-sided alpha p = 0.05;
Bolding indicates statistical significance after correction for multiple adverse events ($p < 0.003$)

Figure 2. Relative risks of adverse events after THA in patients with insulin dependent diabetes mellitus vs patients without DM

Conclusion

The results of the current study show that insulin dependence is an independent risk factor for adverse events following THA. Both NIDDM and IDDM are associated with adverse events after THA, but IDDM is associated with 3 times as many of the adverse events we studied. When both groups of diabetic patients are at increased risk for a given complication, the patients with insulin dependence were at greater risk. This information will be useful for providers for patient selection and management of post-operative expectations, and it may prove useful in mitigating the risks of some complications after surgery. Future studies should investigate the interaction between perioperative glycemic control, insulin use, and the risk of adverse events in patients with DM undergoing THA.

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Ceramic-on-Ceramic Hip Arthroplasty in Young Patients: 12-year Median Follow-Up of Patients Aged 55 Years or Younger

Matthew L Webb, MD[1]
Perry J Evangelista, MD[2]
Andrew Konopitski, MD[3]
Yehuda E Kerbel, MD[1]
Christopher M Scanlon, MD[1]
Charles L Nelson, MD[1]

[1]Hospital of the University of Pennsylvania, Philadelphia, PA

[2]Evangelista Orthopedic Clinic, Scottsdale, AZ

[3]St. Luke's University Hospital, Bethlehem, PA

Introduction

Total hip arthroplasty (THA) in young patients is controversial. Many of these patients develop arthritis secondary to avascular necrosis (AVN) of the hip, post-traumatic arthritis, developmental dysplasia of the hip (DDH), or history of slipped capital femoral epiphysis (SCFE). When non-operative management fails, THA may provide the young active patient with the best chance for pain relief and restoration of function. A major concern for the patient and surgeon is the risk for revision surgery. Historically, THA for cases of osteonecrosis proved to be challenging due to poor implant survivorship with an average revision rate of 40% at mid-term followup.[1,2] With newer techniques and advancements in prosthetic design, such as third generation ceramic-on-ceramic (CoC) components, THA in patients treated for osteonecrosis has demonstrated promising results at mid and long-term follow-up with revision rates ranging from 0% to 1%.[3-5] The purpose of this study is to evaluate the clinical and functional outcomes at long-term follow-up from THA with modern CoC bearings in young, active patients.

Methods

This is a single-surgeon, single-institution retrospective review of cases of a fellowship-trained arthroplasty surgeon at an academic center between years 2003 and 2010. All operations were performed by the senior investigator (C.L.N.) via a posterolateral approach with posterior soft-tissue repair. Stryker (Mahwah, NJ) or DePuy (Warsaw, IN) ceramic-on ceramic bearings were implanted in all patients. In the immediate postoperative period all patients were made weight-bearing as tolerated. Representative pre- and post-op images of bilateral CoC hip replacements are shown in figures 1 and 2.

Revision surgery for any reason was the primary study endpoint. Patient-centered clinical and functional scores were secondary endpoints. Preoperative and postoperative Western Ontario and McMaster University Arthritis Index (WOMAC) and University of California at Los Angeles Activity scores (UCLA) were collected via telephone survey. A questionnaire of squeaking described by Lee and coworkers was included.[6] This questionnaire assesses several squeaking issues: presence, nature, time of onset, frequency,

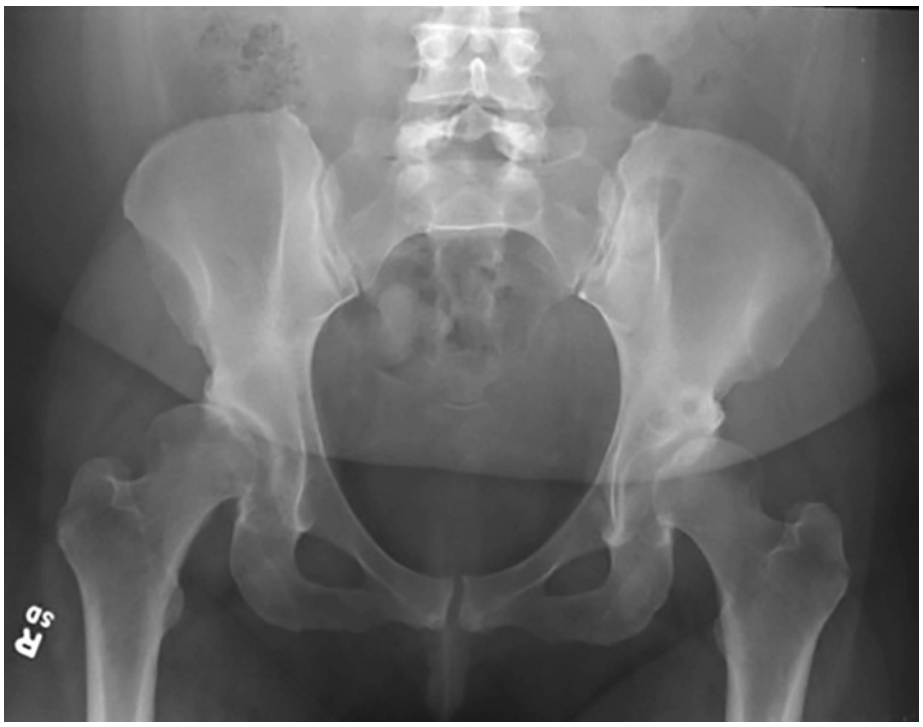

Figure 1. Representative preoperative image of a patient from our sample with bilateral dysplastic hips.

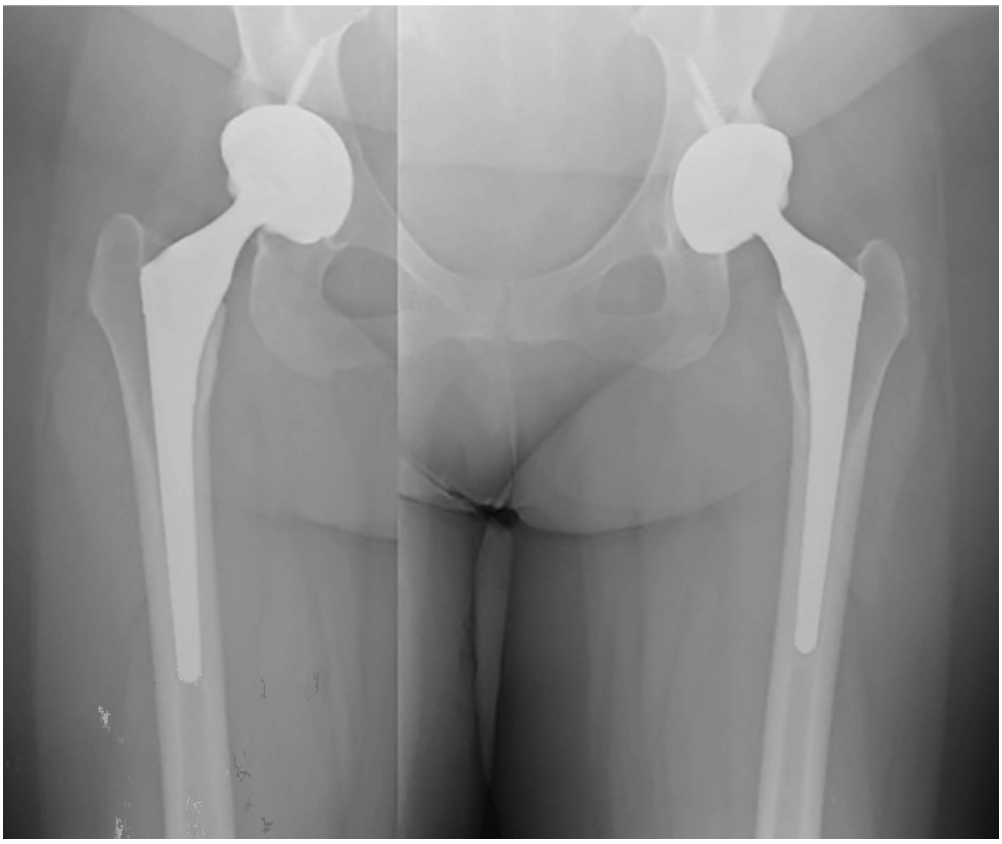

Figure 2. Postoperative radiographs of the patient shown in figure 1, status post bilateral ceramic-on-ceramic hip replacements

associated activities, awareness by other people, intensity over time, associated pain, and how the noise affects the quality of life. Institutional review board approval was obtained prior to data collection. All postoperative complications were recorded.

Demographic data was analyzed descriptively. Student's t-tests were used to determine significance between preoperative and postoperative WOMAC and UCLA scores. A p-value of less than 0.05 was considered significant. All data were tabulated with SPSS software (Version 15.0; SPSS Inc, Chicago, IL).

Results

In this cohort of 108 hips the median age at time of THA was 39 (range 14-55) and the median interval of follow-up was 12.4 years (range 9-16). Forty-two percent had a diagnosis of AVN, 12% had post-traumatic osteoarthritis, 8% had a history of DDH, and 5% had a history of SCFE. Average preoperative BMI was 27 (range 19-40). WOMAC scores (1-100 scale) increased from preoperative mean of 39.1 (range 6.3-78.9) to postoperative mean 84.6 (range 23.1-100) at latest follow-up ($p < 0.05$). WOMAC scores improved on average 46.1 points. UCLA scores (1-10 scale) improved from a preoperative mean of 3.1 (range 1-10) to postoperative 7.2 (range 2-10) at latest follow-up ($p < 0.05$). UCLA scores improved on average 4.2 points. Forty percent of patients were highly active with UCLA scores between 8 and 10.

There were no dislocations, deep infections, or ceramic component failures. At 12.5 years median follow-up, 4 patients had undergone revision surgery. One patient underwent early revision for femoral component loosening, one underwent revision for chronic pain at another institution, one hip was revised for instability at 5 years post-op, and one was revised for traumatic fracture at 10 years postoperatively. Six patients noted some squeaking sounds from the hip. The mean time of onset of squeaking was 9 years postoperatively (range 1-12). None of these patients reported that the squeaking had any effect on self-reported quality of life.

Many patients have regained previous high-level functionality. Two patients have resumed long distance running, including marathons. Another patient is a division one collegiate volleyball player, and several others have resumed occupations involving manual labor such as construction.

Discussion

With the advancements in surgical technique, implant designs, and improved instrumentation, THA has been consistently successful treatment for advanced hip arthritis. Younger and more active patients have been enjoying the benefits of THA, and literature supporting its use in this patient population has been growing.[7-10] A recent literature review reports a 97% implant survival rate for patients treated with THA for the most common risk factors and diagnoses of osteonecrosis since 1990.[11] At long-term follow-up Nich and colleagues report on 52 consecutive hips treated with CoC bearings and found no cases of osteolysis, even at maximum 24 years post-THA.[12] The choice to implant CoC bearings in this population is based on characteristics of low clinical

wear, low rates of osteolysis, and the continuing success of third generation ceramic technology, particularly in the young and active patient population.[13-17] Our findings support the idea that THA with CoC bearings affords high activity level with excellent clinical outcomes and component longevity in young, active patients.

In 2006, Seyler and associates produced a prospective, randomized, multicenter study of patients with osteonecrosis treated with third generation CoC components. Of the 79 hips assessed at an average of 4.2 years postoperatively, they reported a 95.5% implant survival rate (confidence interval 86.5% to 98.6%).[18] They had three revisions in the CoC osteonecrosis cohort, a revision rate of 3.8% and this is similar to our revision rate.[18] One of their revisions was for pain, another for a femur fracture, and a third for recurrent dislocations.[18] In comparison to our current study, we similarly had a patient who was revised at an outside institution exclusively for pain. Most importantly, revisions did not occur in either study due to osteolysis and subsequent loosening.

Populations of young patients engage in more strenuous physical activity when compared to aging populations.[19] Despite cautioning patients regarding activity modifications post-THA, several patients in this cohort have resumed previous strenuous activity without any complications as of this publication, including marathon running, division one collegiate volleyball, and manual labor. One of the female marathon athletes qualified for and ran in the Boston Marathon. While this mid-term study in no way supports impact activity following THA, patients today have high expectations with regard to activity, and a longer-term follow-up of these patients may help us understand whether these high activity goals will lead to high failure rates. This is particularly important as we continue to investigate the role of alternatives to THA such as hip resurfacing and joint preservation procedures.

Conclusion

Our study has several limitations. Some limitations include our retrospective design and lack of control groups. Furthermore, the use of phone surveys utilizing WOMAC and UCLA questionnaires have inherent variability due to patient subjectivity and researcher questioning. Despite these, all efforts were made to control variability by using one telephone interviewer and a standard set of survey questions. There are also challenges in assessing the activity levels of young and very active patients who may encounter a ceiling effect on UCLA survey. Alternatively, patients with multiple comorbidities or prior poly-trauma patients may have clinical or functional limitations that are not related to their THA.

Despite these limitations, this study shows that at long-term follow-up young patients who underwent total hip arthroplasty with ceramic-on-ceramic bearing surfaces had high activity levels with excellent clinical outcomes and component longevity. The strengths of this study include a consecutive series from a single surgeon and institution, as well as the use of modern third generation CoC components in all patients. Surgeons should feel comfortably treating young patients suffering from advanced hip arthritis with THA if necessary, and this study shows that ceramic components in young active patients can provide long-term success with low risk of revision.

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Late Presentation of a Retained Stingray Spine in the Plantar Medial Hindfoot

David P. Falk, MD
Sreenivasulu Metikala, MD
Viviana Serra Lopez, MD, MS
Matthew Stein, MD
Karim Mahmoud, MD
Wen Chao, MD

Department of Orthopaedic Surgery,
Hospital of the University of Pennsylvania

Case Report

A 29 year-old healthy female presented to clinic in October of 2018 with new onset of left ankle redness and swelling at the posteromedial aspect of the ankle along the tarsal tunnel. She denied recent trauma, but recalled that she was stung by a stingray in the left plantar medial hindfoot in August of 2017 while at the beach in New Jersey. The patient did not seek medical attention initially because pain from the sting resolved within 24 hours.

Approximately three months following the initial injury, the patient presented to an outside emergency department with worsening left medial ankle pain. Radiographs of the left foot and ankle were negative for bony pathology and no foreign body was visualized. She continued to have pain, and MRI was obtained in March 2018 at the recommendation of the patient's primary care physician. The radiology read was significant for an accessory navicular, posterior tibial tendon tenosynovitis, flexor hallucis longus (FHL) and flexor digitorum longus (FDL) synovitis, and a moderate ankle effusion. There was no mention of retained foreign body. She was treated in a CAM boot and completed a short course of physical therapy with no improvement. Her symptoms remained stable until October 2018, when she developed a tender erythematous lump over the posteromedial aspect of her left ankle along tarsal tunnel, causing her to seek orthopaedic treatment.

At the initial visit at Foot & Ankle clinic, the patient denied new trauma, fevers, or other constitutional symptoms. Physical examination of the left foot and ankle revealed a 2.5 cm fluctuant mass along the tarsal tunnel with overlying cellulitis. She had mild tenderness at the posterior tibial tendon proximal to the mass, and pain with range of motion at the ankle. The patient was able to bear weight with an antalgic gait on the left side. The remainder of the physical exam was unremarkable. She was instructed to obtain an updated MRI. Oral antibiotics were prescribed to treat the cellulitis.

Two days later, the patient returned to clinic for follow up. Thick, purulent fluid was draining from the inflamed area along left tarsal tunnel (Figure 1). She remained afebrile and the remainder of her exam was unchanged. White blood cell (WBC) count, Erythrocyte Sedimentation Rate (ESR), and High Sensitivity C-Reactive Protein (hsCRP) were all within normal limits [WBC 6.5 (nml 4.0-11.0 THO/ul); ESR 3 (nml 0-30 mm/h); hsCRP 0.5 (nml<7.4 mg/L)]. MRI was reviewed, which showed 2-3 thin linear foreign bodies at the quadratus plantae and tarsal tunnel, with subcutaneous edema of the medial ankle (Figure 2a and 2b). Of note, closer review of the previously obtained MRI from March 2018 also demonstrated the presence of foreign bodies. Surgical exploration and extraction of foreign bodies under anesthesia were recommended.

Intra-operatively, an incision was made along the tarsal tunnel centering at the draining wound. Purulent fluid was encountered just deep to the skin. The laciniate ligament was then identified and found to be extremely thickened. This was excised and sent to Pathology. Culture of the cloudy fluid was obtained and was sent to Microbiology. The neurovascular bundle was carefully retracted posteriorly using a blunt retractor. There was a small piece of the retained stingray barb superficial to the FHL tendon sheath and anterior to the neurovascular

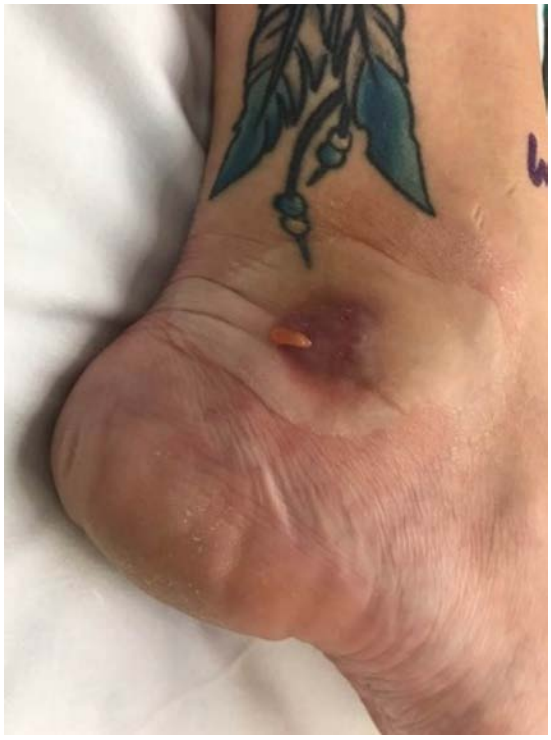

Figure 1. Swelling of posteromedial aspect left ankle with a sinus draining purulent fluid with surrounding cellulitis.

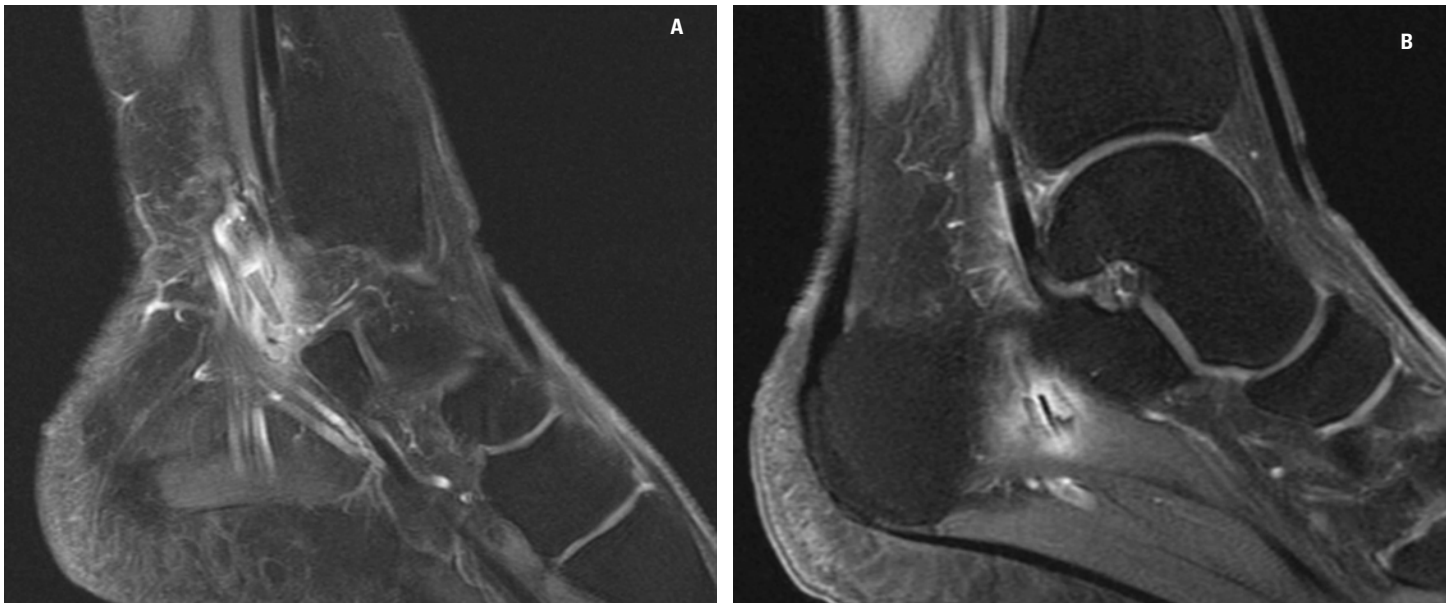

Figure 2. Sagittal T2 MRI, showing **(A)** 2-3 thin, linear low signal intensity foci within the quadratus plantae muscle, compatible with foreign bodies; **(B)** A large linear low signal intensity focus within the tarsal tunnel, compatible with a foreign body.

bundle. This was removed using forceps. The FHL tendon sheath was then incised. There was evidence of tenosynovitis surrounding the FHL tendon. The FHL tendon itself was intact with no evidence of tear. Tenosynovectomy was performed along the FHL tendon. The FHL tendon was then carefully retracted in anterior direction.There was a large stingray barb just posterior to the FHL tendon which was removed using forceps (Figure 3a). Further exploration in deeper planes revealed multiple pieces of stingray barb in quadratus plantae, which were removed using a pair of forceps and a small curved mosquito clamp (Figure 3b). The wound was then irrigated with 3 L of gentamicin-containing solution using urology tubing. Two grams of Ancef was given intravenously by the Anesthesia team after the soft tissue culture was obtained prior to removal of foreign bodies. The friable skin edges were excised using a #15 scalpel blade. Skin closure was then made with 3-0 nylon sutures and the patient was placed into a CAM boot post-operatively.

Microbiology analysis of the intra-operative specimen was unrevealing. Gram stain showed occasional PMNs, but no

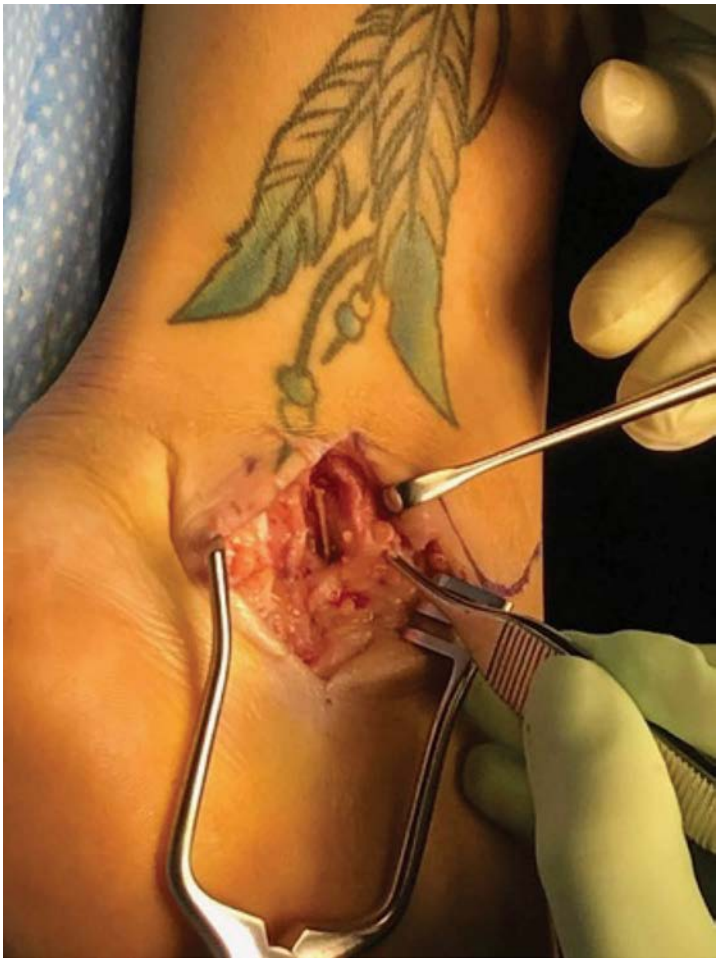

Figure 3. (A) Intra-operative image showing a large piece of retained stingray barb in tarsal tunnel; **(B)** Multiple pieces of broken stingray barb extracted from the patient.

organisms. Operative cultures finalized as no growth at 5 days. Pathology showed fibrous tissue with granulation tissue, acute and chronic inflammation, and granuloma formation. Acid-Fast Bacilli (AFB) and fungal stain were negative.

At 6 week follow-up, the patient's incision was well-healed. Other than mild numbness at the plantar-medial hallux, the patient's exam was unremarkable. At 12 week follow-up, she has resumed full activities except for running.

Discussion

Stingrays are responsible for stinging more humans than any other fish in the sea, affecting at least 2,000 individuals annually in the United States alone.[1] These flattened, cartilaginous fish with muscular wings share their ancestral roots with sharks, and can range in size from several inches up to 12 feet long.[1,2] The stingray's whip-like tail is uniquely structured, possessing 1 to 6 stiletto-sharp spines, also known as barbs, along its length.[3] Each spine is lined with retro-serrated edges and encased by a thin integumentary sheath, which serves to house the venom located along the underside of the spine.[1]

Despite this powerful tail, stingrays are usually thought of as docile, non-aggressive scavengers who only attack when their habitat is unintentionally invaded during recreational and occupational activities. Most victims are young males in their 20s who sustain an injury to an extremity.[4,5] The dorsal and plantar aspects of the foot, as well as the ankle and lower leg are the most commonly implicated body parts among unsuspecting beachgoers or divers who step on a stingray buried in the sand.[2,5] Fisherman are also susceptible to hand injuries, sustained while disentangling stingrays from hooks or nets.[2]

When disturbed, the stingray's tail reflexively whips forward in an effort to embed a spine into the victim.[3] On contact, a 2-part injury occurs.[4] First, there is direct trauma to the affected body part in the form of a laceration or puncture wound. The second part of the injury is caused by envenomation. As the stingray spine plunges into a victim's skin, the integumentary sheath containing the stingray's venom is ripped open, and venom is released into the wound.[2] The venom, composed of heat-labile 5'-nucleotidase, phosphodiesterase, and serotonin can cause both local and systemic symptoms. Classically, envenomation causes localized pain and swelling that peaks within an hour of injury.[1] Systemic signs of envenomation can include weakness, nausea/vomiting, diarrhea, tachycardia, arrhythmias, hypotension, syncope, seizures, muscle cramps or fasciculations, paralysis, and in rare cases, death.[1] Often, pieces of the spine itself or sand and debris from the surrounding environment remain lodged in the wound, increasing the risk of prolonged envenomation, infection, wound breakdown, and granulomatous foreign body reactions.[2]

Management of stingray injuries should begin at the scene. Initial treatment focuses on identifying the extent of anatomic damage, reducing the effects of the venom, controlling pain, and preventing infection.[6] Following assessment of cardiopulmonary stability, the wound should be irrigated to remove non-embedded spine fragments and debris. Initial irrigation may be performed with seawater, though it is preferred to soak the wound in hot water up to 45° C [113° F] for 30–90 minutes as the hot water is thought to promote breakdown of the heat-labile venom.[1,2] If the spine is retained and located superficially within the wound, it may be removed at the scene to minimize exposure to venom. Under the rare circumstance that the spine deeply penetrates the abdomen, chest, or neck, it should be left in place and secured until the patient can be evaluated in an operating room.[1]

Following transfer to a medical facility, patient's should receive tetanus prophylaxis and pain control should be initiated.[2] Oral or parenteral analgesics, non-epinephrine containing local anesthetics, and regional nerve blocks may be necessary to achieve adequate analagesia, though hot water immersion alone has also been found to be effective.[1,7]In addition to these standard methods to alleviate pain, a single case report from Australia found that pain control can also be achieved by applying half of an onion bulb to the stingray wound.[8]

Once pain is controlled, the wound should again be irrigated and explored to evaluate for retained spine fragments or debris. Radiographs of the affected body part can then be obtained to rule out the presence of gas in the tissues, suggestive of bacterial infection, and for further evaluation of retained fragments.[1,9]Although multiple studies have found hyperdense, radio-opaque pieces of retained spine on plain film x-ray, fragments are not always visibly apparent as the spine itself is composed of a cartilagenous material known as vasodentin.[2,9,10] Ultrasound can be utilized in cases with high index of suspicion for a retained foreign body despite negative radiographs, as it has been shown to be effective in identifying radiolucent objects in wounds.[11] MRI also has utility in cases of established infection.[12]

In addition, prophylactic antibiotic therapy should be initiated, directed at common marine bacteria including *Staphylococcal, Streptococcal,* and *Vibrio* species.[4] While evidence on the efficacy of prophylactic antibiotics is limited, Clark et al. found a higher rate of return visits to the emergency department with symptoms suggesting wound infection among patients who did not receive antibiotics prior to discharge from their initial visit following a sting.[7] These authors advocate for a 5-day course of quinolone therapy following stingray injury, though other authors recommend trimethoprim/sulfamethoxazole.[2]

The majority of reports on stingray injuries to the foot and ankle reflect acute injuries, and delayed presentations such as this case are rare. Of these delayed presentations, authors have described multiple reports involving wound complications related to infection and one case of acquired adult flatfoot deformity, all of which occurred within 1-2 months following the initial sting.[12–15] None were associated with a retained spine.

To our knowledge, this is the first case to describe complications in the foot and ankle from a retained stingray spine in the tarsal tunnel sustained from a sting more than one year prior to presentation. Interestingly, Saunders et al.

reported a unique case of a 44 year-old male who presented with a coronary artery occlusion due to a retained spine, which had been implanted when he was stabbed in the chest with a stingray spine 17 years prior to presentation.[16] Both cases demonstrated the potential for stingray spines to migrate over time.

This case is unique because of the extended delay in diagnosis and treatment of a retained sting ray spine in the foot and ankle. It also emphasizes both the importance of obtaining a detailed history and the need to always personally review the patient's diagnostic images in the context of the injury or trauma history.

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Limited Scar Resection for Chronic Achilles Repair: Use of a Rat Model

Matthew Counihan, MD
Courtney Nuss, AS
Joseph Newton, BS
Louis Soslowsky, PhD
Daniel Farber, MD

McKay Orthopaedic Research Laboratory, University of Pennsylvania, Philadelphia, PA

Introduction

Acute rupture of the Achilles tendon is misdiagnosed in up to 24% of patients.[1] Without acute intervention, the tendon ends retract, the injury gap fills with scar tissue, and treatment becomes more difficult.[2] Current treatment of chronic Achilles tendon ruptures involves debridement of scar tissue back to normal tendon ends, followed by interposition of healthy graft tissue to fill the gap, such as in the gastrocnemius fascia turndown (GFT) technique.[3] Direct repair with the limited scar resection (LSR) technique offers a less invasive alternative, allowing for primary repair of the tendon without a graft, avoiding donor site morbidity.[4] However, LSR has not been adopted as a common surgical alternative due to concern that scar tissue does not heal as well as healthy donor graft tissue. Therefore, the objective of this study was to define and compare the healing properties of the Achilles tendon after chronic injury reconstruction with GFT or LSR, utilizing an animal model to control the injury and treatment strategies. We hypothesized that LSR would have superior healing properties to the GFT and non-repair control groups in a chronic Achilles injury model.

Methods

After facility acclimation, 90 male Sprague Dawley rats (400-450g) were used (IACUC approved). Animals were randomized equally into three groups: non-repair (NR), gastrocnemius fascia turndown (GFT), and limited scar resection (LSR). Chronic Achilles injury was generated via unilateral blunt transection of the right Achilles tendon in each rat, followed by 1 week of immobilization of the injured limb in a maximally dorsiflexed position and 5 weeks of cage-activity without immobilization. 6 weeks after the index surgery, GFT and LSR groups underwent chronic Achilles reconstruction. In the GFT technique, all interposed scar tissue was debrided, then the gastrocnemius fascia was flipped on a distal hinge to bridge the gap, reconstructing the tendon. In the LSR technique, a small midsection of the scar tissue was removed to restore the tendon to pre-injury length, followed by end-to-end primary repair of the remaining scar tissue ends. A modified Kessler repair was used in both techniques. The hind limb was immobilized in plantarflexion after the index surgery. Animals were sacrificed at 3 and 6 weeks after repair. The NR group was sacrificed at 9 and 12 weeks from the index procedure to match sacrifice points for all three groups. All rats underwent biweekly in vivo assessments including ambulatory kinetics and kinematics, passive ankle joint mechanics, and ultrasound. Ex vivo assessments included mechanical testing and histology. Cycles to failure comparisons were made using a nonparametric Kruskal-Wallis ANOVA. Other ex-vivo comparisons were made using 1-way ANOVAs. In-vivo assessment comparisons were made using a 2-way ANOVA with repeated measures on time with follow-up t-tests between groups at each time point. Significance was set at $p < 0.05$ for all tests.

Results

Ultrasound

Ultrasound assessment showed successful post-injury elongation of the Achilles tendon in all groups which is critical to the chronic Achilles injury model. The cross-sectional area of each of the repaired tendons was significantly increased compared to the NR tendons at both time points. The LSR repair had increased vascularity compared to NR in the post-repair period, with increased contrast wash-in rate and decreased contrast time to peak at the 9 week time point.

Mechanical Testing

Stiffness of LSR and GFT repairs was significantly lower compared to NR at 3 weeks. At 6 weeks, LSR and GFT tendon stiffness improved, such that there was no longer a difference between the three groups. Modulus was significantly lower in both LSR and GFT groups at both 3 and 6 weeks. Cycles to failure (CTF) was significantly higher in NR at 3 weeks as compared to both LSR and GFT. CTF improved in both repair groups at 6 weeks such that there was no longer a difference between the three groups.

Passive Joint Mechanics

Passive joint mechanics revealed significantly increased dorsiflexion stiffness in the GFT repair group at the first post-repair time point

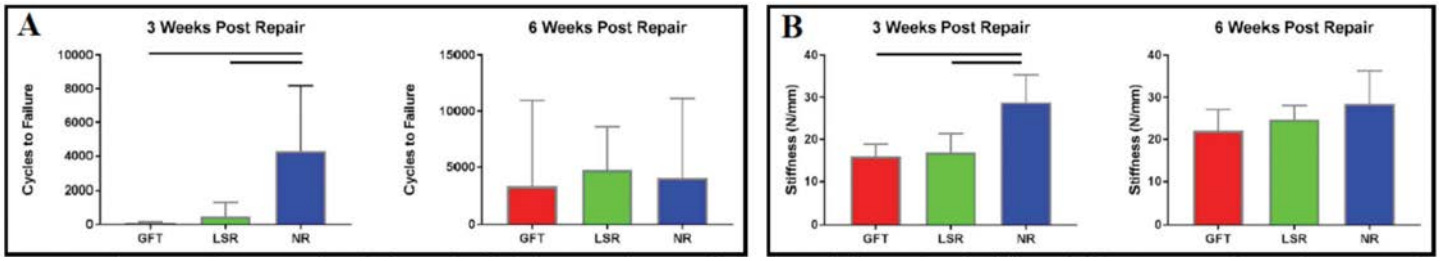

Figure 1. Both GFT and LSR repair techniques similarly improve in strength (cycles to failure, **A**) and stiffness **(B)** between 3 and 6 weeks post repair.

at 8 weeks when compared to NR. LSR repair had increased dorsiflexion stiffness that trended toward significance at the 8 week time point compared to NR. Both LSR and GFT groups had significantly decreased range of motion at the 8 week post-repair time point as compared to NR.

Ambulatory Assessment

Gait analysis of the GFT and LSR repair groups had significantly decreased ground reaction forces (peak vertical force, peak propulsion forces) as compared to the NR group at the first post-repair assessment 8 week time point. Ground reaction forces were recovered quickly in the LSR group, with no significant difference from the NR group at 10 and 12 weeks. Ground reactive forces for the GFT group remained significantly decreased from the NR group at both 10 and 12 weeks without recovery.

