The University of Pennsylvania Orthopaedic Journal

Volume 28 June 2018

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The University of Pennsylvania Orthopaedic Journal

Volume 28, June 2018

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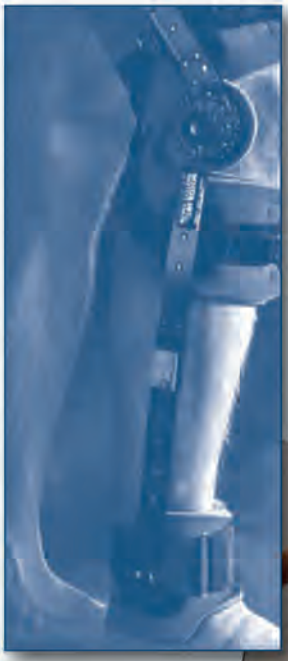

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Letter from the Editors

Adnan Cheema, MD and Michael Eby, MD

We are pleased to welcome you to the 28th edition of the University of Pennsylvania Orthopaedic Journal. This journal began in 1986 under the leadership of Dr. Carl T. Brighton and was the first journal of orthopaedic surgery created and run entirely by residents. We are proud to continue this tradition and carry forward the legacy. We also would like to recognize the countless surgeons and scientists that have contributed to the journal's contents over the past three decades.

We are thrilled to announce our dedication of this year's edition to Dr. Marvin Steinberg, a longstanding pillar of our department. Despite no longer practicing, he is well known to the current residents given his continued attendance at grand rounds, a testament to his commitment to orthopaedics and to the University of Pennsylvania.

The editorials of this year focus on the increasingly important intersection of business and medicine. This arose from our department's view of a changing landscape in medicine and the unique challenges that will place on the physicians of tomorrow. Under the guidance of our chair, Dr. Levin, we have developed a curriculum that will seek to develop important character skills to position our residents as leaders in the field of orthopaedics. This curriculum includes readings, lectures and a collaborative leadership conference with The Wharton School this June. The editorials touch on some of the aspects that we found particularly germane to physicians today.

Beyond the editorials, this year's edition includes an in-depth update on the many facets of our ever changing department including our multiple new faculty and facility additions. The research included is performed here at Penn and includes original basic science and clinical research in addition to case reports and technique articles that highlight interesting aspects of our distinctive practice.

While there are many who contribute to the journal, we would like to thank Dr. Levin first and foremost for providing an atmosphere where exceptional research and clinical excellence can thrive together. We would also like to thank Dr. Samir Mehta and Dr. Jaimo Ahn for their support as faculty advisors for the journal.

This edition is available online (including mobile) for free at www.upoj.org, along with archives of previous editions. We hope you enjoy this edition of the University of Pennsylvania Orthopaedic Journal.

Sincerely,
Adnan Cheema, MD and Michael Eby, MD
Editors-in-Chief

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2018 Dedication: Marvin E. Steinberg, M.D.

By David R. Steinberg, M.D.

It is a great honor to dedicate the 28th edition of the University of Pennsylvania Orthopaedic Journal to Dr. Marvin E Steinberg, who has been a pillar of the local and international orthopedic communities, and a leader and staunch supporter of our Department for over fifty years.

The son of Russian immigrants, Marvin was born and raised in New Brunswick, New Jersey. He attended Phillips Academy in Andover, Massachusetts before returning to Central New Jersey to matriculate at Princeton University. After graduating in 1954, he attended medical school, followed by internship, at the University of Pennsylvania. It was during this time that he married Delores, followed 2 years later by the birth of their first son, David. After training for 1 year in a general surgery residency at Tufts University Medical Center in Boston, Marvin returned with his family to complete his orthopedic residency training at Penn. From 1963-1964, he was a Fulbright Scholar at Worcester College, Oxford University and simultaneously underwent fellowship training with Professor Josep Trueta at the Nuffield Orthopedic Centre in Oxford. After living for almost a year in England, Marvin & Delores took their now 3 young children to western Europe behind the "Iron Curtain" to communist Poland & Russia, before returning to Philadelphia.

Marvin was asked to join the faculty of the Department of Orthopaedic Surgery at Penn by Dr. Edgar Ralston, and eventually became the Director of the Research Laboratory. His research interests included osteoporosis, arthritis, electrical properties of bone, and osteonecrosis. Although he started out performing general orthopaedic surgery, Marvin quickly became a world-renowned expert in hip pathology and joint reconstruction. His many publications and presentations led to his promotions to Associate Professor and then Full Professor in 1980. He has since authored over 195 peer-reviewed publications and given 300 national and international presentations. He has been an editorial consultant and reviewer for numerous medical and orthopaedic journals, and served as Associate Editor for the Journal of Bone and Joint Surgery. Marvin has been involved with local, national and international societies. He was a founding member and later President of the Eastern Orthopaedic Association. He has served as President of both the Philadelphia and Pennsylvania Orthopaedic Societies. He is one of the only non-rheumatologists to have served as President of the Eastern Pennsylvania Chapter of the Arthritis Foundation. He is an active member and past chairman of the Girdlestone Society.

One might not be aware of these and many other accomplishments, for Marvin Steinberg is a selfless and humble individual. He has edited two textbooks on Disorders of the Hip and Revision Total Hip Arthroplasty. He is an inventor: he developed a pneumatic power impactor for removing cement during revision arthroplasty (the "Steinberg Revision System"). He is considered one of the world's experts on osteonecrosis of the femoral head - he was on the forefront of advances in treatment and diagnosis of this condition. He developed a classification system for avascular necrosis that is both comprehensive and yet practical; while Marvin refers to it as the "University of Pennsylvania System," everywhere else it is referred to as the "Steinberg Classification System."

Marvin Steinberg's loyalty and love for Penn Orthopaedics has been demonstrated by his dedication and service to our Department. He was Director of both the Hip Clinic and the Joint Reconstruction Center, served as Vice Chairman from 1977 to 2000, and was both Acting and Interim Department Chairman. He has been a strong advocate for our Department, acting as sage counsel to those Chairmen who have served during Marvin's tenure at Penn. At the same time, he has been there for his colleagues, residents and staff as the Department has grown over the years. For them he has been a sounding board, a purveyor of wisdom, and a moral anchor. He has been a role model for me, and for countless other medical students, residents, fellows and orthopedists. Although Marvin became Professor Emeritus and retired from clinical practice sixteen years ago, his passion for orthopaedics did not abate. He continues to come in to work every week, still writing papers and acting as a consultant reviewer for many publications, including the Journal of Bone and Joint Surgery. He still spends time with medical students, teaching his clinical acumen, patient advocacy, and deep-seated ethics. He still attends conferences and Grand Rounds, imparting his knowledge and wisdom to those who listen.

As dedicated as he has been to orthopedics and to Penn, Marvin Steinberg has been equally dedicated to his wife, Delores, and his family. As children, we would routinely eat dinners at 9 PM, so we could share stories with our father, who had just come home from a long day at the hospital. He had the same routine every weekend: after spending Saturday morning at work, my dad would come home for a late lunch, before taking me on errands to the hardware store, followed by a game of catch in the front yard. On Sundays, mom and dad would take my three siblings and me on day trips. Every August he would take a four-week vacation, spending it with the family at the Jersey shore. In retirement, Marvin and Delores continue to spend time with their four children (David, Jim, Susan and Julie) and their spouses, their 12 grandchildren, and two great-grandchildren.

In conclusion, Marvin has been a beacon of wisdom for the department over his long and enduring tenure at Penn. His innumerable accomplishments, devotion to family, and tireless commitment to education make him deserving of this dedication. Through innovation that continues to provide relief to the ailing and leadership that continues to inspire

the young, he has changed the face of modern orthopaedics forever. Many years of trainees have benefited from Marvin's clinical intuition, sound judgment, and vast experience. They continue to disseminate his knowledge and build upon his achievements, enriching a legacy that will last for many generations to come.

Marvin Steinberg with his son David.

Marvin Steinberg with his wife Delores

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Professor of Surgery (Plastic Surgery)

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Penn Medicine

Leading in Changing Times—Reflections of the Penn Orthopaedics Chairman

L. Scott Levin, M.D., F.A.C.S.

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

Historically leaders in academic medicine, particularly those in surgery, are individuals who have ascended to the position of Department Chairman based mainly on their ability as surgeons. Occasionally research accomplishments or clinical innovations result in leadership roles in Departments. Rarely does gifted teaching ability, financial or administrative talent lead to Chair appointments.

Over the last 25 years, the requirements for a successful leader in academic medicine, and specifically orthopaedic surgery, center around the leader's ability to be regarded as a outstanding clinician, by distinguished himself or herself in a particular field within orthopaedic surgery. They must be an individual who understands basic, translational, and clinical science and has demonstrated commitment to education. They also should have demonstrated a proven track record as a Division Chief or Section leader based on fiscal accountability as well as the ability to organize and mentor others. While these requirements may be considered formidable attributes, these are exactly the qualifications that a Chancellor for Health Affairs or Dean of a medical school looks for when selecting leaders for departments of orthopaedic surgery.

My comments in this article are based on more than three decades of observation of outstanding leaders in academic medicine. Several of these are surgeons, but others emanate from different fields of medicine. All have a distinct ability to coach effectively, and create career opportunities for their faculty without micromanaging them. Effective Department Chairs must realize that they often must place their personal career needs and goals secondary to the plans of institutional leaders (Deans and CEOs), fellow chairs and faculty.

The scientific question of "nature vs. nurture," is frequently debated in athletics, academia, or business. "Are leaders born or are they created?" Are those leading in academic medicine today naturally gifted with the leadership qualifications that I have listed? Perhaps they have studied and learned how to be effective leaders or grown into their roles based on self-analysis, didactic course work and reading, outside coaching, 360 reviews, and feedback from their faculty and the leadership within their health systems?