Discussion

The present study supports that both LSR and GFT reconstruction techniques are viable options for treatment of the chronic Achilles tendon injury in a rat model. We established that the injury surgery successfully recreated the elongated Achilles tendon typical of the chronic Achilles injury. Both reconstruction techniques established increased dorsiflexion stiffness and decreased range of motion across the ankle joint. This is representative of the re-establishment of normal length and tension of the Achilles complex in both of the repair groups, which is critical to the success of operative management of a chronic Achilles injury. Ground reaction forces were expectedly decreased after surgery, but quickly recovered in the LSR group, while the GFT group remained significantly decreased through the study. This is reflective of the decreased morbidity incurred by the LSR technique, allowing for a significantly shorter recovery time. Vascular analysis provided evidence of adequate microcirculation and vascularization of this tissue, contesting the notion that a lack of circulation in scar tissue would be a barrier to healing in this technique. Mechanical testing results raise the question of whether these tendons fared better with non-operative management compared to either reconstruction technique. However, it must be noted that at the 3 week and 6 week post-repair sacrifice points, the NR tendons are actually matured to 9 and 12 weeks, respectively. The difference in the relative maturity of the tendon in NR vs GFT/LSR groups inherently introduces a difference in stiffness and strength between the groups. Importantly, the repair groups were able to match the stiffness and strength of the NR group at the 6 week time point, when they have had relatively half the time for healing and scar maturation as the NR group. A limitation of the rat model is that the gastrocnemius muscle of the rat is relatively thinner with a larger soleus as compared to humans, and as such the GFT procedure may cause relatively larger morbidity to the gastrocnemius muscle in the rat.

Significance

This study supports that the limited scar resection technique is a viable surgical alternative, particularly when minimizing postoperative morbidity and surgical time are paramount. The study also suggests the non-operative management of chronic Achilles injuries may yield similar results as compared to operative management, which necessitates further research into conservative treatment modalities for this condition.

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Liquid Poly-N-Acetyl Glucosamine (sNAG) Improves Achilles Tendon Healing in a Rat Model

Courtney Nuss, AS[1]
Julianne Huegel, PhD[1]
Sergio Finkielsztein, BS[2]
Louis Soslowsky, PhD[1]

[1]McKay Orthopaedic Research Laboratory, University of Pennsylvania

[2]Marine Polymer Technologies, Inc. Burlington, MA

Introduction

The Achilles tendon, while the strongest and largest tendon in the body, is frequently injured. Even after surgical repair, patients risk re-rupture and typically have long-term deficits in function, with a low rate of return to pre-injury levels of activity.[1] Various forms of biological augmentation have been utilized in an attempt to improve tendon repair.[2] Poly-N-acetyl glucosamine (sNAG) polymer has been shown to increase the rate of healing of venous leg ulcers, with an 86% success rate clinically.[3] Additionally, use of this material improved tendon-to-bone healing in a rat model of rotator cuff injury and repair.[4] However, whether this nanofiber material, in an injectable liquid formulation, could improve soft tissue tendon healing after Achilles injury is unknown. Therefore, the purpose of this study was to investigate the healing properties of sNAG containing membranes in a rat partial Achilles tear model. We hypothesized that sNAG would improve tendon healing as measured by improved mechanical properties and cellular morphology.

Methods

Study Design

32 adult male Sprague-Dawley rats (400-450g) were used in this IACUC-approved study. All animals underwent a partial-width, full thickness injury using a 1.5 mm biopsy punch through the right Achilles tendon as described.[5] After injury, animals were randomized into two groups, receiving either 10 µl of 0.9% saline (control group) or 10 µl of 20 mg/ml sNAG polymer gel (sNAG group). Animals were allowed normal cage activity after surgery, without immobilization. Animals received repeat saline or sNAG injections at the site of the injury through the skin at one and two weeks post-surgery. All animals were sacrificed three weeks after injury.

Ex Vivo Assessments

The Achilles-calcaneus complex was immediately harvested and processed for histological analysis including quantitative collagen fiber organization analysis (n = 6/group). All other animals (n = 10 per group per time point) were frozen at −20°C and later thawed for dissection and mechanical testing. For testing, the Achilles tendon and foot complex were dissected and the calcaneus was potted in poly(methyl methacrylate). While immersed in 37°C phosphate-buffered saline and in a physiologic orientation, the Achilles tendons were gripped and subjected to a mechanical loading protocol consisting of: preloading, stress relaxation at 6% strain, dynamic frequency sweeps, and fatigue cycling under load control until specimen failure.

Statistics

Mechanical testing and collagen fiber organization data were evaluated using two-tailed t-tests after confirming data normality. Semi-quantitative histological comparisons were made using Mann-Whitney U tests. Significance was set at $p < 0.05$ for all comparisons.

Results

Mechanical properties

At three weeks after injury, there was no difference in tendon cross-sectional area (not shown). Tendon stiffness was improved with sNAG treatment (Fig 1A), but modulus was not different between groups (Fig 1B). Frequency sweeps demonstrated an increase in dynamic modulus across tested frequencies (Fig 1C), but tanδ, a measure of force dissipation, was not different (not shown). Fatigue testing demonstrated increases in tendon secant stiffness (Fig. 1D) and tangent stiffness (Fig. 1E) throughout fatigue life for sNAG-treated tendons compared to controls. There was no difference in cycles to failure (Fig. 1F), or other properties measured (not shown).

Histologic observations

Semi-quantitative grading did not demonstrate differences in cell density (Fig. 2A) or cell shape (Fig. 2B) at the injury region. Collagen alignment in this region was also not different between groups (Fig. 2C). Representative images of the injury region for both groups are shown in Figure 2D.

Discussion

This study investigated the effects of repeated sNAG polymer application on tendon healing after partial Achilles injury. Although several parameters did not exhibit differences between

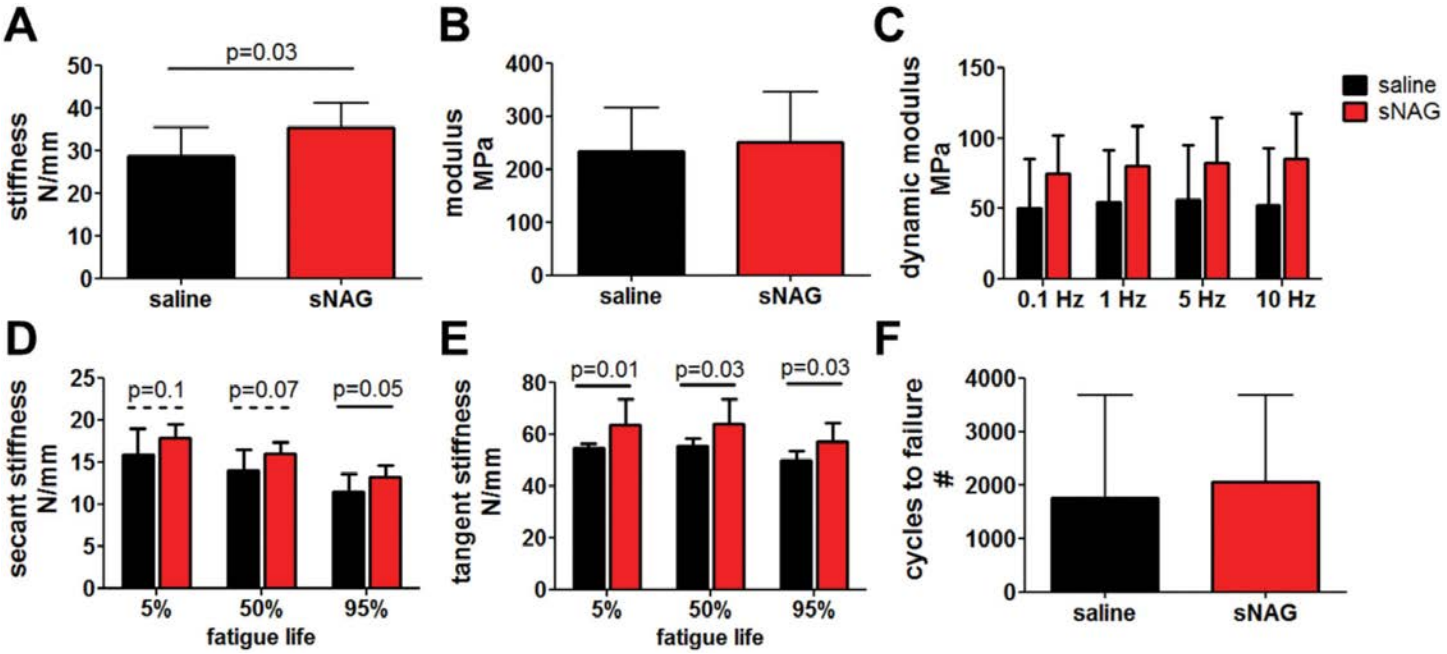

Figure 1. Mechanical Properties. Three weeks after injury, sNAG treated tendons had **(A)** increased stiffness; **(B)** no change in modulus; **(C)** increased dynamic modulus across testing frequencies; **(D)** increased secant stiffness and; **(E)** increased tangent stiffness. There were no changes in **(F)** cycles to failure between groups. Data shown as mean+SD.

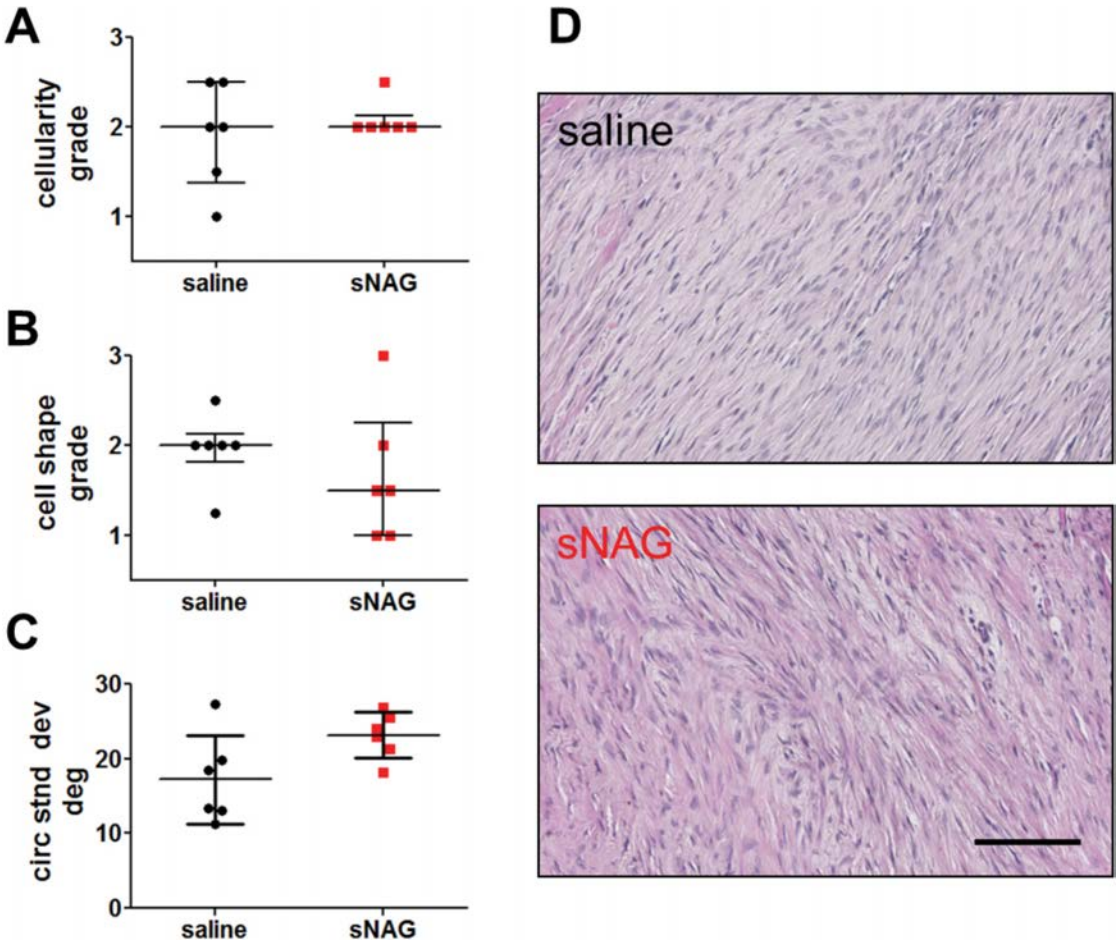

Figure 2. Histological Properties. There were no differences between groups for **(A)** cellularity; **(B)** cell shape; or **(C)** collagen alignment. Representative images of the injury region are shown in **(D)**. Data represented as median±IQR in A and B, and as mean±SD in C. Scale bar in D: 100 μm.

treatment groups, other results demonstrate that sNAG has a positive effect on rat Achilles tendon healing at three weeks after a full thickness, partial width injury. Quasistatic testing demonstrated increased tendon stiffness with sNAG treatment, which continued during fatigue cycling, as shown in increased tangent and secant stiffness across fatigue life. Increased dynamic modulus also suggests improved viscoelastic properties with sNAG treatment. Importantly, use of this

material did not have any negative effects on any measured parameter. Previous studies suggest that this material may mitigate pain after rotator cuff injury.[4] Functional testing such as gait assessment might be valuable, potentially expanding the use of this material as a less invasive treatment for painful Achilles tendonitis.[6] Additionally, dosage studies and number of repeated sNAG injections may optimize the use of sNAG for soft tissue tendon healing. Finally, studies to elucidate the mechanism of action for the changes identified are important.

Significance

Repeated injections of sNAG polymer improve Achilles tendon properties after partial tear. These results support further study of this material as a minimally invasive treatment modality for tendon healing.

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Microdialysis as a Longitudinal, In Vivo Assessment of Achilles Tendon Healing in a Rat Model

Joseph B. Newton, BS
Snehal S. Shetye, PhD
Courtney A. Nuss, AS
Matthew M. Counihan, MD
Daniel C. Farber, MD
Louis J. Soslowsky, PhD

McKay Orthopaedic Research Laboratory, University of Pennsylvania, Philadelphia, PA

Introduction

The Achilles tendon is the most frequently ruptured tendon, leading to significant pain, loss of function, and healthcare costs.[1] In vivo assessment of healing after an Achilles tendon rupture can provide valuable metrics not only to monitor healing, but also to guide treatment options.[2,3] Specifically, in vivo assays such as ultrasound imaging, passive joint mobility assessments, and functional gait analysis can provide longitudinal measures of structural and functional properties of the healing tendon. However, these assays do not provide insight into the biologic changes in the healing tendon.[4-6] While microdialysis has been used to assess tendon healing in humans, it has not been used in an animal model of Achilles tendon injury.[7,8] Therefore, the objective of this study was to develop and pilot a novel use of microdialysis in vivo to directly measure key biologic markers of tendon healing and matrix deposition in the rat Achilles tendon. We hypothesized that, following Achilles injury, metabolite and procollagen concentrations would significantly increaseindicating higher metabolic activity and collagen synthesis, respectively.

Methods

Experimental Design

After facility acclimation, six, 4-month male Sprague Dawley rats underwent unilateral blunt transection of the right Achilles tendon without repair (IACUC approved). The right hind limb was immobilized for 7 days. Microdialysis measurements were taken before injury and 7, 14, and 21 days post injury.

Dialysate Collection and Analysis

Under isofluorane anesthesia and ultrasound guidance, a microdialysis catheter (CMA 71; CMA Microdialysis AB; 100kDa molecular cutoff, 0.5mm outer diameter; 4mm in length) was introduced from the proximal aspect of the tendon towards the calcaneus. The active part of the membrane was placed in the rupture site and a perfusion fluid of artificial CSF with 3% 500kDa dextran (Sigma Aldrich) was used. The fluid was pumped through the inner tube of the catheter into the space between the inner tube and the semipermeable catheter membrane, where the exchange between the interstitial and perfusion fluid takes place. The resultant dialysate solution was transmitted from the catheter and collected in a 1.5mL vial (Microvial, CMA Microanalysis AV). With a perfusion speed of 1.0 μL/min, samples were collected for 2.5 hours. Due to fluid pump adjustment during the first few minutes, trauma from the probe insertion, and to remain conservative, the first 30 minutes of dialysate was discarded. Lactate, pyruvate, glucose, glutamate, glycerol, and procollagen type I N propeptide (PINP), concentrations were quantified via ELISAs.

Statistics

All comparisons were made using the nonparametric Kruskal-Wallis ANOVA followed by Dunn's post hoc tests, which compared values at 7, 14, and 21 days post injury to preinjury values.

Results

Lactate (Fig.1A) and pyruvate (Fig.1B) concentrations significantly increased 7 days post-injury, with no changes in lactate:pyruvate ratio at any time points (Fig.1C). Glucose concentration 7 days post-injury showed significant increases (Fig.1D). Glutamate was elevated 21 days following injury (Fig.1E). No changes were found in glycerol concentration following injury (Fig.1F). PINP concentrations were decreased at each post-injury time point compared to pre-injury measures (Fig.2).

Discussion

Results indicate an early increase in overall metabolic activity and simultaneous decrease in collagen I production following Achilles injury. Increases in lactate and pyruvate 7 days post-injury indicate increased anaerobic and aerobic metabolic activity, respectively, as the resident cell population begins tissue repair. No changes in the lactate:pyruvate ratio demonstrate that the local environment is sufficiently oxygenated, as aerobic and anaerobic activity levels are maintained throughout healing.[7] Under normal healing conditions, angiogenesis peaks around day 7 in a healing tendon,[9] which is supported by the early increase in glucose concentration. This increase in glucose concentration may also indicate increased metabolic activity immediately following injury, concurrent with the lactate and

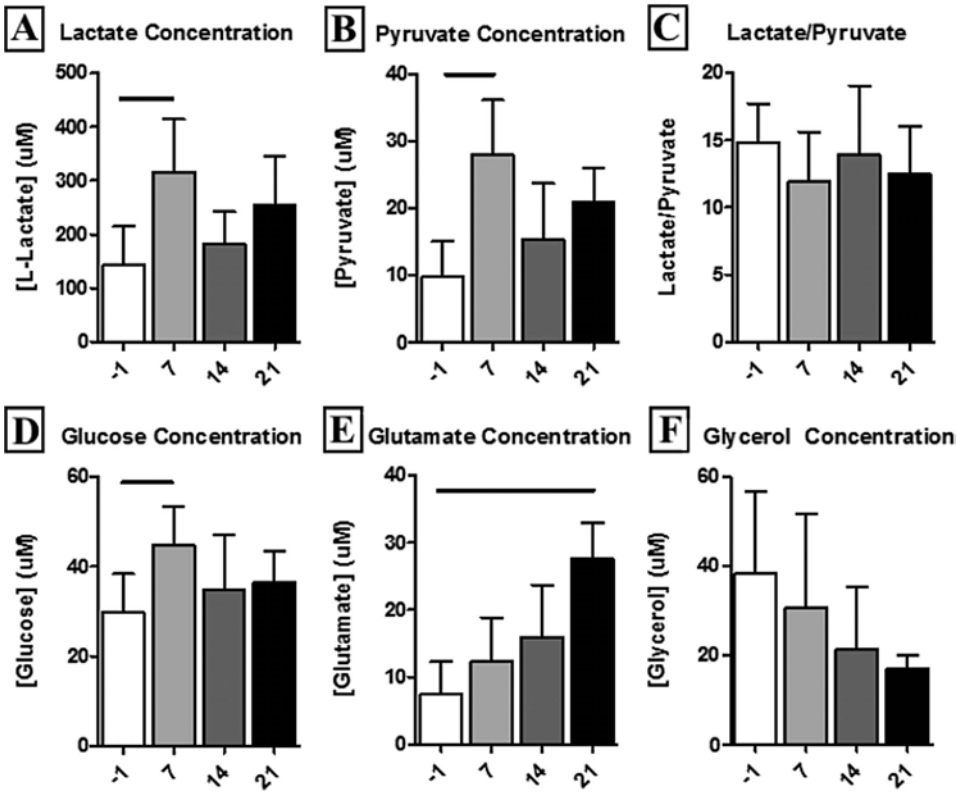

Figure 1. ELISA results from dialysate prior to injury (−1) and 7, 14, and 21 days post injury. Lactate **(A)** and pyruvate **(B)** concentrations peaked at 7 days postinjury while their relative ratio **(C)** was maintained. Glucose **(D)** peaked at day 7. Glutamate (E) was significantly increased at day 21. No changes were found in glycerol **(F)**. Data as mean +/− standard deviations; bar indicates significance.

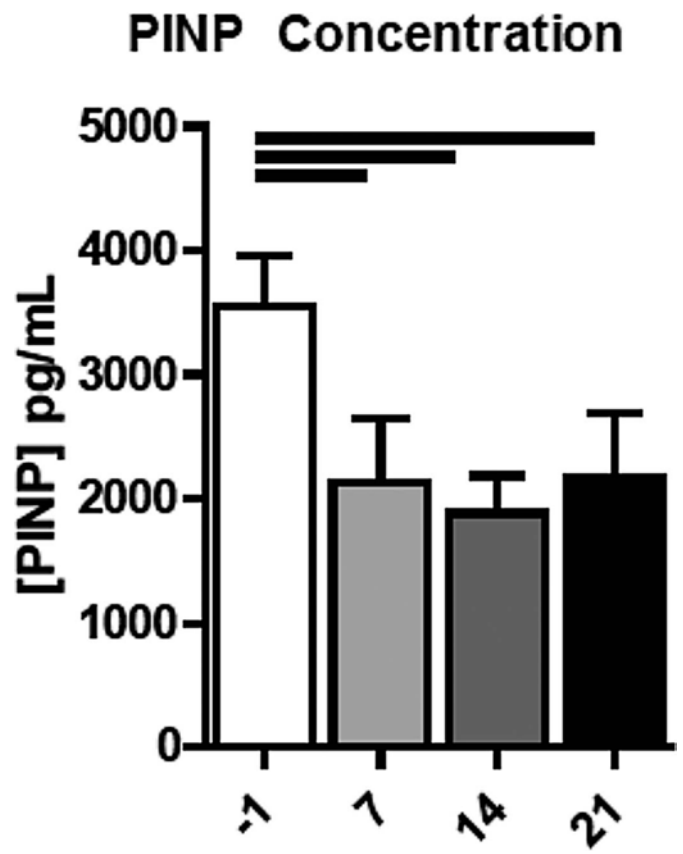

Figure 2. ELISA results showed a decrease in PINP concentration throughout healing compared to pre-injury levels. Data as mean +/− standard deviations; bar indicates significance.

pyruvate changes shown. Glutamate concentration peaks at 21 days post-injury in congruence with nerve ingrowth.[7] Glycerol is a marker for cellular damage, and results show no changes in the metabolite's concentration, thus the severity of cellular damage remains unclear in our injury model.[7,8] PINP decreased immediately following injury, demonstrating a reduction in collagen I production. The study timeline was likely not long enough to see the expected increase in collagen I production as the tendon begins the remodeling phase of healing in which collagen III in the fibrotic scar tissue is replaced by more aligned collagen I.[2] Future studies will investigate changes in the biological environment of a healing Achilles tendon in response to exercise and new modalities to improve healing outcomes.

Significance

This study demonstrates that microdialysis is a viable in vivo, longitudinal measure of Achilles tendon healing in a rat model. This technique will provide valuable metrics to monitor the biological environment in healing Achilles tendons.

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The Role of Weight-Bearing Computed Tomography Scan in Hallux Valgus

Karim Mahmoud, MD
Sreenivasulu Metikala, MD
Samir D. Mehta, MD
George W. Fryhofer, MD, MTR
Daniel C. Farber, MD

Department of Orthopaedic Surgery, Hospital of the University of Pennsylvania

Introduction

Hyperpronation of the 1st metatarsal in hallux valgus (HV) is poorly understood by conventional weightbearing radiography and is not always linked to the tibial sesamoid position.[1,2] We aimed to evaluate this parameter using weightbearing computed tomography (WBCT) and to understand its association with other standard measurements.

Methods

Retrospective evaluation of WBCT and weightbearing radiographs (WBXR) was performed for 20 patients with hallux valgus (HV) feet and 20 controls with no such deformity. Axial CT images of both groups were compared for 1st metatarsal pronation angle (α angle) and tibial sesamoid subluxation (TSS) grades (Figure 1). The hallux valgus angle (HVA), first-second intermetatarsal angle (IMA), 1st metatarsal-medial cuneiform angle (MMCA), Meary's angle, and calcaneal pitch (CP) angle of the study and control groups were compared on both WBXR and the corresponding 2D images of WBCT. All the measurements were independently studied by a dedicated musculoskeletal radiology fellow. All statistical analyses were performed in R v3.5.2.[3] Mean comparisons were made using either t-test (for normally distributed data) or Wilcox rank-sum test (for non-normal data and for subluxation grade). Univariate analysis was performed using Fisher's test. Receiver operating characteristic (ROC) curves were fit to data using the "pROC" package.[4] Example "optimal" ROC thresholds were calculated using Youden's J statistic.[5]

Results

The HV group demonstrated significantly higher values for TSS grade ($p < 0.001$) but not for α angle ($p = 0.19$) compared to controls (Table 1). Likewise, significantly elevated HVA and IMA were noted in the HV group on both imaging modalities while no such differences were observed for the CP angle and Meary's angle. On the other hand, higher MMCA in the study group was evident only on WBXR ($p = 0.009$) but not WBCT ($p = 0.076$).

Among all, the receiver operating characteristic (ROC) curves demonstrated the greatest area under curve (AUC) for HVA followed by IMA (Table 2). The a angle performed just within the range of a chance (AUC 0.64, 95% CI: 0.49 to 0.66). The Pearson's correlations of the α angle, in the HV group, revealed no significant linear relationship with TSS grades, IMA and MMCA, and only a moderate positive correlation was identified between α angle and HVA as per the WBXR ($r = 0.38$, $p = 0.014$) but not by the WBCT images ($p = 0.084$).

Discussion

The existing methods to assess sesamoid position using weightbearing AP radiograph have been found to be unreliable as they fail to capture the rotational component of HV deformity.[6-9] Previous studies utilizing true full WBCT have shown a tendency of the first metatarsal to pronate during weightbearing with a mean pronation angle of eight degrees in patients with HV, though this difference was not always statistcailly significant.[10] In our study, similar full weightbearing was practiced while taking the CT images, and we obtained a mean α angle of 18.2 degrees in the HV study group,

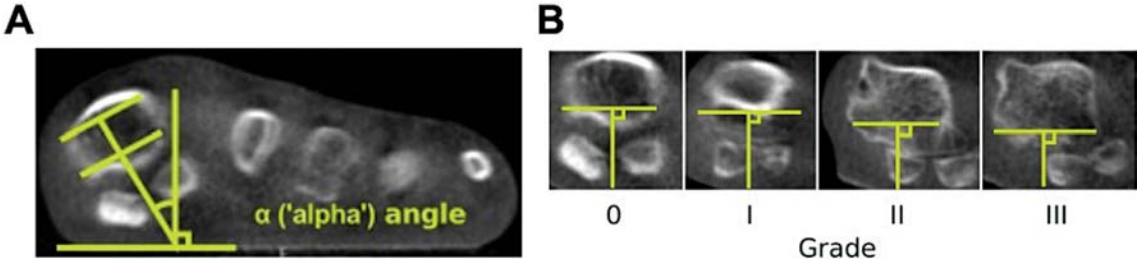

Figure 1. Parameters assessed by musculoskeletal radiologist. **(A)** Measurement of alpha angle in using weightbearing computed tomography (WBCT). **(B)** Measurement of sesamoid grade based on the location of the medial sesamoid with respect to the intersesamoid ridge. WBCT images of the hallux of the left foot are shown.

Table 1. Comparison of radiographic (XR) and computed tomography (CT) parameters in individuals without hallux valgus versus patients with known hallux valgus. P values shown were obtained by t-test, except where * indicates the use of Wilcox test for data with a non-normal distribution.

		Normal		Hallux Valgus		95% CI			P
		Mean	*(SD)*	*Mean*	*(SD)*				
α angle (deg)	CT	14.7	(7.8)	18.2	(9)	(−1.8	-	8.8)	0.19
TSS (grade)	CT	0	(0.2)	2	(1.1)	(1.4	-	2.4)	< 0.001*
HVA (deg)	*CT*	11.6	(3.8)	30	(7.4)	(14.6	-	22.2)	< 0.001
	XR	8.9	(5.2)	25.7	(7.1)	(12.8	-	20.7)	< 0.001
1-2 IMA (deg)	*CT*	10.3	(2.2)	14.9	(4.2)	(2.4	-	6.7)	< 0.001
	XR	8.2	(2.4)	11.7	(3.9)	(1.5	-	5.6)	0.003*
Meary's angle (deg)	*CT*	6.8	(5)	9.1	(8.2)	(−2	-	6.7)	0.449*
	XR	4.5	(3.5)	8.8	(7.8)	(0.4	-	8.3)	0.066*
Calcaneal pitch angle (deg)	*CT*	16.7	(7.2)	17.4	(5.1)	(−3.2	-	4.7)	0.718
	XR	16.5	(7.2)	17.2	(7.2)	(−3.9	-	5.3)	0.765
MMCA (deg)	*CT*	0.8	(0.7)	2.4	(2.7)	(0.3	-	2.9)	0.076*
	XR	0.6	(0.5)	2.5	(2.5)	(0.6	-	3)	0.009*

Table 2. Receiver operating characteristic (ROC) models were created using populations with and without a diagnosis of hallux valgus. The area under curve (AUC) value for each parameter is shown, describing how well each parameter can predict a diagnosis of hallux valgus. AUC values greater than 0.5 indicate that a parameter will predict hallux valgus better than a simple "coin flip". Optimal "threshold" values (obtained using Youden's J statistic) for each parameter are also shown, along with threshold-specific specificity and sensitivity.

	Threshold (deg)	Specificity (%) (for predicting hallux valgus)	Sensitivity (%) (for predicting hallux valgus)	AUC	AUC 95% CI		
				AUC	*95% CI*		
Hallux valgus (CT)	18.4	95	100	1	(0.98	-	1)
Hallux valgus (XR)	14.2	86	100	0.98	(0.94	-	0.98)
1st-2nd IMT (CT)	13.7	95	90	0.83	(0.87	-	0.94)
1st-2nd IMT (XR)	9.4	95	65	0.78	(0.7	-	0.83)
MMCA(XR)	2	76	75	0.74	(0.63	-	0.78)
Meary' s (XR)	1.9	100	45	0.67	(0.58	-	0.74)
MMCA(CT)	2.5	40	90	0.66	(0.5	-	0.67)
Alpha (CT)	19.2	100	40	0.64	(0.49	-	0.66)
Meary's(CT)	6.7	81	55	0.57	(0.46	-	0.64)
Calcaneal pitch (CT)	14.3	57	60	0.54	(0.39	-	0.57)
Calcaneal pitch (XR)	15.1	43	80	0.52	(0.36	-	0.54)

which was also not significantly different from controls. Moreover, nine out of 20 feet in the control group had an abnormal α angle greater than 16 degrees, suggesting that hyperpronation may be observed in non-HV feet as well. Also, the α angle performed just within the range of a simple coin flip (AUC 0.64) when measured in the ROC model, indicating its poor diagnostic ability in the diagnosis of HV deformity

There are a few limitations to this retrospective study.

First, a small sample size of study and control groups (N = 20, in each). Recruitment of larger numbers could affect the results as one might expect the normal group to trend to more normal α angle values. Secondly, the WBCT images in the control population were obtained for indications unrelated to HV condition (e.g. ankle arthritis).

Conclusions

In conclusion, our study showed that the α angle—a measure of abnormal hyperpronation of the first metatarsal —is an independent factor that may co-exist with other parameters in HV, but in isolation has limited diagnostic utility. "Abnormal" α angles may even be observed in individuals without HV deformity. An increase in the HVA, IMA, MMCA or TSS grade is not necessarily associated with a similar increase in the α angle and hence, the severity of HV deformity may not be judged on this parameter alone. The WBCT is a reliable method to assess hyperpronation and guide physicians during surgical management.

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Ultrasound Echogenicity is Associated with Fatigue Damage and Failure of Achilles Tendon in a Cadaveric Loading Model

Elaine C. Schmidt, MS
Todd J. Hullfish, BS
Kathryn O'Connor, MD
Michael W. Hast, PhD
Josh R. Baxter, PhD

Department of Orthopaedic Surgery, University of Pennsylvania, Philadelphia, PA

Introduction

Achilles tendon disorders are one of the most common conditions observed by sports medicine physicians and one of the most difficult to predict with current clinical tools.[1] One in twenty patients with tendinopathy will eventually sustain an Achilles tendon rupture.[2] Clinical diagnoses currently rely on patient-reported symptoms of pain, a reduction in ankle range of motion, and tendon swelling. However, by the time Achilles tendinopathy becomes symptomatic, many degradative changes to the tendon have already been initiated.[3] Developing clinical imaging tools sensitive enough to detect and quantify markers of Achilles tendon damage may lead to better treatment and improved outcomes for patients. Therefore, the purpose of this study was to determine whether clinical ultrasound images can be assessed with computational algorithms to detect in vitro fatigue-induced degradation of Achilles tendon mechanical properties. We hypothesized that slight alterations in mean echogenicity (ME) could be linked to changes in vitro tendon fatigue life.

Methods

Achilles tendons were harvested from 10 fresh-frozen cadaveric feet (3 matched pairs, 7 unmatched; 4M, 3F; 60 ± 15 years old). Calcanei were potted in surgical cement and tendons were cut into dog-bone shapes to ensure failure at the mid-substance. The proximal end of the tendon was secured in custom 3-D printed clamps.Tendons were tested in a 37°C circulating PBS bath and were loaded using a universal test frame (Fig 1A). To fatigue the tendon, we utilized the following cyclic loading protocol: First, 500 sinusoidal cycles were applied under load control between 10-20 MPa at 1 Hz (Fig 1B). Next, we applied 2 'stress test' loads at 0.25 Hz and acquired continuous ultrasound images at 41 Hz using an 18MHz transducer. This two-step process was repeated until tendons failed at mid-substance (Fig 1C). Using a custom MATLAB script, we analyzed the change in mean echogenicity (%ME) of ultrasound images captured during stress tests throughout testing. To determine if this echogenicity measurement differed between tendons that failed and tendons that survived the fatigue loading, we compared the two groups using an unpaired t-test ($P < 0.05$)

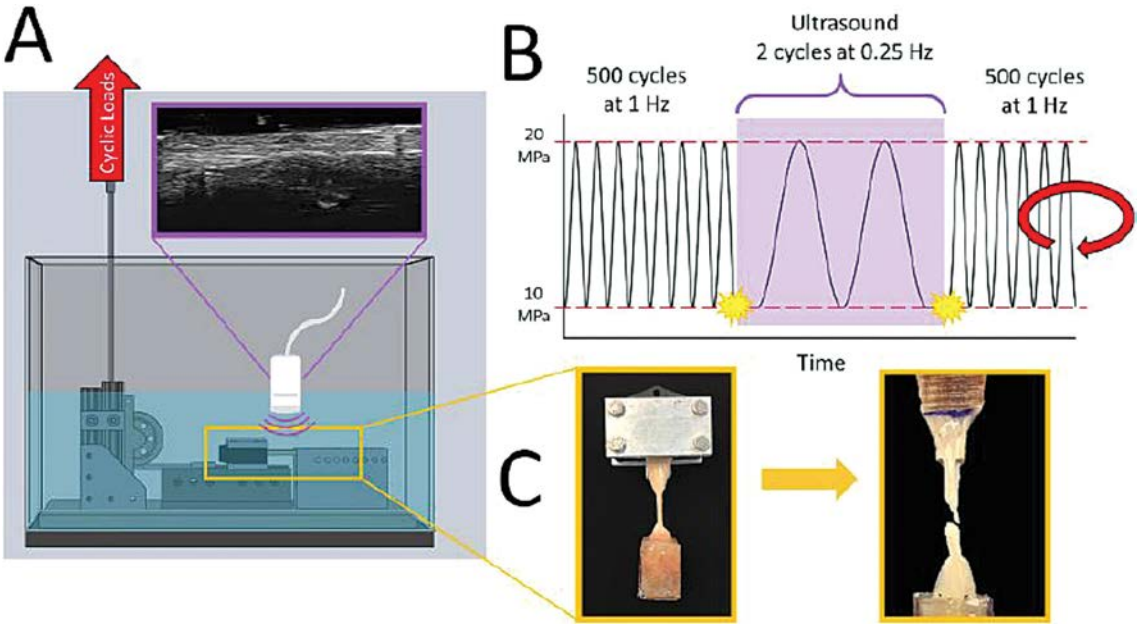

Figure 1. (A) Computer-aided representation of tank water bath testing setup, showing pulley, linear track, and tendon carriage setup. **(B)** Cyclic testing protocol applied to tendon. Ultrasound (purple) was captured every 500 cycles and initiated via a trigger signal (yellow bursts). **(C)** This protocol was repeated until tendon failure or until 150,000 cycles was achieved.