The next question becomes "what defines leadership?" Do we lead based on what we have seen others do or do we wake up one day and say, "I want to lead?" My first exposure to strong leadership was growing up in a household with a father who served as a naval captain on a minesweeper in Korea. A sense of work ethic, self- discipline, respect for regulation and regimentation, tough love and principal-based leadership were lessons that I learned at an early age from my father. Following medical school, I was influenced by the late David C. Sabiston, Jr, MD., who was a disciple of Alfred Blalock at Johns Hopkins. It has only been recently that I have understood the influence of Dr. Sabiston, who chaired the Department of Surgery at Duke University School of Medicine for more than three decades. For those of you who have not read the book, Genius On the Edge, by Gerald Imber, I recommend it to you. It has only been a little more than 100 years since the American School of Surgery evolved under the leadership of William Halsted at Johns Hopkins. Halsted's development and contributions as a surgeon and scientist, despite his cocaine and morphine addiction, led to remarkable discoveries and advances in surgery and established the principles of modern surgical education. Halsted's influence permeated David Sabiston's training experience at John Hopkins under Alfred Blalock, and this influence was ultimately passed down to me. I inculcated and embraced the standards for patient care that Dr. Sabiston established. He always had high expectations and espoused the concept that one's work was never done; and that one achievement should lead to another. Resting on one's laurels, whether it is a grant award, a manuscript accepted for publication, a chapter written or a productive fiscal year as an operative surgeon was unacceptable. My exposure to Dr. Sabiston and the Halsted traditions at an early point in my career (1982-1984) predated the 80-hour work week and the Libby Zion rule. Working every other night on call resulted in two of the most formidable training years of my career.

Dr. Sabiston chaired one of the most pre-eminent departments of surgery in the United States. Trainees worked without duty hour restrictions, internet, or cell phones. Surgical residents came to appreciate that the most important commodity in the life of a house officer was not money, not sleep, but time. *Time* that we spent with patients, making rounds late at night or early in the morning, time in the operating room, and caring for sick patients with a commitment to continuity of care, set the stage for lifetime lessons that allowed me to become a successful clinician. The template for much of my career was based on what Dr. Sabiston expected. As Osler stated-"the key to success is hard work." There is no question that the technology explosion

such as the electronic medical, the internet, and all the other technology that now exists in modern health care, have been advances. I question whether the values and our current generation of trainees, particular with restricted duty hours will ever understand my generation and the value our training experiences produced without the tools that we routinely use today. Viewing a digital picture of a wound or x-ray is not a substitution for examining the patient at the bedside.

J. Leonard Goldner (James B. Duke Professor and Chairman of Duke Orthopaedic Surgery) was a renaissance surgeon who was as comfortable doing an anterior lumbar fusion as he was correcting a child's clubfoot. Dr. Goldner was an outstanding leader for several reasons. He led by example. He was the consummate clinician. He was a voracious reader. He knew about those around him, such as the names of the children of his residents, and had a sixth sense that if somebody was in trouble, he would engage them in conversation and help by just talking out a situation, providing an opinion and wisdom. Having established the Piedmont Orthopedic Foundation with Jack Hughston, he set the stage for sustained excellence in orthopaedics that continued under my mentor in microsurgery, James R. Urbaniak, who ably led the department following the retirement of Dr. Goldner and took it to even higher planes.

My exposure to great surgical leaders included Harold Kleinert (Louisville), who was the pied piper of hand surgeons from around the world. He was always humble, always available, always kind, and outworked everyone on his faculty as well as his 21 international fellows.

Great leaders should demonstrate a strong work ethic. A prime example of this is Dr. Fu-Chan Wei (Chang Gung Memorial Hospital-Taipei Taiwan). Dr. Wei is a plastic surgeon with expertise in reconstructive microsurgery. Dr. Wei has established an empire in reconstructive microsurgery and plastic surgery at Chang Gung Memorial Hospital. As a fellow I observed his incredible surgical skill, commitment to basic science research, and skills such as an educator. Dr. Wei had a profound influence on me because of his humility and kindness to those who would visit him from around the world. I have emulated the "open door" policy of Goldner, Urbaniak, Kleinert and Wei, and enjoy a continued stream of visitors to my Department from around the world. It enriches the learning environment for residents and fellows, and we always learn something from those that visit regardless of their seniority or experience.

The common defining all of these great men, is a sense of strong work ethic, humility and their propensity to always ask the question, "What's next?" and "What can we do better as individuals and as a team?" My style of leadership is an amalgamation of those that I have already mentioned.

I am a great believer that there is much that is written about leadership that should be embraced and studied, particularly by those who ascend rapidly to positions of leadership at a young age. Inherently, in such situations, faculty that a new Chairman may be leading are older and more established as clinicians. Senior faculty may have a stronger research track record, and will occasionally challenge the new leader to see what he or she is made of.

Historically, medicine has been isolated from the business world, but we all know that today medicine is very much a business as well as a profession. The lessons from Wall Street, corporate board rooms, philosophies of CEO's, and innovation and globalization in business can provide many lessons for physician leaders of today. Jim Collins, the Stanford business Professor, has written several books. The most important of these, I believe, is the book, Good To Great, that describes about how to take a good company and make it great. How do we make a good department or not-so-good department and make it great? What are the key ingredients to this recipe? According to Collins, the first objective is that we must set a vision. We must attract and encourage the right people to join our organization. The goal of any leader in academic orthopaedics should be to become a Level 5 leader- who will "build enduring greatness, blending humility and professional will." I translate this into the concept of "the servant leader." Whether it is right or wrong, it is how I believe one should lead. Leaders earn respect; they do not command it. Distinguished leaders from the business world that I have studied include Jack Welch- who believed investing in people, setting goals and expectations. I remind you of his 70-20-10 rule, and his desire to "have fun." The "have fun principle" is something that Jim Urbaniak taught me. Dr. Goldner's philosophy used to be, "How do I wake up in the morning and stay out of trouble?" Jim Urbaniak's philosophy was always, "Stay out of trouble but have fun!" Other exemplary leaders included Rudolph Giuliani. His management of the 9/11 crisis is legendary. The book, The Real Deal by Sandy Weill, reflects on his life building an empire in the financial management business. Athletic coaches, have a lot to say about leadership, and the writings of Mike Krzyzewski, such as Leading From the Heart and Five-Point Play talk about people working together as one to achieve a common goal. Coach K's. principles include setting standards, establishing trust, communicating well, evaluating individual goals and empowering those to do the right thing in an organization. I refer to the book The Gold Standard often when I talk about how to make quality improvements in our operating rooms, in O. R. turnover, and in our practice efficiency. Just following his principles have helped me a tremendous amount.

Vincent Lombardi has had a lot to say on leadership, and I have studied his quotations that ring true, particularly for a new leader in academic orthopaedics who inherits a department that is not firing on all cylinders. "We would accomplish many more things if we did not think of them as impossible." Lombardi said, "Perfection is not attainable, but if we chase perfection, we can catch excellence." How true is that? Lombardi, again: "The measure of who we are is what we do with what we have." How many times has a faculty member asked for the "moon" rather than demonstrating to his division chief or the department chairman that, with a limited amount of resources that you allocate, much can be done. My personal philosophy is to see what people can do with limited resources, particularly when departmental resources and discretionary funds are scarce. As they improve, whether it is obtaining grants, increasing clinical productivity,

or developing new educational programs, additional resources can be provided. Lombardi also said "Confidence is contagious, so is lack of confidence." The goal of a good leader is to make students, residents, fellows, faculty and division leaders confident.

Based on my father's history in the Navy, and my opportunity to be in the Army Reserves, I have rubbed elbows with a number of military commanders for whom I have great respect. There has been an entire generation of surgeons who served in Vietnam and, more recently academic leaders who have served in Operating Enduring Freedom and Operation Iraqi Freedom. It is a personal bias of mine, but I say: "give me a military man or woman any day." I seek these individuals as residents, and am proud to appoint them to my faculty. They are disciplined and have an understanding of the chain of command, which is important for any organization to prosper. Colin Powell has written a tremendous amount on leadership and is the epitome of a modern military leader who has set forth a series of principles that are absolutely essential for an academic leader to understand. Powell says, "Leadership is solving problems. The day people stop bringing you their problems is the day you stop leading them. They have either lost confidence that you can help or concluded that you do not care. Either is a failure of leadership." The privilege of leadership is something else that Powell talks about. "Leadership requires that one take responsibility. The ultimate responsibility is that of your team. Understand that you cannot please everyone, and leadership is not a popularity contest. Once a decision is made, stay with the decision despite opposition if you think it is right. It is very important that your constituents be supported." It is also important to praise those around you in public for what they have accomplished and criticize in private what has not been accomplished. One must lead by example and not decree, and crediting others with a team's success is probably one of the most powerful force multipliers one can do. Other lessons by Colin Powell are to discount organizational charts. Titles mean little, and certainly title of Department Chairman means nothing if you are dissociated from your division chiefs, residents, ancillary health personnel, administrative support staff and the hospital administration. A leader must be perpetually optimistic because this is a force multiplier and as one builds a department, one needs to look for people who have loyalty, integrity and energy. Realize that command is lonely, and one must also know when to exit. As Powell said, "Leadership is ultimately responsibility, and it's the ultimate responsibility."

As a disciple of leaders that I have mentioned and a student of those I have read about, I can summarize my perspective as a Chair. One needs to maintain a positive attitude, champion an integrative win-win approach with the health system, enforce personal discipline, and be responsive. You must be a competitor. You always must set the bar high. You are hired not for the easy decisions but the difficult ones. For example- hiring faculty is based on mission-based needs. A good leader creates succession plans and understands the need for a marketplace strategy.

Malcolm Forbes believed that first class leaders recruit people better than themselves; second class leaders recruit third-class people. I believe this. There are Red flags regarding when not to hire faculty. A potential recruit may be talented however if there is no room in a section, division or for another faculty member you will create a problem that is difficult to manage. In such cases you will create conflict by having too many mouths to feed with not enough work to do, or not enough resources to provide for those that are already there. Any individuals making frequent career moves, (you should vet carefully). If one's gut tells you that they are not a good fit, they are not a good fit.

Accountability is something that I am particularly keen on. There should be mission-based goals set each year for faculty. Frequent communication with section leaders is essential. Quality and safety goals are built into our compensation plan that ultimately benefits our health system. There are team goals, individual goals, and certainly, citizenship is important. Leading is motivating and encouraging those around you by cheerleading, mentoring, compensating, providing ownership, providing opportunity and fulfilling dreams of those that you work with.