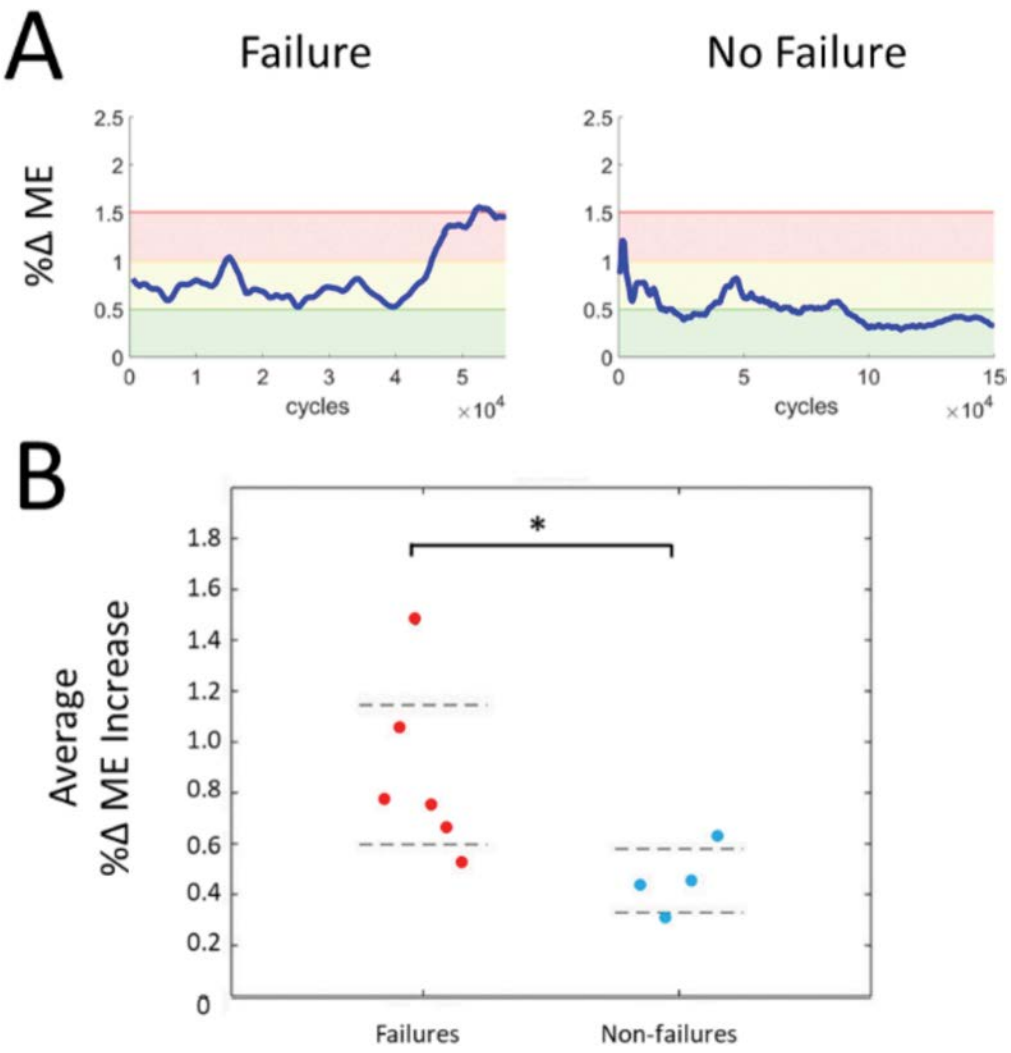

Figure 2. (A) The percent change of mean echogenicity (%ME) profile over fatigue life for a tendon that failed and a tendon that survived. **(B)** Statistical differences between the failure (red datapoints) and non-failure (blue data points) groups for average % ME (left). Dashed lines indicate 95% confidence intervals. Asterisks indicate $p < 0.005$.

Results

Of the ten tendons that were tested, six failed at the mid-substance and four did not fail after 150,000 cycles. On average, the tendons that failed did so at 12.5±1.1% strain while the tendons that survived the fatigue loading protocol underwent less strain (7.1 ± 1.6%). Tendons that did fail spent more time in the zone above 0.5 %ME and eventually surpassed 1.0 %ME(Fig 2A). Conversely, tendons that survived the fatigue loading "settled" below 0.5 %ME (Fig 2A). The average increase in %ME was greater in the tendons that failed compared to those that did not ($p = 0.031$) (Fig 2B).

Discussion

In this study we combined biomechanical loading with ultrasound imaging to assess the fatigue life behaviors of cadaveric Achilles tendons. We found that changes in mean echogenicity measurements increased under tension with increased tendon damage. Ultrasound imaging is an attractive clinical tool because it is relatively inexpensive, portable, and non-invasive. Using ultrasound to identify patients that are at risk of Achilles tendon rupture based on quantitative metrics would be a highly convenient and cost-effective way to alleviate the physical and healthcare costs of these debilitating injuries. The magnitude of change in mean echogenicity that was found in this study was relatively small (< 1.5%ME) and would not be visible to the clinician's eye. Therefore, machine learning may be the next logical direction for future work on establishing a predictive model for Achilles tendon injuries.

Significance/Clinical Relevance

Mean echogenicity is a promising marker for quantifying fatigue damage in Achilles tendons. Future work will focus on developing computer-based predictive tools to assess Achilles tendinopathy risk in physically active adults.

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Reflection: A Light in the Darkness

Andrew Summers, MD

Department of Orthopaedic Surgery
University of Pennsylvania

Three doors. Three patients. Three stories. Each encounter served as a window into understanding how powerful the art of medicine can be in the field of orthopaedic oncology.

Behind the first door, an elderly woman sits quietly. Anxious hands address a fold in her loose-fitting floral sundress. She had woken up early today, double-checked her appointment time, and headed out to one of many postoperative visits following an above the knee amputation two months prior. She brings her hand to her mouth and quickly stifles a cough. A small nuisance, she thinks little of it as she waits patiently for her surgeon.

The air was thick with worry, her face betraying her thoughts. She was afraid. The patient didn't seem to notice his entry into the small clinic room. The surgeon lightly touched her shoulder and softly spoke her name with an air of familiarity. Seeing the surgeon now, she immediately recognized the somber look on his face and grasped him by the arm, securing herself to the white coat.

With eyes closed and voice trailing she said, "It's back."

"Yes," he replied as he enveloped the patient in a long embrace.

Three words were exchanged between a long-time patient and her surgeon. They needed to say no more, as they already shared the most intimate of bonds. Their embrace wasn't just an empathetic gesture, or a social cue picked up by someone who genuinely cared for others, this embrace was different. Sadness and pain emanated from them both.

This surgeon *knew* her. He had made a connection. He had been both the original bearer of bad news and her champion of hope. He had fought and won clear margins in the operating room. He had helped her through recovery and its difficult setbacks. He cheered all of her successes, celebrating many of them with her family.

However, it was her recurrence which brought them all closer. Her strength and resolve on display as she signed consent for him to take her leg knowing full well her time was borrowed.

She wasn't a patient. She had become his friend. The twenty-minute visit went well beyond as he turned the monitor to show numerous PET-avid spots now in her lungs.

He held her hand the entire time.

We all have a persona, an identity, a unique mosaic of our likes, passions, and aspirations. It is the restoration of a patient's identity through the reconstruction of form and the renewal of function that lies at the heart of orthopaedics.

Is a person a runner if they can no longer walk? Can one say they are a climber if they have lost their ability to grip? Can one identify themselves as a musician if their instrument permanently lays silent?

"If I am no longer who I was, then who am I now?"

Through the practice of orthopaedics, many patients will not have to ask themselves this difficult and life changing question at the hands of acute injury or musculoskeletal disease.

The second door slides open silently. The unmistakable sound of an alerting ventilator cuts through the dim ICU room. A man lays in the bed grimacing, fighting the ventilator. Soon the respiratory therapists and house-staff will pull out the endotracheal tube and he will take his first of few precious remaining breaths. He has known he will die soon, that he will likely miss the birth of his first grandchild, that his life has been cut short. He fights for every moment. His orthopaedic surgeon enters the room with the ICU physicians. The patient's wife and his pregnant daughter wait outside the room, a nurse sharply draws the curtain.

It had happened a few nights prior, cleaning up after his wife had made his favorite for dinner.

Opening the plate cupboard, he lifted two dinner plates from the drying rack to put them away. The sound of the plates shattering on the tile brought his wife at a run, she found him kneeling, right arm flaccidly hanging at his side. Tears streamed down her husband's face.

On the day of surgery, he had been uncharacteristically yet understandably withdrawn. He looks up at his orthopaedic surgeon, his head covered with a blue bouffant cap. Tears forming in his eyes, the certainty that he would spend the "few months" he had left showing his wife how much he loved her was fading.

His voice breaking, he asks, "Will I ever hold my wife again?"

His orthopaedic surgeon, gently took his patients hand in his own, and smiled. His smile carried with it the knowledge of who his patient

is and the reassurance and confidence that he could make this man whole.

A simple "Yes," was all that needed to be said.

The postoperative X-ray showed a well-placed intramedullary nail that spanned an impressive pathologic midshaft humerus fracture.

The man's first word after his extubation was his wife's name. He called out to her. The curtain is flung back and he sees her like it's for the first time. He instinctively lifts his previously non-functional arm and embraces her. His daughter presses in and joins.

The nail does its job.

The third door is the hardest to open.

"Is it cancer?"

A little girl played while sitting on her mother's lap, unaware of the hyperintense lesion in her leg. The mother was panicked, uncertain and fearful of her only daughter's future, her voice cracked as she discussed the need for surgery her surgeon. He was masterful in the way he assuaged her anxiety. As he spoke, her terror began to fade and her posture relaxed. As the conversation continued, trust began to form, and then something amazing happened. She began to breathe, angst evaporating, and then she emotionally released her daughter to his care. A man she had just met. The most humbling of experiences, an honor and privilege that can only be described as a bond formed between a patient and their surgeon.

The trust that we are given is sacred—as an orthopaedic surgeon it allows us to intervene in the most invasive and decisive manner to save form, function, and even life.

To hold the limp body of a small child, someone's little girl, to blink and see my son in my arms; I have no words. I have opened up a child. I have cut deep into someone else's child. I have operated on an only child. She did not come into this world on a whim. Her parents prayed for her, they cried for her, they strived for her. A new future realized.

We made the cut, followed our approach, and exposed the mass. To see disease, to physically put my hands on it, and to remove it from this little girl was emotionally overwhelming. My mask was fogged with concentration and love for my patient.

We stop. Arms crossed maintaining sterility, we wait. Small talk. We tower over our tiny patient.

The phone rings.

"Clear margins."

Orthopaedic oncologists have the skill and knowledge to resect disease, to alter outcomes, to be able to say to another human being, "you are cancer free." Families frequently come to their clinics surrounded in darkness. Yet, perspective is everything. The lens with which we view the world is ours to choose. There is beauty in everything, even in death We have the ability to wade into the darkness with them, hold their hands, and show them there is light still.

Through my experiences I have come to believe that everything happens for a reason. Whether you call it spirituality, a belief in a higher power, or fate is irrelevant. It is what we do with the life we are given that matters most.

Being witness to these encounters, being a part of these stories, and reflecting on them throughout my training has redefined what the "art of medicine" means to me. As providers, we have the opportunity to become powerful agents of healing. Strip away the coat, medical jargon, the structural confines of our healthcare system. Sit in front of your patients and open yourself to them.

Listen. Be vulnerable. Connect. Know who your patients *are,* better than you know their disease.

It is through the process of purposefully establishing and cultivating true human connection that our work becomes meaningful. Every encounter is a precious opportunity. Don't waste them. We have the ability to act on our patients and heal them in a way that chemotherapy, antibiotics, and surgery cannot.

U·P·O·J

Orthoplastics Tips & Tricks: The Posterior Interosseous Artery Reverse Flap for Coverage of Distal Upper Extremity Defects

Agnes Z. Dardas, MD, MSc
L. Scott Levin, MD, FACS, FAOA

Introduction

First described in 1985 by Zancolli and Angrigiani at the 6th European Hand Surgery Course and published in 1986, the posterior interosseous artery flap is a regional fasciocutaneous flap from the posterior forearm that can be used to cover distal defects in the hand and fingers.[1] The vascular supply is based on reverse arterial flow from the anterior interosseous artery (AIA) to the posterior interosseous artery (PIA) via its distal anastomosis classically described 2cm proximal to the dorsal distal radioulnar joint (DRUJ). Blood supply is provided superficially via septocutaneous perforator branches. Venous drainage occurs through one or two large interconnecting venous perforators that connect to the venae comitantes of the posterior interosseous artery.[1,2] The flap centers on an axis between the lateral epicondyle of the humerus and the DRUJ.A point is marked 1cm distal to the middle of this line, marking the medial pedicle which includes the medial cutaneous branch of the PIA and venous perforator.[2] Proximally, the flap can extend up to 4 cm distal to interepicondylar line.[3,4] Distally, it can extend up to the wrist joint.[2] Originally described up to 7-8cm wide,[1] the largest reported dimensions to date have been 16cm x 10cm with respect to width[5] and 22cm x 6cm with respect to length.[6]

Indications/ Contraindications

Originally described to electively address severe adduction contractures of the thumb and dorsal hand defects, its indications have since expanded to include treating emergent traumatic hand defects,[4] volar hand defects, distal digital reconstruction,[7,8] and deep three-dimensional defects of the hand.[9]

Contraindications are mainly limited to pre-operative identification of possibly poor vascular perfusion either due to anatomic variability described below or traumatic soft tissue injury to the dorsal wrist or forearm. Cosmetically, it is contraindicated if the patient self-identifies hair growth at the recipient site as an intolerable cosmetic outcome, such as women with hairy forearms.

Advantages

This flap provides several advantages over other reconstructive options when considering distal upper extremity coverage. As a regional flap, it can be performed under a regional block as a same-day outpatient surgery. With respect to donor site morbidity, it does not sacrifice a major artery in the forearm. Furthermore, if the flap is limited to 3-4cm in width, the surgeon can close the donor site primarily.[1] For larger defects where the donor site cannot be primarily closed, a split thickness skin graft will suffice over the exposed extensor carpi ulnaris (ECU) and extensor digiti quinti (EDQ) muscle bellies. Cosmetically, it is a thin flap and requires few, if any, revision surgeries for debulking. As a fasciocutaneous flap, the fascial and cutaneous segments can be separated partially to have the fascia serve as a gliding surface for a tendon over bone or hardware or fill in deeper hand defects.[9] More recently, Jakubietz et al described use of the flap as a pure fascial flap with a split thickness skin graft for final coverage.[10]

Disadvantages

This flap is a more technically challenging dissection compared to some of the other regional alternatives as demonstrated by increased reported operative times in the literature, averaging to 2 hours 40 minutes.[11-13]

This can be further complicated by variant anatomy of the posterior interosseous artery and its distal anastomosis to the anterior interosseous artery. The PIA has been reported to be absent anywhere from 1-5.7% of the time.[2, 14, 15] However, it has been proposed that in those cases, the dorsal aspect of the forearm is supplied by the dorsal recurrent branch of the AIA and its cutaneous branches.[2] In those with a complete PIA, the distal anastomosis was found to be absent 1.5-3% of the time[14,16] and inadequate in caliber 3% of the time.[16] In one early reported case in a 29 year-old blacksmith, inadequate retrograde flow necessitated conversion to a free flap.[17] In that case, the surgical team anastomosed the proximal aspect of the PIA to the radial artery in the anatomic snuffbox and the vena comitantes of the PIA to one of the radial artery.[17] As such, pre-operative planning and proper informed consent are of the utmost importance.

Pre-Operative Assessment

As with any soft-tissue coverage planning in an elective setting, optimization of patient risk factors, such as nutrition and smoking cessation, is advised.

With respect to assessing variant arterial anatomy, a portable Doppler during the clinic visit can be used to assess the distal anastomosis and trace the perforators of the posterior interosseous artery proximally. If there is doubt, some investigators will order color Duplexes or CT arteriograms, the results of which have significantly impacted surgical plans when variant anatomy has been identified.[18,19]

Surgical Technique

The patient is placed supine on a bed with a hand table extension and is inducted under regional anesthesia. The extremity is prepped and draped in a standard fashion. A sterile Doppler can be used to confirm the distal anastomosis 2cm proximal to the DRUJ and the PIA perforators proximally. The tourniquet is inflated to 250 mm Hg with an Esmarch bandage for exanguination. Loupe magnification can be used for the procedure. The recipient site is prepared, ensuring a healthy viable soft tissue bed. The size of the defect can be traced on sterile surgical glove paper and cut out to be traced over the donor site. The dimensions of the flap should be increased 10% to account for flap thickness.

Attention is then turned to flap harvesting. A longitudinal incision from the ulnar head proximally is carried out designing a posterior interosseous flap over the middle third of the forearm centered over the axis between the lateral epicondyle and DRUJ. The skin and subcutaneous tissue are divided on the proximal aspect of the forearm over the ECU muscle. Dissection is carried down subfascially to the level of perforators to the posterior interosseous artery. An ulnar-based incision is made around the flap, with the dissection taken down to the ECU fascia from ulnar to radial, coming down on the intermuscular septum between the EDQ and the ECU, thereby identifying the perforators to the posterior interosseous artery flap. Continue dissecting on either side of the septum, laterally and medially, taking care to avoid injury to the posterior interosseous nerve fibers to the extensor compartment. Clip the proximal pedicle with double hemoclips and divide it. Continue dissecting distally to identify the perforator at the level of the ulnar head where the two arteries anastomose. The tourniquet should be let down at this point to confirm flap perfusion. The remainder skin bridge to the defect can then be incised to bring the flap over for insetting. Alternatively, the flap can be carefully tunneled subcutaneously to the recipient site but this is not recommended because tunneling can compromise venous outflow. Insetting and closure can be done in a standard fashion with post-operative immobilization type dependent on the recipient site where one would like to provide soft-tissue immobilization.

Post-Operative Care

The same institutional protocol can be followed as other regional flaps.

Complications

Partial flap necrosis has been reported to occur in 4-21% of cases, most of which do not seem to warrant treatment other than local wound care or at most a split thickness skin graft.[2, 5-8, 12, 15, 20-23] Complete flap necrosis has been reported to occur in 1-12% of cases.[2, 7, 15, 20, 22] Extensor weakness or paralysis is a rarely reported complication cited in few papers with incidences of 5-9%.[5, 7]

Case Report

To highlight the versatility of the fasciocutaneous nature of this flap and its utility in the hand, we present the case of a 40 year-old right-hand dominant police officer who presented to us with right small finger extrinsic tightness as a complication of a prior right 5th metacarpal shaft fracture treated at an outside hospital 2 years prior with open reduction internal fixation, followed by removal of hardware 6 months later, and extensor tenolysis 8 months after that. Given his deficient, contracted soft-tissue envelope over the 5th metacarpal, the decision was made to proceed with an extensor tenolysis, 5th MCP joint capsulotomy, and posterior interosseous artery reverse flap to provide adequate soft-tissue coverage. At time of insetting, given the extensive scarring over the metacarpal bone, the fascia of the PIA flap was interposed between the bone and extensor tendon to allow for a smooth gliding surface and minimize post-operative tendon adhesions (Fig 1). The patient improved dramatically with increased digital flexion, primarily due to the augmentation of the hand's soft tissue envelope with a well-vascularized soft tissue flap.

Final Considerations

In summary, the posterior interosseous artery flap can be a powerful tool in the Hand Surgeon's armamentarium in addressing distal soft-tissue defects in the volar and dorsal hand and fingers. While a technically challenging procedure, it can provide superb cosmesis to both donor and recipient sites and restore an adequate soft-tissue envelope to the recipient site while minimizing the need for future surgical interventions.

Since its original description 35 years ago, numerous variations and technical tricks have been described to tackle different problems. Many advocate raising the flap with a wide base or surrounding fibrofatty sleeve to both increase the perforating branches from the AIA and PIA and the venous/lymphatic drainage.[8, 20, 21] To increase pedicle length and allow the flap to reach more distal areas, a myriad of modifications have been recommended. Some describe carrying the dissection distally along the transverse anastomotic branch[16] or extending the pivot point to the anastomosis of the PIA to the dorsal intercarpal artery via the fifth extensor compartment artery.[24] Others have described immobilizing the wrist in extension[3] or exteriorizing the pedicle, wrapping it in a split thickness skin graft, and immobilizing in plaster with a plan to return for delayed flap sectioning.[7, 8] If there is concern for development of venous congestion, the flap can be designed with a superficial venous anastomosis.[20, 25] Lastly,

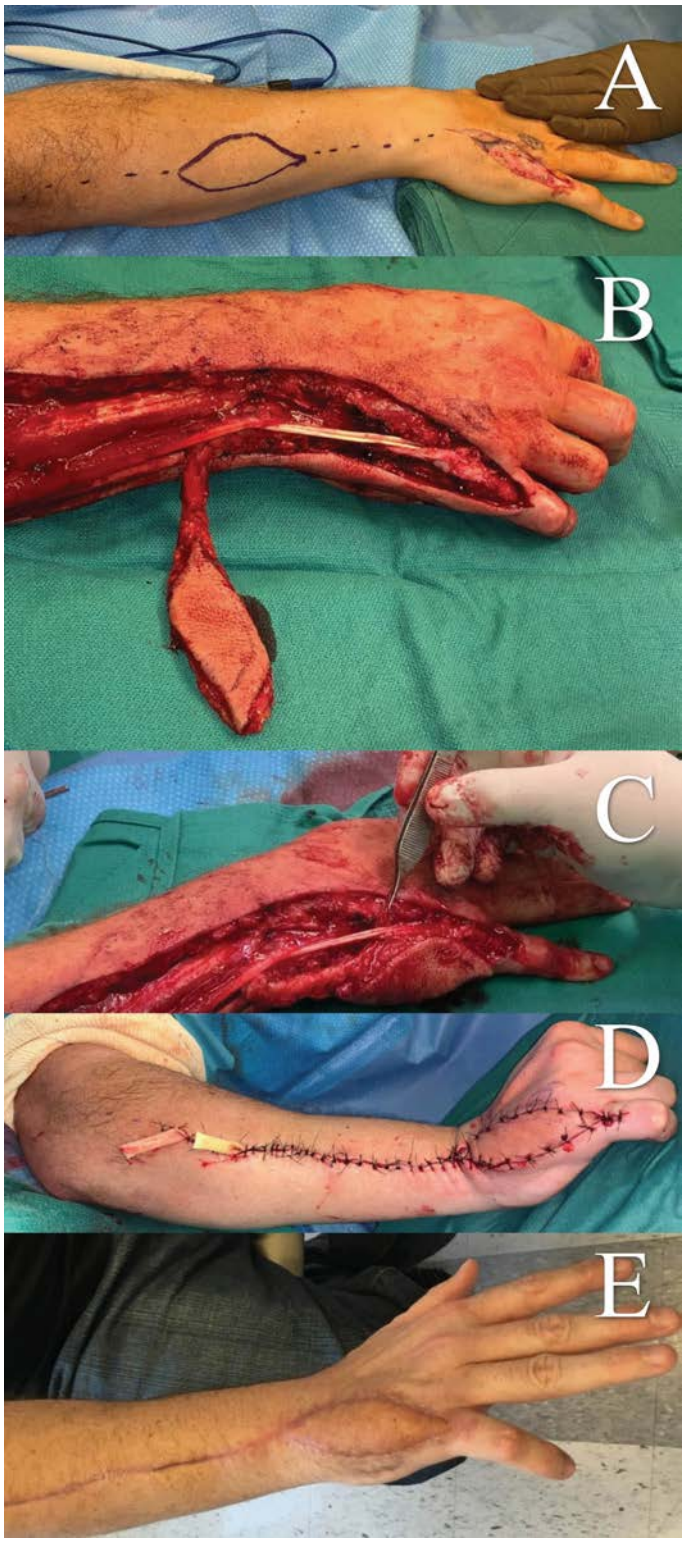

Figure 1. 40 year-old male police officer with extensive scarring of the small finger extensor tendons and dorsal overlying soft-tissue contracture. **(A)** Intra-operative marking of the flap parameters based off the dimensions of the soft-tissue defect; **(B)** Elevation of the PIA reverse flap after further recipient wound bed preparation; **(C)** Insetting the PIA reverse flap with the fascia under the extensor tendon to facilitate tendon glide and reduce post-operative tendon adhesion formation; **(D)** Cosmetic appearance and demonstration of improved small finger flexion immediately post-operatively; **(E)** 3.5 weeks post-operatively, the flap has incorporated well and the patient continues to work with Hand therapists to maintain finger flexion and prevent scar formation.

despite the best pre-operative planning, in the worst case scenario of inadequate intra-operative perfusion, this flap can be converted to a free flap with the proximal perforator as the site of anastomosis.[20]

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Single Cell Transcriptome Analysis of Aging Effect on Bone Marrow Mesenchymal Progenitors

Lutian Yao, MD[1]
Leilei Zhong, PhD[1]
Robert J. Tower, PhD[1]
Yulong Wei, MD[1]
Zhen Miao, PhD[2]
Jihwan Park, PhD[3]
Rojeshi Shrestha[3]
Luqiang Wang, MD, PhD[1]
Yulong Wei, MD[1]
Yejia Zhang, MD, PhD[1]
Katalin Susztak, MD, PhD[3]
Mingyao Li, PhD[2]
Jaimo Ahn, MD, PhD[1]
Ling Qin, PhD[1]

[1]Department of Orthopaedic Surgery University of Pennsylvania

[2]Biostatistics, Epidemiology and Informatics University of Pennsylvania

[3]Renal Electrolyte and Hypertension Division University of Pennsylvania

Introduction

Bone marrow mesenchymal lineage cells are a heterogeneous cell population involved in bone homeostasis and diseases such as osteoporosis. While it is long postulated that they originate from mesenchymal stem cells (MSCs), the true identity of MSCs and their in vivo bifurcated differentiation routes into osteoblasts and adipocytes remain poorly understood. Previously we and others reported that Td labels the entire bone marrow mesenchymal lineage cells in *Col2-Cre Rosa-tdTomato* (*Col2/Td*) mice.[1] Here, we applied large scale single cell RNA-sequencing (scRNA-seq) on sorted bone marrow Td$^+$ cells from *Col2/Td* mice at various ages to identify the subpopulations of mesenchymal progenitors and to examine the aging effects on them.

Methods

Animals

All animal work performed was approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Pennsylvania. *Col2/Td* was generated by breeding *Rosa-tdTomato* mice with *Col2-Cre* mice. α*SMA-CreER Rosa-tdTomato* (α*SMAER/Td*) was generated as described previously[2]. Mice received Tamoxifen (Tam) injections (75 mg/kg) for 2 days at 1 mo of age and bones were harvested 3 mo later.

Sorting bone marrow Td$^+$ cell for scRNA-seq-

Endosteal bone marrow cells were isolated using an enzymatic digestion method as we described previously[3] and resuspended into FACS buffer for sorting Td$^+$ cells. A total of 4 batches of single cell libraries were constructed from 1-(2 batches, n = 5), 3-(1 batch, n = 3), and 16-mo-old (1 batch, n = 3) male *Col2/Td* mice. Libraries were generated by Chromium controller (10X Genomics) and sequencing was performed on an Illumina HiSeq platform. Unsupervised clustering was conducted by Seurat and trajectory analysis was conducted by Monocle.

Whole mount immunofluorescence

Freshly dissected bones were processed for cryosections and fluorescent imaging.

Statistics

All analyses were conducted using t-tests.

Results

In all age groups, sorted Td$^+$ bone marrow cells from *Col2/Td* mice contained all the CFU-F forming cells as unsorted cells and almost all CFU-Fs were Td$^+$, suggesting that Td$^+$ cells include all bone marrow mesenchymal progenitors. Large scale scRNA-seq of those Td$^+$ cells yielded 5102, 1693, and 7066 bone marrow mesenchymal cells from 1-, 3-, and 16-mo-old mice, respectively. Seurat revealed a similar cell clustering pattern among 3 age groups (Fig. 1A). Examination of lineage-specific markers identified clusters with gene signatures of osteoblast, osteocyte, and adipocyte (Fig. 1B). In each group, pseudotemporal trajectory analysis always placed cluster 1 cells at one end while osteoblast/osteocytes and adipocytes, at the opposite ends (Fig. 1C), suggesting that cluster 1 cells are the ancestor of other mesenchymal cells and that they undergo bi-differentiation routes into osteoblasts and adipocytes. In 1 and 3 mo datasets, cluster 1-4 had gradually increased osteogenic gene expression. Thus, clusters 2 and 3 were named late MSC and mesenchymal bi-potent progenitor (MBP), respectively. Cluster 6 is lineage committed progenitor (LCP) due to its distribution around the branch point. Cell cycle analysis revealed that MSCs are quiescent among progenitors and adipocytes and osteocytes are non-proliferative (Fig. 1D). Lacking the late MSC cluster, 16 mo dataset had marked reduced

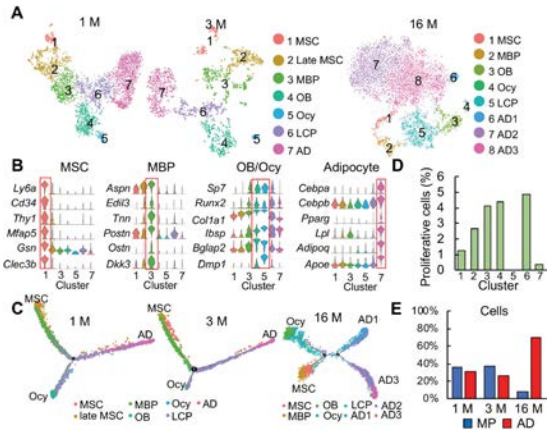

Figure 1. Single cell transcriptomics analysis of bone marrow mesenchymal lineage cells of 1-, 3-, and 16-mo old mice. **(A)** tSNE plots of 3 age datasets. **(B)** Violin plots of cluster-specific makers in 1 mo dataset. The patterns are same in the other 2 datasets. **(C)** Monocle trajectory of mesenchymal lineage cells. **(D)** The percentage of proliferative cells (S/G2/M phase) among each cluster are quantified. **(E)** The percentages of mesenchymal progenitors (MSCs, late MSCs, and MBPs) and adipocytes (ADs) are quantified

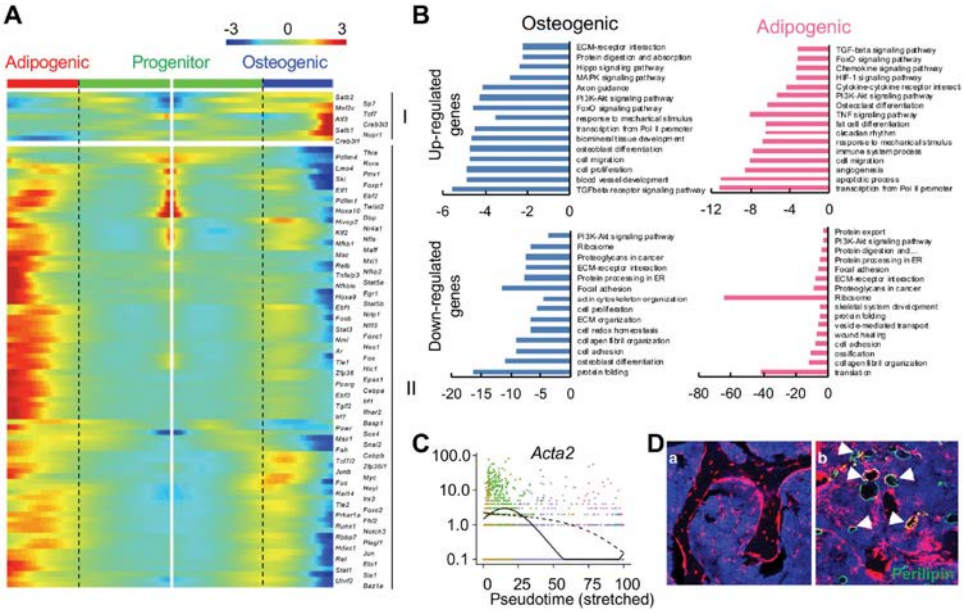

Figure 2. The bifurcated osteo- and adipo-lineage differentiation routes of in vivo bone marrow MSCs. **(A)** Pseudotemporal depiction of differentially expressed transcription factors. **(B)** GO term and KEGG pathway analyses of genes during osteogenic and adipogenic differentiation. **(C)** *Acta2* (α*SMA*) expression peaks at MBP. **(D)** In 4-mo-old α*SMAER/Td* mice, Td labels osteoblasts, osteocytes (a) and many adipocytes (b, arrows).

mesenchymal progenitors and increased adipocytes compared to young ones (Fig. 1E). Positioning individual cells along a linear pseudotimeline with MSCs as the root revealed transcription factors (TFs) differentially expressed after the branch point of osteogenic and adipogenic lineages (Fig. 2A). Consistent with its longer pseudotime, adipogenic differentiation required much more unique TFs than osteogenic differentiation, including *Pparg* and *Cebp*α. Analyzing differentiated expressed genes (DEGs) revealed that up-regulated genes are distinct for each lineage whereas there is considerable overlap between down-regulated genes. Pathway analyses of DEGs found unique and common features of osteogenic and adipogenic differentiation processes (Fig. 2B). Our seq data indicated α*SMA* as a MBP marker (Fig. 2C). This was confirmed in αSMAER/Td mice, in which Td labeled many osteoblasts, osteocytes, and bone marrow Perilipin$^+$ adipocytes (Fig. 2D). Combining all datasets generated similar clusters and pseudotime trajectory as individual ones (Fig. 3A). While MSCs and MBPs in 1- and 3-mo datasets were more centered at the starting point of pseudotime, those cells in 16 mo dataset shifted toward differentiated status, particularly the adipocyte end (Fig. 3A). Furthermore, adipocyte markers in 16-mo dataset were expressed at higher levels in mesenchymal subpopulations (MSC and MBP) than in young ones (Fig. 3B), suggesting an adipocytic drift of progenitors during aging.

Discussion

Our large scale scRNA-seq revealed the in vivo identity of MSC population, which expresses several common adult stem cell markers (Ly6a, CD34, and Thy1) but not most previously reported MSC markers, including LepR. Indeed, in our analysis, LepR is an adipocyte marker with an age-related increase in MSCs (Fig. 3C). The same pool of MSCs followed by the same hierarchy differentiation pattern is responsible for bone formation by mesenchymal lineage cells at adolescent, adult, and aging stages. During aging, MSCs are not only reduced in numbers but drifted toward more adipocyte status, which might further account for the loss of progenitor activity.

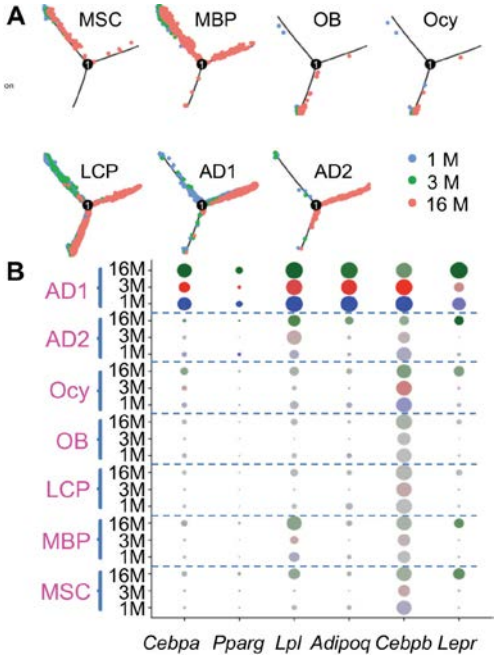

Figure 3. Aging causes an adipocytic drift of mesenchymal progenitors. **(A)** Monocle trajectory of mesenchymal lineage cells of integrated database. Cells are labeled based on age groups. **(B)** Dotplot of *Cebpa, Pparg, Lpl, Adipoq* and *Lepr* in Seurat clusters across different age groups. The circle size is proportional to the percentage of cells expressing the gene and the transparency of circle is reversely correlated with the gene expression level.

Significance

Understanding of the mechanism of in vivo bone marrow mesenchymal progenitor subpopulations and discovery of their adipocytic drift during aging will shed light in treating age-related osteoporosis.

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Identification of a Novel Adipose Lineage Cell Population that Regulates Bone Marrow Environment

Leilei Zhong, PhD[1]
Lutian Yao, MD[1]
Robert J. Tower, PhD[1]
Yulong Wei, MD[1]
Luqiang Wang, MD, PhD[1]
Yulong Wei, MD[1]
Yejia Zhang, MD, PhD[1]
Yanqing Gong, MS, PhD[2]
Fanxin Long, PhD[1]
Patrick Seale, PhD[3]
Chider Chen, PhD[4]
Jaimo Ahn, MD, PhD[1]
Ling Qin, PhD[1]

[1]Department of Orthopaedic Surgery University of Pennsylvania

[2]Division of Transnational Medicine and Human Genetics University of Pennsylvania

[3]Cell and Developmental Biology University of Pennsylvania

[4]Department of Oral and Maxillofacial Surgery University of Pennsylvania

Introduction

Bone marrow adipocytes are conventionally viewed as large cells containing unilocular lipid droplets. Originally considered as space fillers, they are now thought to be a negative regulator of osteogenesis because both adipocytes and osteoblasts are derived from bone marrow mesenchymal stem cells (MSCs). We recently applied single cell RNA-sequencing (scRNA-seq) on sorted bone marrow mesenchymal lineage cells from 1-mo-old mice that has very few marrow adipocytes. Unexpectedly, we identified a large mesenchymal subpopulation that expresses many mature adipocyte markers (*Pparg, Cebpa, Adipoq, Apoe*, and *Lpl*) but not liqid droplet-associated genes (*Perilipin* and *Fabp4*). Here, we constructed mature adipocyte-specific *Adipoq-Cre(ER) Rosa-tdTomato (Adipoq(ER)/Td)* mice to validate this novel cell population and study their actions in bone.

Methods

Animals

All animal work performed was approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Pennsylvania. *Col2/Td*, *Adipoq/Td, AdipoqER/Td* mice were obtained by crossing *Rosa-tdTomato* mice with *Col2-Cre*, *Adipoq-Cre, Adipoq-CreER* mice, respectively. *Adipoq/Td/DTR* mice were generated by breeding *Adipoq/Td* mice with *Rosa-DTR* mice. *AdipoqER/Td* mice received Tamoxifen (Tam) injections (75 mg/kg/day) at P6 and P7 and euthanized at 1 mo of age. *Adipoq/Td/DTR* mice received vehicle or diphtheria toxin (DT, 50 μg/kg) every other day for 2 wk. For focal radiation, mouse right femur received a clinically relevant radiation dose of 5 Gy using small animal radiation research platform (SARRP).

Immunofluorescence

Bones were processed for 50 μm-thick whole mount cryosections and stained with indicated antibodies.

Transplantation

Freshly FACS-sorted Td^+ cells ($5x10^4$/transplant) were mixed with Gelfoam and placed under the kidney capsule of 2-mo-old *C57Bl/6* mice. 4 wk later, mice received calcein injection (15 mg/kg) 1 day before harvesting grafts.

Statistics

All analyses were conducted using t-tests.

Results

Td labeled all $Perilipin^+$ adipocytes, many $CD45^-$ stromal cells, and pericytes, but not osteoblasts, osteocytes, and chondrocytes in 1-mo-old *Adipoq/Td* mice (Fig.1A). The majority of Td^+ cells (99.8%) did not harbor lipid droplets

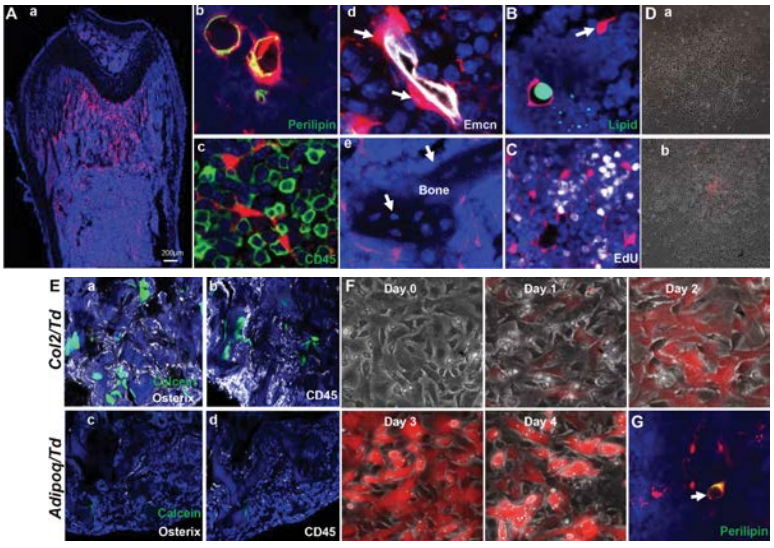

Figure 1. Mouse bone marrow contains abundant non-lipid-laden adipocytes. **(A)** In a 1-mo-old *Adipoq/Td* femur (a), Td labels $Perilipin^+$ adipocytes (b), $CD45^-$ stromal cells (c), pericytes (d), but not osteoblasts and osteocytes (e). **(B)** BODIPY lipid staining shows a Td^+ stromal cell (arrow) with no lipid. **(C)** Td^+ cells do not incorporate EdU. **(D)** all CFU-F colonies are made of Td^- cells (a) while some Td^+ cells do attach to the dish (b). **(E)** Td^+ cells from *Col2/Td* mice, but not *Adipoq- Td* mice, form bone-like structure. **(F)** In vitro adipogenic differentiation assay of Td^- mesenchymal progenitors from *Adipoq/Td* mice. The same area was imaged daily. **(G)** Bone marrow $Perilipin^+$ adipocytes are derived from non-lipid-laden Td^+ adipocytes in 1-mo-old *AdipoqER/Td* mice (Tam injections at P6, 7 when no $Perilipin^+$ cells can be detected in the bone marrow).

and none of them incorporated EdU (Fig.1B,C). Td$^+$ cells constituted ~18% of CD45$^-$Ter119$^-$ bone marrow cells. After isolation, they attached to the culture dish but did not form CFU-F colonies (Fig. 1D). While Td$^+$ cells from *Col2/Td* mice (in which Td labels mesenchymal progenitors) formed bony structure after transplantation, freshly sorted Td$^+$ cells from *Adipoq/Td* mice did not (Fig.1E), indicating that they are not mesenchymal progenitors. Upon adipogenic differentiation, Td$^-$ mesenchymal progenitors from *Adipoq/Td* mice first became Td$^+$ cells with no lipid droplets and then evolved into Td$^+$ cells with lipid (Fig. 1F). Similar cell culture results were also obtained with *AdipoqER/Td* mice. Fate mapping in postnatal *AdipoqER/Td* mice confirmed that Perilipin$^+$ lipid-laden adipocytes are derived from non-lipid-laden Td$^+$ adipocytes (Fig. 1G). In the bone marrow of young *Adipoq/Td* mice, all pericytes identified by PDGFRβ or Laminin staining in a peri-capillary location were Td$^+$ (Fig. 2A). Strikingly, using whole mount sectioning and confocal scanning, we found that bone marrow Td$^+$ stromal cells and pericytes form a 3D network made of cell processes to communicate amongst themselves and other components of bone, including vessel walls (Fig 2B). Ablating those cells in 1-mo-old *Adipoq/Td/DTR* mice after 2 wk of DT injections disrupted bone marrow vasculature and caused drastic *de novo* bone formation in the diaphyseal bone marrow (Fig. 3), suggesting that those cells function in maintaining vessel integrity and inhibiting osteogenesis. Focal radiation on long bones rapidly expanded the non-lipid-laden Td$^+$ cells at d3, accompanied with vessel dilation and a loss of Td$^+$ pericytes (Fig. 4). By d7, both vessel structure and Td$^+$ pericyte density returned to relatively normal levels. These data implied a role of Td$^+$ adipocytes in the repair and stabilization of marrow vessels after radiation injury.

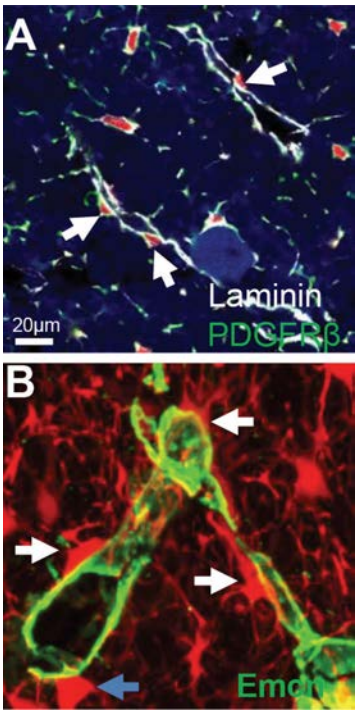

Figure 2. Non-lipid-laden Td$^+$ cells are stromal cells and pericytes forming a 3D network inside the bone marrow. **(A)** All PDGFRβ$^+$ and Laminin$^+$ cells with a pericyte morphology are Td$^+$ (arrows). **(B)** Td$^+$ stromal and pericytes are morphologically similar with many cell processes.

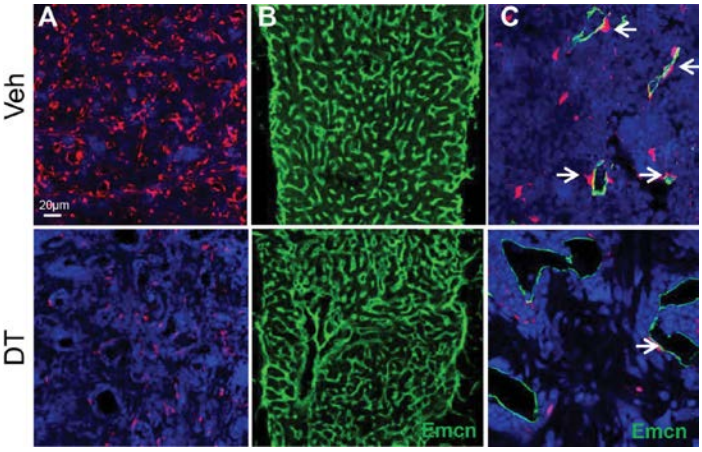

Figure 3. Ablation of adipocytes reveals their roles in maintaining vasculature and bone. **(A)** Bone marrow Td$^+$ cells in *Adipoq/Td/DTR* mice were ablated by DT. **(B)** DT altered bone marrow vessel structure. **(C)** High magnified image showed that vessels were dilated coinciding with a depletion of Td$^+$ pericytes **(D)** 3D μCT images show drastic *de novo* bone formation in femoral midshaft after DT injections.

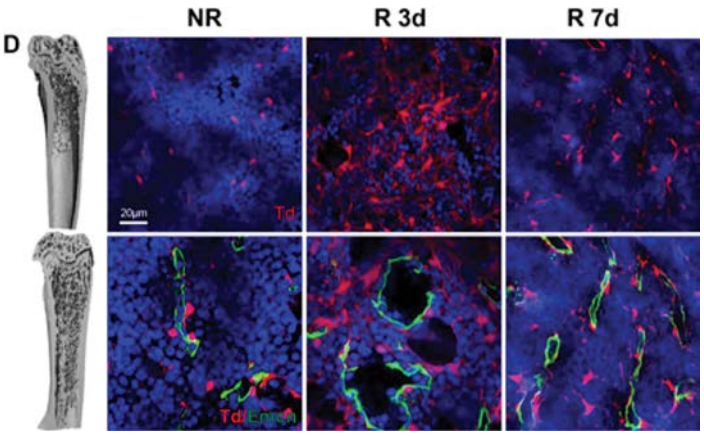

Figure 4. Adipocytes are required for the recovery of bone marrow vasculature after radiation injury. Fluorescent images of total Td$^+$ cells (top) and pericytic Td$^+$ cells (bottom) in the bone marrow of 1-mo-old *Adipoq/Td* femurs before (NR) and after (R) focal radiation (3 and 7 days).

Discussion

Our study demonstrate that bone marrow contains a large number of non-proliferative, mature adipocytes with no significant lipid stores. Those cells represent a stable transitional cell type situated after mesenchymal progenitors and before classic lipid-laden adipocytes along the adipogenic differentiate route. They are morphologically and functionally distinct from traditional adipocytes. Existing as stromal cells or pericytes, they possess numerous cell processes to form a vast 3D network structure in bone marrow. Our scRNA-seq data suggest that they express many secretory factors, including angiogenic factors. Most likely through secreting these factors into marrow environment, they play pivotal roles in maintaining marrow vasculature, suppressing osteogenic differentiation of mesenchymal progenitors, and participating into vessel repair after radiation injury. Therefore, we name them marrow environment regulating adipose cells (MERAs).

Significance

We discovered a novel type of adipose lineage cell population that regulates bone marrow environment.

Biophysical Cues Regulate Nanoscale Chromatin Organization in Mesenchymal Stem Cells

Su-Jin Heo, PhD[1]
Shreyasi Thakur, PhD[1]
Claudia Loebel, MD, PhD[1]
Peter Relich, PhD[1]
Boao Xia[1]
Jason Burdick, PhD[1]
Melike Lakadamyali, PhD[1]
Robert Mauck, PhD[1]

[1]University of Pennsylvania

Introduction

Mesenchymal stem cells (MSCs), a promising cell source for musculoskeletal therapies, are subjected to mechanical forces during regeneration and repair.[1,2] Exogenous biophysical cues, such as changing substrate stiffness (SS) and fluid-induced shear stress (FSS), can direct lineage specification via chromatin reorganization.[2,3] We recently showed that dynamic tensile loading or FSS caused rapid chromatin reorganization (within 30 min) in MSC nuclei, mediated by histone methylation (e.g. H3k27me3).[3,4] These changes in chromatin organization resulted in changes in gene expression and cell differentiation.[5] However, since the length scale of chromatin complexes in the nucleus is very small (< 100 nm), obtaining well-resolved images of their interaction using conventional microscopy remains challenging. Here, we assessed how biophysical cues (SS or FSS) altered the organization of histone-H2B (H2B) at the nanoscale in MSCs, as well as the spatial localization of specific histone modifications, using a super-resolution nanoscopy [i.e. stochastic optical reconstruction microscopy (STORM)].

Methods

Human MSCs were isolated from unprocessed human bone marrow (male, 22 years, LONZA). To investigate the effect of SS, MSCs (passage #1; 3,000 cells/cm^2) were cultured on 2 well-chambered cover glass (Glass;Stiff) or 5 kPa (soft) methacrylated hyaluronic acid hydrogels (MeHA) modified with RGD to promote cell adhesion.[6] followed by 2 days of culture in basal cell growth media. To investigate the role of the histone H3k27 methyltransferase EZH2 in chromatin reorganization, cells were treated with GSK343 (GSK, 2.5μM, Sigma) for 1 day before imaging. To investigate the effects of FSS, a custom-PDMS microfluidic chamber was developed[4] to impose FSS to MSCs seeded on a chambered cover glass (500 cells/mm^2) at different shear stress conditions (1 or 5 dyne/cm^2) and for different durations (30 min or 2 hour). After the cessation of loading, cells were immunostained for histone-H2B (H2B, Proteintech) or H3k27me3 (a mark for condensed chromatin and transcriptional inactivation, Abcam), and then incubated with secondary antibodies custom-labeled with activator-reporter dye pairs (Alexa Fluor 405-Alexa Fluor 647, Invitrogen) for STORM imaging (Nanoimager, ONI).[7] STORM images were analyzed and rendered using Nanoimager software (ONI). For quantitative analysis, Voronoi tessellation of the H2B localizations was adapted to segment super-resolution images in MATLAB[7], and heat maps based on the density of H2B localizations were generated.[8]

Results

Super-resolution images of Histone-H2B in MSC nuclei were successfully obtained, revealing the histone nanodomains, which could not be observed with conventional microscopy (Conventional, Fig. 1A). STORM images and Voronoi tessellation analysis showed that, while H2B localizations clustered to form discreet and spatially separated nanodomains in MSC nuclei on glass (Fig. 1), nuclei on soft 5kPa MeHA substrates contained smaller domains (Fig. 1 A-C). Interestingly, heat maps showing the density of H2B or H3k27me3 localizations revealed that these marks were primarily localized at nuclear periphery on soft substrates (Fig. 1D, E) with no change in the total number of H2Bs per nuclear area (not shown). However, when GSK, an inhibitor of the histone H3k27 methyltransferase EZH2, was added to MSCs seeded on soft MeHA hydrogels, the distribution and localization of H2B throughout the MSC nuclei increased (Fig. 1 F, G). Similarly, STORM imaging revealed that FSS caused marked histone H2B reorganization in MSCs (Fig. 2), depending on the magnitude or duration of FSS (Fig. 2). Voronoi cluster analysis showed that FSS increased the number of localizations per histone cluster and the cluster size (Fig. 2). FSS also increased repressive histone modifying marks (i.e., H3k27me3 localizations) in these nuclei (not shown).

Discussion

In this study, we investigated the role of biophysical cues on nanoscale chromatin reorganization in MSC nuclei using STORM imaging. Our findings showed that substrate stiffness regulates chromatin organization at the nanoscale, with stiff substrates resulting in H2B and H3k27me3 nanodomains that

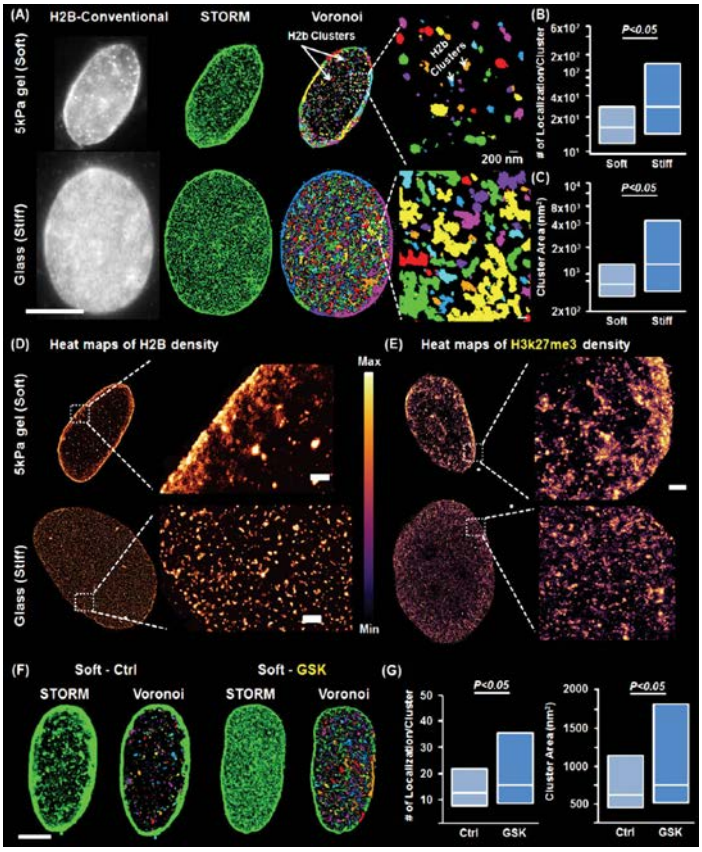

Figure 1. (A) Conventional image, STORM image, and Voronoi cluster analysis of H2B localizations in MSC nuclei on soft and stiff substrates, scale bar = 5 μm; (B and C) Quantification of the number of H2B localizations per cluster and the cluster area (n ≥ 12,345 clusters from 5 cells); (D, E) heat maps showing H2B or H3k27me3 localization density on soft and stiff substrates, scale bar = 500 nm. (F, G) STORM image, Voronoi cluster analysis, and quantifications of H2B localizations for cells on soft substrates with/without GSK treatment for 1 day (scale bar = 5 μm, n ≥ 11,227 clusters from 5 cells). The box and line correspond to the interdecile range (IDR, 10th~90th percentile) and median, respectively.

were distributed throughout the nuclei. Conversely, on soft substrates, these domains shifted to the nuclear periphery, a region in which heterochromatin dominates and methyltransferases are abundant.[9] When MSCs on these soft substrates were treated with GSK, an inhibitor of histone H3k27 methyltransferase EZH2, the localization to the nuclear periphery was prevented. This suggests that physical forces, acting through EZH2, may play an important role in nanodomain translocation to the nuclear periphery. We also noted that other physical forces, such as FSS, caused rapid histone condensation and reorganization, as well as

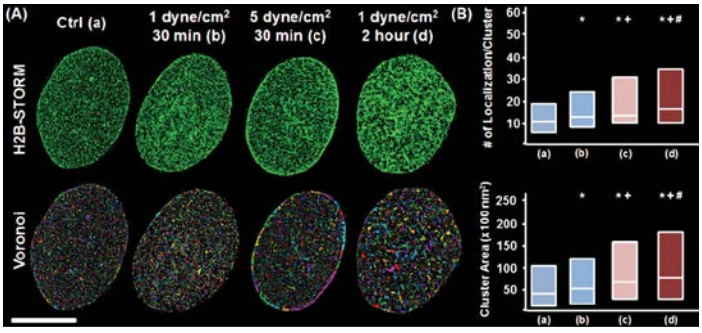

Figure 2. (A) STORM image and Voronoi cluster analysis of H2B localizations in MSC nuclei in response to FSS, scale bar = 5 μm; (B) Quantification of the number of H2B localizations per cluster and cluster area (n ≥ 10,545 clusters from 5 cells. The box and line correspond to the interdecile range (IDR, 10th~90th percentile) and median, respectively (*p<0.05 vs. a, +p<0.05 vs. b, #p<0.05 vs. c).

increases in H3k27me3. Taken together, this study suggests that biophysical perturbations regulate nanoscale chromatin spatial organization through histone methylation in MSCs. Ongoing studies are focused on elucidating how these histone reorganizations and modifications by biophysical cues act to regulate gene expression and enforce lineage specification in MSCs.

Significance

Here, we show that biophysical cues regulate chromatin organization at the nano-scale using super-resolution imaging. These studies may help to elucidate epigenetic mechanisms regulating stem cell differentiation and enhance their use in regenerative medicine applications.

Acknowledgements

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Abnormal Vascularity and Extracellular Matrix Remodeling are Associated with Impaired Secondary Ossification in Mucopolysaccharidosis VII

Zhirui Jiang PhD[1,2]
Casey P. Johnson, PhD[3]
Olli Nykänen, PhD[4]
Mikko Nissi, PhD[4,5]
Yian Khai Lau[1,2]
Meilun Wu[1,2]
Kai D. Ludwig, PhD[3]
Jutta Ellerman, MD[3]
Margret L. Casal, DVM, MS, PhD[6]
Lachlan J. Smith, PhD[1,2]

[1]Mckay Orthopedic Research Laboratory
University of Pennsylvania

[2]Department of Neurosurgery
University of Pennsylvania

[3]Department of Radiology
University of Minnesota

[4]Department of Applied Physics
University of Eastern Finland

[5]Department of Diagnostic Radiology
University of Oulu

[6]School of Veterinary Medicine
University of Pennsylvania

Introduction

Mucopolysaccharidosis VII is a genetic, lysosomal storage disease characterized by deficient beta-glucuronidase activity, which results in accumulation of poorly degraded glycosaminoglycans (GAGs) in cells and tissues.[1] MPS VII patients exhibit severe skeletal abnormalities, including dysplasia of the vertebrae and long bones. Resulting impaired mobility, pain and paralysis negatively impact quality of life.[2] Previous studies in our lab using the naturally occurring canine MPS VII model showed that formation of secondary ossification centers (SOCs) is markedly delayed in both vertebrae and long bones.[3] Conversion of cartilage to bone in SOCs is a multi-stage process that requires step-wise differentiation of chondrocytes, vascularization, cartilage matrix resorption and formation of mineralized bone matrix.[3] We showed previously that MPS VII chondrocytes in SOC epiphyseal cartilage exhibit impaired hypertrophic differentiation capacity.[4] Our objectives in the current study were to establish whether abnormal cartilage vascularity and impaired matrix resorption and mineralization also contribute to delayed SOC formation in MPS VII dogs, using novel, contrast-free MRI-based susceptibility-weight imaging (SWI)[5,6] and histological assays.

Methods

With IACUC approval, thoracic vertebrae were obtained postmortem from control (heterozygous) and MPS VII-affected dogs at 9 days-of-age.This is the age immediately preceding commencement of secondary ossification in controls.[4]

Cartilage Vascularity

Vertebrae (n = 3) were imaged on a 9.4T MRI scanner using a high-spatial-resolution (91 μm isotropic) 3D gradient echo sequence with magnetic susceptibility weighted to provide detailed visualization of epiphyseal cartilage vascularity.[5,6] Images were post-processed using a quantitative susceptibility mapping (QSM) pipeline to better visualize and quantify cartilage vessels,[5,6] Vessel density, thickness, branching and connectivity were then quantified using uCT Ray v4.0 software.

Cartilage Matrix Remodeling

For assessment of enzyme activity in epiphyseal cartilage, coronal, calcified cryosections of vertebrae (n = 5) were stained for either alkaline phosphatase (ALP, a marker of matrix mineralization) or tartrate-resistant acid phosphatase (TRAP, a marker of matrix resorption). The number of TRAP-positive chondroclasts per cartilage canal was quantified. Additional vertebrae (n = 5) were processed for paraffin immunohistochemistry, with sections stained for matrix metalloproteinase-9 (MMP-9, required for neovascularization).The number of MMP-9-positive epiphyseal chondrocytes was quantified

Statistical Analysis

Differences in quantitative metrics between control and MPS VII were established using Mann-Whitney tests ($p < 0.05$).

Results

Cartilage Vascularity

SWI and QSM were successfully applied to reveal detailed 3D renderings of vertebral epiphyseal cartilage vascularity (Figs 1A and B). While vessel thickness was similar in MPS VII compared to controls (Fig 1B), quantitative assessments revealed lower vessel density and connectivity (branching) in MPS VII vertebrae (~70% and 22% of control, respectively; Figs 1C and D), although the differences did not reach statistical significance.

Cartilage Matrix Remodeling

The number of MMP-9-positive chondrocytes was significantly lower for MPS VII (~33% of control, Fig 2).There was punctate ALP staining surrounding chondrocytes in control epiphyses; however, staining was completely absent in MPS VII (Fig 3A). Finally, the number of TRAP-positive chondroclasts per cartilage canal was a significantly lower in MPS VII (~13% of control, Figs 3B and C).

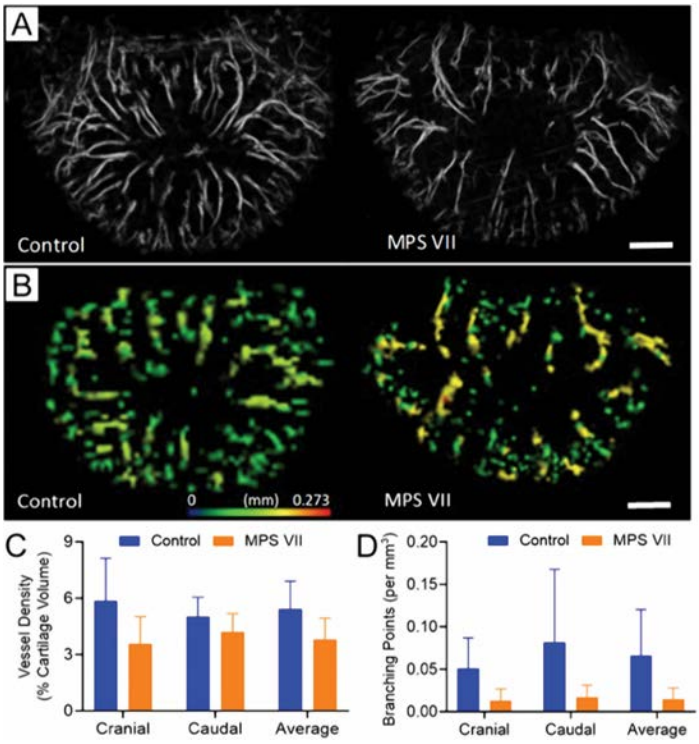

Figure 1. Analysis of vascularity in control and MPS VII dog vertebral epiphyseal cartilage using susceptibility-weighted MRI. **A.** 3D visualization of cartilage vessels (axial view). **B.** Heat map of vessel thickness. **C.** quantification of vessel density and **D.** number of branching points. Bar = 1mm

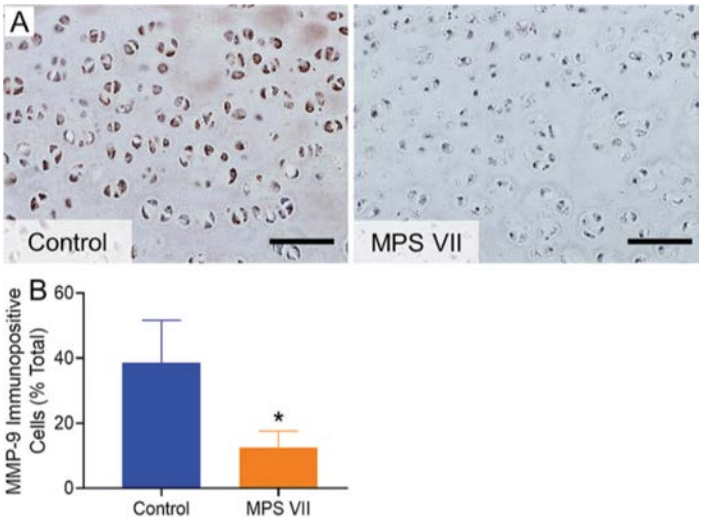

Figure 2. A. Representative MMP-9 immunostaining of control an d MPS VII epiphyseal chondrocytes. **B.** quantification of percent MMP-9 immuno-positive cells. *p<0.05 vs control. Bar = 100μ

Discussion

Vascularization and matrix remodeling are critical for effective cartilage-bone conversion during the process of endochondral ossification. We successfully applied novel, contrast-free SWI and QSM MRI-based techniques for detailed visualization of vascularity in canine vertebral epiphyseal cartilage. Preliminary findings suggest that vessel density and architecture may be abnormal in MPS VII, but this should be confirmed through analysis of additional samples and at additional skeletal sites. The lower number of MMP-9-positive chondrocytes in MPS VII supports our previous mRNA results,[8] and suggests impaired cartilage neovascularization, while altered TRAP and ALP expression likely reflect the diminished matrix resorption and mineralization capacity, respectively, of MPS VII cartilage cells. Ongoing studies seek to establish the molecular mechanisms linking lysosomal storage and GAG accumulation to altered cartilage vascularization and matrix remodeling, with the long term goal of developing improved therapies to normalize bone formation in MPS VII patients.

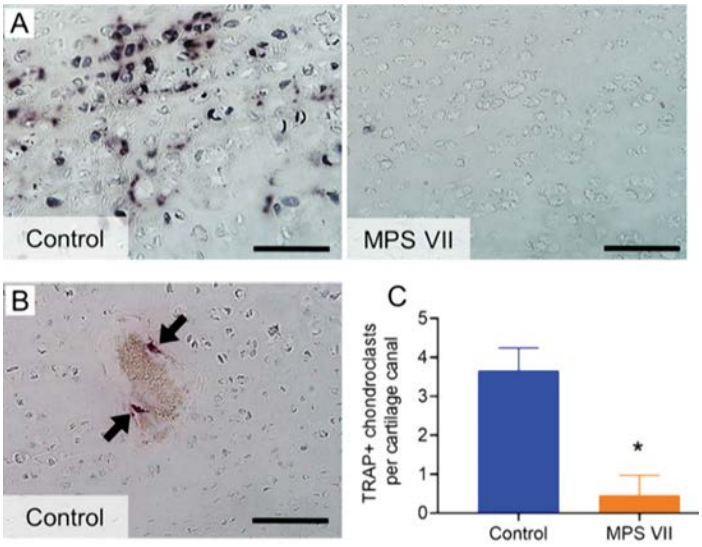

Figure 3. Impaired matrix turnover and mineralization in MPS VII epiphyseal cartilage. **A.** ALP staining is present in controls but absent in MPS VII cartilage. **B.** TRAP-positive chondroclasts (arrows) in a cartilage canal of a control. **C.** Number of TRAP-positive chondroclasts per cartilage canal. (*p<0.05 vs control). Bar = 100 μ

Significance

MPS VII patients exhibit crippling skeletal deformities for which there are no effective treatments. In this study we provide novel insights into the mechanisms underlying impaired bone formation in MPS VII using a clinically-relevant large animal model.

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Cellular pathogenesis in mucopolysaccharidosis dogs at the onset of postnatal growth

Zhirui Jiang, PhD[1,2]
Yian Khai Lau[1,2]
Margret L. Casal, PhD[3]
Lachlan J. Smith, PhD[1,2]

[1]McKay Orthopaedic Laboratory, University of Pennsylvania

[2]Department of Neurosurgery, University of Pennsylvania

[3]School of Veterinary Medicine University of Pennsylvania

Introduction

The mucopolysaccharidoses are a family of inherited lysosomal storage disorders caused by deficiencies of enzymes that degrade glycosaminoglycans (GAGs).[1] GAGs accumulate in cells and tissues resulting in multi-organ manifestations. Progressive skeletal abnormalities, including kyphoscoliosis and joint dysplasia, are hallmarks of most subtypes including MPS I (alpha-L-iduronidase deficiency) and VII (beta-glucuronidase deficiency). In previous work using naturally-occurring canine models of these diseases, we showed that both MPS I and VII dogs exhibit failures of endochondral ossification during postnatal growth, including delayed cartilage-bone conversion in secondary ossification centers,[2-4] and low bone volume and mineral density in primary ossification centers.[4] The underlying cellular basis of these abnormalities remains poorly understood. The objective of this study was to conduct an ultrastructural examination of lysosomal storage and quantify pathological changes to other organelles across different skeletal cell types in MPS I and VII dogs at the onset of postnatal growth.

Methods

With IACUC approval, vertebral bodies were obtained postmortem from 9-day-old normal (control), MPS I and MPS VII-affected dogs (each n = 5), fixed in glutaraldehyde/paraformaldehyde overnight and decalcified. Samples were post-fixed in 2% osmium tetroxide prior to *en bloc* staining with 2% uranyl acetate. Thin (80nm) sections were stained with uranyl acetate and lead citrate and imaged using transmission electron microscopy (TEM; JEOL JEM-1010). Ultrastructural analyses were performed for resting, proliferating and hypertrophic growth plate chondrocytes (RC, PC and HC, respectively), and osteoblasts (OB) and osteocytes (OCY) in primary ossification centers. The following parameters were measured using ImageJ software: cell area occupied by vacuoles (lysosomal storage, %), rough endoplasmic reticulum (ER) lumen diameter, and number of mitochondria and Golgi. For each sample, measurements were performed for 3 cells of each type, with results averaged prior to statistics. Detection of apoptotic cells was carried out on paraffin sections from thoracic vertebrae using in situ cell death (TUNEL assay) detection kit (Sigma, USA) following manufacture's instruction. Statistical differences were established via ANOVA with pairwise post-hoc Tukey's tests ($p < 0.05$).

Results

All skeletal cell types examined from MPS VII vertebrae exhibited significantly elevated lysosomal storage (vacuoles as a percent of cell area) compared to control cells (Figs. 1 and 2). Storage was greatest and most striking for MPS VII osteocytes, occupying ~ 50% of the total cell area. Storage was also elevated in MPS I compared to control, but did not reach significance for any cell type. Rough ER lumen were significantly dilated for MPS I resting chondrocytes compared to both control and MPS VII (Figs. 3A and B). Rough ER lumen were also dilated in MPS VII resting chondrocytes, but not significantly compared to control. There were no significant differences in ER lumen diameter between groups for other cell types. There was elevated TUNEL staining in MPS VII epiphyseal cartilage compared to controls, indicating increased apoptosis of resting chondrocytes secondary to storage (Fig. 3C). There were no significant differences in the number of mitochondria or Golgi between groups for any cell type.