The academic leader in 2018 derives credibility from clinical skills, demonstrates commitment to education, respects research, is enthusiastic about team building and coaching, has a business sense, anticipates road blocks, avoids calamities and continually collaborates with those around him or her. A leader must be able to do is to admit mistakes. Apologize when needed, take risk, maintain humility, and remember that you are only as good as your last quarter! A Chair's responsibility is to set vision, develop strategies, set standards, establish accountability and, lead by example. Earn respect; it cannot be mandated. Respect your work force, and know that people are your most important asset. One's work is never done. Take a long term view, and build by supporting others. This is the key to success in leadership. Time will change. Challenges in health care delivery will change. Principles of leadership are time honored and consistent throughout the history of medicine. As I reflect on the last nine years as Chairman of the Department of Orthopaedic surgery at the University of Pennsylvania, I am proud of the team that we have built to address all missions.

Nine years ago was a time of tremendous uncertainty in our department's history. A new Chairman was appointed from the outside, an increasingly competitive marketplace threatened practice growth, economic volatility in our country limited investments in our enterprise, and faculty insecurity overshadowed teamwork. Today, our culture is proudly defined as "a blue collar work ethic imbedded in an Ivy league university". Our faculty is almost tripled, our educational programs are among the best in the country, and our aggregate research abilities are unrivaled in the US. We have a MSKR center, a MSKR service line, and eight hospital sites compared with three when I began. Our goal for the next nine years is to build on this early success, remain humble, committed and determined. It is a privilege to lead this outstanding team. Onward!

Letter from Program Director

Craig Israelite, M.D.

It is again my pleasure to update the orthopedic community on the current state of the Penn Orthopedic Residency Program. I use the word pleasure because it truly is a pleasure as we continue to have one of the most balanced and indepth residencies in the nation. This has led to th applications for our residency from the top candidates in the country. Of the 800 or so applicants we interviewed this current year, all but one matched at a top tier orthopedic program. Additionally, our incoming class for next year ranks among the finest group of young men and women in the country.

While I may have some implicit bias, the Orthopedic Department at Penn has the most committed group of faculty in every division. Divisions are led by its directors who oversee the clinical and academic missions of its subdivision. This has led to the continuous development of some of the finest clinical educators in the country as evidenced by our graduates becoming leaders in many of the most prestigious medical centers. These young talented individuals carry the Penn pedigree as program directors and division chiefs throughout the medical community.

I continue to believe that this continued success stems from the leadership of our Chairman, L. Scott Levin, M.D. Though he is most certainly the busiest individual in our department, he manages to personally meet with each resident class in order to continue to build upon the already stellar program.

In addition to his input, our residents comprise the majority of our graduate medical education committee which meets monthly to continuously improve our programs and offerings. This leads to constant changes which benefit the residency as a whole. Our current chief residents, Drs. Joshua Rozelle, Joshua Steere and Zachary Zimmer have continued to push our program forward and not rest on our reputation alone. Just a few examples of implementations this past year include a video library showcasing faculty doing representative cases, conference schedules which are more robust and comprehensive as ever and the visiting professor series that is second to none. Additionally, several non-clinical programs have been developed which include programs in leadership training as well as the business of medicine.

As a result, our residents upon graduation continue to pursue fellowships in the most competitive programs. The feedback that I constantly receive is that our residents serve Penn proudly and have become coveted faculty at their own fellowship locations.

This column does not afford me enough space to document all of the recent developments to our program. Suffice it to say all pillars are strong as ever. The clinical diversity and talent of our dedicated faculty and residents, and the research arm led clinically by Dr. Mehta and basic research by Dr. Soslowsky are as solid as ever. There have been numerous grants, awards, presentations, and peer reviewed journal articles. But what really sets us apart is the dedication of the faculty who constantly are there to provide mentorship and clinical expertise. The faculty and residents are truly the foundation of the program.

Additionally I would be remiss if I did not acknowledge the dedication of the other program directors, Drs. Ahn and Sheth, who continue to dedicate their time and efforts without hesitation. Lastly, our program coordinator, Shanna Kurek, has to be one of the most talented in the country. Her organizational skills and dedication are undoubtedly responsible for the implementation of it all.

I continue to be indebted to all of these exceptional individuals that I am privileged to work with in one of the finest institutions in the nation.

In Memoriam: Dean Gerard Lorich, MD (1963-2017)

David L. Helfet, MD

Orthopaedic Trauma Service, Hospital for Special Surgery & New York Presbyterian Hospital, Weill Cornell Medicine

We write this obituary with heavy hearts — we lost Dean Lorich suddenly and prematurely on December 10, 2017. He was a remarkable colleague, surgeon, researcher, educator, role model and of course father, and will be sorely missed by for whom he made a profound impact.

Dean G. Lorich was born in Aliquippa, Pennsylvania on July 10, 1963. Beginning in 1981 he attended University of Pennsylvania, played collegiate football, and graduated in 1985 with a major in Chemistry, with honors (Summa Cum Laude, Deans list, Alpha Chi Omega). He continued his education at University of Pennsylvania as a medical student (1985-1990); completed with honors (Penn Medical Scholar). He was accepted for Orthopaedic Residency in 1991 at University of Pennsylvania completing his residency training in 1995 and during which he completed multiple research projects. Dr. Lorich then was then selected as an Orthopaedic Trauma Fellow (1995-1996) on the Orthopaedic Trauma Service of the Hospital for Special Surgery under the direction of David L. Helfet, MD. Subsequently, he undertook the prestigious and world-renowned Martin Allgöwer Traveling Trauma Fellowship with further specialized training in orthopaedic trauma by Rheinhold Ganz (2001). Dr. Lorich started as an Orthopaedic Surgeon and Assistant Professor at University of Hawaii (1996) and subsequently went on to Albert Einstein School of Medicine, New York (NY) becoming Chief of Orthopaedic Trauma (1998) and Jacobi Medical Center, NY, Chief of Orthopaedic Surgery (1998). In 2002, Dr. Lorich returned 'home' to Weill Cornell Medicine, NY Presbyterian Hospital, and Hospital for Special Surgery (HSS) as Associate Professor of Orthopaedic Surgery and Associate Director Orthopaedic Trauma Service. He also was elected to the Board of Trustees for the NY State Orthopaedic Society, Associate Team Physician for the NY Rangers and AO/ASIF Foundation teaching faculty. He won numerous awards including the HSS Philip D.Wilson Resident Teacher of the Year (2006), Department of Defense Orthopaedic Visiting Scholar (in collaboration with the Orthopaedic Trauma Association and American Academy of Orthopaedic Surgeons), Landstuhl Regional Medical Center (2007) and Roger E. Joseph Prize for Humanitarian Medical Rescue Work award (2010).

During the prolific course of his orthopaedic career, Dr. Lorich was principal investigator on 230 scientific presentations at orthopaedic conferences of which 92% were presented by an Orthopaedic Resident, Fellow or medical student he mentored. Dr. Lorich published 197 articles in his career with an average of 15 articles per year over the past 10 years, multiple chapters in textbooks and numerous additional manuscripts currently accepted for publication. He received 12 grant awards for his research and was editor or reviewer for 10 orthopaedic journals.

His research contributions focused on improving outcomes through surgical innovation, and optimizing patient outcomes and vascular research. His 11 vascularity research articles led to new innovation in the treatment of hip, proximal humerus and patella fractures, all which were a central clinical interest. He then published new surgical techniques and outcomes studies based on these vascular research findings including novel use of a mesh plate to better protect the patella vasculature and novel techniques for fibula allograft augmentation for treatment of select femoral neck fractures. Other significant contributions include his recognition of an alarming complex fracture associated with long-term alendronate therapy (atypical femur fractures).

His publications include 38 ankle fracture articles, 38 hip fracture articles, 28 proximal humerus articles, 11 quantitative vascularity articles, 6 articles on atypical femur fractures, 14 patella fractures articles, 6 clavicle fracture articles. He also published numerous other groundbreaking innovations and research findings which have helped advance the specialty of Orthopaedic Trauma and other orthopaedic specialties.

Most of all Dr. Lorich was a devoted family man and is survived by his wife Deborah and three daughters, Tristan, Bianca, and Tatiana. His incredible legacy will live on through his research, and all he impacted so positively including the patients whose thousands of lives and limbs he restored and of course the residents, fellows, students, and colleagues who all benefited from his teaching and remarkable surgical skills.

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Utilizing a unique biocompatible membrane, MACI offers potential benefits over traditional ACI through minimal incision, simplified delivery, and suture-free fixation for the treatment of articular cartilage defects of the knee.

INDICATION

MACI® (autologous cultured chondrocytes on porcine collagen membrane) is an autologous cellularized scaffold product that is indicated for the repair of single or multiple symptomatic, full-thickness cartilage defects of the adult knee, with or without bone involvement.

MACI is intended for autologous use and must only be administered to the patient for whom it was manufactured. The implantation of MACI is to be performed via an arthrotomy to the knee joint under sterile conditions.

The amount of MACI administered is dependent upon the size (surface in cm2) of the cartilage defect. The implantation membrane is trimmed by the treating surgeon to the size and shape of the defect, to ensure the damaged area is completely covered, and implanted cell-side down.

Limitations of Use

Effectiveness of MACI in joints other than the knee has not been established.

Safety and effectiveness of MACI in patients over the age of 55 years have not been established.

VERICEL

IMPORTANT SAFETY INFORMATION

MACI is contraindicated in patients with a known history of hypersensitivity to gentamicin, other aminoglycosides, or products of porcine or bovine origin. MACI is also contraindicated for patients with severe osteoarthritis of the knee, inflammatory arthritis, inflammatory joint disease, or uncorrected congenital blood coagulation disorders. MACI is also not indicated for use in patients who have undergone prior knee surgery in the past 6 months, excluding surgery to procure a biopsy or a concomitant procedure to prepare the knee for a MACI implant.

MACI is contraindicated in patients who are unable to follow a physician-prescribed post-surgical rehabilitation program.

The safety of MACI in patients with malignancy in the area of cartilage biopsy or implant is unknown. Expansion of present malignant or dysplastic cells during the culturing process or implantation is possible.

Patients undergoing procedures associated with MACI are not routinely tested for transmissible infectious diseases. A cartilage biopsy and MACI implant may carry the risk of transmitting infectious diseases to healthcare providers handling the tissue. Universal precautions should be employed when handling the biopsy samples and the MACI product.

Final sterility test results are not available at the time of shipping. In the case of positive sterility results, health care provider(s) will be contacted.

To create a favorable environment for healing, concomitant pathologies that include meniscal pathology, cruciate ligament instability and joint misalignment, must be addressed prior to or concurrent with the implantation of MACI.

Local treatment guidelines regarding the use of thromboprophylaxis and antibiotic prophylaxis around orthopaedic surgery should be followed. Use in patients with local inflammations or active infections in the bone, joint, and surrounding soft tissue should be temporarily deferred until documented recovery.

The MACI implant is not recommended during pregnancy. For implantations post-pregnancy, the safety of breast feeding to infant has not been determined.

Use of MACI in pediatric patients (younger than 18 years of age) or patients over 65 years of age has not been established.

The most frequently occurring adverse reactions reported for MACI (≥5%) were arthralgia, tendonitis, back pain, joint swelling, and joint effusion.

Serious adverse reactions reported for MACI were arthralgia, cartilage injury, meniscus injury, treatment failure, and osteoarthritis.

For more information, please see Highlights of Prescribing Information about MACI, or visit MACI.com

1. Saris D, Price A, Widuchowski W, et al. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: Two-year follow-up of a prospective randomized trial. Am J Sports Med. 2014;42(6):1384-94.

maci

autologous cultured chondrocytes on porcine collagen membrane

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MACI safely and effectively. See full prescribing information for MACI.

MACI® (autologous cultured chondrocytes on porcine collagen membrane)

Cellular sheet for autologous implantation

Initial U.S. Approval: 2016

RECENT MAJOR CHANGES

Dosage and Administration, shaping the MACI implant (2.2) 06/2017

INDICATIONS AND USAGE

MACI® is an autologous cellularized scaffold product indicated for the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults. (1)

Limitations of Use

- Effectiveness of MACI in joints other than the knee has not been established.
- Safety and effectiveness of MACI in patients over the age of 55 years have not been established.

DOSAGE AND ADMINISTRATION

For autologous implantation only.

- Contact Vericel at 1-800-453-6948 or www.MACI.com regarding training materials for surgical implantation of MACI. (2)
- The amount of MACI implanted depends on the size (surface area in cm^2) of the cartilage defect. (2.1)
- MACI should be trimmed to the size and shape of the defect and implanted with the cell-side down. (2.2)

DOSAGE FORMS AND STRENGTHS

Each 3 x 5 cm cellular sheet (MACI implant) consists of autologous cultured chondrocytes on a resorbable porcine Type I/III collagen membrane, at a density of at least 500,000 cells per cm^2. (3)

CONTRAINDICATIONS

- Known history of hypersensitivity to gentamicin, other aminoglycosides, or products of porcine or bovine origin. (4)
- Severe osteoarthritis of the knee. (4)
- Inflammatory arthritis, inflammatory joint disease, or uncorrected congenital blood coagulation disorders. (4)
- Prior knee surgery (within 6 months), excluding surgery to procure a biopsy or a concomitant procedure to prepare the knee for a MACI implant. (4)
- Inability to cooperate with a physician-prescribed post-surgical rehabilitation program. (4)

WARNINGS AND PRECAUTIONS

- Safety of MACI in patients with malignancy in the area of cartilage biopsy or implant is unknown. Expansion of malignant or dysplastic cells present in biopsy tissue during manufacture and subsequent implantation may be possible. (5.1)
- Because patients undergoing procedures associated with MACI are not routinely tested for transmissible infectious diseases, cartilage biopsy and MACI implant may carry risk of transmitting infectious diseases. (5.2)
- Local inflammation or active infection in the bone, joint, and surrounding soft tissue, meniscal pathology, cruciate ligament instability, and misalignment should be assessed and treated prior to or concurrent with MACI implantation. (5.3)
- Final sterility test results are not available at the time of shipping. (5.4)

ADVERSE REACTIONS

The most frequently occurring adverse reactions (≥5%) reported for MACI were arthralgia, tendonitis, back pain, joint swelling, and joint effusion. (6)

Serious adverse reactions reported for MACI were arthralgia, cartilage injury, meniscus injury, treatment failure, and osteoarthritis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Vericel at 1-800-453-6948 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch for voluntary reporting of adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy: Because MACI implantation requires invasive surgical procedures, use in pregnancy is not recommended. (8.1)

VERICEL

See 17 for PATIENT COUNSELING INFORMATION Revised: 06/2017

For more information, please see Full Prescribing Information on MACI.com

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My Executive Masters in Business Administration Experience

Derek J. Donegan, MD, MBA(c)

The current day Orthopaedic surgeon, or any physician for that matter, wears many different hats. The obvious ability to have clinical acumen and the skill set to take care of patients are learned in great depth in medical school, residency and fellowship. The necessary skills to be a leader and manage the business side of medicine are largely underemphasized. As I have matured in my career and practice, I realized these skills that are glossed over in the majority of our medical education are just as important as the skills that are hammered in to us for easily over a decade. A quote that I have heard more recently was: "Healing is an art, medicine a profession, health care a business." This is something that I have experienced first-hand over the past few years. As the focus of modern day medicine has shifted from providing quality care to providing quality care at a low cost, the ability to marry the art, the profession, and the business of health care has become critical to one's success.

When I initially sought out to pursue my MBA degree, I was looking to gain a more formal educational experience on business fundamentals, leadership, and economics that I could apply to the healthcare environment. I was interested in learning the principles of statistical analysis, negotiation strategies, team management, and strategic formulation to be more successful at navigating our complex health care system and to provide the most effective, cost-conscious care to my patients.

As I am only one month away from finishing my journey through this process, I have come to appreciate that this has been more than just acquiring another skill set. This has actually been a transformative experience that will cause me to exit a much different individual than when I entered. There have been three reasons suggested for an MD to get an MBA and I thought that I would provide my personal experience behind them as I have matriculated through Temple University's Fox School of Business EMBA program. These three reasons are: developing a new perspective, acquiring skills, and building bridges.

Developing a New Perspective

If an MBA would do nothing more for an MD than to help develop a new perspective, then that would be enough to justify any cost incurred for the degree. It is easy to lose perspective when you are constantly surrounded by like-minded individuals doing the same thing on a daily basis. The ability to expand outside of your comfort zone and interact with people from many different industries has been one of the biggest assets of obtaining this MBA degree. It is often stated that the intent of your action does not matter as much as how others perceive it. Gaining a better appreciation for how others perceive and react to your actions can provide significant insight to how you approach different situations. This better understanding can lead to heightened self-awareness and overall improved emotional intelligence. As part of the Temple EMBA program, we were put into groups of 6 to work as a team for the duration of the program. My group consists of a Senior Vice President for an air-fleet management group, a General Manager for GMC, a Global Project Manager for Jansen Pharmaceuticals, Legal Counsel for Discovery Inc., and the CFO for the City Counsel of the City of Philadelphia. This deep immersion with a new group of people from diverse backgrounds provided many opportunities to develop a new perspective. The beauty of it was that with every business lesson we learned, I was able to glean a perspective from each of these individuals and their industries that I could apply to the health care sector and my current position. Additionally, the "real-life" experience that each member contributed to the class discussions proved to be invaluable.

Acquiring Skills

Matriculating as an EMBA student has brought with it commonly thought of classes such as Corporate Strategy, Finance, Marketing, and Operations Management. These classes were completely new to me. While I was accustomed to learning new skills from a technical perspective in the operating room, these skills proved to tax a different part of my brain. As the process unfolded, my grasp of the financial nuances became stronger and my ability to apply these concepts to the health care sector improved. The terms "Net Present Value" and "Internal Rate of Return" actually meant something to me and started to help me form a strategy for thought and discussion at a higher level. These skills I acquire will also help me view medicine and the cost of healthcare from a very different lens. It will also allow me to take a more holistic approach to understanding the extremely complex environment that we work in and enhance my ability to ask the appropriate question and expect the appropriate answer.

While the analytical skills mentioned above proved to be useful, the greatest return was my development as a leader. The leadership and professional development throughout my EMBA curriculum has provided incredible insight into both my strengths and my weaknesses as a leader. It has also provided the opportunity to hone my strengths and improve my weaknesses. These skills will prove to be priceless as I continue to advance in my career.

Building Bridges

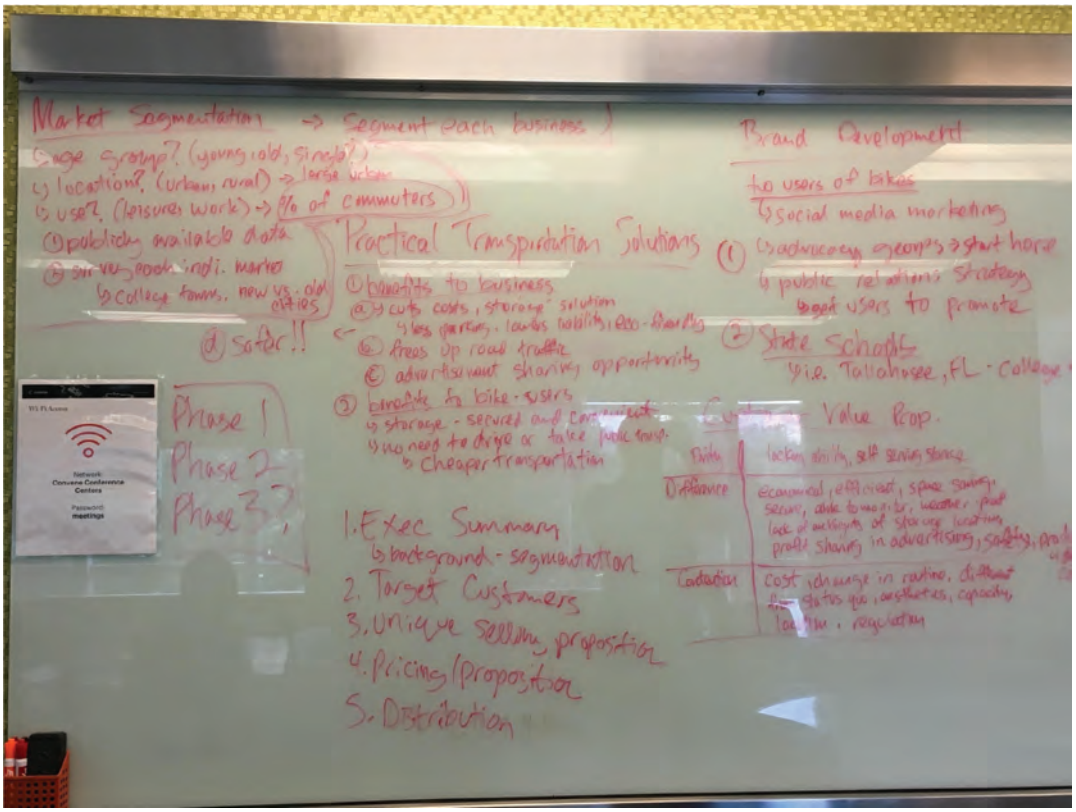
Finally, the concept of building bridges has been a constant thought throughout my time at the Fox School of Business. When I initially heard this, I immediately thought of building the bridge between clinicians and administrators in the health care sector. This seemed to be obvious given the reasons most choose to pursue this degree. As I have ventured through this, I must admit that the new perspective I have gained and the newly acquired skills have facilitated building these bridges, and I imagine that as I continue to mature in my career, this will continue to grow and develop with me.