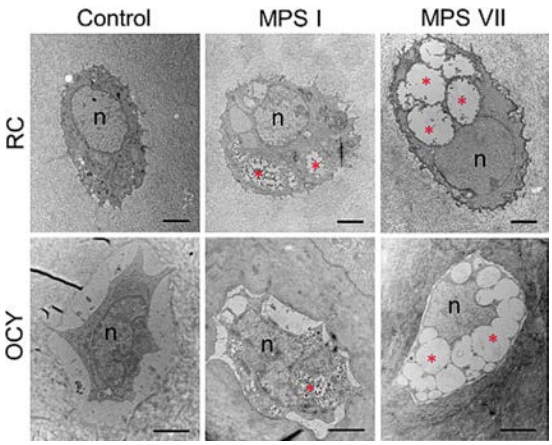

Figure 1. TEM of resting chondrocytes (RC) and osteocytes (OCY) in the vertebrae of 9-day-old control, and MPS I and VII-affected dogs. Bar =2μm. Asterisks = vacuoles (lysosomal storage); n=nucleus

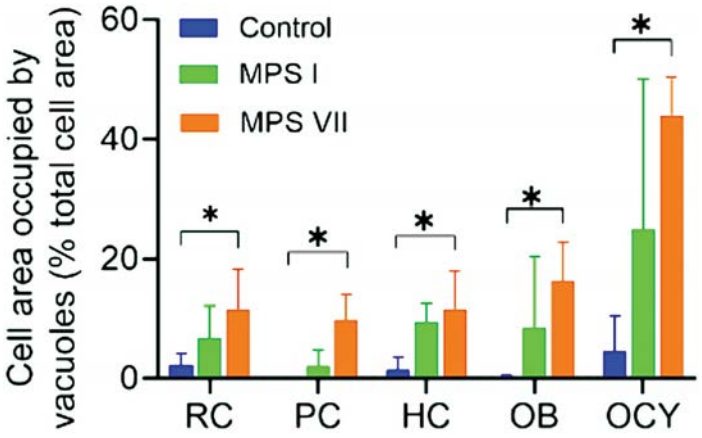

Figure 2. Relative lysosomal storage (cell area occupied by vacuoles) in resting (RC), proliferating (PC) and hypertrophic (HC) chondrocytes, osteoblasts (OB) and osteocytes (OCY) of 9-day-old control, and MPS I and VII affected dogs. *p < 0.05 vs control.

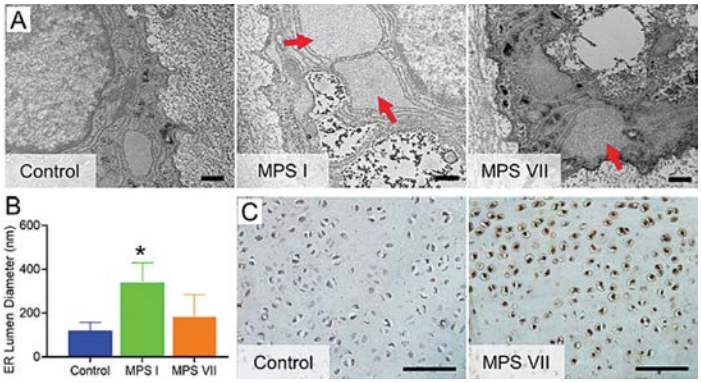

Figure 3. A. Representative images showing dilated rough ER lumen (arrows) in resting chondrocytes of 9-day-old MPS I and VII dog vertebrae. Bars = 500 nm. **B.** Quantification of rough ER limen diameter; * p < 0.05 vs control and MPS VII. **C.** TUNEL staining showing elevated numbers of apoptotic resting chondrocytes in MPX VII vertebral epiphyseal cartilage. Bars = 100μ.

Discussion

Abnormal development of the vertebrae and long bones is a hallmark of skeletal disease in MPS patients; however, the underlying cellular mechanisms remain poorly understood. In general, skeletal manifestations are more severe in MPS VII compared to MPS I. In the current study we showed that both bone and cartilage cells from MPS VII dog vertebrae exhibit significantly elevated lysosomal storage from early in postnatal life. Storage in chondrocytes may impair proliferation and differentiation ability, contributing to delayed epiphyseal cartilage-bone conversion and longitudinal bone growth. Storage in osteoblasts and osteocytes likely negatively impacts bone formation and turnover. Interestingly, storage was greatest in MPS VII osteocytes, potential reflecting the relative age of these cells. Once entombed within the bone matrix, osteocytes are relatively inaccessible to exogenous drugs, which may in part explain why bone disease is recalcitrant to treatments such as enzyme replacement therapy. Rough ER dilation (highest for MPS I resting chondrocytes) is a marker of ER stress and may negatively impact protein synthesis and cell health. In conclusion, these results highlight the importance of very early diagnosis and intervention for preventing the progression of skeletal manifestations of MPS, and the need for new therapies that effectively target skeletal cells that reside in dense, avascular microenvironments.

Significance

MPS patients exhibit severe skeletal disease for which there are currently no effective treatments. The results of this study provide insights into how storage differentially effects major skeletal cell types, and highlights the need for early and target delivery of therapeutic agents to these cells to prevent progression of crippling skeletal deformities.

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An Adaptable CT-Derived 3D-Printed Alignment Fixture Minimizes Errors in Whole-Bone Biomechanical Testing

Jordan V. Inacio[1]
Danielle M. Cristino, PhD[2]
Michael W. Hast, PhD[2]
Hannah L. Dailey, PhD[1]

[1]Lehigh University

[2]Biedermann Lab Orthopaedic Research
University of Pennsylvania

Introduction

Benchtop cadaveric biomechanical testing represents the gold standard for evaluating mechanical properties of bone and developing orthopaedic implants. Virtual tests (i.e. finite element models) can be used for the same purposes, but the validation of such models is critical to their utility. When validating virtual models with physical experiment data, most test configuration parameters (e.g. specimen geometry, applied loads, loading rates, etc.) are well documented and controlled. It is known that differences in specimen alignment during physical testing can introduce unwanted variability in comparative outcome measures, yet standardized alignment methodologies are not well documented. Therefore, the objective of this preliminary study was to design and test the functionality of an adaptive potting fixture that produces precise specimen alignment. This was accomplished using specimen-specific 3D computed tomography (CT) scans of human radii bones. The hypothesis was that accurate specimen alignment using this novel tool would improve the agreement between physical and virtual mechanical tests, while malalignment would introduce errors in the comparison between virtual and physical tests.

Methods

Six radii from 3 donors (1 male, 2 females; 83-89 y.o.) underwent clinical CT scanning in a Siemens Somatom Definition Edge scanner (Siemens Healthcare GmbH; Erlangen, Germany). An axial slice thickness of 0.5 mm was used and a bone density calibration phantom (QRM-BDC/6; QRM GmbH) was included in all scans. 3-D renderings of the radii were segmented using Mimics Innovation Suite v21.0 (Materialise Inc.) (see Fig. 1a-b). The following virtual realignment protocol was used to ensure identical orientation of all models: First, the 3-D location of anatomic landmarks (articular surfaces, styloid process) were defined and a coordinate system was created and aligned with the mechanical axis of the test frame (Fig. 1c). Next, the proximal and distal portions of each radius model were cropped at a depth equal to the widest portion of the distal end. This step was performed to ensure potted bone was not included in the simulations (see Fig. 1d). Tetrahedral meshes were added to each model, and element-specific material properties were assigned by converting radiodensity ρHU (HU) to bone mineral density ρQCT (mgHA/cm3) using the phantom calibration data (see Figure 1.) Finally, Young's modulus was assigned on a voxel-by-voxel basis, using a published density-modulus equation.[1] The aligned virtual models were used to create the specimen specific 3D-printed holders. Specifically, negative molds of mid-shaft geometries were created (Fig 2b), and custom clamps held the bone in place as they were potted in urethane (Master Dyna-Cast, Freeman Manufacturing and Supply, Mount Joy, PA) (Fig. 2c). During testing, both the physical specimens and the virtual models were subjected to controlled axial compressions of 100 N and torsions up to ± 1.5 N-m (physical) or ± 5 deg (virtual remote displacement with calculated moment reaction). Physical testing was conducted on a universal testing frame (TA Electro-Force 3550; Eden Prairie, Minnesota) equipped with a 1,110 N/14.1 N-m load/torque cell. Virtual mechanical testing was carried out in ANSYS Workbench Mechanical (ANSYS Inc.). All virtual models were also tested with deliberate malalignments created by introducing a shift of 13 mm (~ 0.5 in) anterior, posterior, medial, and lateral to the intended aligned axis. In all cases, axial stiffness [N/mm] and torsional rigidity [N-m2/deg] were calculated and compared between physical and virtual models.

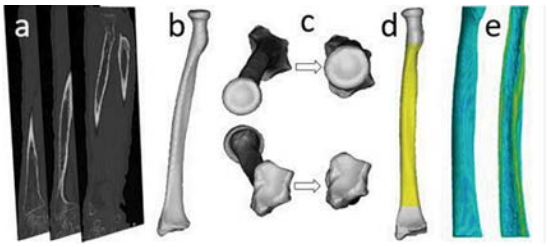

Figure 1. The workflow followed to prepare each radius model for finite element analysis: (a) CT scan image stack (b) Segmented radius (c) Alignment protocol (d) Cropping protocol (e) Element specific material properties assigned (solid body/section view)

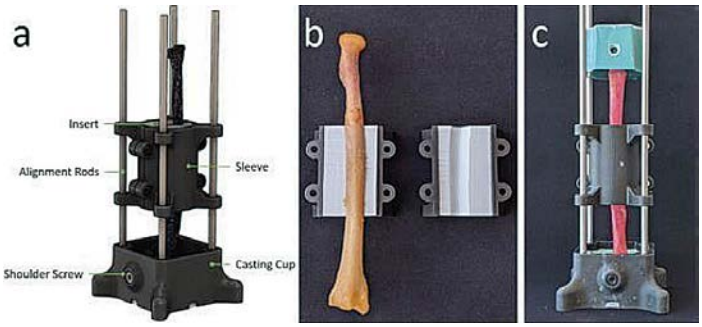

Figure 2. (a) 3D model of the radius alignment fixture indicating critical fixture components. (b) Patient-specific 3D-printed insert positions radius in the same orientation as in the virtual model. (c) Radius alignment fixture with an aligned cadaver radius fully potted.

Results

For all six radii tested with identical specimen alignments achieved through the use of the CT-based 3D-printed fixture, a strong and statistically significant correlation between the physical and virtual test results was observed (axial stiffness: $R2 = 0.756$, $p = 0.031$, torsional rigidity: $R2 = 0.986$, $p < 0.001$). The physical samples could only be potted once, so for comparison, deliberate malalignment was introduced into the virtual models for all specimens. Comparing these anterior, posterior, medial, and lateral offsets to the perfectly aligned scenario resulted in 39.2%, 16.8%, 18.8%, and 48.1% average percent errors, respectively, in the axial loading condition (see Fig. 3). The off-centered torsional loading conditions resulted in 1.8%, 1.0%, 1.7%, and 1.4% average percent errors, respectively.

Discussion

As hypothesized, small specimen malalignments of 13 mm between the intended aligned axis and machine test axis caused significant errors in measured axial stiffness of the virtual bone models. Torsional rigidity measures had higher correlations to physical test results and were robust to deviations from ideal alignment, with errors less than 2% in all directions. This suggests that, whenever appropriate, torsion tests should be used preferentially as a summary mechanical measure, or as a supplement to axial compressive tests. When more challenging modes of loading are required, pretest clinical-resolution CT scanning can be effectively used to create potting fixtures that allow for precise specimen alignment. In some applications, this may be important for increasing the correlation and reducing the error between physical and virtual mechanical tests.

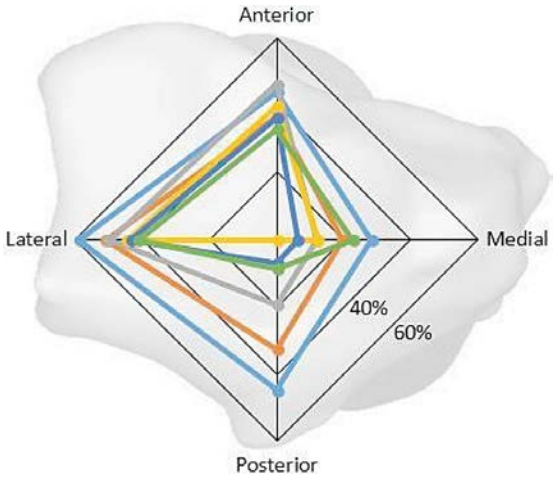

Figure 3. Distal-to-proximal view of an aligned radius. Radar chart illustrates the average percent error relative to the aligned condition for all six radii virtually tested under malaligned conditions. Axial stiffness was highly sensitive to malalignment, whereas torsional rigidity was not.

Clinical Relevance

CT scans are increasingly being used to assess bone quality in biomechanical research. Opportunistic use of these scans together with additive manufacturing techniques allows for fabrication of adaptable specimen potting jigs that guarantee the desired sample alignment and reduce omechanical testing errors from alignment artifacts. This may be particularly important for more sensitive biomechanical tests (e.g. axial compressive tests) that may be needed for industrial applications, such as implant design.

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Dynamic Changes in the Porcine Meniscus and Articular Cartilage After Meniscal Injury

Sonia Bansal, BA[1,2]
Liane M Miller, MD[1,2]
Jay M Patel, PhD[1,2]
Kamiel S Saleh, BA[1,2]
Brendan D Stoeckl, MSE[1,2]
Dawn M Elliott, PhD[3]
Michael W Hast, PhD[4]
Miltiadis H Zgonis, MD[1,2]
Robert L Mauck, PhD[1,2]

[1]McKay Orthopaedic Research Laboratory
University of Pennsylvania
Philadelphia, PA

[2]Translational Musculoskeletal
Research Center
Philadelphia VA Medical Center
Philadelphia, PA

[3]Multi-Scale Fiber-Reinforced Tissue
Biomechanics Laboratory
University of Delaware
Newark, DE

[4]Biedermann Laboratory for
Orthopaedic Research
University of Pennsylvania
Philadelphia, PA

Introduction

The meniscus is an integral load-bearing tissue in the knee[1] that is commonly injured.[2] The functional role of the meniscus has been widely studied in small animal models in service of understanding controlled joint degradation after meniscus destabilization.[3] However, these studies focus primarily on the cartilage and joint rather than on the impact of injury on the meniscus itself due to the small size of the rodent meniscus. A number of studies suggest, however, that even smaller injuries may have long term deleterious effects on the joint, as is evidenced by the early onset of OA in humans with small excisions of meniscus tissue to treat tears in the inner zone.[4,5] While post-injury joint degeneration is an established clinical problem, progression of disease in the meniscus itself is not well studied. In previous work, we evaluated the short-term (one month) effects of arthroscopic meniscus injury in a Yucatan minipig model on whole joint, meniscus, and cartilage mechanics, and on meniscus and cartilage histopathology. That study indicated that destabilization of the medial meniscus (DMM) via detachment of the anterior horn led to altered transfer of load across the tibial plateau, decreased cartilage mechanics, and a loss of proteoglycans in both the cartilage and the meniscus at this early time point. Conversely, a longitudinal vertical defect, which maintains meniscus-mediated load transfer in the knee, resulted in few changes in any of these quantitative outcomes. Here, we evaluated the longer term (three and six month) outcomes of these meniscal injuries in order to evaluate the progression of multiscale changes of the meniscus and joint.

Methods

Surgical experimental design

Juvenile (6 month old) Yucatan minipigs underwent bilateral arthroscopic surgery and each limb received one of the following injuries to the medial meniscus: sham, DMM via complete transection of the anterior attachment, or a vertical longitudinal tear (1/5 arc length, red-white zone, n = 5-7/group/time point). Animals were euthanized at one, three, or six months following surgery, and joints were harvested for a series of macro-, meso-, and micro-scale analyses.

Macroscopic load transfer and joint degeneration

In macro-scale tests, intact joints were compressed to 1x body weight (400 N) at a flexion angle of 45° using a custom rig and universal test frame. Thin film pressure sensors (TekScan #6900-110) were inserted into the joint to measure load transfer through the medial compartment.[6] Next, joints were assessed for macroscopic changes to the meniscus and for cartilage wear (using India ink).

Meniscus mechanics and ECM remodeling

Subsequently, medial menisci were harvested and sectioned (350 micron thickness in the horizontal plane within the body) and trimmed to a dog bone shape for mechanical tensile testing (tensile ramp to failure, 0.1% strain/sec). Menisci were also sectioned (16 micron thickness, vertical plane in the anterior and posterior horns) for histological analysis of proteoglycans (PGs, Safranin O/Fast Green).

Osteochondral evaluation

Osteochondral segments from the medial tibial plateau were isolated and indented using a spherical indenter (2 mm diameter) to determine cartilage mechanical properties in the regions covered by the meniscus and cartilage.[7] Next, microCT analysis of the subchondral bone was performed. Samples were then decalcified, embedded, sectioned, and stained for PGs (Safranin O/Fast Green).[8] Sections were graded using the OARSI scoring method[9] by five blinded observers (scale: 0-25, best to worst).

Results

Macroscopic load transfer and joint degeneration

When joint-level mechanics were assessed, DMM-treated joints showed an increase in peak contact pressure and decreased contact area on the tibial plateau compared to Sham and Vertical samples at one month. This effect did not persist to three or six months (Fig. 1). in sham-operated joints, menisci showed no macroscopic evidence of degeneration at any time point. However, DMM-treated joints showed evidence of degeneration at each time point, with anterior fibrovascular scars forming at the injury site

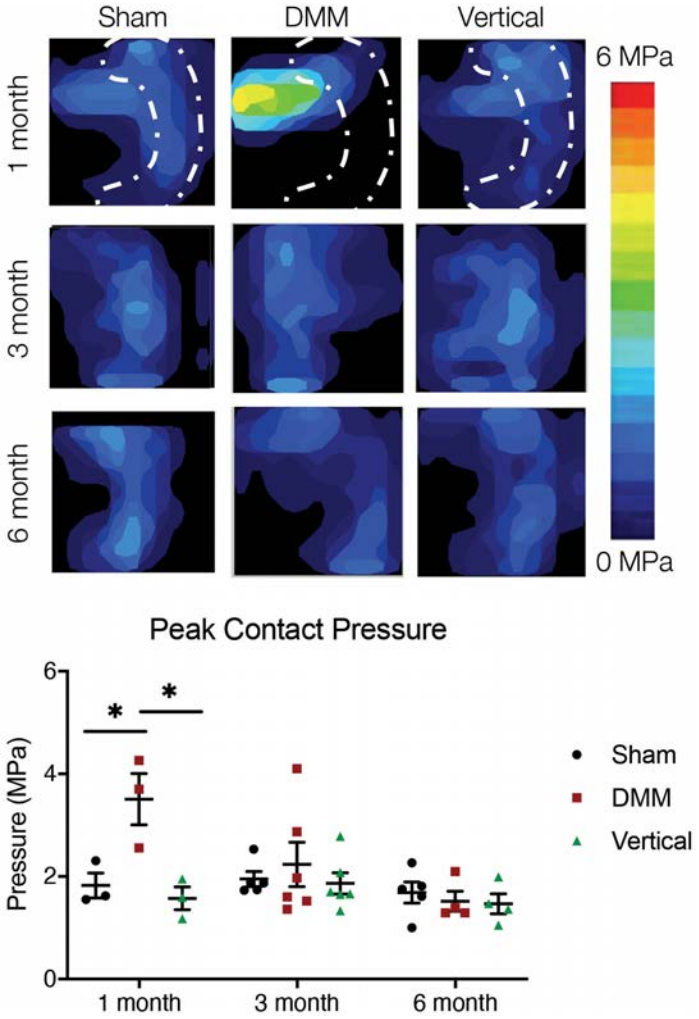

Figure 1. Contact pressure maps (top) and quantification of peak contact pressure.

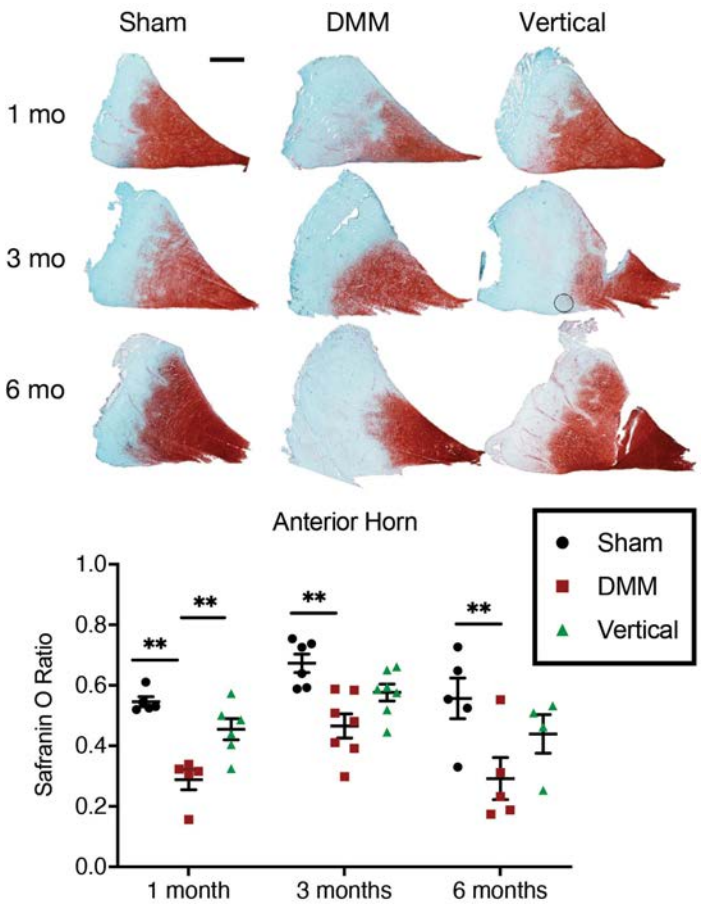

Figure 2. Safranin-O/Fast Green histology of the anterior horn of the meniscus (scale = 2 mm, top) and quantification.

in most samples at all time points and meniscal narrowing present at both 3 and 6 months. Vertical tears were visible in the majority of samples at 3 and 6 months; this did not result in marked degeneration of the cartilage surfaces (data not shown).

Meniscus mechanics and ECM remodeling

Bulk tensile mechanics were not significantly different across treatment groups at each time point (data not shown). However, DMM-treated menisci had less intense staining for PGs compared to sham-operated menisci at one month, and this was sustained through to both three and six months. Menisci subjected to a vertical tear did not show a decrease in staining compared to sham at six months though the tear was visible at three and six months (Fig. 2).

Osteochondral evaluation

While there were no changes to subchondral bone (not shown), cartilage indentation modulus in the cartilage-meniscus contact region decreased in DMM operated joints at one month and continued through three months. Interestingly, joints in which menisci were subjected to a vertical tear showed no change in cartilage mechanics at 1 month, but a decrease in indentation modulus at 3 months. These detrimental changes resolved by 6 months in both treatment groups (**Fig. 3**). OARSI scoring significantly increased, indicating osteoarthritic changes, in DMM joints at one month. This effect was somewhat attenuated, but remained significantly elevated, at three months. Vertical tears did not result in a change in OARSI scoring at either time point (data not shown)

Discussion

This study investigated meniscal and joint remodeling in a minimally invasive (arthroscopic) large animal surgical model of meniscus injury. Interestingly, we found that load transfer through the meniscus was significantly altered at 1 month post-DMM, but that this had returned to sham levels by 3 and 6 months. This was potentially due to a wide, fibrovascular scar tissue noted at the site of detachment, which had developed at 1 month and matured by 3 months to restore load transmission. The effects of DMM-injury and early unloading caused a transient decrease in cartilage mechanics in the tibial cartilage, as well as increased cartilage histopathology scores at 3 months. Interestingly, the meniscus showed sustained and worsening loss of proteoglycan content after injury in DMM menisci and in menisci subjected to vertical tears at

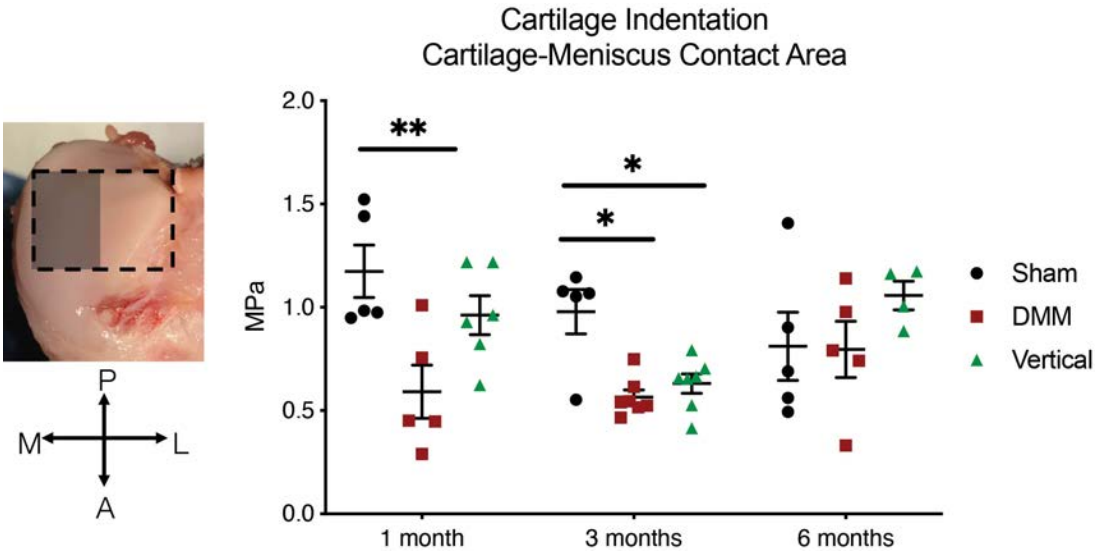

Figure 3. Cartilage-Meniscus contact area and cartilage indentation modulus in this region.

6 months. This may indicate a dynamic remodeling process, wherein the healing of the severed meniscal attachment in the DMM group restored load transfer and slowed the rate of joint degeneration compared to sustained degenerative changes in the meniscus. Current work is investigating a wider range of outcome measures of cartilage and meniscal post-injury remodeling in these animals to determine the scope of these changes. Understanding the progression of joint disease after meniscal injury in this large animal model may improve surgical decision making and inform novel repair strategies to combat osteoarthritis after meniscal tear.

Acknowledgments

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Fabrication of Integrated Multi-Phasic MSC-Laden Composite Scaffolds for Osteochondral Repair

George W Fryhofer, MD, MTR[1,2]
Hannah M Zlotnick, BS[1,2,3]
Brendan D Stoeckl, MSE[1,2]
Megan J Farrell, PhD[1,2,3]
David R Steinberg, MD[1,2]
Robert L Mauck, PhD[1,2,3]

[1]Dept. of Orthopaedic Surgery
University of Pennsylvania
Philadelphia, PA, USA

[2]Translational Musculoskeletal Research Center
Philadelphia VA Medical Center
Philadelphia, PA, USA,

[3]Dept. of Bioengineering
University of Pennsylvania
Philadelphia, PA, USA

Introduction

Osteoarthritis (OA) is the most common degenerative joint condition in the United States.[1] In addition to OA in older patients that often requires total joint replacement, full thickness cartilage defects are present in the knees of as many as 36% of younger athletes.[2] While some biologic joint-sparing treatments do exist, their efficacy and long term durability in large defects are either limited or unknown. We recently developed, in a Yucatan minipig model, a rapid fabrication method to produce patient-specific engineered osteochondral hydrogel/porous PCL units that can be implanted to completely replace an entire articular surface.[3] That prior work represented only a proof of concept, however, given that it included a hydrogel alone—without cells to provide sustained matrix production. To extend this work, the purpose of this study was to couple a cell-laden hydrogel (methacrylated hyaluronic acid, MeHA) with the porous polycaprolactone (PCL) bone interating phase. Constructs were formed into cylindrical units and mesenchymal stem cells (MSC) viability, matrix elaboration, and construct mechanical properties were evaluated over time in culture in comparison to cell-free controls.

Methods

Construct fabrication

Poly(ε-caprolactone) (PCL) was dissolved in chloroform at 20% wt/vol and mixed with NaCl crystals sieved to ~106 μm. The slurry was poured into a polydimethylsiloxane (PDMS) cylindrical mold (height: 3.5mm, diameter, 5mm), and the solvent was evaporated. PCL units were salt-leeched, sterilized in ethanol, and placed into an array of cylindrical (diameter: 5mm) PDMS casting wells. Juvenile bovine MSCs (passage 3) were suspended ($20x10^6$/mL) in 1% methacrylated hyaluronic acid (MeHA) with 0.05% LAP crosslinker, and pipetted (~40μl) onto the surface of the PCL units. Constructs underwent UV-crosslinking within a nitrogen chamber. Cell-laden constructs were cultured in chemically defined media supplemented with 10ng/mL TGF-β3 (10mL of media per construct) changed two-three times weekly for up to 8 weeks.

MicroCT.

Cell-free constructs (n = 2) were also created using MeHA spiked with zirconium powder (2.5% w/v) and imaged by μCT (Scanco).

Live/dead assay

Constructs (n = 2) were diametrically halved, labeled with Calcein-AM (live), Ethidium Homodimer-1 (dead), and Hoechst stain, and imaged after 4 weeks of culture using a confocal microscope. Maximum projection images were compiled from multiple focal planes using FIJI.

Matrix staining

Following the live/dead assay, constructs (n = 2) were paraffin embedded, sectioned, and stained with Alcian blue (proteoglycans) and nuclear fast red.

Mechanical testing

Thickness and diameter of acellular (n = 6) and cell-laden constructs (n = 4, after 8 weeks of culture) were measured followed by unconfined compression testing. Hydrogels were separated from PCL constructs prior to testing, which consisted of: 1) ramp to 0.2 N; 2) stress relaxation to 10% strain; 3) and dynamic compression (1% strain at 0.5 Hz).

Biochemical analysis

Dimethylmethylene blue (DMMB) assay was used to determine GAG content following proteinase K digestion (n = 4).

Statistics

Data are presented as the mean ± SD. Significance was set at $p < 0.05$. Fig. 3 utilized an unpaired two-tailed t-test.

Results

MeHA/PCL composite scaffolds were reproducibly fabricated in PDMS molds. MicroCT demonstrated some interdigitation at the hydrogel/PCL interface (Fig. 1). Live/dead imaging at 4 weeks demonstrated good cell viability in the construct periphery but fewer viable cells in the center of the gel/PCL interface (Fig. 2A). Proteoglycan staining by Alcian blue identified subjectively greater matrix at the hydrogel periphery, in the area of greater cell

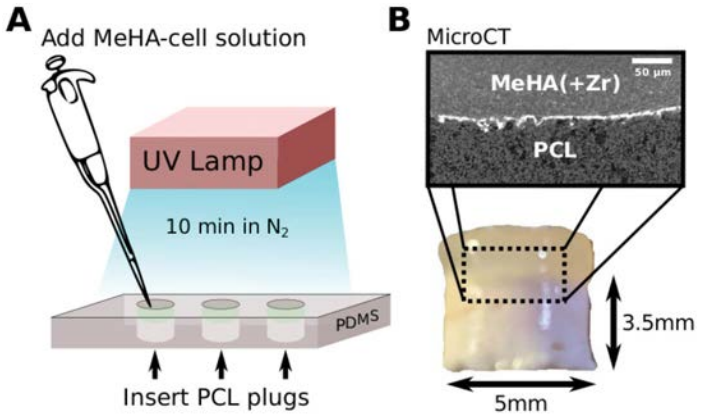

Figure 1. Fabrication of integrated MSC-laden hydrogel/poly-caprolactone composite scaffolds. **(A)** MeHA hydrogels are crosslinked on PCL cylinders under UV light in PDMS casting wells. **(B)** MicroCT of PCL-hydrogel construct with zirconium shows limited interdigitation at the hydrogel-PCL interface.

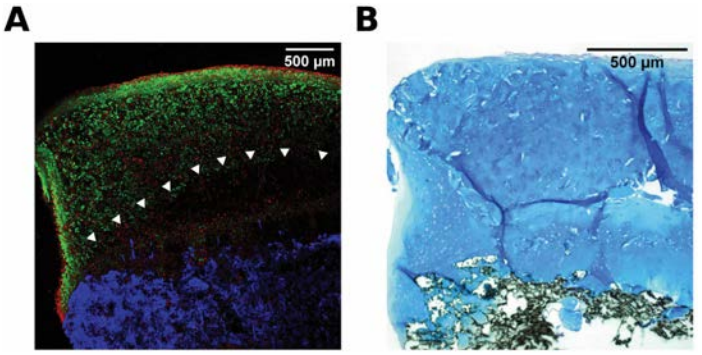

Figure 2. Cell viability and matrix production. **(A)** Live (green)-dead (red) staining with Hoecht's stain (blue) shows live cells in periphery with more dead cells centrally (region demaracated by white triangles). **(B)** Glycosaminoglycan production (Alcian blue) is subjectively more pronounced in peripheral compared to central regions.

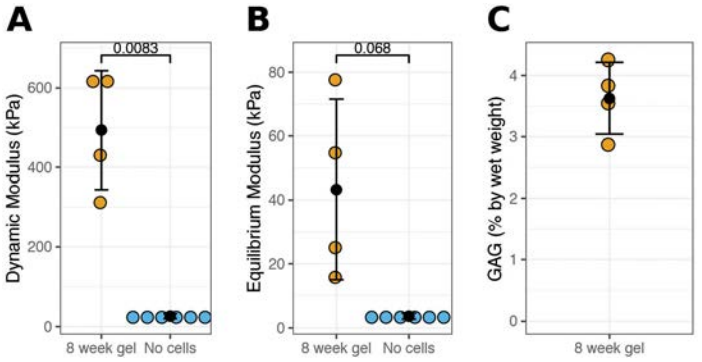

Figure 3. Mechanical and biochemical properties of 8-week cellular (n=4) and acellular (n=6) hydrogel constructs (mean ± SD). **(A)** Dynamic modulus was significantly elevated in cellular constructs after 8 weeks of growth, as was **(B)** equilibrium modulus (trend). **(C)** Mean GAG content after 8 weeks culture was 3.6 ± 0.6%.

viability (Fig. 2B). Mechanical and biochemical properties of the hydrogel portion were assessed after 8 weeks of growth. Mean hydrogel thickness was similar in hydrogels after 8 weeks of growth (2134 ± 337µm) compared to acellular constructs (2179 ± 198µm); however, gel diameter was greater (4.8±0.2mm vs. 3.7 ± 0.3mm, $p < 0.001$). Dynamic modulus was significantly greater at 8 weeks compared to acellular constructs (493.9 ± 149.8 kPa vs. 26.5±6.2 kPa, $p = 0.008$), and a similar trend was observed for equilibrium modulus. At this time point, mean GAG content as a proportion of wet weight was 3.6 ± 0.6%.

Discussion

In this study, we hypothesized that juvenile bovine MSCs could be reproducibly encapsulated within a hyaluronic acid hydrogel/PCL composite scaffold with relatively uniform cell viability and extracellular matrix production. Although reproducible composite scaffold fabrication was achieved, cell viability within the scaffold was not uniform, and instead demonstrated a predilection for greater cell viability in peripheral regions, perhaps driven by greater ease of nutrient diffusion from the culture media at the scaffold periphery. As expected, a GAG-rich matrix was evident after 4 and 8 weeks of growth, accompanied by a significant increase in mechanical properties relative to acellular hydrogels. The dynamic and equilibrium moduli observed here agree with previous results of unconfined compression testing of cell-laden 1% MeHA hydrogels at similar time points.[4] While these results support the overall approach, only one time point was assessed here for histological and mechanical assessment. This prevents assessment of growth trajectory, a factor known to vary among constructs and cell populations.[5] Future studies will evaluate construct maturation at multiple time points and over a longer time course. Additionally, while compression is one of the primary modes of mechanical loading for articular cartilage, shear at the bone-cartilage interface is also critical for function of these implants. Future work will implement "push-off" evaluation of the forming interface with time in culture.[6]

Significance

This study demonstrated the feasibility of reproducibly fabricating viable cell-laden hydrogel/PCL scaffolds with mechanical properties significantly greater than those of cell-free constructs. These findings support the further development of hydrogel/PCL molds with patient-specific geometry, with the ultimate goal of recapitulating native articular geometry and mechanical properties in an implantable osteochondral composite scaffold.

Acknowledgments

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Cellular Dynamics and Zonal Specialization of the Murine Meniscus ECM during Postnatal Growth

Tonia K. Tsinman, BS[1]
Xi Jiang, MS, MD[1]
Lin Han, PhD[2]
Eiki Koyama, PhD, DDS[3]
Robert L. Mauck, PhD[1]
Nathaniel A. Dyment, PhD[1]

[1]McKay Orthopaedic Research Laboratory
University of Pennsylvania,
Philadelphia, PA

[2]Nanobiomechanics Laboratory
Drexel University
Philadelphia, PA

[3]Children's Hospital of Philadelphia
Philadelphia, PA

Introduction

The molecular composition and organization of the extracellular matrix (ECM) is essential for the load bearing function of the adult knee meniscus. In large animals, the body of the meniscus is most often described as having a well-defined cartilaginous, collagen II-rich 'inner' region and fibrous, collagen I-rich 'outer' region. However, heterogeneity in the ECM is observed in both of these regions during aging[1] and with pathologic remodeling following injury.[2] This observation underscores that the understanding of how aberrant compositional changes emerge during meniscus degeneration requires an improved knowledge of how the mature meniscus ECM is established at the cellular and molecular level. To this end, we employ innovative transgenic murine meniscus models to study tissue maturation at the single cell length scale and with fine temporal resolution. Our previous work focused on defining changes in meniscus cell phenotypes throughout inner and outer zones and revealed regionalization of particular cell populations during maturation.[3] Here, we expand the analysis of postnatal maturation by quantifying both cellular and extracellular growth dynamics within the meniscus body.