The other idea of building bridges has been an evolution of thought and my relationship or "networking" with my colleagues and cohorts from different industries. Additionally, I have forged lasting relationships that will continue to add value to my personal and professional life. The opportunity to be involved in innovative ideas and potential game-changing initiatives has significantly increased with these relationships.

In conclusion, the decision to pursue an MBA degree in the early stages of my career as a physician was a long, thought-out process. I had my preconceived notions of what this was going to afford me and the potential opportunities that this experience would create. I have been absolutely amazed at the actual insights that this journey

has allowed me to gain and the perspective that I now carry. It has met and exceeded all of my expectations. I look forward to continue to hone my skills as a leader, an innovator, and a clinician with this newly acquired knowledge.

EMBA Cohort Picture with our visiting students from Columbia



The typical whiteboard after a small-group meeting.

Opportunities Abound For Innovation

Mark A. Turco, MD, FACC

Chief Innovation Officer and Corporate Outreach Officer
Penn Center for Innovation
University of Pennsylvania

"To succeed, jump as quickly at opportunities as you do at conclusions"

-Benjamin Franklin

The opportunities to embrace innovation within healthcare systems and academic medical centers have never been greater, given the current precipice of technology, including the fields of artificial intelligence (AI), genomics, genetics, and machine learning—to name a few. While equipped with these technologies, we as caregivers have never had more scrutiny with regard to value-based care and demonstrating true benefit for the individual and society. We are all part of the race to make these contemporary tools work for us, as no one technology or solution is the end goal because they must always remain the means to improved care.

Transition of Academic Medical Centers

The Bayh-Dole Act of 1980, which gave universities the legal right to take title of inventions that resulted from federal research grants, caused institutions to revamp their technology transfer capabilities[1,2]. During the last three decades, most research universities established a technology transfer office (TTO) to help license new discoveries, resulting in $2.5 billion in licensing revenue for universities in 2015[2]. Over the past 25 years, more than 84,000 U.S. patents were issued to research institutions, with 6680 of these patents issued in 2015 alone[3].

More recently, within research universities and healthcare systems, these TTOs have embraced innovation models, which seek to provide support for researchers, scientists, students and faculty to make them aware of how TTOs can support their needs. In addition, innovation centers and Chief Innovation Officers provide connectivity between researchers and possible industry collaborators, as well as other opportunities to help generate technology co-creation. Chief Innovation Officers within healthcare systems often have a slightly different charge, as they are tasked with driving efficiencies within a large integrated delivery network (IDN) through value-based models. Examples include developing AI-Bot and machine learning technologies that allow for patient engagement and empowerment around adherence to medications and reduction of readmission rates. Further areas of impact around patient-based behavior economics are key areas for investigation and research. Ideally, these entities collaboratively support the mission of the academic research, as well as improve the lives of our patients.

Goals of Innovation

Research universities have integral strengths in many areas but lead in discovery and invention, which complement the innovation process. The ability to rapidly introduce new discoveries and technological advances has the potential to make dramatic changes to the healthcare landscape. The goals of healthcare innovation revolve around three key tenants: improving efficiencies, accessibility, and affordability through key advances in individualized care. Innovation aiding in therapy optimization and outcomes over time are crucial. New medical device development should be aimed away from iterative change and toward transformative value-based idea generation.

The National Science Foundation (NSF) seeks to provide "foundational" support of research for transformative advances within fields of science or engineering. Their criteria for these transformative research grants are reviewed based on two merit review criteria: Intellectual Merit and Broader Impacts[3]. The NSF recognizes that those working on this frontier take "high risks in their research" [3]. Government agencies, like the NSF, help researchers clarify the end-goals and value of their projects, which are increasingly aligned with industry in seeking high risk/high reward impact.

Successful Partnerships Require Shift from Outcomes to Impact

Having had the fortunate opportunity to span a career that includes clinical care, medical device industry and now a firsthand commitment at a premier academic university, I recognize that the prospects and opportunities for innovation have never been more robust or more needed. Outside the research and science that are generated at an academic center, translational opportunities are also clearly outlined. To realize those translational efforts, collaborative relationships with industry partners across sectors are oftentimes needed. However, in order to be successful with industry partners, researchers need to refocus from *outcome* to *impact*[4], as also recognized by the NSF. The main observation that drives discussion is that industry-university collaborations often produce interesting outcomes (i.e., an insightful scientific publication, a new process or pathway, or a innovative computer code) but those outcomes have minor or no impact to society[4].

In fact, to identify best practices, Massachusetts Institute of Technology surveyed 106 projects at 25 multinational companies that engage in research collaborations with a broad base of universities. While approximately 50% of the examined projects resulted in what were seen as major outcomes (i.e., produced new ideas or solutions to problems, developed new methods of analysis or generated new intellectual property of potential benefit for the company), only about 20% of the projects led to major impacts[4]. Thus, we must work to align the outcomes with the impact of the researcher and the collaborator, as well as the academic mission.

Over time, these relationships allow for new technology development to be accelerated and brought to the bedside. Furthermore, developing and aiding cross-functional collaborations are integral to attaining the intended impact. The University of Pennsylvania has committed large resources to a new center for medical devices (Penn Health-Tech) which does just this in bringing together science, research and the clinical community together with engineers.

Innovations at the UPENN

While innovation opportunities at academic institutions globally have grown, the University of Pennsylvania is truly unique in its support of researchers and inventors. As an example, Reuters recently ranked UPenn fourth among for the World's Most Innovative Universities. The Penn Center for Innovation (PCI) has distributed more than $100 million of licensing income and sponsored research funding at Penn. PCI has filed 869 patents, and been issued 111 U.S. patents. In addition, it has executed on 654 commercial agreements.

With all the opportunities available, it is the individual researcher or scientist's choice to seek them out. Therefore, I want to leave you with a challenge from one of the university's founders, Benjamin Franklin: "The height of foolishness is to discard an opportunity without full investigation."The onus is on you—the researchers—to take advantage of all that the university has to offer.

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Pride in Leadership: Penn Orthopaedics

Joshua Rozell, MD & John Kelly IV, MD

A leader is simply a person in a position of power: a CEO, a President, or a team captain. It only logically follows that their role should, therefore, be to lead a company, a country, or a team, respectively. But there are leaders, and there are those who truly lead. The distinction between a leader and those who genuinely lead lies in the belief of a higher purpose, and an unwavering devotion to bettering their organization and its members. Companies such as Apple, Google, Coca Cola, and General Electric are not successful merely because of their fancy products, stock prices, or marketing prowess; these companies' employees (and leaders) genuinely believe in the vision and mission of their company, a belief which their customers also share. The ability of a leader to instill this emotional connection to a company or organization and their product is paramount to being successful. British author and leadership expert Simon Sinek comments that "people don't buy what you do, they buy why you do it." At Penn Orthopaedics, we believe that patient-centered care, innovative research, and clinical education are at the forefront of our vision. We also recognize that great works to advance the common good are only accomplished with leadership skill. Our department's ability to train not only great surgeons but revolutionary leaders and agents of positive change is our committed focus. To this end, the department has taken a keen interest in incorporating leadership-based training into the resident curriculum.

Last year Penn Orthopaedics held its inaugural leadership forum. A symposium of leaders from the Wharton Business School, the Perelman School of Medicine, industry, and sports gave thought-provoking lectures on leadership. This year, while still continuing this forum, we are taking leadership training to the next level. We will be the first orthopaedic program in the country to offer our 42 residents a certified course in leadership in collaboration with the Wharton Business School. This two-day course, sponsored in large part by a gift from Michael P. Kelly Esq., will provide our residents with in-depth leadership training, skills, and tangibles to lay the foundation to become the next generation of leaders in orthopaedics. Wharton professors will discuss topics such as emotional intelligence, leader identity, executing difficult conversations, and leading effective teams.

Michael Kelly, Esq. speaking at grand rounds this year in an installment of our resident curriculum on leadership training.

This endeavor would not have been possible without the vision of Drs. Scott Levin, Derek Donegan, and John Kelly. As residents, we are grateful to have the opportunity to expand our education beyond the field of orthopaedics and into the realm of leadership.

Hip and Knee Arthroplasty Care Pathways: Process Improvement Methods Increase Quality and Lower Care Cost

Eric Hume, MD, Hannah Lacko, Joanne Piscitello

Department of Orthopaedic Surgery, University of Pennsylvania

Introduction

For high volume, elective procedures, including hip and knee arthroplasty, variability is a key factor that degrades value, defined as delivering high-quality care at low cost. Medical education has traditionally focused on individualizing patient care. But as care has become more complex, individualized variation in patient care may not add value. Total hip arthroplasty and total knee arthroplasty clinical teams are challenged to the "memory test" of completing all of the steps of a patient's care, repeated approximately 3,000 times a year within UPHS hospitals. Variability in care delivery increases as providers' preferences and opinions cause care to drift away from evidenced based medicine (EBM). Quality improvement methods rooted in EBM can provide high-value, low-variability care pathways.

A care pathway maps the current-state process of a patient's experience from initial presentation through recovery. Care pathways should be developed to be EBM-driven and appropriately modifiable for unique care needs. Use of a pathway supports EBM-driven care, relieves the memory workload, and frees the care team to focus on value-added variability. Clinical decision support (CDS) is needed in the electronic medical record to guide care variation for individual patient needs. For example, the venous thromboembolism prophylaxis default should be the standard of care. However, for a post-operative mechanical heart valve patient, CDS should prompt team to consider ordering a heparin to Coumadin bridge. Care pathways are effective tools for monitoring opportunities within defined episodes of care (EOC). An EOC is a value-based payment model that includes all services provided to a patient for a particular condition or procedure within a specific period of time across a continuum of care.

Pathways: Preoperative

Pre-admission care for anemia, diabetes, poor nutrition, smoking, obesity, and psychosocial and physical home barriers will improve perioperative and postoperative quality and lower cost. Surgeons and interprofessional teams should work with the patient and his primary care physician to provide personalized preoperative preparation before an elective surgical procedure [1,2].

Pathways: Acute care

Acute-care quality efforts ideally are hospital cost neutral and because DRG payments are fixed, acute care costs will not directly impact EOC costs. For example, mobility programs in the hospital will lower the risk of falls and decrease the length of stay. Lowering the cost of implants and improved OR efficiency are also important for the hospital margin.

Even in a coordinated health system, cost impacts do not precisely align. Postoperative subacute rehabilitation in a skilled nursing facility (SNF) lowers length of stay cost to the hospital, but it is a significant cost within an EOC. Hospitals are reimbursed for readmissions, but readmissions routinely push the EOC cost above the budget. Hospitals do pay penalties for readmissions to Medicare and Independence Blue Cross (IBC) unrelated EOC.

Pathways: Post-Acute Care

Most of the opportunities for EOC cost savings are during the post-acute period where data shows post-acute care variability. Increased quality of post-acute care improves patient safety and lowers post-acute care cost. Lower utilization of skilled nursing facilities (SNF) and inpatient rehab facilities (IRF) and lower readmission rates have led to significant savings from improved post-acute care within Bundled Payment for Care Improvement (BPCI) (Figure 1, 2) and IBC EOC (Figure 3).

Skilled Nursing Facilities

SNF planning has been an important success. Preoperatively, a Risk Assessment and Prediction Tool (RAPT) score assesses post-acute care needs. A RAPT score of 9 or greater predicts a patient can return home safely. UPHS has seen a steady decrease of SNF usage from approximately 66% to approximately 33% of THA and TKA patients. The UPHS readmission rates from home are stable, which confirms we are increasingly returning patients home safely. EOC payments reflect number of patients who go to a SNF and IRF, SNF length of stay and IRF DRG. To meet the goals of returning patients home safely, decreasing utilization of SNF and IRF, and decreasing SNF length of stay, multidisciplinary effort is needed select to high-value post-acute care location.

Physical therapy

Physical Therapy (PT) after surgery has become an important cost within our most recent IBC bundle. Our work to lower SNF use and readmission rates can be seen to directly explain cost savings (Figure 4). With SNF and readmission costs lowered, we now see PT costs (Figure 5) driven by a highly variable distribution of 8 to 30 sessions per patient (Figure 6). We have partnered with our physical therapy colleagues to try to define PT endpoint with metrics based on activity and functional scores. PT should direct the patient toward

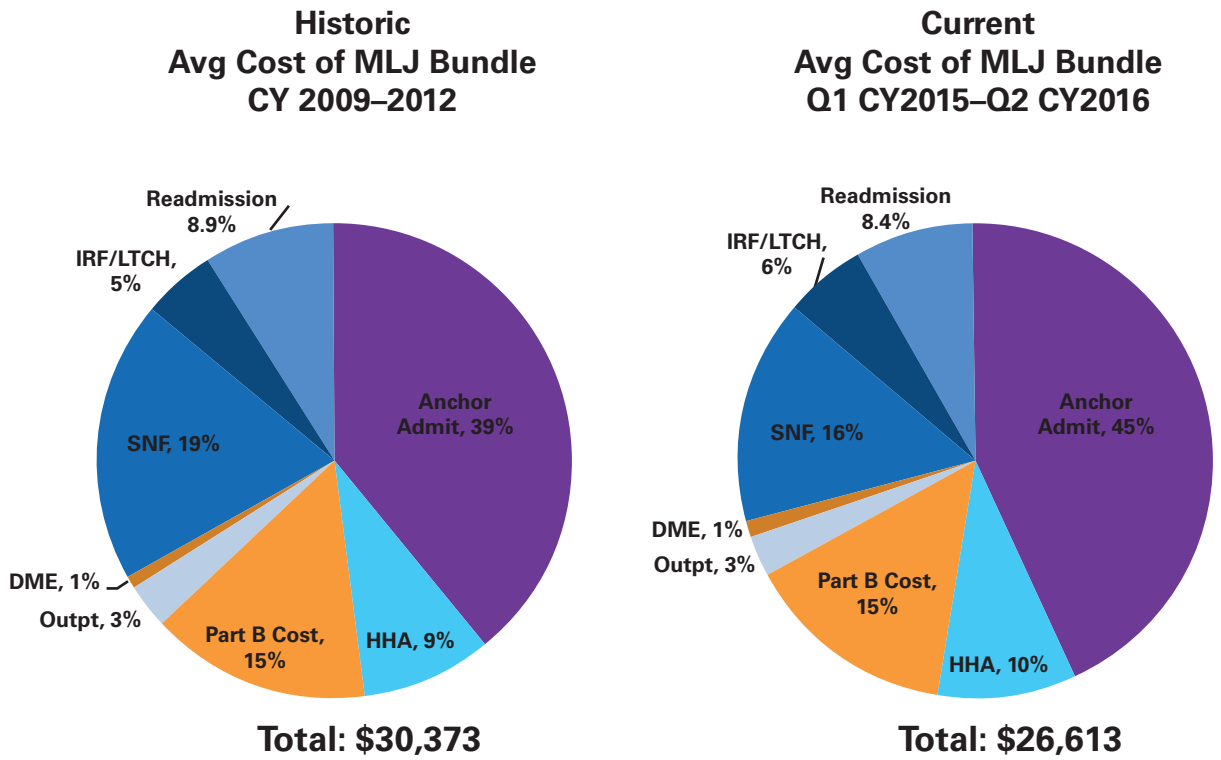

Figure 1. CMS Bundle Payment Care Initiative (BPCI) Historical Costs and Savings.

CMS BPCI Total Spend	2017Q2	
Major joint replacement of the lower extremity	Performance Avg	Performance %
Total Episode Cost	$24,543	
Anchor Admit	$12,033	49%
Part B	$3,626	15%
Skilled Nursing Facility	$2,904	12%
Inpatient Rehabilitation Facility/LTCH	$893	4%
Home Health	$3,122	13%
Outpatient	$802	3%
Readmission	$1,064	4%
Durable Medical Equipment	$98	0%

Figure 2. CMS Bundle Payment Care Initiative (BPCI) Most Recent Reconciled Cost Data.

IBC Hip and Knee Replacement Legacy Bundle			
Period	Performance	Shared Savings (50/50 upside only)	Episodes
Oct '13 - Jun '14	($590,687)	$0	221
Jul-Dec "14	$105,273	$52,637	140
Jan-Jun '15	($391,111)	$0	184
Jul-Dec '15	$318,747	$159,374	169
Jan-Jun '16	$550,008	$275,004	208
Jul-Dec ' 16	$719,612	$359,806	193
Jan- Jun '17	$731,494	$365,747	221

Figure 3. IBC Savings.

a self-directed exercise program, with long-term health benefits. The physical therapy post-acute care cost and value is a new focus for the EOC.

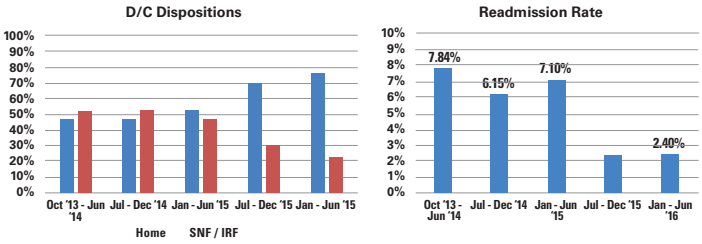

Figure 4. IBC Readmission and SNF Rate Changes Correlate with Figure 3.

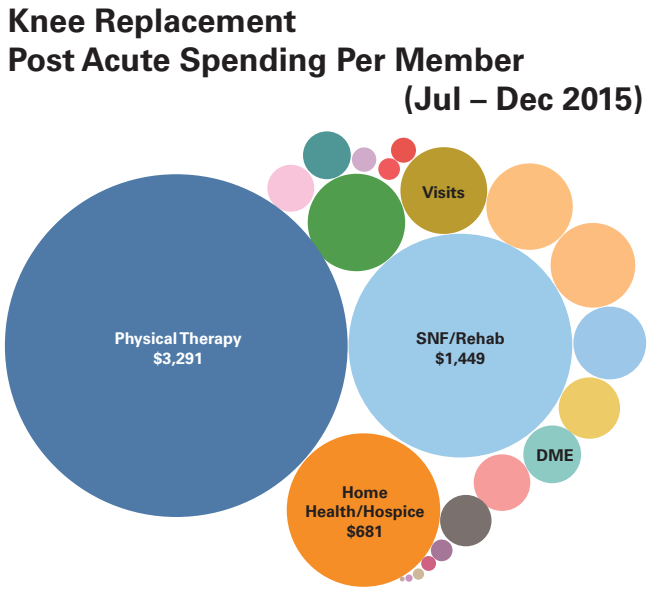

Figure 5. IBC Post-Acute Care Costs.

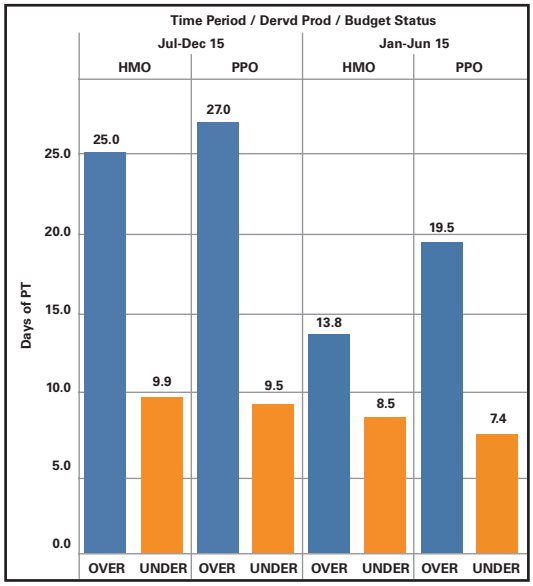

Figure 6. IBC Physical Therapy Session Variability.

Readmissions

Readmissions are poor value, both for low quality and high cost. Readmission prevention starts with preoperative preparation and medical comorbidity risk mitigation. Risk stratification work is focused on patients with multiple medical comorbidities that can be managed preoperatively. Urgent, unplanned patients are high risk, because we do not have the preoperative opportunity to manage comorbid risk. The third high readmission risk group is the patient discharged to SNFs and IRFs. Active collaboration, including sharing pathways and clinical processes supported by nurse navigators, helps manage the risk of readmission for all three groups.