Methods

All animal work was approved by the UPenn IACUC.

Samples

For all analyses, mouse hindlimbs (P0-P28, CD1 background) were harvested, fixed in 4% PFA, embedded in OCT, and cryosectioned (7μm) in the coronal plane as previously described.[4] Only sections containing the body region of the medial meniscus were analyzed.

EdU labeling

3μg/g of EdU was IP injected into mice for two consecutive days prior to sacrifice at P4, P14, or P28. EdU incorporation was assessed using the Click Chemistry Tools kit and Calfluor Azide AF647, followed by DAPI counterstaining, and fluorescent imaging.

Quantification

Tissue area, cell number, and EdU staining was quantified using Fiji plugins.[5] 3-5 sections were quantified and averaged per animal, with 3-5 animals/age group. One-way ANOVA with Tukey post-hoc ($p < 0.01$) was used to determine differences between age groups.

Second harmonic imaging (SHG)

Tissue sections were imaged using a multiphoton microscope and 20X objective. Equal laser power was used between P7 and P28 samples for signal intensity comparison, but was increased to detect the lower signal in P0 samples.

Results

The cross-sectional area of the meniscus body increased exponentially in the first two weeks post-birth (P0-P14) and plateaued thereafter —demonstrating rapid tissue growth (Fig. 1a, b). Cell proliferation did not contribute to the growth, as the cell count per tissue section was similar across timepoints, and minimal EdU incorporation was observed in meniscus cells after P4 (Fig. 1b, c). Increased SHG signal between P7 and P28 indicated accumulation of fibrillar collagen within the tissue (Fig. 2a, top panel), suggesting that matrix deposition is the likely cause of rapid size changes in the postnatal meniscus. Interestingly, proteoglycan (PG) and collagen staining showed a distinct PG-rich inner zone and collagen-rich outer zone already present at P7 (Fig. 2a, arrowheads). Indeed, appreciable inner/outer regional differences in ECM structure were present at birth (P0), with cells of the outer meniscus residing in a circumferentially aligned collagen matrix, while cells of the inner meniscus were not organized in this aligned fibrous matrix (Fig. 2b). By P28, however, PGs were more widespread, intercalated between the fibrous matrix, and enriched within the pericellular spaces (Fig. 2a).

Discussion

As expected, postnatal meniscus growth is characterized by an accumulation of ECM proteins and the introduction of extrinsic mechanical forces (i.e. weightbearing). Given the fact that little cell division is detected within

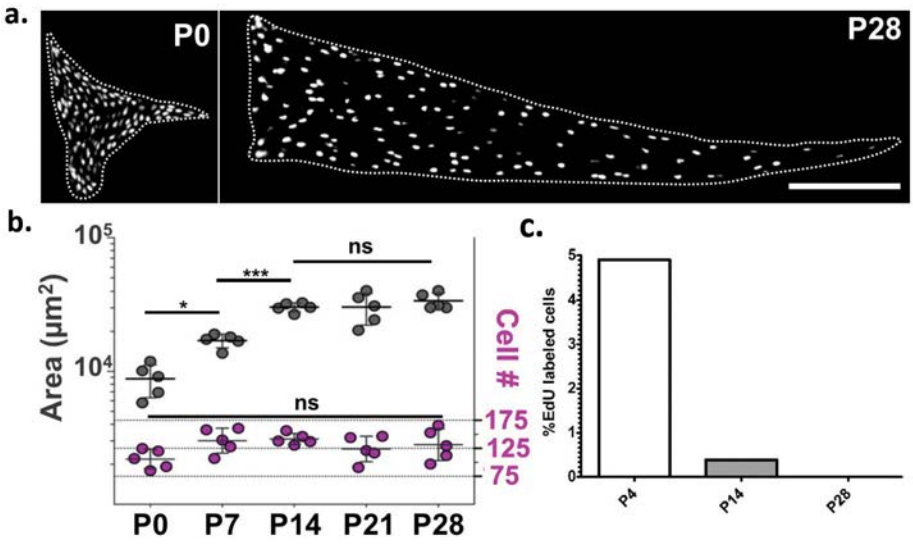

Figure 1. (A) Representative P0 and P28 meniscus body cross sections, with the tissue border outlined by a white dotted line, and cell nuclei stained (with DAPI) in grey. SB: 100mm. **(B)** Cross sectional area plotted on the left axis (mm^2, log10 scale, grey dots) and average cell number per measured cross section plotted on the right axis (linear scale, pink dots). n = 5 animals/age, mean ± s.d. shown. *$p < 0.01$, ***$p < 0.0001$, ns: not significant. **(C)** Average percentage of cells positive for EdU staining within meniscus body sections. n=4 animals/age, mean ± s.d. shown.

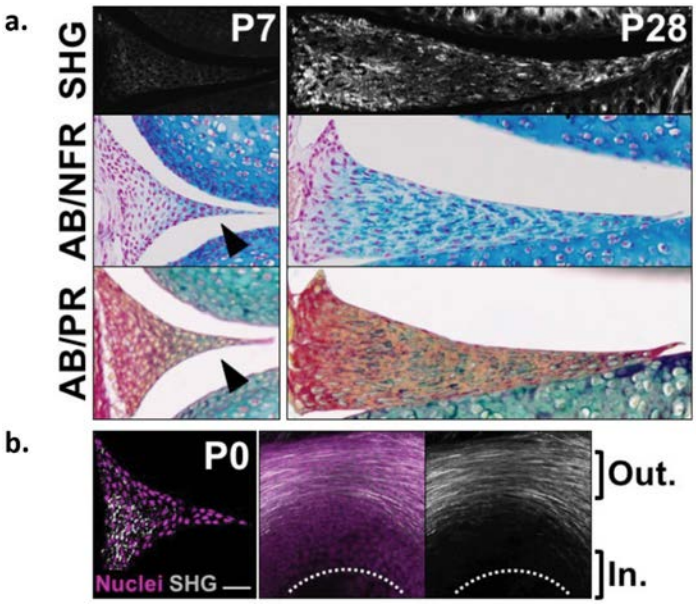

Figure 2. (A) Cross sections at P7 (left) and P28 (right), imaged for: fibrillar collagen using SHG with equivalent multiphoton laser settings (top panel), proteoglycans and nuclei using Alcian blue and nuclear fast red stains (AB/NFR, middle panel), and proteoglycan and collagen matrix using Alcian blue and Picrosirius red (AB/PR, bottom panel). **(B)** SHG imaging of P0 body region in the cross sectional plane (left) and circumferential transverse plane (right) with a DAPI counterstain. Dotted white line indicates inner edge of tissue. "Out": Outer region. "In." Inner region. SB: 20mm.

the tissue by P4, our data also indicate that the resident cells that orchestrate the establishment of the mature ECM are, in fact, present at the time the animal is born (Fig 1). Taken together, these observations show that the same population of meniscus cells is subject to tremendous changes in their microenvironment. As the principles of mechanobiology dictate, such shifts in biophysical cues can in turn alter the behavior of these cell populations. Thus, the observations of pericellular accumulation of PGs after P7 (Fig. 2a) and rapid tissue growth following full weightbearing (P0 to P14, Fig. 1b) may both be evidence of a cellular mechanobiologic response to elevated joint loading. Importantly, our data determine that ECM specialization in the inner and outer zones of the meniscus is present as soon as the animal is born (Fig. 2). In all, these findings suggest that while regional differences in loading patterns may drive changes in matrix deposition at *later* stages of maturation, other mechanisms—such as regional differences in cell origins[6]—may be at play in specifying inner and outer zones during early development.

Significance

Ultimately, defining the cellular and mechanical regulators of hierarchical dense connective tissue formation is pivotal to guiding our repair strategies and providing success benchmarks to establish efficacy. This study is one of our first steps in establishing the cellular and matrix changes that occur during rapid tissue growth in the murine meniscus. Future studies will define the mechanisms that regulate cell fate and ECM organization.

Acknowledgments

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Identification of Gli1 as a Progenitor Cell Marker for Meniscus Injury Repair

Yulong Wei, MD[1]
Hao Sun, MD[1]
Lutian Yao, MD[1]
Leilei Zhong, PhD[1]
Wei Yu[1]
Su Chin Heo, PhD[1]
Lin Han, PhD[2]
Fanxin Long, PhD[3]
Robert L Mauck, PhD[1]
Jaimo Ahn, MD, PhD[1]
Ling Qin, PhD[1]

[1]Department of Orthopaedic Surgery
School of Medicine
University of Pennsylvania

[2]Drexel University School of Biomedical Engineering
[3]Translational Research Program in Pediatric Orthopaedics
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania, USA

Introduction

Meniscal tears are one of the most common injuries of the knee. They are likely to be an important early event in the initiation and later propagation of osteoarthritis (OA) and have been accepted as an important risk factor for OA clinically. As a treatment, meniscal resection has been demonstrated to accelerate degenerative disease and the most commonly performed surgery of partial meniscectomy is not restorative and only delays degeneration. Surgical repair remains a viable treatment for only a small portion of individuals. Various approaches, including stem cell transplantation, have been proposed to repair injured meniscus. However, meniscus-specific progenitors are still largely unknown. Gli1 was recently recognized as a marker for bone marrow and periosteal mesenchymal progenitor.[1,2] In this study, we constructed *Gli1-CreER Tomato (Gli1ER/Td)* mice and analyzed the progenitor properties of Gli1-labeled meniscus cells in development, homeostasis, and injury repair.

Methods

Animals

Gli1-CreER mice were crossed with *Rosa-tdTomato* mice to obtain *Gli1ER/Td*. Mice at various ages received Tamoxifen (Tam) injections (50 mg/kg × 2 days in pups and 75 mg/kg × 5 days in adults).

Surgery

Male mice at 3 mo of age received Tam followed by surgical transection of the medial meniscus in right knees and sham operation in left knees a week later. During the surgery, the joint capsule was opened and the anterior horn of the medial meniscus was cut into two parts. For cell treatment, 5000 FACS sorted meniscus cells (Td^+ or Td^- cells) were injected into the knee joint space right after meniscus surgery. For activator treatment, 2 μl Purmorphamine (1 mM) were injected into the knee joint space right after surgery. All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Pennsylvania.

Cell culture

Primary meniscus cells were enzymatic digested from the meniscus of 4-wk-old *Gli1ER/Td* mice. FACS sorted Td^+ and Td^- cells were used for CFU, migration, proliferation, differentiation, and qRT-PCR assays.

Histology

Knee joints were fixed in 4% PFA, decalcified in 10% EDTA, and processed for cryosections or paraffin sections.

Human meniscus samples

They were prepared from de-identified specimens obtained at the total arthroplasty of the knee joints. Paraffin sections were stained by Safranin O/Fast green to evaluate degenerative stages and neighboring sections were used for Gli1 staining.

Statistics

Data are expressed as means±SEM and analyzed by paired, two-tailed Student's t-test.

Results

In *Gli1ER/Td* mice, Td did not label meniscus cells in newborn pups (Tam at P5-6). In 2-wk-old mice (Tam at P9-14), Td initially labeled the entire anterior meniscus and gradually concentrated at the superficial cells by 8 wk of age. Td started to label the posterior meniscus in 4-wk-old mice and also later focused on superficial cells only. In adult animals, Td^+ cells only occurred in the superficial layer of meniscus right after Tam injections and long term tracing did not detect their expansion (Fig. 1). In culture, Td^+ cells generated much more CFU-Fs (2.55-fold) and grew much faster than Td^- cells (Fig. 2A). Using an activator (Purmorphamine) and an inhibitor (GANT-61) of hedgehog (Hh) pathway, we found that primary meniscus cells proliferate and migrate in an Hh-dependent manner (Fig. 2B, **C**). Td^+ meniscus cells also had the abilities to differentiate into osteoblasts and adipocytes (Fig. 2D). During meniscal differentiation, Td^+ cells expressed 2.9-fold more *Col1a1* and 61.2% less *Col2a1* than Td^- cells. After meniscus injury, Td^+ cells quickly emerged at the injury ends and proliferated (Fig. 3). Without treatment, two ends remained separated 3 mo later. However, injection of Td^+ cells, but not Td^- cells, from *GliER/Td* meniscus into the joint capsule of *WT* mice right after injury resulted in the

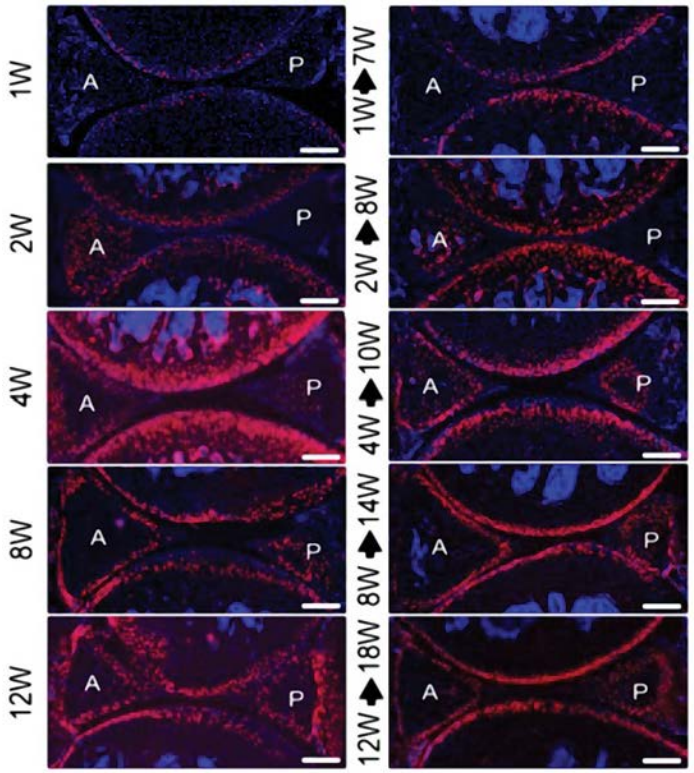

Figure 1. The distribution of Gli1$^+$ cells and their progenies in mouse meniscus during development and homeostasis. *Gli1ER/Td* mice received Tam injections at various ages and their joints were harvested right after injections (left panel) or 6 weeks later (right panel) for sagittal cryosections. A and P represent the anterior and posterior side of meniscus, respectively. n = 5/age.

reconnection of two ends within a month (Fig. 4). Injection of Purmorphamine also exhibited a strong repair effect. After meniscus injury, OA generally developed in the cartilage 2 mo later. Strikingly, injection of Td$^+$ cell or Hh activator right after surgery significantly delayed OA initiation (Fig. 5). Analyzing human meniscus samples from OA patients confirmed an increase of Gli$^+$ cells in meniscus during degeneration (Fig. 6).

Discussion

By using a lineage tracing line, cell culture, and a meniscus injury model, we demonstrated that Gli1 is a mesenchymal progenitor marker in mouse meniscus. Gli1-labeled cells contribute to meniscus development and injury response. Activation of Gli1/hedgehog signaling in adult meniscus leads to accelerated meniscus healing process in response to surgically induced meniscus degeneration, indicating a protective role of hedgehog signaling on meniscus against degeneration. Analyzing Gli1 expression profile in human meniscus samples with different meniscus degenerative stages strongly implicates the clinical relevance of our study

Significance

Our studies uncover the critical role of Gli1 in adult knee meniscus and provide proof-of-principle evidence for targeting this novel pathway as meniscus injury therapy for preventing OA development.

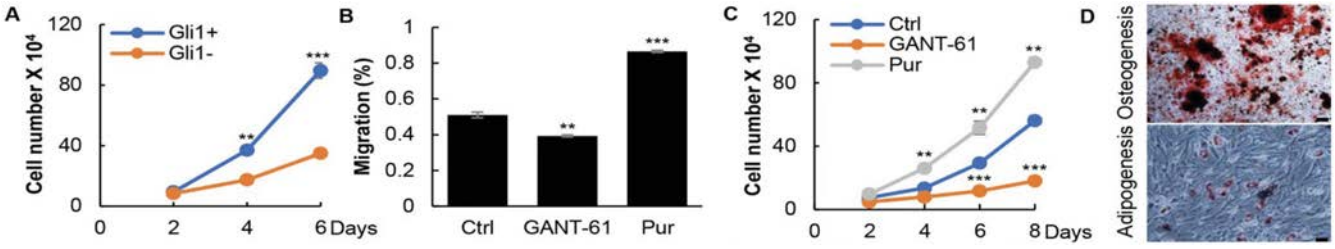

Figure 2. Gli1$^+$ cells exhibit mesenchymal progenitor properties in vitro. **(A)** The growth curve of sorted Gli1$^+$ and Gli1$^-$ meniscus cells. **(B, C)** The growth curve **(B)** and migration ability **(C)** of primary meniscus cells treated with GANT-61 (1 mM) or Purmorphamine (0.1 mM). **P < 0.01, ***P < 0.001 vs Control. **(D)** Osteogenic (Alizarin Red staining) and adipogenic (Oil Red O staining) differentiation of sorted Gli1$^+$ primary meniscus cells. n = 3/group.

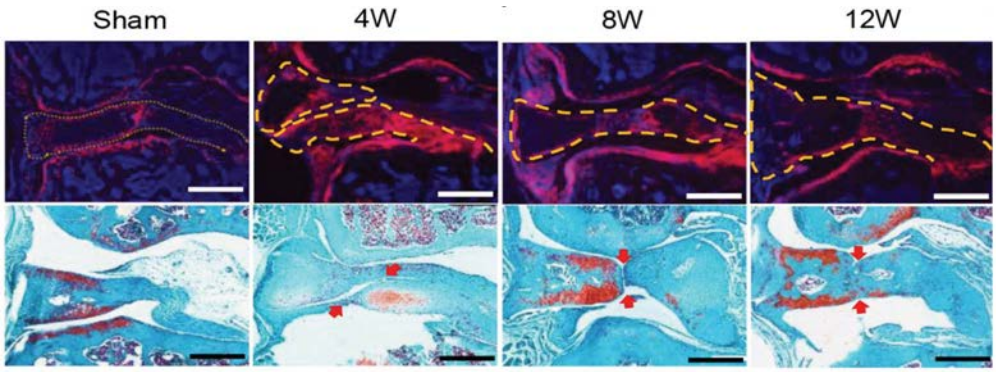

Figure 3. Mouse meniscus does not heal at 3 mo post injury. *Gli1ER/Td* mice received Tam injections at 12 wk of age followed by meniscus injury. Joints harvested at various times were sectioned at a coronal plane for fluorescent image of Td signal (top panel) and Safranin O/Fast Green staining (bottom panel). n = 8/group. Red arrows point to injury sites.

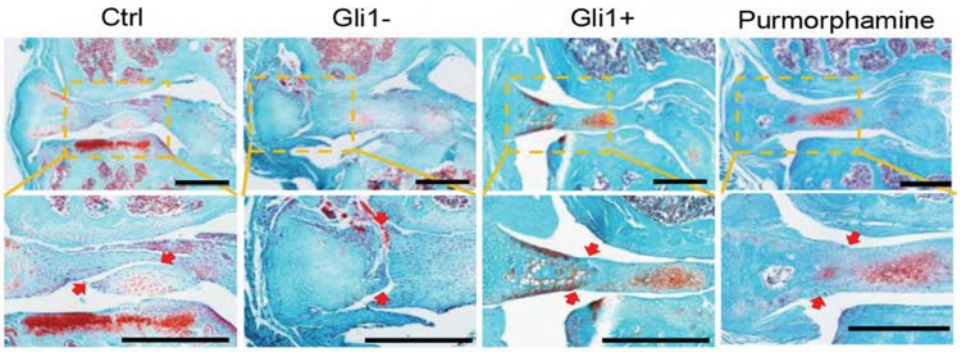

Figure 4. Activating Hh signaling promotes meniscus repair. At 4 wk post injury, mouse knees received Gli1-labeled meniscus cells or Purmorphamine injections right after surgery showed reconnection of two meniscus ends. Red arrows point to prior meniscus injury sites. n = 8/group. Bottom panels are magnified images of top panels.

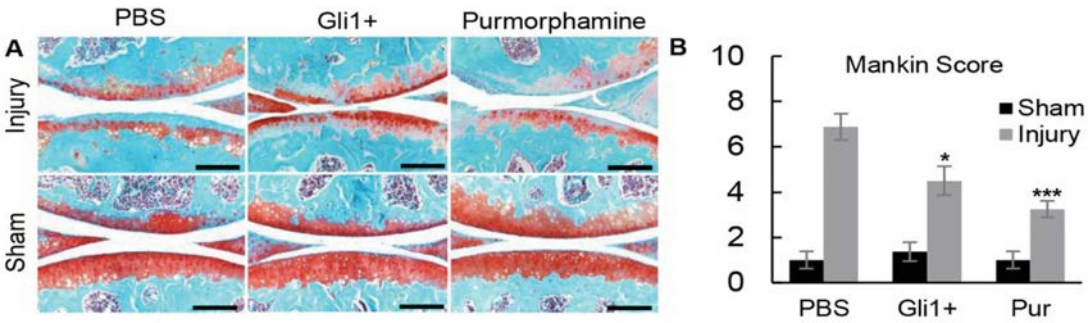

Figure 5. Meniscus repair delays OA initiation. **(A)** Safranin O staining of mouse knee joints (sagittal sections) at 8 wk postsurgery. Mice received PBS, Gli1^{+} cell or Purmorphamine treatment right after surgery. **(B)** The OA severity was measured by Mankin score. n = 10/group. *P < 0.05, ***P < 0.001 vs PBS injury.

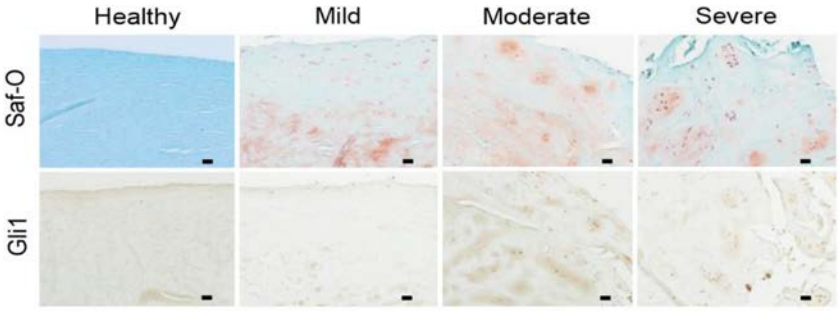

Figure 6. Human meniscus samples from OA patients show a positive correlation between meniscus degeneration severity and Gli1 expression. n = 5/group. Scale bar in all images, 200 mm.

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Gli1 Labels a Subpopulation of Fap Cells that Respond to Muscle Injury

Lutian Yao, MD[1]
Elisia D. Tichy, PhD[1]
Leilei Zhong, PhD[1]
Luqiang Wang[1]
Foteini Mourkioti, PhD[1,2,3]
Ling Qin, PhD[1]

[1]Department of Orthopaedic Surgery
University of Pennsylvania

[2]Department of Cell and Developmental Biology
University of Pennsylvania

[3]Penn Institute for Regenerative Medicine, Musculoskeletal Program
Perelman School of Medicine
University of Pennsylvania

Introduction

Skeletal muscle has a remarkable capacity for regeneration after injury. Recently, a new type of muscle-resident progenitor cell, referred to as fibro-adipogenic progenitors (FAPs), was identified to be critical in supporting the process of injured muscle regeneration.[1] To date, FAPs remains a poorly defined, heterogeneous population without any specific genetic markers. Gli1 was recently recognized as a marker for bone marrow and periosteal mesenchymal progenitor.[2, 3] In this study, we used *Gli1-CreER* to label FAPs and characterized their changes in healthy, aged, and diseased muscle.

Methods

Animals

All animal work performed in this report was approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Pennsylvania. Gli1-CreER Rosa-tdTomato (Gli1ER/Td) mice were generated by breeding Rosa-tdTomato mice with Gli1-CreER. Gli1ER/Td/mdx mice were generated by breeding Gli1ER/Td mice with mdx^{4cv} mice.[4] To induce CreER activity, mice received tamoxifen (Tam) injections (75 mg/kg/day) at 2 months of age for 5 days. Acute muscle injury was induced by injection of 10 μl Notexin (10 μg/mL) into Tibialis Anterior (TA) muscle.

Histology

TA muscle samples were fixed in 4% PFA for 1 day, and then immersed into 30% sucrose at 4°C overnight. They were processed for cryosections followed by H&E, WGA, Biodipy, Sca1, PDGFRα, or αSMA antibodies staining.

FAP cell isolation

Hindlimb muscles (quadriceps, gastrocnemius, and tibialis anterior) were dissected and enzymatically dissociated with 0.1% collagenase and 4.8 units/mL dispase in DMEM using the gentleMACs system. The cell slurry was pulled through a 21-gauge needle until all remaining muscle tissue was broken apart, after which the cell solution was filtered through a 40 μm cell strainer. After red blood cell lysis, cells were stained with lineage cell markers (CD45, CD31, CD11b), Sca1, α7-integrin (Itga7) and CD34 antibodies for flow analysis.

Statistics

Data are expressed as means±SEM and analyzed by unpaired, two-tailed Student's t-test.

Results

In the TA muscle of *Gli1ER/Td* mice, Td^+ cells were exclusively located in the interstitial area of myofibers after Tam induction (Fig. 1A). The majority of them were co-stained with FAP markers, PDGFRα and Sca1 (Fig. 1B). Quantification revealed that $Gli1^+$ cells constitute a small portion of $PDGFR\alpha^+Sca1^+$ FAPs (Fig. 1C). In flow analysis, FAPs are defined by $Lin^-Sca1^+CD34^+Itga7^-$. In line with the staining data, Td^+ cells were mostly FAPs (97.4% Lin-, 78.5% $Sca1^+$, 78.2% $CD34^+/Itga7^-$, Fig. 1D) and they labeled 3.2 ± 0.1% and 7.6 ± 0.5% of digested muscle cells at P66 and P72, respectively (Tam at P61-65). Meanwhile, 10.9 ± 0.7% and of 17.3 ± 0.3% FAPs at P66 and P72, respectively, were Td^+ cells (Fig. 1E). In 1-year-old mice, the percentage of FAP cells in digested muscle cells decreased to 7.94 ± 0.6% and *Gli1-CreER* labeled cells (95.15 ± 4.45 cells/mm^2) reduced drastically compared to adult mice (147.09 ± 14.98 cells/mm^2, n = 3/age, $p < 0.05$). Though initially presented at a low level in freshly digested muscle cells, Td^+ cells constituted 40% of confluent cells after culturing (Fig. 2A). Sorted Td^+ cells exhibited fibroblastic and adipogenic differentiation abilities, but not osteogenic differentiation ability (Fig. 2B). To investigate their in vivo function, *Gli1ER/Td* mice received Notexin intramuscularly at P72 (Tam at P61-65) to create acute muscle injury. Td^+ cells peaked at day 3 post injury, gradually decreased at day 6, and almost receded to normal levels by day 9 (Fig. 3A, B). To further validate the role of Gli1-labeled cells in chronic injury, we crossed *Gli1ER/Td* mice with dystrophic mdx^{4cv} mice. After Tam at P61-65, Td^+ cells were significantly increased in the interstitial area of myofibers of *Gli1ER/Td/mdx* muscle compared to *Gli1ER/Td* control muscle (P72, control: 198.81 ± 22.66 cells/mm^2, mdx: 360.33 ± 53.70 cells/mm^2, n = 6/group, $P < 0.05$, Fig. 3C).

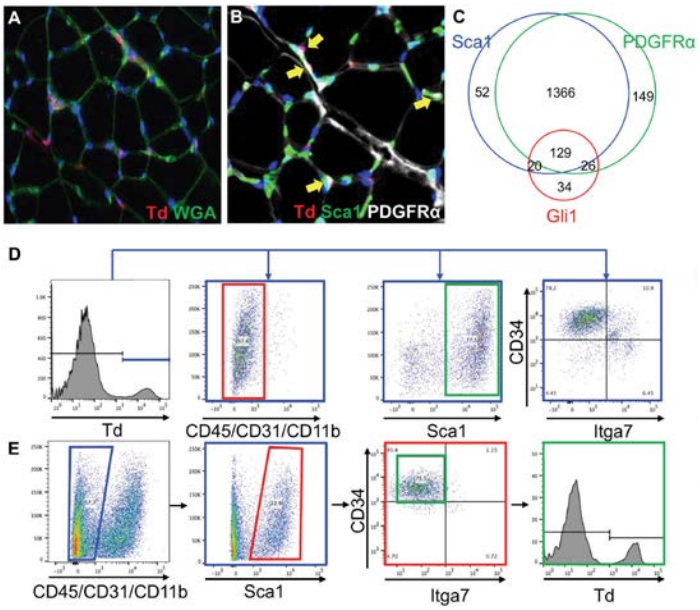
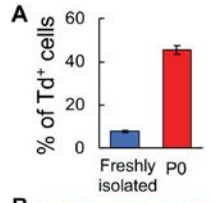


Figure 1. Td in the muscle of *Gli1ER/Td* mice labels a subpopulation of FAPs. **(A)** Td$^+$ cells located in the interstitial area of TA muscle in *Gli1ER/Td* mice. **(B)** Td$^+$ cells co-express FAP staining markers, Sca1 and PDGFRα (yellow arrows). **(C)** Venn diagram of Sca1$^+$, PDGFRα$^+$, and Td$^+$ cells in TA muscles. **(D)** Examination of FAP flow markers on Td$^+$ cells. **(E)** A portion of FAPs identified by flow are Td$^+$.



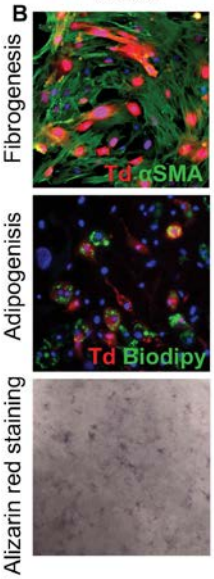


Figure 2. Td$^+$ cells in the muscle of *Gli1ER/Td* mice are FAPs in vitro. **(A)** The percentage of Td$^+$ cells in freshly digested muscle cells and in cultured P0 cells. **(B)** Sorted Td$^+$ cells can differentiate into fibroblasts (αSMA$^+$) and adipocytes (biodipy$^+$) but not osteoblasts (Alizarin red staining).

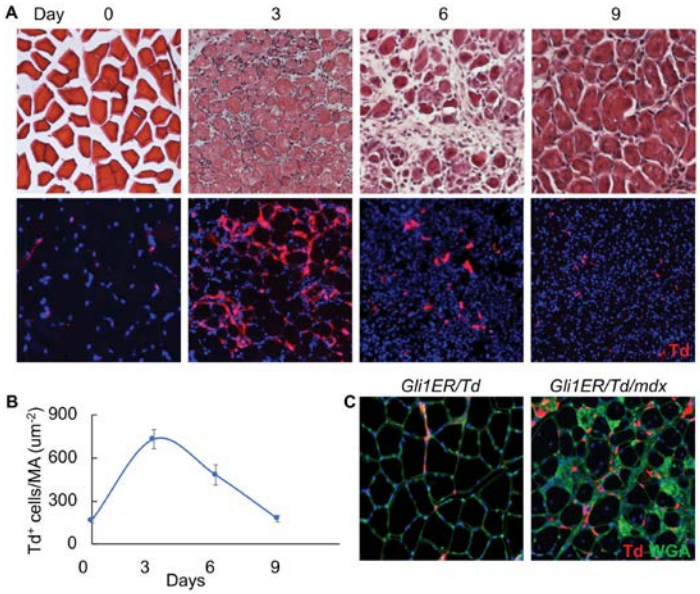


Figure 3. Td$^+$ cells in the muscle of *Gli1ER/Td* mice rapidly response to muscle injury. **(A)** HE staining (top panel) and immunofluorescence of Td$^+$ cells (bottom panel) in TA muscles at day 0, 3, 6 and 9 post Notexin-induced muscle injury. **(B)** The time course of Td$^+$ cells after injury. MA: muscle area. **(C)** Immunofluorescence of Td$^+$ cells in TA muscles of control and dystrophic *mdx^{4cv}* mice.

Discussion

In our study, we demonstrated that *Gli1-CreER* labels a subpopulation of FAP cells that undergo age-dependent reduction. Interestingly, they show the same response kinetics of FAPs after acute and chronic muscle injury, suggesting that Gli1-labeled subpopulation of FAP cells play a predominant role in the regeneration process of injured skeletal muscles. Since Gli1 is an effector of Hedgehog (Hh) signaling, our data also implied a possible role of Hh signaling in regulating FAP action.

Significance

We identified *Gli1-CreER* as a suitable model to genetically target a subpopulation of FAPs that respond to muscle injury. Understanding the cellular and molecular mechanism of FAPs is crucial for designing new treatments to promote muscle regeneration under aging and diseased conditions.

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Injury and Healing Effect on Fatigue Properties of Collagen V Haploinsufficient Female Murine Tendons

Jaclyn Carlson, M.Eng[1]
Zakary Beach, BS[1]
Stephanie Weiss, BS[1]
David Birk, Ph.D[2]
Louis Soslowsky, Ph.D[1]

[1]McKay Orthopaedic Research Laboratory
University of Pennsylvania

[2]Department of Molecular Pharmacology and Physiology
University of South Florida

Introduction

Patients with Classic Ehlers-Danlos Syndrome (*c*EDS), a disorder characterized by mutation in the *COL5* genes with *COL5a1* haploinsufficiency being the most common, suffer from articular hypermobility, skin hyperextensibility, tendon/ligament fragility and abnormal wound healing.[1,2] Furthermore, human studies have shown that females have decreased collagen synthesis and fibroblast activity[3-5] as well as altered gene expression during repair,[6] potentially exacerbating detrimental changes present in *c*EDS tendons. Quasi-static loading of the mouse patellar tendon[7-9] demonstrates decreases in modulus, failure stress, failure load, and stiffness due to reduced collagen V throughout healing. Although the hierarchical structure of the tendon has been implicated in changes following cyclic fatigue loading, and collagen V is essential in regulating collagen fibrillogenesis, fatigue properties have not been examined in *c*EDS tendons.[7,10] Therefore, the objective of this study was to define the fatigue properties of female patellar tendons following injury, as well as the effect of a reduction in collagen V on these properties. We hypothesized that reduction in collagen V following injury will delay improvements in the fatigue properties compared to wild-type tendons.

Methods

Adult female wild-type (WT) C57/BL6 and heterozygous *Col5a1*$^{+/-}$ mice, a model for *c*EDS, at 120 days of age (n = 60) were used (IACUC approved). Mice were randomly divided into uninjured and injured groups, with injured mice undergoing bilateral patellar tendon injury surgery as described.[11] Injured mice were sacrificed early in the remodeling healing phase (3w) or later in remodeling (6w) and uninjured age-matched mice were sacrificed.

Mechanics

The patella-patellar tendon-tibia complexes of all mice were dissected and prepared for mechanical testing.[12] Cross-sectional area was measured using a custom laser device.[13] Tendons underwent a fatigue protocol, consisting of pre-conditioning and 1 Hz cyclic loading until failure. Cyclic loads corresponded to 20% and 55% maximum stress (previously determined from quasi-static testing). Fatigue parameters were analyzed at the end of the primary phase (BP1) and secondary phase (BP2) of fatigue life, capturing changes in material parameters that occur with fatigue damage, including peak cyclic strain, tangent modulus, secant modulus, tangent stiffness, secant stiffness, hysteresis, and laxity. Secant modulus and stiffness are calculated in reference to the zero displacement point and tangent modulus and stiffness are calculated from a specific loading cycle.

Statistics

Two-way ANOVAs with post-hoc Bonferroni tests were used to assess the effects of genotype (collagen V expression), injury time-point, and their interaction on fatigue mechanical properties. Significance was set at $p \leq 0.05$ and trends at $p \leq 0.1$.