Conclusion

Total joint arthroplasty pathways start when a patient signs surgical consent and continue through 90 days of postoperative care. All components of the pathway are amenable to reducing variability. Formal pathways can manage the majority of our patients. Process metrics allow us to understand quality impact. The resulting decreased variability has improved safety and lowered EOC costs. Realization of these opportunities comes with the Home Safely program and with preferred provider SNF and IRF collaboration. To prevent readmissions, we focus on improving care delivery across the whole episode of care. We have added a new focus with physical therapy progression to a self-directed exercise program to develop the healthy lifestyle that should start with a total hip or total knee replacement. We have been pleased that efforts aimed at improving quality have led directly to episode of care cost savings.

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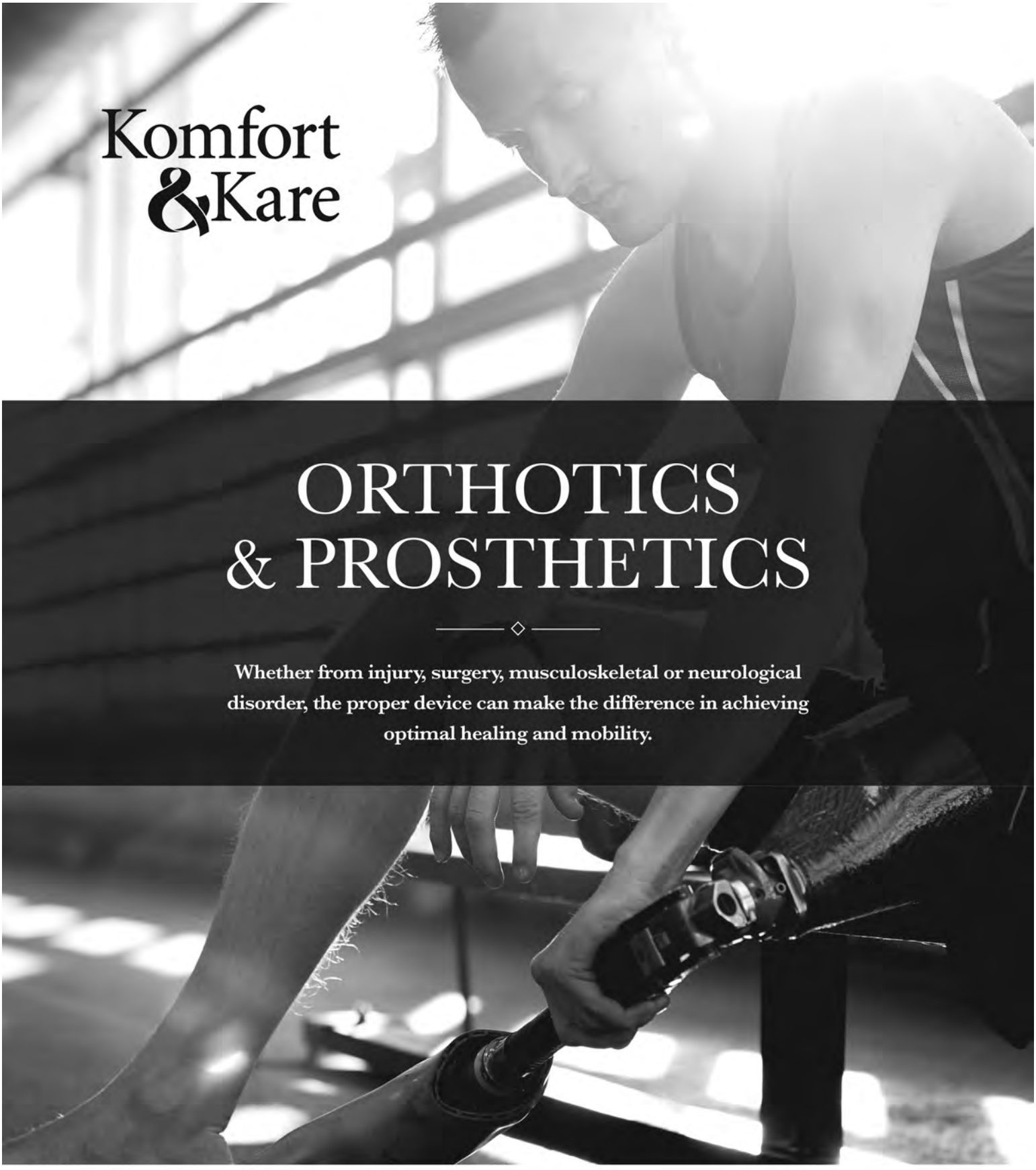
2. Yao DH, Keswani A, Shah CK, Sher A, Koenig KM, Moucha CS. Home Discharge After Primary Elective Total Joint Arthroplasty: Postdischarge Complication Timing and Risk Factor Analysis. *J Arthroplasty.* 2017 Feb;32(2):375-380.



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Kristy Weber to be first female president of AAOS

The Penn community looks forward to next year with great excitement as our own Kristy Weber will become the first female president of the American Academy of Orthopaedic Surgeons, serving from 2019-2020.

Dr. Weber serves as the Chief of Orthopaedic Oncology here at Penn. Residents look forward to being on her service, where difficult tumor resections and complex limb reconstructions are performed in pediatric and adult patients. She is also the Director of the Abramson Cancer Center Sarcoma Program, which gives residents a first class experience of how to efficiently organize a multidisciplinary team of doctors to provide the highest quality care for patients with complex diagnoses.

A tireless advocate for her patients, she is equally energetic outside of the operating rooms and clinics. She has dedicated herself to guiding the future of orthopaedics having served on the board of directors of the AAOS, American Orthopaedic Association, Orthopaedic Research Society, Musculoskeletal Tumor Society, Ruth Jackson Society and the Connective Tissue Oncology Society. She was also the recipient of the 2006 Kappa Delta Elizabeth Winston Lanier Award for her work in metastatic bone disease.

There are many challenges on the horizon facing the field of orthopaedics, but we look to the look forward to the future of our profession knowing that it rests in the most capable of hands.

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2017 Berton Rahn Research Award Recipient: Robert Mauck, PhD

We are proud to report Dr. Mauck was the recipient of the 2017 Berton Rahn Research Award. Dr. Mauck is the Mary Black Ralston Professor of Education and Research in Orthopaedic Surgery as well as the Director of the McKay Orthopaedic Research Laboratory at the University of Pennsylvania. This award, which recognizes young investigators for their contributions to the their field, comes with little surprise to the academic community at Penn given Dr. Mauck's incredibly decorated career, which includes the 2015 Kappa Delta Young Investigator Award from the American Academy of Orthopaedic Surgeons. He is active in numerous national and international academic organizations and serves on the editorial board for multiple journals, including a recent appointment of c-Editor–in-Chief of the new *Journal of Orthopaedic Research – Spine.* Dr. Mauck's lab has served as a launching pad for academic careers of numerous past and present residents. He helps to guide the lab year residents forward with many of them returning to participate as collaborators in translational research. Much of his work focuses on translational tissue engineering of musculoskeletal tissues such as cartilage, meniscus and intervertebral discs, and work from his lab can be found throughout the research sections of this journal.

L. Scott Levin, MD, FACS—President-Elect, American Society for Surgery of the Hand (ASSH)

Dr. Levin was recently elected as the future president of the American Society for Surgery of the Hand. Board-certified in plastic and reconstructive surgery, Dr. Levin is the chairman of Orthopaedic Surgery at the Perelman School of Medicine at the University of Pennsylvania, Director of the Penn Hand Transplant Program, Professor of Surgery in the Division of Plastic Surgery, and the Paul B. Magnuson Professor of Bone and Joint Surgery. Dr. Levin has also previously served as President of the American Society for Reconstructive Transplantation and the American Society of Reconstructive Microsurgery. His expertise in the field of microsurgery and exemplary leadership have been cited as reasons for his appointment as President.

The ASSH was established in the years following WW II with 35 hand surgeons from several hand centers across the country, under the leadership of Dr. Sterling Bunnell. Its first meeting was held at the Blackstone Hotel in Chicago in January, 1946 and has since grown every year to become a predominant surgical society. The ASSH works to advance hand and upper extremity surgery through research and education, as well as advocating on behalf of both patients and practitioners. It is this legacy that Dr. Levin inherits and will continue to foster during his time in office.

Leading by example: Dr. Levin offering to be the "patient" while visiting professor Dr. Luis Scheker teaches the residents how to examine the DRUJ

Louis Soslowsky, PhD—H. R. Lissner Medal

The H. R. Lissner medal is awarded by the American Society of Mechanical Engineers (ASME) in recognition of outstanding achievement in the field of bioengineering. The award was established in 1977 and named in honor of H. R Lissner, a professor at Wayne State University, for his work in the field of biomechanics. This award is given to one individual per year and is the single highest honor that can be achieved in the field of bioengineering.

Dr. Soslowsky received the award in 2018 "for outstanding contributions toward the understanding, prevention and treatment of musculoskeletal injuries to tendinous and ligamentous tissues; and for internationally recognized leadership in the biomechanics community". He is set to deliver a plenary lecture and receive his award at the World Congress of Biomechanics in Dublin, Ireland in the summer of this year.

Dr. Soslowsky is the Associate Dean for Research Integration at the University of Pennsylvania and the Founding Director of the Penn Center for Musculoskeletal Disorders. His lab operates as part of the McKay Orthopaedic Research Laboratory. When asked about his research, Dr. Soslowsky states, "My group is involved in a number of exciting studies in tendon and ligament injury and repair. We are making strong efforts in understanding fundamental structure-function relationships, that is, how the composition and organization of a tissue relate to its mechanical function". He continues to work on translating basic science bench research into clinically applicable diagnoses and treatments.

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 μCT 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 145 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 faculty members for more than 12 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.