Results

WT patellar tendons 3w post-injury (PI) showed a significant decrease in tangent modulus (BP1 and BP2) (Fig.1A,B), tangent stiffness (BP1 and BP2 [trend]) (Fig.1C,D), and secant modulus (BP1 and BP2) (not shown) when compared to uninjured controls. The decrease in tangent modulus at BP2 persisted to 6w PI. However, no other parameters had differences at 6w PI. *Col5a1*$^{+/-}$ patellar tendons 3 and 6w PI exhibited reduced tangent modulus (Fig.1A,B), tangent stiffness (Fig.1C,D), and secant modulus at both BP1 and BP2 when compared to uninjured controls. There were no differences in *Col5a1*$^{+/-}$ tendons compared to uninjured tendons in peak strain (Fig.2C) or secant stiffness (not shown) at BP1. However, 3w PI at BP2, there was an increase in peak strain (Fig.2D) and a trending decrease in secant stiffness (not shown), with no differences 6w PI. Hysteresis was significantly higher in WT tendons 3w PI when compared to uninjured and 6w tendons at BP1. However only a trending difference was seen at BP2 between uninjured and 3w PI (Fig.2A,B). *Col5a1*$^{+/-}$ tendons showed no differences in hysteresis at BP1, but had significantly higher hysteresis 3 and 6w PI compared to uninjured tendons at BP2, and a trending increase between 3 and 6w PI (Fig.2A,B). Differences between genotypes, were primarily seen in the uninjured groups, with WT tendons having a significantly lower tangent

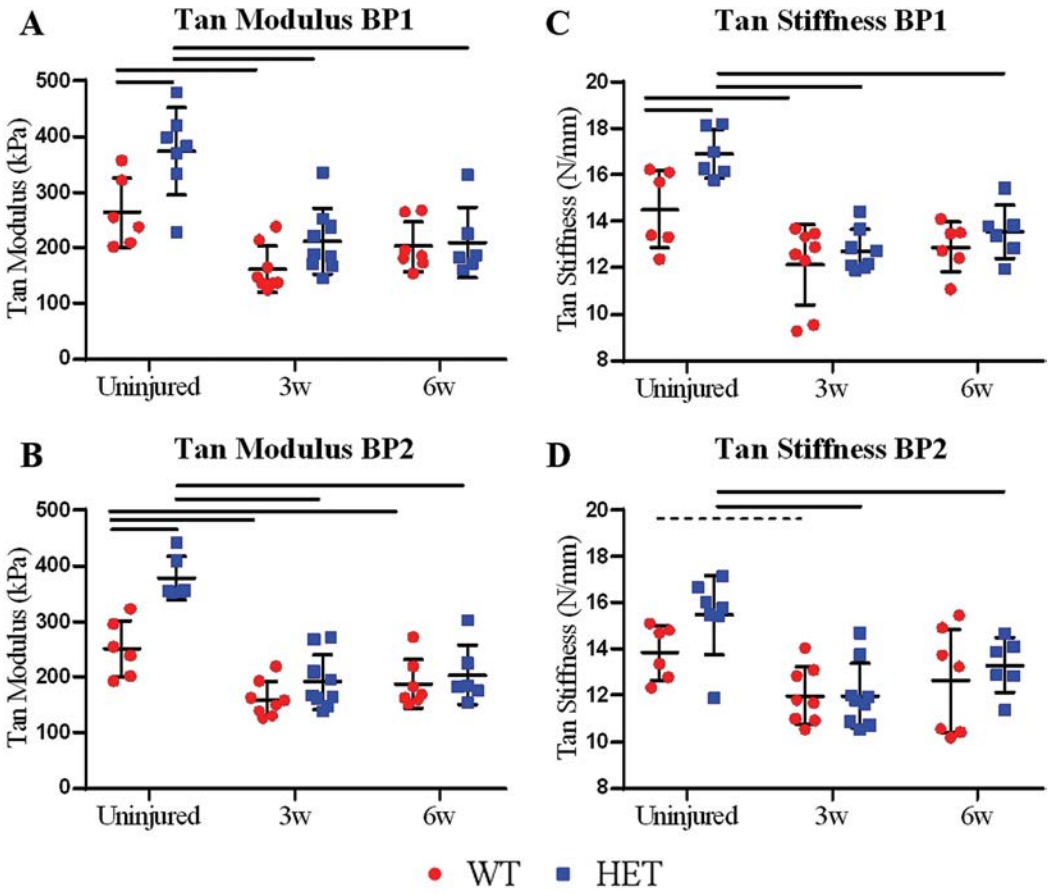

Figure 1. Tangent Modulus BP1 (A) and BP2 (B). Tangent Stiffness BP1 (C) and BP2 (D). *Col5a1*$^{+/-}$ tendons had persistent decreases in tangent modulus and tangent stiffness 3 and 6w PI at BP1 and BP2. WT tendon decreases in tangent modulus and tangent stiffness seen 3w PI were only persistent to 6w PI in tangent modulus at BP2. Solid lines denote significance and dashed lines denote trends.

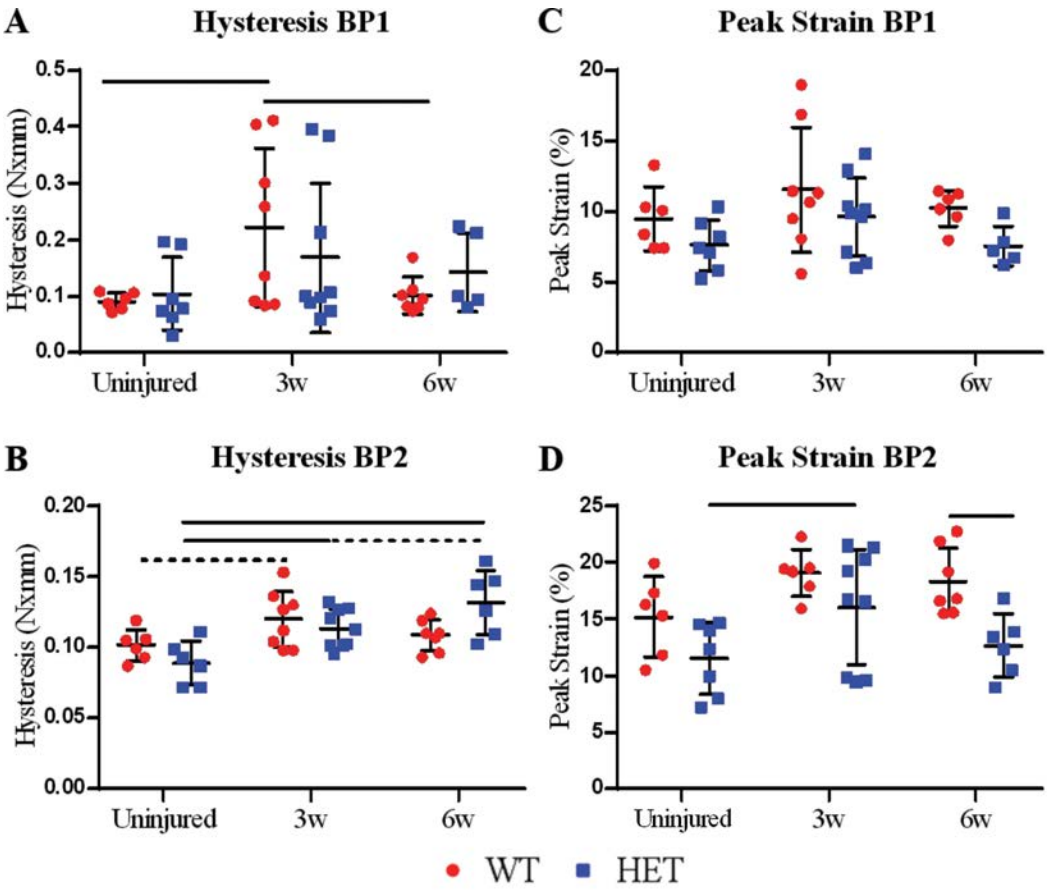

Figure 2. Hysteresis BP1 (A) and BP2 (B). WT tendons had increased hysteresis at BP1 3w PI, while *Col5a1*$^{+/-}$ tendons had increased hysteresis 3 and 6w PI at BP2. **Peak Strain BP1 (C) and BP2 (D).** Peak strain was increased 3w PI in *Col5a1*$^{+/-}$ tendons at BP2. Solid lines denote significance and dashed lines denote trends.

modulus (BP1 and BP2) (Fig.1A,B), tangent stiffness (BP1) (Fig.1C), and secant modulus (BP1 and BP2) (not shown), and a significantly higher laxity (BP1) (not shown). When compared to WT tendons, *Col5a1*$^{+/-}$ tendons at 6w PI had a decreased peak strain (BP2) (Fig.2D) and increased secant stiffness (BP1 [trend] and BP2) (not shown).

Discussion

This study evaluated the fatigue properties of the patellar tendon in uninjured and injured mice as well as the role of collagen V. Cyclic fatigue loading mimics the *in vivo* loading pattern of the patellar tendon, and therefore is a relevant approach to study mechanic properties. Overall, fatigue properties of *Col5a1*$^{+/-}$ tendons were persistently affected to a later time-point post-injury, while the fatigue properties of WT tendons showed minimal differences later in healing. Therefore, as hypothesized, collagen V deficient mice have a delayed healing response, with changes persisting to 6w PI, while WT tendon fatigue properties recover by 6w PI. Additionally, genotypic differences in uninjured tendons indicate that collagen V plays a role in the tendon response to cyclic loading. However, these differences are not consistently present PI. This shows that WT and *Col5a1*$^{+/-}$ tendon fatigue properties are affected to different degrees following injury, and the diminished healing of *Col5a1*$^{+/-}$ tendons could be obscuring genotypic differences post-injury. Lastly, hysteresis analysis indicates that energy loss is different throughout fatigue life between WT and *Col5a1*$^{+/-}$ tendons following injury, as WT tendons show increased hysteresis at the end of the primary phase, while *Col5a1*$^{+/-}$ tendons show increased hysteresis at the end of the secondary phase. More energy is lost at the end of fatigue life in *Col5a1*$^{+/-}$ tendons, while the opposite is true for WT tendons. This indicates that collagen V affects the ability of the tendon to heal in a manner that resists microstructural damage associated with cyclic use. Therefore, this study demonstrates that collagen V plays a role in the tendon's ability to respond to fatigue loading, and following injury, collagen V plays a crucial role in the tendon healing process.

Significance

This study demonstrates that WT tendon fatigue properties recover following injury while a decrease in collagen V results in a delayed healing response, highlighting the importance of evaluating the effect of collagen V in the tendon healing process.

Acknowledgements

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Determining the Roles of Decorin and Biglycan in Tendon Healing Using Conditional Deletion at Time of Injury

Ashley Fung[1]
Stephanie Weiss[1]
David Birk[2]
Louis Soslowsky[1]

[1]McKay Orthopaedic Research Laboratory
University of Pennsylvania

[2]Department of Molecular Pharmacology and Physiology
University of South Florida

Introduction

Tendon injury leads to a healing cascade of inflammatory, proliferative, and remodeling phases, but the mechanisms underlying these processes remain unclear. Small leucine-rich proteoglycans (SLRPs) such as decorin (Dcn) and biglycan (Bgn) are regulators of fibrillogenesis and matrix assembly and play important roles throughout tendon healing. Previous studies using conventional $Bgn^{-/-}$ and $Dcn^{-/-}$ mice showed that absence of Dcn impaired the healing response with no improvement in dynamic modulus between 3- and 6-weeks post-injury, while absence of Bgn had a moderate effect on early tendon healing, together suggesting differential roles of these SLRPs throughout the injury response.[1] However, these results are confounded by the cumulative effects of SLRP deficiency on altered development and growth, and the isolated roles of Dcn and Bgn on tendon healing are unknown. Therefore, the objective of this study was to determine the regulatory role(s) of Dcn and Bgn on the mechanical properties of healing tendons in mature mice using conditional deletion at the time of tendon injury resulting in an isolation of Dcn, Bgn, and both Dcn/Bgn knockdown. We hypothesized that induced deletion of Dcn, Bgn, and both Dcn and Bgn expression would impair the healing response compared to wild type mice leading to reduced improvement in tendon mechanical properties post-injury. Because Dcn has been shown to mediate all stages of healing while Bgn is primarily important in the inflammatory phase, we hypothesized that deletion of Dcn would result in greater impairment.

Methods

Female $Dcn^{+/+}/Bgn^{+/+}$ control (WT, n = 48), $Dcn^{flox/flox}$ (I-$Dcn^{-/-}$, n = 32), $Bgn^{flox/flox}$ (I-$Bgn^{-/-}$, n = 32), and compound $Dcn^{flox/flox}/Bgn^{flox/flox}$ (I-$Dcn^{-/-}/Bgn^{-/-}$, n = 32) mice with a tamoxifen inducible Cre (B6.129-Gt(ROSA)26Sortm1(cre/ERT2)Tyj/J, Jackson Labs) were utilized[2] (IACUC approved). At 120 days old, Cre excision of conditional alleles was induced in all mice via two (injured mice) or three (uninjured mice) consecutive daily IP injections of tamoxifen. WT mice also received tamoxifen to account for any potential side effects. WT mice (n = 16) were designated as uninjured controls, and remaining mice were divided into 3- or 6-week post-injury groups to represent the early and later remodeling phases of healing (n = 16/genotype/time point). At time of induction, mice in injury groups underwent bilateral patellar tendon injury surgery as described[3] and were sacrificed 3- or 6-weeks later. Uninjured groups were sacrificed at 150 days old. The patellar tendon-bone complex from one limb of each animal was dissected and prepared for mechanical testing to assess potential differential effects in both the midsubstance and insertion regions of the tendon.[4] Tendons were subjected to a testing protocol consisting of preconditioning and a quasi-static ramp to failure. Dynamic collagen fiber realignment was measured throughout the ramp-to-failure using a crossed polarizer setup. Images were used to optically measure moduli in the insertion site and midsubstance regions. To evaluate the effect of genotype on tendon healing, one-way ANOVAs with Bonferroni corrections were conducted for 3- and 6-week post-injury groups. Significance was set at $p \leq 0.05$; trends at $p \leq 0.1$.

Results

WT, I-$Dcn^{-/-}$, and I-$Bgn^{-/-}$ mice had significantly reduced insertion site modulus compared to uninjured controls at both 3- and 6-weeks post-injury, while insertion site modulus was reduced in I-$Dcn^{-/-}/Bgn^{-/-}$ mice only at 6-weeks (Fig. 1A,B). Midsubstance modulus in I-$Dcn^{-/-}$ mice was significantly lower than uninjured and I-$Dcn^{-/-}/Bgn^{-/-}$ groups and trended lower compared to I-$Bgn^{-/-}$ mice 3-weeks post-injury (Fig 1C). Similarly, midsubstance modulus was significantly lower in I-$Dcn^{-/-}$ mice compared to uninjured and I-$Bgn^{-/-}$ groups 6-weeks post-injury (Fig 1D). Midsubstance modulus in I-$Dcn^{-/-}/Bgn^{-/-}$ mice also trended lower compared to I-$Bgn^{-/-}$ mice (Fig 1D). For failure properties, maximum stress trended lower in I-$Dcn^{-/-}$ and I-$Dcn^{-/-}/Bgn^{-/-}$ groups compared to uninjured mice 3-weeks post-injury (Fig 1E), while maximum stress trended lower in I-$Dcn^{-/-}/Bgn^{-/-}$ mice compared to I-$Bgn^{-/-}$ mice at 6-weeks (Fig 1F). Finally, normalized circular variance in the midsubstance at 3-weeks was higher (indicating less collagen fiber alignment) in I-$Bgn^{-/-}$ and I-$Dcn^{-/-}/Bgn^{-/-}$ groups at strains between 1 and

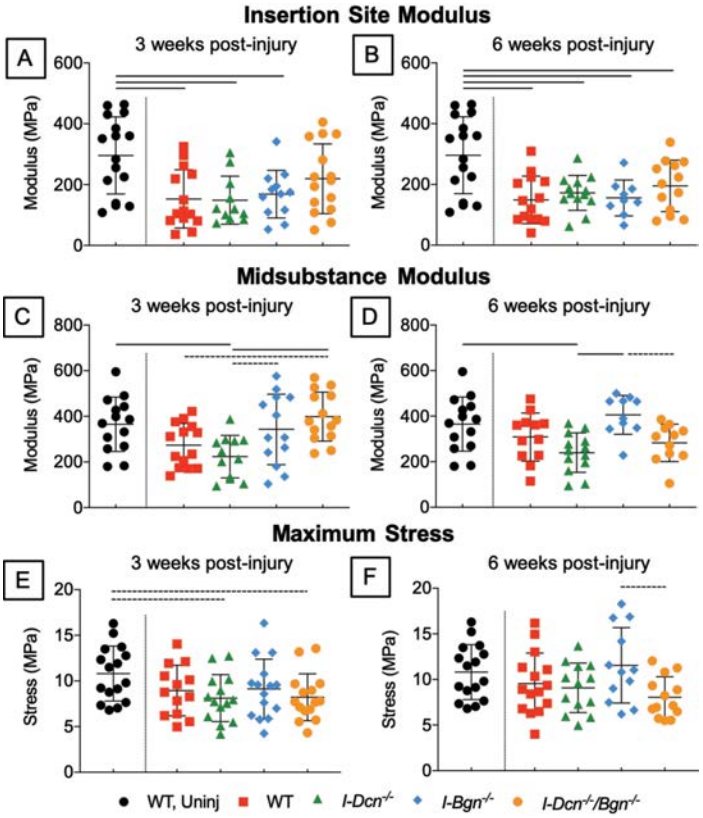

Figure 1. Quasi-static mechanical properties. Insertion site modulus was lower in injured tendons at (A) 3- and (B) 6-weeks post-injury. Only I-Dcn$^{-/-}$ groups exhibited reduced midsubstance modulus compared to uninjured at both (C) 3- and (D) 6-weeks post-injury. Maximum stress trended lower in I-Dcn$^{-/-}$ and I-Dcn$^{-/-}$/Bgn$^{-/-}$ compared to uninjured 3-weeks post-injury but (F) not at 6-weeks post-injury. Solid lines denote significance for $p < 0.05$ while dashed lines denote trends for $p < 0.1$.

4%. (Fig 2C). Few differences were observed at the insertion site or at 6-weeks (Fig 2A,B,D).

Discussion

This study investigated the roles for Dcn and Bgn in determining tendon mechanics after injury using conditional deletion of Dcn, Bgn, and both Dcn and Bgn at the time of injury. As hypothesized, results revealed that absence of Dcn negatively impacts tendon healing. Modulus within the midsubstance region, the location where the injury is introduced, was only significantly lower in I-*Dcn*$^{-/-}$ mice at both 3- and 6- weeks post-injury compared to uninjured controls.This healing response is consistent with our previous studies using conventional *Dcn*$^{-/-}$ mice,[1] further highlighting the critical role of Dcn in all stages of tendon healing. However, contrary to our hypothesis, induced knockout of Bgn did not impair the healing response compared to WT control animals. These findings contrast those observed in the conventional *Bgn*$^{-/-}$ model suggesting that altered growth, especially considering the important role of Bgn in tendon development and fibrillogenesis, may impair the tendon healing response. Interestingly, midsubstance modulus in I-*Dcn*$^{-/-}$/*Bgn*$^{-/-}$ mice was significantly greater than I-*Dcn*$^{-/-}$ mice 3-weeks post-

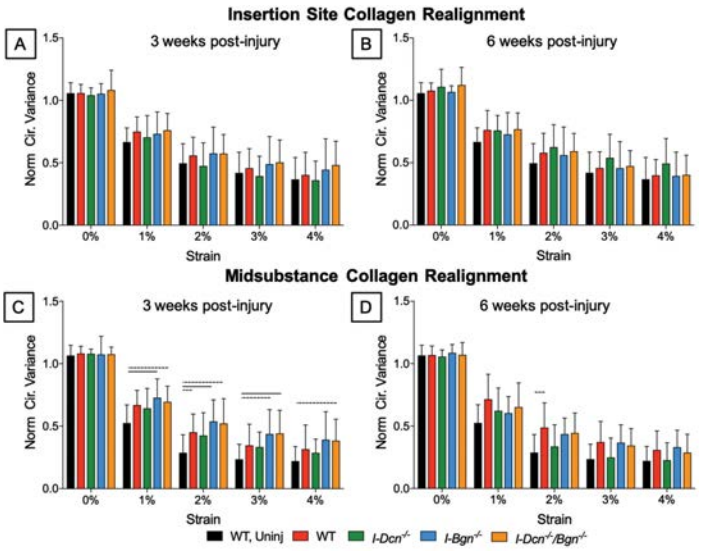

Figure 2. Collagen fiber realignment. There were no differences in collagen fiber realignment at (A) 3- or (B) 6-weeks post-injury within the insertion site region. However, (C) normalized circular variance was higher in I-Bgn$^{-/-}$ and I-Dcn$^{-/-}$/Bgn$^{-/-}$ groups at values of strain between 1 and 4%, and these differences were not sustained to (D) 6-weeks post-injury. Solid lines denote significance for $p < 0.05$ while dashed lines denote trends for $p < 0.1$.

injury, indicating there may be a compensatory or protective effect for Bgn against detrimental changes due to deletion of Dcn. However, these differences were not evident in the insertion site, suggesting the regulatory roles of decorin and biglycan are regionally dependent. Additionally, increased circular variance in both I-*Bgn*$^{-/-}$ and I-*Dcn*$^{-/-}$/*Bgn*$^{-/-}$ groups in the midsubstance at 3-weeks reveal that deletion of Bgn may alter how fibers in healing tendons respond to changes in load. However, the mechanisms driving differences in tendon modulus during healing remain unknown, and ongoing work to assess changes in gene expression, matrix composition, and fibril structure will further elucidate how Dcn and Bgn impact tendon healing.

Significance

In contrast to biglycan, induced deletion of decorin at time of injury has a detrimental effect on mechanics of healing tendons. Elucidating the isolated roles of decorin and biglycan in the response to tendon injury will contribute largely to understanding mechanisms that drive poor tendon healing.

Acknowledgements

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The Differential Roles of Decorin and Biglycan in the Early Proliferative and Remodeling Phases of Tendon Healing

Thomas Leahy, BS[1]
Ashley Fung, BS[1]
Stephanie Weiss, BS[1]
David Birk, PhD[2]
Louis Soslowsky, PhD[1]

[1]McKay Orthopaedic Research Laboratory University of Pennsylvania

[2]Department of Molecular Pharmacology and PhysiologyUniversity of South Florida

Introduction

Tendon matrix consists of highly organized collagen fibrils with small leucine rich proteoglycans (SLRPs) bound to the fibril surface. SLRPs decorin and biglycan play a critical role in regulating tendon healing processes. Specifically, using conventional $Bgn^{-/-}$ and $Dcn^{-/-}$ mice, the absence of biglycan diminished initial tendon healing following injury while the absence of decorin reduced late tendon healing.[1] However, these studies have confounding effects due to the absence of decorin and biglycan during development[2] and do not allow the roles of these SLRPs to be defined at specific phases (inflammation, proliferation, remodeling) of healing. Therefore, the objective of this study was to define the roles of decorin and biglycan in specific healing phases using inducible knockouts. We hypothesized that a complete knockout (i.e., a Bgn-Dcn double knockout) earlier in the healing process would have the greatest negative effect since both SLRPs would be absent throughout the proliferative and remodeling phases. Further, we hypothesized that decorin knockout would result in more pronounced negative effects on healing compared to biglycan knockout regardless of time of induction and that decorin knockout would reduce tendon healing similarly when knocked out during early or late stage healing due to its known role in the later remodeling phase.

Methods

Study Design

Female wildtype (WT, n=48), $Dcn^{flox/flox}$ (I-$Dcn^{-/-}$ n = 48), $Bgn^{flox/flox}$ (I-$Bgn^{-/-}$, n = 48), and compound $Dcn^{flow/flox}$/$Bgn^{flox/flox}$ (I-$Dcn^{-/-}$/$Bgn^{-/-}$, n = 48) mice with a tamoxifen (TM) inducible Cre, (B6.129-Gt(ROSA)26Sortm1(cre/ERT2)Tyj/J, Jackson Labs) were utilized (IACUC approved). At maturity (120 days), mice underwent bilateral patellar tendon injury surgery as described.[1,3] Following surgery, Cre excision of the conditional alleles was induced via two consecutive daily IP injections of tamoxifen (2 mg/40g body weight). WT mice received tamoxifen injections at 120 days and were evenly divided between the uninjured control group, which were sacrificed at 150 days, and surgery groups which were sacrificed at 3 or 6 weeks post-injury, representing the early remodeling and mid-remodeling phases of tendon healing, respectively. Mice from knockout genotypes underwent surgery and were evenly divided between Cre-induction during the early proliferative period (tamoxifen injections beginning at 5 days, termed TM5) or during the remodeling period (tamoxifen injections beginning at 21 days, termed TM21). TM5 animals were sacrificed at 3 or 6 weeks post-injury, while TM21 mice were sacrificed at 6 weeks post-injury (n = 16/genotype/induction timepoint/sacrifice timepoint).

Mechanical Testing Protocol

The patellar tendon-bone complex from one limb of each animal was dissected and prepared for mechanical testing. Tendons were then subjected to mechanical testing consisting of preconditioning followed by a quasi-static ramp to failure. Material properties of the tendons were calculated from the load-displacement data via optical tracking of stain lines on the tendon using MATLAB. Throughout mechanical testing, dynamic collagen fiber realignment was quantified using cross-polarization imaging, and regional fiber alignment data was interpolated with a polynomial fit as a function of strain from the load-displacement data between 0 and 4% tendon strain.

Statistics

Comparisons were made between genotypes and the relevant uninjured and WT controls at each induction timepoint-sacrifice timepoint combination (TM5-3wk, TM5-6wk, and TM21). Mechanical properties were compared with three separate one-way ANOVAs with Bonferroni post-hoc corrections with significance at $p \leq 0.05$ and trends at $p \leq 0.1$. Fiber realignment properties were compared between strain levels and genotypes with a two-way ANOVA. If the effect of strain level or genotype was significant, a one-way ANOVA with Bonferroni post hoc corrections was performed (if strain had a significant effect, multiple comparisons were made from 0% strain to all strain levels and between adjacent strain levels) with significance set at $p \leq 0.05$.

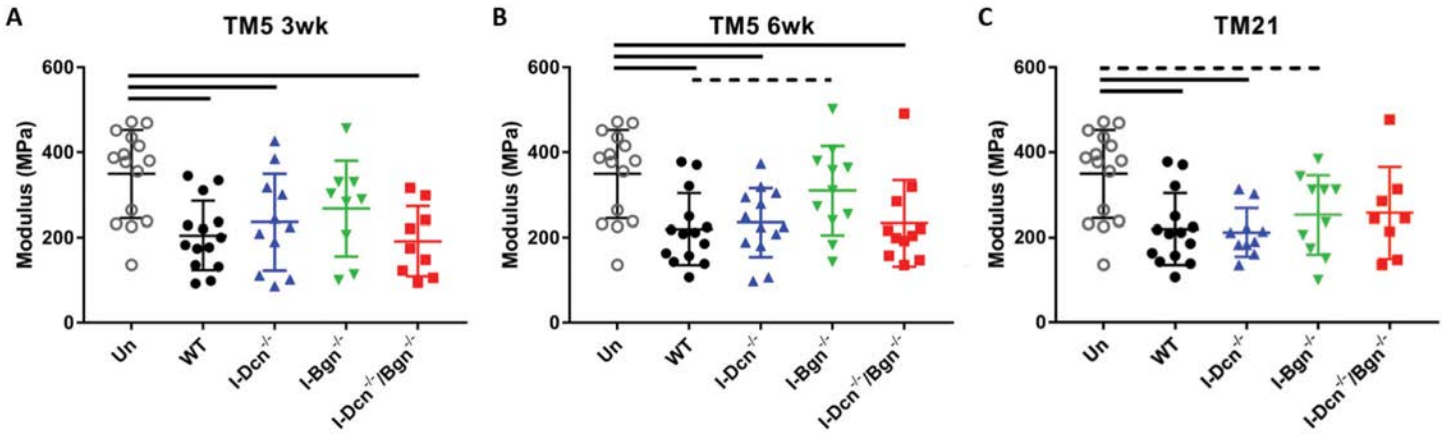

Figure 1. Tendon modulus comparisons at TM5-3wk **(A)**, TM5-6wk **(B)**, and TM21 **(C)**. The TM5 I-Bgn$^{-/-}$ group abolished differences with injury, while TM5 and TM21 I-Dcn$^{-/-}$ groups showed consistent effects on mechanics. Solid bars represent significance ($p \leq 0.05$) and dotted bars represent trends ($p \leq 0.1$).

Results

Injury significantly reduced modulus at both 3 and 6 weeks in the WT tendons (Fig 1). Decreased modulus was maintained in both the TM5 I-*Dcn*$^{-/-}$ and TM5 I-*Dcn*$^{-/-}$/*Bgn*$^{-/-}$ groups but not in the TM5 I-*Bgn*$^{-/-}$ group at either 3 or 6 weeks. In the TM21 groups, a decreased modulus was maintained in the I-*Dcn*$^{-/-}$ group with a trending decrease in the I-*Bgn*$^{-/-}$ group and no difference between the uninjured and I-*Dcn*$^{-/-}$/*Bgn*$^{-/-}$ groups. There were no changes in max stress with injury or between genotypes, except for a trending decrease in max stress at 6 weeks in the I-*Dcn*$^{-/-}$ group (data not shown). All tendons showed significantly increased fiber realignment with increasing strain in both the insertion and midsubstance regions (Fig 2, insertion data not shown). There were no differences in realignment between genotypes, except in the midsubstance region of the TM5 I-*Dcn*$^{-/-}$ tendons at 6 weeks, which showed significantly less realignment relative to the uninjured control.

Discussion

Contrary to our hypothesis, the TM5 I-*Dcn*$^{-/-}$/*Bgn*$^{-/-}$ and TM21 I-*Dcn*$^{-/-}$/*Bgn*$^{-/-}$ groups did not exhibit significantly reduced tendon healing at 3 or 6 weeks relative to the WT control. Moreover, decorin knockout did not show a significant negative effect on tendon mechanics compared to biglycan knockout at either TM5 or TM21. Interestingly, biglycan knockout appeared to reduce the negative effects of tendon injury, as there were no negative mechanical effects of injury at 3 or 6 weeks in the TM5 I-*Bgn*$^{-/-}$ tendons. Further, these results suggest that biglycan plays a negative role in early healing, as TM21 I-*Bgn*$^{-/-}$ had negative changes with injury not present in TM5 I-*Bgn*$^{-/-}$. Finally, while TM5 I-*Dcn*$^{-/-}$ and TM21 I-*Dcn*$^{-/-}$ had similar effects on tendon mechanics as hypothesized, TM5 I-*Dcn*$^{-/-}$, but not TM21 I-*Dcn*$^{-/-}$ showed altered fiber realignment behavior at 6 weeks, suggesting that decorin plays a role in regulating fiber organization in early stage tendon healing. These results contrast with previous studies using conventional knockout mice that suggested that *Bgn*$^{-/-}$ mice had impaired early tendon healing and *Dcn*$^{-/-}$ mice had clearly diminished late stage tendon healing,[1] underscoring the importance of using inducible animals to distinguish the specific temporal roles of these SLRPs in tendon healing. Future work will elucidate the underlying mechanisms behind altered tendon healing with temporal deletion of decorin and biglycan by investigating gene expression, matrix composition, and fibril structure in these tendons.

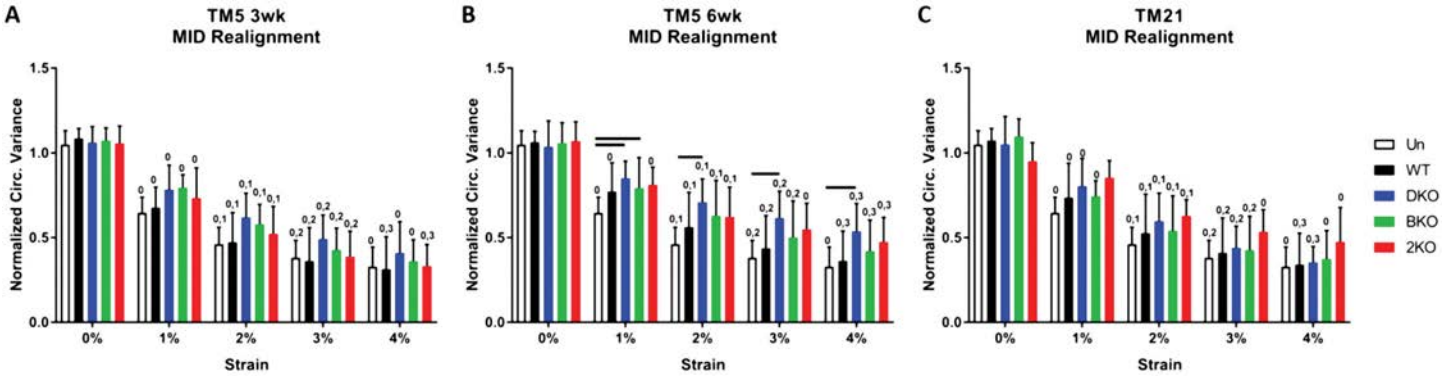

Figure 2. Midsubstance realignment data for TM5-3wk **(A)**, TM5-6wk **(B)**, and TM21 **(C)**. All groups showed increased alignment with increasing strain. TM5 I-Dcn$^{-/-}$ group showed altered fiber realignment behavior relative to uninjured. Solid bars represent significance ($p \leq 0.05$) between genotypes. Numbers above indicate significance from noted strain values given the comparisons performed (see methods).

Significance

This study used novel inducible knockout mice for decorin and biglycan to investigate the temporal roles of these SLRPs during the early proliferative and remodeling phases of tendon healing. This data suggests that biglycan plays a significant negative role in tendon healing, particularly in the early proliferative phase, while decorin does not play a drastic temporal role in tendon healing.

Acknowledgements

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Collagen V Deficiency during Healing Mitigates the Quasi-Static Mechanical Deficits of Injured Tendons

Ryan Leiphart, BS[1]
Stephanie Weiss, BS[1]
David Birk, PhD[2]
Louis Soslowsky, PhD[1]

[1]McKay Orthopedic Research Laboratory
University of Pennsylvania

[2]Department of Molecular Pharmacology and Physiology
University of South Florida

Introduction

Classic Ehlers-Danlos Syndrome (cEDS) is characterized by genetic mutations of collagen V, a matrix protein present in tendon.[1] Two hallmarks of cEDS are connective tissue hyperelasticity and poor wound healing, and a murine model of cEDS demonstrates impaired tendon healing.[2,3] It is unknown whether this impaired healing response is due to the regulatory role of collagen V during tendon healing or due to pre-existing differences in collagen V-deficient tendons. Therefore, the objective of this study was to determine the isolated role of collagen V on healing tendon mechanics. Due to its role in fibrillogenesis, we hypothesized that acute knockout of collagen V following injury would result in decreased tendon mechanical properties at both intermediate and late healing time points.

Methods

Animals

Male wild-type (WT) (n = 45) and bitransgenic *Col5a1*$^{flox/+}$ (n = 30) and *Col5a1*$^{flox/flox}$ (n = 30) mice with a tamoxifen (TM)-inducible Cre were used in this study (IACUC approved). At 120 days old, mice received bilateral, full thickness, partial width patellar tendon injuries under sterile conditions.[4] For Cre-mediated excision of the *Col5a1* gene, mice received two consecutive daily doses of TM (2mg/40g body weight) beginning on the day of injury. Mice were sacrificed at 3 or 6 weeks post-injury. Healthy WT control mice received TM doses (3 days of 4mg/40g body weight) at 120 days old and were sacrificed 30 days later. Tibia-patellar tendon-patella complexes were harvested and prepared for mechanical testing as previously described.[5]

Mechanical Testing

Uniaxial, viscoelastic testing was performed with an Instron 5848. The testing protocol consisted of 10 cycles of preconditioning, followed by stress relaxations at 3%, 4%, and 5% strain. Following each stress relaxation, frequency sweeps of 10 cycles at 0.1, 1, 5, and 10Hz were performed. A ramp-to-failure followed the 5% stress relaxation. Percent relaxation, dynamic modulus (E*), and phase shift (δ) were quantified for each stress relaxation and frequency sweep. Stiffness, modulus, maximum load, and maximum stress were quantified from the ramp-to-failure data.

Statistics

For all mechanical properties, one-way ANOVAs with Bonferroni post-hoc tests were used to compare across genotypes and uninjured controls at each healing time point. Significance was set at $p \leq 0.05$, and trends were set at $p \leq 0.1$.

Results

Injury effects

Compared to uninjured tendons, injured WT tendons had increased cross-sectional area (CSA) (Fig 1).

Quasi-Static Mechanics

Compared to uninjured tendons, injured WT tendons were less stiff (Fig 2A), had no differences in max load (data not shown), had decreased modulus (data not shown), and lower max stress (Fig 2B).

Stress Relaxation

Compared to uninjured tendons, injured WT tendons had greater stress relaxation at 3%, 4%, and 5% strains (data not shown).

Dynamic Mechanics

Compared to uninjured tendons, injured WT tendons had decreased dynamic moduli at all

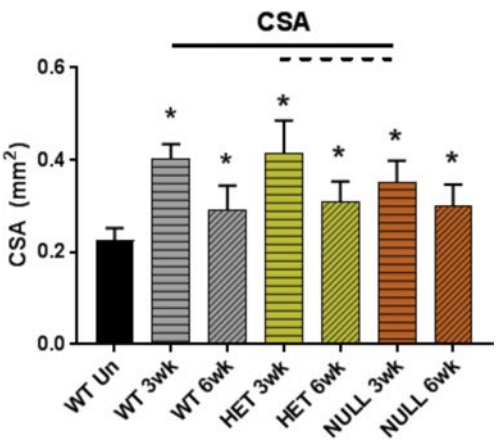

Figure 1. Cross-sectional area. Injured tendons across all genotypes and healing time points had larger CSA than uninjured tendons. * indicates $p < 0.05$ compared to uninjured tendons. Solid bars indicate $p < 0.05$, and dashed bars indicate $p < 0.1$.

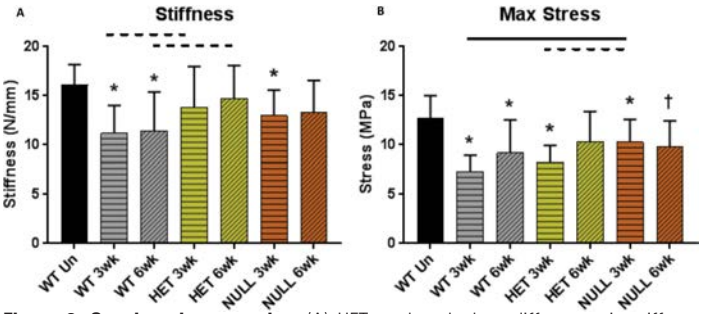

Figure 2. Quasi-static properties. (A) HET tendons had no differences in stiffness compared to uninjured tendons but trended towards higher stiffness compared to WT at both healing time points. (B) 6-week HET tendons had no differences in max stress compared to uninjured tendons. * indicates $p < 0.05$, and † indicates $p < 0.1$, compared to uninjured tendons. Solid bars indicate $p < 0.05$ and dashed bars indicate $p < 0.1$.

strains and frequencies, larger tan(δ) values at 3 and 4% strain and for most frequencies at 5% strain for 6-week WT tendons (data not shown).

Genotype effects

Injured *Col5a1*$^{+/-}$ (HET) and *Col5a1*$^{+/+}$ (NULL) tendons had increased CSA relative to uninjured (Fig 1). At 3 weeks post-injury, NULL tendons had decreased CSA relative to WT and a trend towards smaller CSA relative to HET.

Quasi-Static Mechanics

No differences in stiffness were observed between HET and uninjured tendons (Fig 2A). HET tendons trended towards higher stiffness relative to injured WT tendons at both healing time points. 3-week NULL tendons were less stiff than uninjured tendons, but this decrease did not persist at 6-weeks. 3-week HET tendons had lower max stress than uninjured tendons, but this decrease did not persist at 6-weeks (Fig 2B). 3-week NULL tendons had lower max stress than uninjured tendons, and this difference persisted as a trend at 6-weeks. 3-week NULL tendons had higher max stress than 3-week WT tendons and trended towards higher max stress relative to 3-week HET tendons. HET and NULL tendons had decreased modulus compared to uninjured. No differences in max load were observed between knockout and uninjured tendons. No differences in max load or modulus were observed between injured genotypes.

Stress Relaxation

HET and NULL tendons had increased stress relaxation at 3% and 4% strain relative to uninjured. 3-week HET and NULL tendons exhibited increased stress relaxation at 5% strain relative to uninjured, which persisted for 6-weeks HET but not for 6-week NULL tendons. No differences in stress relaxation were observed between injured genotypes at any strain.

Dynamic Mechanics

HET and NULL tendons had decreased dynamic moduli relative to uninjured. For most frequencies at 3% and 4% strain, HET and NULL tendons had larger tan(δ) values than uninjured, while at 5% strain, 6-week HET tendons had larger tan(δ) values than uninjured. No differences in tan(δ) values were observed between 6-week NULL and uninjured tendons. No differences in dynamic modulus or tan(δ) values were observed between injured genotypes at any strain or frequency.

Discussion

Injured tendons exhibited substantial deficits in mechanical properties relative to uninjured tendons. Contrary to our hypothesis, however, acute knockout of collagen V did not further impair the mechanical properties of these healing tendons. Instead, stiffness did not decrease through healing in HET tendons. Injured HET tendons were stiffer than WT tendons at each healing time point. No decreases in max stress were seen with 6-week HET tendons. These results demonstrate that while healing tendons have impaired mechanical properties, collagen V deficiency during healing does not further diminish these properties. Instead, collagen V haploinsufficiency during healing mitigated the decreases in stiffness and max stress seen in WT injured tendons. Impaired tendon healing in cEDS patients may not be due to the regulatory role of collagen V during healing and may instead be due to pre-existing deficiencies of the tissue. A previous study found that fibroblasts from a murine model of cEDS demonstrated decreased proliferation, migration, and wound healing relative to WT fibroblasts.[6] Results of the present study support the notion that poor wound healing in cEDS patients is due to differences in tissue properties that existed prior to injury. A limitation of this study is the global nature of the collagen V knockouts, which could cause confounding effects on neighboring tissues. The inducible knockout models used here lessen these effects due to the short period of knockout. Future studies will analyze the composition and gene expression of these tendons to identify other differences in healing, collagen V-deficient tendons. Overall, this study demonstrates that collagen V deficiency does not impair the mechanical properties of injured tendons beyond the normal healing response, and instead mitigates some of these mechanical deficits.

Significance

This study reveals that the quasi-static mechanical deficits of injured tendons are not worsened, and are instead mitigated, by collagen V deficiency. These results provide a further understanding of the role of collagen V in tendon healing.

Acknowledgements

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Acute Reduction in Collagen V Expression Increases Viscoelasticity in Mature Tendons

Ryan Leiphart, BS[1]
Stephanie Weiss, BS[1]
David Birk, PhD[2]
Louis Soslowsky, PhD[1]

[1]McKay Orthopedic Research Laboratory
University of Pennsylvania

[2]Department of Molecular Pharmacology and Physiology
University of South Florida

Introduction

Classic Ehlers-Danlos Syndrome (cEDS) is a disease caused by mutations in the gene encoding collagen V, a fibrillogenic protein present in tendon.[1] cEDS patients experience joint hypermobility, which is likely caused by connective tissue dysregulation in the absence of collagen V.[2] Tendon-specific knockout of collagen V decreases tendon mechanical properties due to an aberrant development of tissue fibrils.[3] However, the regulatory role of collagen V in tendon homeostasis has not been distinguished from its role in development. Understanding this homeostatic role is critical for establishing the baseline effect of collagen V knockdown in both healthy and injured mature tendons. Therefore, the objective of this study was to determine the effect of acute knockdown of collagen V on the mechanical properties of mature tendons. Since the tendon fibril network is well-established by tissue maturity, we hypothesized that acute knockdown of collagen V in mature tendons would result in minimal changes to tendon mechanical properties.

Methods

Animals

Male wild-type (WT) (n = 15) and bitransgenic *Col5a1*$^{flox/+}$ (n = 15) and *Col5a1*$^{flox/flox}$ (n = 15) mice with a tamoxifen (TM)-inducible Cre were used in this study (IACUC approved). At 120 days old, mice received 3 consecutive daily TM doses (4mg/40g body weight) for Cre-mediated excision of the *Col5a1* gene. Mice were sacrificed 30 days later. Tibia-patellar tendon-patella complexes were harvested and prepared for mechanical testing as previously described.[4]

Mechanical Testing

Uniaxial, viscoelastic testing was performed with an Instron 5848. The testing protocol consisted of 10 cycles of preconditioning, followed by stress relaxations at 3%, 4%, and 5% strain. Following each stress relaxation, frequency sweeps of 10 cycles at 0.1, 1, 5, and 10Hz were performed.A ramp-to-failure followed the 5% stress relaxation. Percent relaxation, dynamic modulus (E*), and phase shift (δ) were quantified for each stress relaxation and frequency sweep. Stiffness, modulus, maximum load, and maximum stress were quantified from the ramp-to-failure data.

Statistics

For all mechanical properties, one-way ANOVAs with Bonferroni post-hoc tests were used to compare across genotypes. Significance was set at $p \leq 0.05$, and trends were set at $p \leq 0.10$.

Results

No differences in cross-sectional area (CSA) were observed between genotypes (data not shown).

Quasi-Static Mechanics

Col5a1$^{-/-}$ (NULL) tendons had a decreased modulus relative to WT tendons (Fig 1). No differences in stiffness, max load, or max stress were observed between genotypes (data not shown).

Stress Relaxation

Col5a1$^{+/-}$ (HET) tendons exhibited increased stress relaxation compared to WT tendons at 4% strain (Fig 2). NULL tendons trended towards increased stress relaxation compared to WT tendons at 4% strain. No differences were observed in stress relaxation between genotypes at 3% and 5% strain.

Dynamic Mechanics

At 3% strain, NULL tendons had increased tan(δ) values compared to WT tendons at 0.1Hz

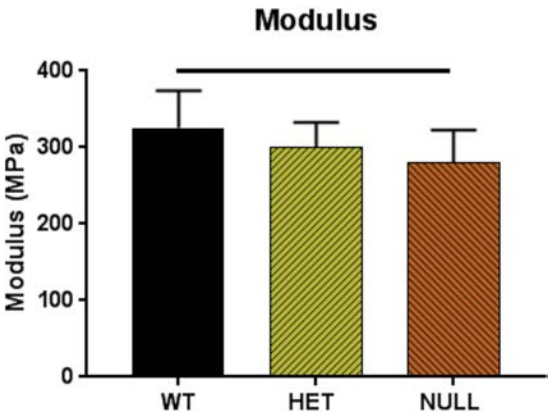

Fig 1. Elastic modulus. NULL tendons exhibited a decreased modulus relative to WT tendons. Solid bars indicate $p \leq 0.05$.

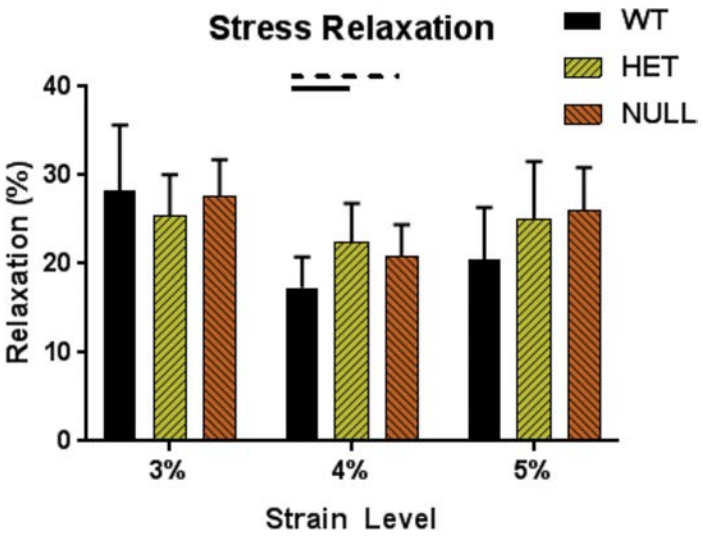

Figure 2. Stress relaxation. HET and NULL tendons displayed increased stress relaxation compared to WT tendons at 4% strain. Solid bars indicate $p \leq 0.05$, and dashed bars indicate $p \leq 0.1$.

(trend), 1Hz, and 5Hz and had increased tan(δ) values compared to HET tendons at 0.1Hz (data not shown). HET tendons had increased tan(δ) values compared to WT tendons at 1Hz and 5Hz (trend). At 4% strain, NULL tendons had increased tan(δ) values compared to WT tendons at all frequencies and trended towards higher tan(δ) values relative to HET tendons at 0.1Hz and 1Hz (Fig 3A). HET tendons had increased tan(δ) values compared to WT tendons at all frequencies (trend at 0.1Hz). At 5% strain, NULL tendons had increased tan(δ) values compared to WT tendons at all frequencies (Fig 3B). NULL tendons had increased tan(δ) values compared to HET tendons at 1Hz and 5Hz, with trending increases at 0.1Hz and 10Hz. No differences in dynamic moduli were observed between genotypes across strain levels and frequencies (data not shown).

Discussion

Surprisingly, acute reduction in collagen V expression in mature tendons led to numerous changes in tendon viscoelastic properties. NULL tendons exhibited increased stress relaxation at 4% strain and increased tan(δ) values at nearly every strain and frequency. HET tendons exhibited increased stress relaxation at 4% strain and displayed intermediate tan(δ) values between those of WT and NULL tendons. These results are in direct contrast to our hypothesis, as knockdown of collagen V increased tendon viscoelasticity in an allele dosage-dependent manner. While mature tendons were generally believed to be quiescent tissues, there is growing evidence that tendon fibril networks are dynamic and remodel on shorter time scales than previously thought.[5] Results of this study strongly support the notion of these dynamic networks, with collagen V playing a large role in regulating fibril properties beyond the developmental time frame. While this study is limited by global knockout models and potential confounding effects on neighboring tissue, the induced and short period of knockdown minimizes these effects. Future studies will analyze the composition and gene expression of these collagen V-knockdown tendons to further elucidate the surprising regulatory role of collagen V in mature tendons. Overall, this study demonstrates that acute reduction of collagen V expression in mature tendons leads to an increase in their viscoelastic properties.

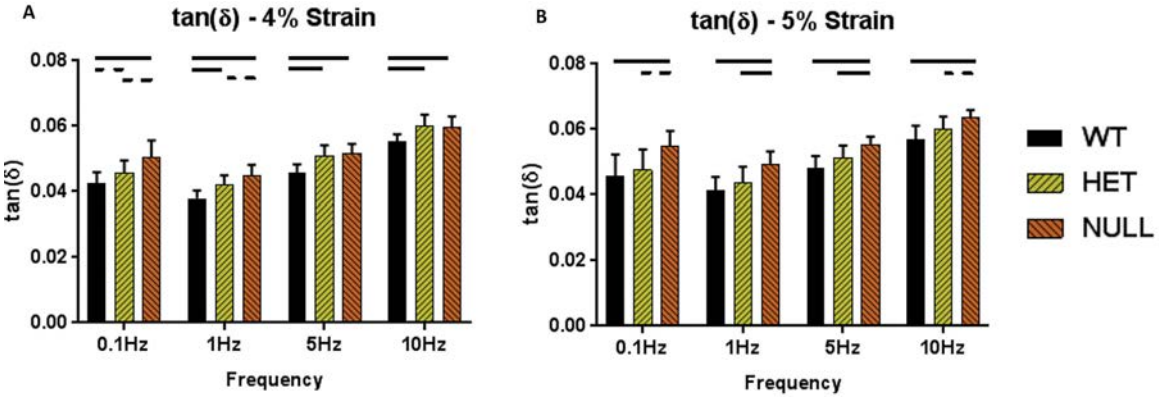

Figure 3. Phase shift. (A,B) NULL tendons had higher tan(δ) values than WT tendons at every frequency of both strains. HET tendons exhibited intermediate tan(δ) values between those of WT and NULL tendons. Solid bars indicate $p < 0.05$, and dashed bars indicate $p < 0.1$.

Significance

This study reveals that acute reduction in collagen V expression increases viscoelasticity in mature tendons. These results provide further insight into the surprising role of collagen V in regulating mechanical properties during tendon homeostasis.

Acknowledgements

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Role of Ligamentous Restraints During Anterior-Posterior Drawer Tests of the Murine Knee

Snehal Shetye, PhD[1]
John Bova, BS[1]
Andrew Kuntz, MD[1]
Miltiadis Zgonis, MD[1]
David Butler, PhD[2]
Nathaniel Dyment, PhD[1]

[1]McKay Orthopaedic Research Laboratory
University of Pennsylvania

[2]Biomedical Engineering Program
University of Cincinnati

Introduction

Murine models of altered knee loading are frequently employed to study the pathogenesis of osteoarthritis and more recently, to investigate tendon-bone attachments within the ensuing bone tunnels.[1,2] Human cadaveric and large animal model demonstrated that the anterior cruciate (ACL) and posterior cruciate (PCL) ligaments are the primary restraints to anterior or posterior tibial translation, respectively. Even though murine knee destabilization models are common, the specific contributions of the cruciate ligaments have not been quantified. Further, the role of other murine knee ligaments that provide secondary restraints, such as the medial and lateral collateral ligaments (MCL, LCL) under anterior/posterior loading remains unknown. Therefore, the objective of the study was to investigate the role of ligamentous restraints in the murine knee during anterior-posterior loading. We hypothesized that the ACL and PCL will be the primary restraints to anterior and posterior drawer, respectively. Based on murine knee ligament anatomy, we also hypothesized that the MCL will be the secondary restraint in anterior drawer and the LCL will be the secondary restraint in posterior drawer.

Methods

Experimental Design

All animals and procedures were approved by UPenn's IACUC. CD1 mice (4 male, 3 female, n = 7) 16 weeks of age were assessed for anterior-posterior drawer stability in a custom fixture recently described by our group.[2] Briefly, following sacrifice, 7 hindlimbs (6 right, 1 left) were isolated, all extraneous soft tissue removed, and all capsule ligaments, including the cruciates and collaterals, along with the menisci left intact. The patellar tendon was removed based on its previously described role in anterior posterior loading.[3] The distal half of each tibia was potted in an acrylic tube using PMMA. This construct was then loaded onto a material testing machine. The potted tibial end was fixed in a custom fixture that allowed for adjustment of tibial plateau angle. The distal end of the femur was lowered into another acrylic tube affixed to a custom fixture that could control knee flexion by rotating the femur around the joint center of rotation. The knee was set up at 90 degrees of flexion for all tests. The knee joint was tested for anterior and posterior stability by cyclic loading under displacement control between ± 0.3mm for 5 cycles and the 5th cycle was used to quantify stability for all cases

Selective Cutting Procedure

The intact knee joint loads were evaluated at ± 0.3mm (+ve = anterior drawer, -ve = posterior drawer) to establish the baseline conditions. Following this, a 27G needle was used to carefully cut the ACL with an anterior approach. This procedure was performed on the testing machine itself to not lose the initial knee joint zero reference position. The stability test was repeated at ±0.3mm to quantify the contribution of the ACL. Next, the PCL was carefully transected, and the stability test repeated to quantify PCL contribution. After transection of the ACL and PCL, the knee joint was substantially unstable and barely registered any loads at ± 0.3mm. Thus, to quantify MCL and LCL contributions, the drawer tests were modified to reach ±1.0mm, as described previously in cadavers.[3] This allowed for quantifying MCL and LCL contributions as secondary restraints. The transection of each ligamentous structure was not randomized since it has been shown previously to not have an effect if tests are conducted under displacement control to a specified peak displacement.[3]

Results

Primary Restraints

The peak anterior restraining force for the intact knee was 1.24 ± 0.17N at 0.3mm of displacement. The peak posterior restraining force for the intact knee was 0.82±0.1N at −0.3mm of displacement. Transection of the ACL dropped the peak anterior restraining force at 0.3mm to 0.06 ± 0.04N indicating that ACL contributed to 95.01 ± 3.30% of the restraining force. Interestingly, ACL transection also reduced the peak posterior load by 14.0 ± 9.83%. Transection of the PCL dropped the posterior restraining force at −0.3mm to −-0.1 ± 0.07N, which translated to a contribution of 89.55 ± 6.96% of the peak restraining force in the posterior direction at -0.3mm by the PCL. Primary restraint contributions can be seen from a representative sample in Figure 1.

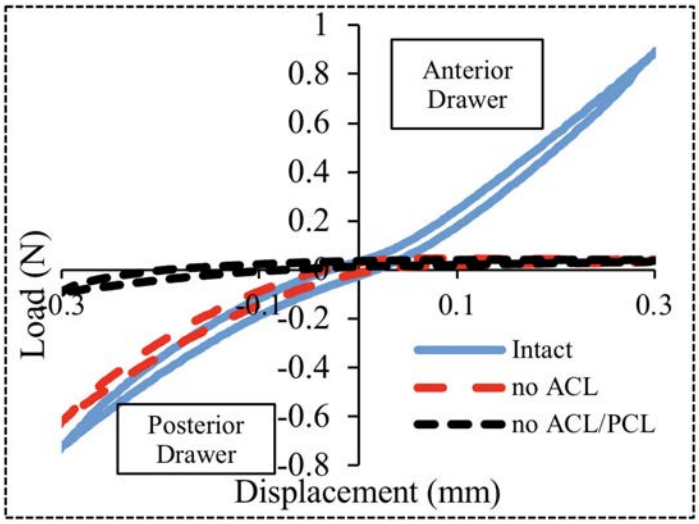

Figure 1. Representative sample plots that show the effect of transecting the ACL and PCL on anterior and posterior drawer loads.

Table 1: **ACL and PCL force contributions at 0.3mm drawer. Values are reported as Mean (S.D.).**

Anterior Drawer (n=7)			Posterior Drawer (n=5)			
Intact Force	Anterior Cruciate Force	ACL Contribution	Intact Force	Posterior Cruciate Force	PCL Contribution	ACL Contribution
(N)	*(N)*	*(%)*	*(N)*	*(N)*	*(%)*	*(%)*
1.24(0.17)	1.18(0.18)	95.01(3.3)	−0.82(0.1)	−0.58(0.09)	89.55(6.96)	14.0(9.83)

Secondary Restraints

After ACL and PCL transections, the peak restraining forces at ± 1.0mm of displacements were found to be 0.32 ± 0.19N and −0.52 ± 0.31 in the anterior and posterior directions, respectively. Transection of the MCL only influenced the anterior peak force whereby the force dropped by 86.13 ± 8.3%. Transection of the LCL only influenced the posterior peak force whereby the force dropped by 85.12 ± 11.89%.

Discussion

To better understand molecular and genetic mechanisms that regulate osteoarthritis pathogenesis in murine models, it is crucial to understand the mechanical stability of the knee joint before and after destabilization and how the joint adapts with time post-injury. The data presented here provide a baseline for studies creating these OA models by transecting supporting ligamentous structure involved in knee stability. We found that, similar to the human knee, the ACL and PCL are the primary structures providing anterior and posterior stability, respectively, in the murine knee. Interestingly, we did see an approximately 14% contribution by the ACL to posterior stability, which has not been observed in humans. Further, at a knee flexion angle of 90 degrees, and in absence of the ACL and PCL, the MCL provides most of the stability in the anterior direction and the LCL provides most of the stability in the posterior direction. While great care was taken to not disrupt other structures such as the menisci during transection of these ligaments, it is possible due to the small size of the murine knee joint. However, future studies will use contrast MicroCT to verify damage to each structure. Our data suggest that the menisci did not play a major role in anterior-posterior knee stability since the peak load were close to 0N after transection of these ligaments. This agrees with a previous study that followed a displacement control protocol as presented here.[3] However, other studies that employed a load-control protocol have shown that the menisci play a role in knee stability at lower flexion angles.[4,5] Furthermore, our study did not apply a compressive load to the knee, which might be necessary for the menisci to be loaded. Alternatively, a case could also be made for the menisci to be more important in varus-valgus knee stability, which was not investigated here. Further studies will investigate the influence of knee flexion angle, compression joint load, and the menisci to anterior-posterior stability of the murine knee.

Significance/Clinical Relevance

This methodology can be applied to murine knee destabilization PTOA models over the time course of OA progression, correlating with biological changes to the joint. In addition, methods to restabilize the knee[2] to attenuate OA progression can be verified.

Acknowledgements

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Knockdown of Collagen V during the Inflammatory Healing Phase Significantly Affects Quasi-Static Tendon Mechanics

Brittany Taylor, PhD[1]
Ryan Leiphart, BS[1]
Stephanie Weiss, BS[1]
David Birk, PhD[2]
Louis Soslowsky, PhD[1]

[1]McKay Orthopaedic Research Laboratory
University of Pennsylvania

[2]Department of Molecular Pharmacology and Physiology
University of South Florida

Introduction

Collagen V is a quantitatively minor component of collagen fibrils with major regulatory roles throughout tendon healing. Our established murine model of collagen V haploinsufficiency demonstrated diminished recovery of mechanical properties and altered fibril morphology following tendon injury; which supports the important modulatory role of collagen V in tendon injury repair.[1] However, these studies utilized conventional mouse models of collagen V deletion and therefore the lack of collagen V during development and maturation *and* the effect on the injury response is confounding. Thus, the isolated role of collagen V at defined phases of tendon healing following injury remains unknown. Therefore, the objective of this study was to elucidate the specific mechanistic regulatory role(s) of collagen V in the late inflammatory and remodeling responses of tendon healing in a normal matrix using inducible collagen V null and heterozygous models. We hypothesize that decreased collagen V during the inflammatory and remodeling phases will result in significantly decreased dose-dependent tendon mechanical properties during both phases.

Methods

Animal Surgery

Adult male wild-type (WT) (n = 15), $Col5a1^{flox/+}$ (n = 45), and $Col5a1^{flox/flox}$ (n = 45) mice with a tamoxifen (TM) inducible Cre were utilized for this study (IACUC approved). Bilateral partial width, full thickness patellar tendon injury was performed on the $Col5a1^{flox/+}$ and $Col5a1^{flox/flox}$ mice at maturity (120 days) under sterile conditions as described.[2] Cre-induced excision of the conditional alleles of the transgenic mice was performed at 5 days following surgery during the late inflammatory phase (TM5) and 21 days following surgery during the remodeling phase (TM21) via two consecutive daily IP injections of tamoxifen (2mg/40g body weight). The TM5 mice were sacrificed at 3 and 6 weeks post-injury and the TM21 mice were sacrificed 6 weeks post injury (n = 15/genotype/timepoint). The WT uninjured control mice were administered TM doses (3 days of 4mg/40g body weight) at 120 days old and were sacrificed 30 days later. The patellar-tendon-tibia complexes were harvested and prepared for uniaxial mechanical testing.

Mechanical Testing

The tendons were subjected to viscoelastic mechanical testing, which consisted of 10 cycles of preconditioning and stress relaxations at 3%, 4%, and 5% strain. Each stress relaxation was followed by 10 cycles of frequency sweeps, quasi-static ramp to failure, and 5% stress relaxation. The ramp to failure data was used to determine stiffness, modulus, maximum load, and maximum stress. Percent relaxation was quantified for each percent strain level.

Statistics

One-way ANOVAs with Bonferroni correction post-hoc tests were performed to compare the WT uninjured and injured controls to the injured $Col5a1^{flox/+}$ (HET) and $Col5a1^{flox/flox}$ (NULL) tendons at each Cre-induction and healing time point (TM5 at 3 weeks, TM5 at 6 weeks, TM21 at 6 weeks) to define the specific effect of collagen V at each healing phase. Significance was set at $p \leq 0.05$ and trends were set at $p \leq 0.1$.

Results

Cross-sectional area and stiffness of the injured tendons were significantly increased compared to the uninjured WT tendons at both induction and healing time points. The injured WT tendons trended towards increased cross-sectional area compared to HET tendons at TM5 induction after 3 weeks of healing, but the opposite trend was observed between the injured WT and HET at TM5 and TM21 induction after 6wks (data not shown). The injured WT tendons were significantly stiffer than the injured HET and NULL tendons at TM5 after 3 and 6 weeks of healing (Fig. 1A & 1B), but these differences were not seen with TM21 at 6 weeks (data not shown). Max load of the uninjured WT was significantly greater than the injured WT tendons at TM5 after 3 weeks of healing, injured NULL tendons at TM5 after 3 and 6 weeks of healing, and injured HET tendons at TM5 and TM21 after 6 weeks of healing (Fig. 2). Injured WT tendons also had increased max load compared to injured HET tendons at TM5 after 3 (Fig. 2A) and 6 weeks of healing (Fig. 2B). Decreasing trends in max load were

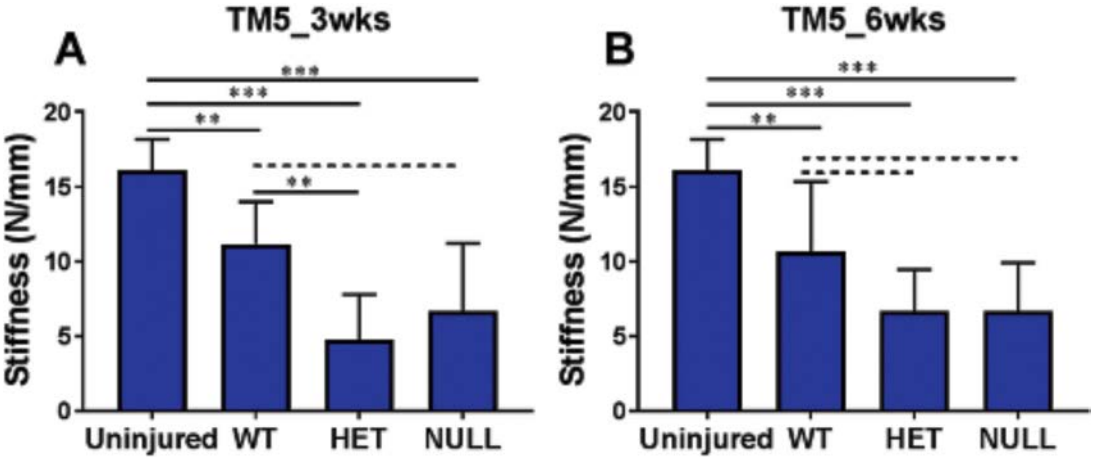

Figure 1. Stiffness. Uninjured tendons exhibited increased stiffness compared to injured tendon and injured WT tendons were stiffer than the HET and NULL tendons when collagen V was knocked out of 5 days post-surgery (TM5) after **(A)** 3 and **(B)** 6 weeks of healing ***: $p \leq 0.001$, **: $p \leq 0.01$, *: $p \leq 0.01$.

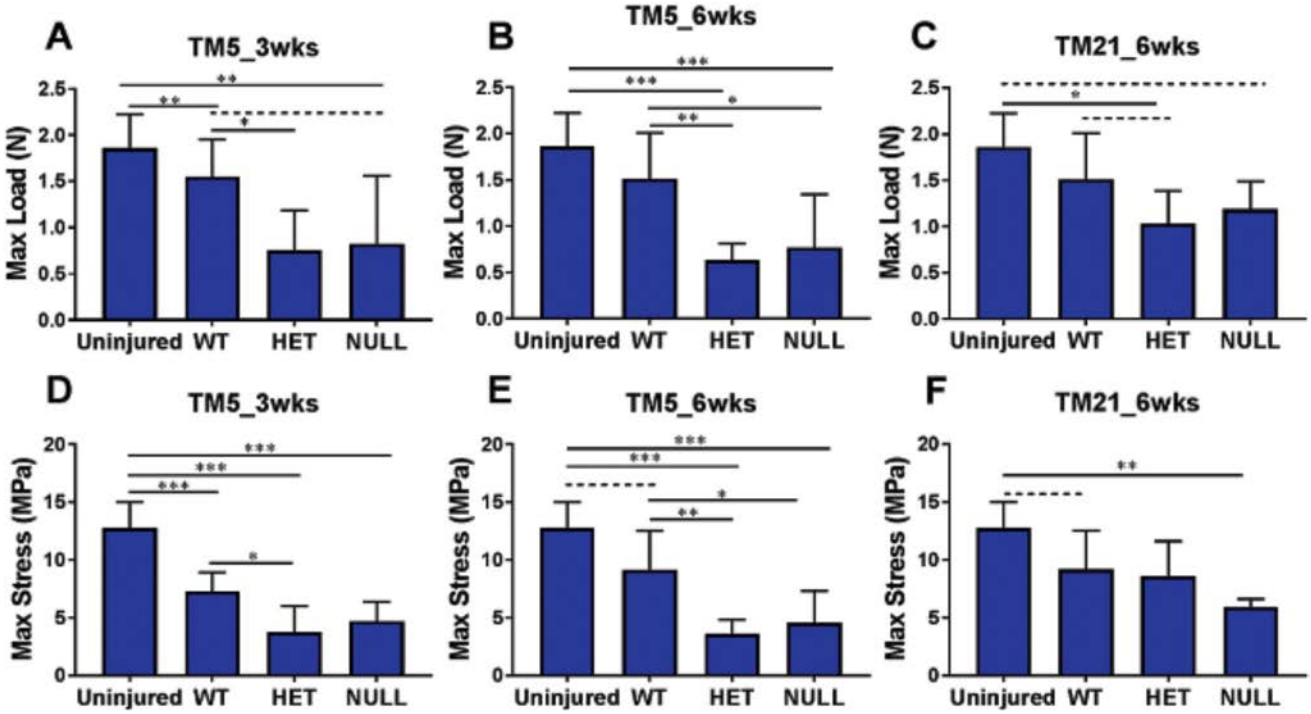

Figure 2. Max Load and Max Stress. Injured tendons exhibited decreased **(A-C)** max load and **(D-F)** mas stress compared to uninjured WT when collagen V was knocked ouut at 5 days post-surgery after **(A&D)** 3 and **(B&E)** 6 weeks of healing. These differences were lessened at the 21 day induction time point and 6 weeks of healing **(C&F)**. ***: $p \leq 0.001$, **: $p \leq 0.01$, *: $p \leq 0.05$, ---: $p \leq 0.01$.

observed between injured WT and NULL at TM5 after 3 weeks of healing (Fig. 2A), and at TM21 after 6 weeks of healing between uninjured WT and injured NULL, and injured WT and HET tendons (Fig. 2C). Significant differences in max stress were observed between the uninjured WT tendons and injured tendons at TM 5 after 3 weeks, injured HET and NULL tendons after TM 5 after 6 weeks, and injured WT (trend) and NULL tendons at TM21 after 6 weeks (Fig. 2D-F). The injured WT tendons also exhibited increased max stress compared to the injured NULL at TM5 after 6 weeks and injured TM5-induced HET tendons at both healing time points (Fig. 2D & 3E). Stress relaxation of the injured tendons at 3 and 4% strain was increased compared to the uninjured WT tendons at both induction and healing time points (data not shown). Statistical differences in stress relaxation were observed with TM5 after 3 weeks of healing between injured WT and HET tendons at 4% (trend), injured WT and NULL tendons at 3% and 4% (data not shown). Stress relaxation at 5% strain was increased for the injured HET and NULL tendons compared to the uninjured WT at TM 5 and TM21 (trend) independent of healing time, and decreased for the injured WT tendons compared to the injured HET and NULL tendon at TM5 after 3 weeks (data not shown). No differences were observed between the injured HET and NULL tendons across all parameters, induction, and healing time points.

Discussion

This study investigates the mechanistic regulatory role(s) of collagen V in the late inflammatory and remodeling phases of tendon healing in a normal matrix using inducible

collagen V null and heterozygous models. Overall, the injured tendons exhibited significantly altered material and structural properties independent of genotype. Contrary to our hypothesis, these differences were not allele dose-dependent as no differences were observed between the HET and NULL tendons. This is contrary to the dose-dependent response observed in a previous study where collagen V knockdown induced at the time of surgery resulted in trending differences in cross-sectional area and max stress between injured HET and NULL tendons. This demonstrates that the degree of collagen V deficiency does not have a significant effect on the healing response in the late inflammatory and remodeling phases. Interestingly, knocking down collagen V during the late inflammatory phase resulted in substantial deficits in tendon mechanics, and this effect was not as pronounced when collagen V was altered during the remodeling phase. This observation confirms the direct correlation between collagen V production and tendon inflammation as concluded in a study where collagen V was substantially increased in chronically inflamed connective tissue and supports the unique binding and connecting role of collagen V during the inflammatory process. Further investigation is required to elucidate the mechanistic role of collagen V at the gene and protein level and to define the pathologic and functional significance of collagen V.

Significance

This study demonstrates the role collagen V on tendon repair at defined healing phases and provides mechanistic insights toward understanding the healing response of a normally developed tendon in a collagen deficient healing environment.

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