2017 Cartilage Repair Symposium

Mackenzie Sennett

In April 2017, coinciding with the Penn Relays, the University of Pennsylvania Department of Orthopaedic Surgery was thrilled to host the Penn Orthopaedics 2017 Cartilage Repair Symposium. This multidisciplinary event, organized by James L. Carey, MD, MPH, and Robert L. Mauck PhD, brought orthopaedic surgeons, engineers, and basic scientists together from across the United States and World. Symposium topics included basic science and biology of cartilage, translational considerations for cartilage repair, and the latest surgical and clinical techniques for cartilage repair and rehabilitation. Invited keynote speakers included Farshid Guilak, PhD (Washington University in St. Louis, St. Louis, MO) and Daniel B. Saris, MD, PhD (Mayo Clinic, Rochester, MN). Day one of the symposium included Dr. Guilak's keynote lecture, *"An Engineering Perspective on Biologic Joint Replacement,"* and concluded with an evening cocktail hour and poster session. Day two of the symposium included the keynote lecture by Dr. Saris, "*SUMMIT Trial – MACI Experience in Europe".* The day concluded with a surgical skill session in the Human Tissue Lab, moderated by Miltiadis Zgonis, MD. Under the leadership of Drs. Carey and Mauck, the symposium continues to grow in popularity and promises to be a gathering of the foremost cartilage repair specialists for years to come.

We hope to see you at the annual Penn Cartilage Repair Symposium this year, taking place on September 7th and 8th, 2018. For more details, please visit:

http://pennmedicine.org/CartilageRepair

Orthoplastics Division

Stephen J. Kovach, III, MD and L. Scott Levin, MD, FACS

Multidisciplinary care of patients has become commonplace within modern medicine. The medical and surgical knowledge required to take appropriate care of patients is too vast for any one physician to master. The combination of the principles of Orthopaedic Surgery and Plastic Surgery or Orthoplastic surgery is the epitome of the multidisciplinary approach to patient care. Orthoplastic surgery harnesses the best aspects of each specialty and applies them to the care of the patient. The care of the orthopaedic patient encompasses meticulous fracture reduction and fixation, hand surgery, well executed arthroplasty, and tumor resection. Without special attention to the soft tissue envelope, each of these endeavors may be for naught. Whether it is microvascular coverage of a IIIB tibia fracture, prophylactic soft tissue coverage to allow for revision knee arthroplasty, or reconstruction of a musculoskeletal tumor defect to allow for limb salvage, the principles are the same: achieve the most functional outcome for the patient with the least risk and morbidity.

Our reconstructive abilities have continued to improve since Orthoplastic surgery was first described in 1993 (Levin LS. The Reconstructive Ladder - An Orthoplastic Approach. Orthopaedic Clinics of North America, J.B. Lippincott Co., 24(3):393-409, July 1993). The idea of combining the beneficial aspects unique to each specialty in the care of the orthopaedic patient has served as the basis of Penn's Musculoskeletal Institute. Orthoplastic surgery has made great strides since it was first described. At Penn, we have contributed to the evolution of microvascular perforator flaps to minimize patient morbidity, combined ringed fixators and free tissue transfer, used minimally invasive approaches to joint arthroplasty, and allowed for revision arthroplasty with prophylactic soft tissue augmentation. Perhaps the ultimate confluence of orthoplastic surgery has been the successful performance of 3 bilateral hand transplants. The coordination of care between orthopaedic and plastic surgery was paramount to the success of our vascularized composite allotransplantation program. Penn has remained fertile ground for the care of complex musculoskeletal patients, and orthoplastic surgery has blossomed as part of the Musculoskeletal Institute's dedication to improving care of patients.

Penn is uniquely qualified to care for patients with complex reconstructive needs of their musculoskeletal system. In addition to the trauma, joint, hand, and tumor surgeons, the Musculoskeletal Institute has plastic and microsurgeons whose focus remains reconstruction of the orthopaedic surgical patient. Plastic and orthopaedic surgical principles are a powerful tool, but stronger when applied in combination. Orthoplastic surgery is not unique to a finite group of faculty as the principles permeate the practices of all the members of the Department of Orthopaedic Surgery. We are all "orthoplastic" surgeons at heart.

Our goal continues to be to deliver the finest orthoplastic care to patients and to grow our individual programs within the Musculoskeletal Institute. We will continue to work together in a coordinated fashion to attract patients regionally, nationally and internationally. As Orthoplastic surgeons, we have a unique skill set and ability to work together for the betterment of patients and physicians alike.

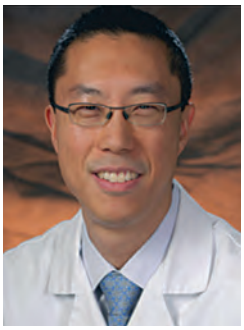
Multidisciplinary orthoplastics team for bilateral hand transplantation (Children's Hospital of Philadelphia).

Orthopaedic Trauma Division

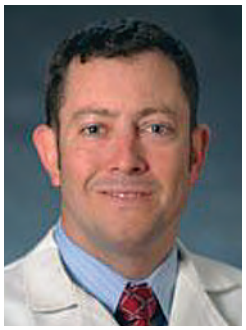
Samir Mehta, MD

Orthopaedic Trauma Faculty

Samir Mehta, MD



Jaimo Ahn, MD, PhD



Derek Donegan, MD

L. Scott Levin, MD, FACS

The Orthopaedic Trauma and Fracture Service in the University of Pennsylvania of Health System continues to expand its footprint in the Delaware Valley. Anchored by a tremendous general surgery trauma service, expanded infrastructure at Penn Presbyterian Medical Center, and dedicated and determined housestaff and advanced practice providers, the Division of Orthopaedic Trauma strives to compete at a high level across all missions of the Health System and School of Medicine. The clinical program has expanded to include peripheral sites including Radnor and Cherry Hill. Thanks to the help of our administration and our clinical partners, the Division has finally realized a Geriatric Hip Fracture program – an idea nearly a decade in the making. In addition, the Division continues to explore and build relationships with Penn's newest partners – Chester County Hospital, Lancaster General Hospital, and Princeton Hospital. Services that are provided to our sister hospitals as well as our regional orthopaedic community include complex fracture care, limb salvage, deformity correction, periprosthetic fracture reconstruction, and infection management. Our clinical program continues to utilize advanced technologies such as 3D printed implants, lengthening nails, and ring fixators. Our ability to provide care necessary to our patients in a 24/7/365 fashion would not be possible without the house staff, our nurse practitioner, our physician assistants, and the faculty who continue to take call on nights, weekends, and holidays.

Through the tireless efforts of our clinical research coordinators, the research program continues to expand. Several prospective funded studies are currently underway, including ones funded by industry examining the changes with suprapatellar nailing, the Department of Defense assessing infection control in open fractures, the REGAIN hip fracture trial through PCORI, and better understanding the flora of open fractures through the AO Foundation. In addition, a generous grant from the Wyss foundation continues to support our work examining the biomarkers predicting fracture healing which was recently highlighted at the AAOS Annual Meeting. Engaging in pragmatic trials allowing us to refine our approach to trauma and fracture care is a critical component of our work at Penn.

Ultimately, the orthopaedic trauma and fracture service is most proud of its continued dedication to resident education. The current complement on service includes a PGY1, 2 PGY2s, PGY3, PGY4, and PGY5. While there are occasional visiting fellows, these learners do not interfere with the education of the residents, who are the primary focus for the service. The residents continue to work hard on this service rewarded with opportunities in leadership, technical skill development, decision-making, and communication. Several teaching tools are utilized in the resident growth and development including critical and timely feedback, online education, written pre-operative plans, case-based teaching, and trauma conference.

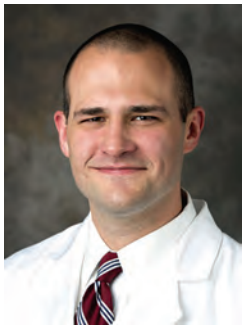
Spine Division

Vincent Arlet, MD

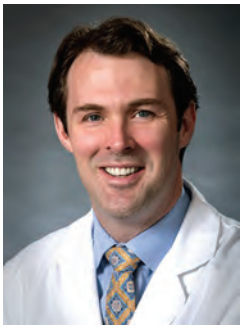
Spine Faculty


Vincent Arlet, MD


Harvey Smith, MD


Andrew Milby, MD


Comron Saifi, MD


Michael Murray, MD

The new academic year has seen lots of positive changes for the spine division.

Recruitment:

Three additional Spine surgeons came onboard our busy Spine Division. Dr. Milby who is a former resident from Penn came back after a one year spine fellowship at Emory. Dr Milby is currently working at the VA, Penn Presbyterain Medical Center and Radnor. His research and clinical interests lie in degenerative spine disorders. Dr. Michael Murray left his successful private practice at Christiana in Delaware to start a new Practice at Penn Chester County Hospital. His research and clinical interest lie in minimal invasive spinal surgery and degenerative spine disease. Dr. Comron Saifi , a graduate from Columbia, finished his Spine fellowship at Rush and is interested in degenerative spinal conditions and spinal deformities. Dr. Saifi works primarily at Pennsylvania Hospital and at Yardley.

With now five spine surgeons in the orthopedic division, we cover the whole spectrum of spine surgery from minimally invasive surgery to complex spinal reconstruction, including adult and pediatric spinal deformities, spinal tumors, and treatment of cervical diseases with motion sparing technologies such as cervical disc replacement or laminoplasty. Our referral for revision spinal surgery coming from outside the Penn system has also increased dramatically and our clinical activity is forecasted todouble in the year to come.

Spine trauma coverage:

In partnership with our neurosurgical colleagues, we now cover spine emergencies including fractures, emergent tumors and infections. This has had a huge impact on the education of our residents who so far had limited exposure to spine trauma. Dr. Harvey Smith, our Orthopedic Spine Trauma Program Director, has begun to implement protocols for spine fractures in partnership with the Presbyterian Trauma ICU and our neurosurgical colleagues.

Research:

Under the leadership of Dr. Smith, grants of several million dollars have allowed sustained research on the degeneration and regeneration of the human disc. This research is being conducted at the VA and will hopefully mitigate the need for complex spinal procedures in the near future.

Academic Productivity:

Fifteen peer review publications,abstracts and presentations have come from the spine division. Penn Orthopedics is now represented in most national and international spine societies. The Philadelphia Spine Summit meeting organized with our colleagues from Jefferson is now entering its fourth year and attracts spine surgeons from all over the region.

Outreach Surgery:

Surgery to treat pediatric and adult patients with spinal deformities is still ongoing in Trinidad and Tobago. With more than 100 complex spinal deformities treated in Trinidad, our outreach experience is well recognized nationwide and internationally.

Spine Fellowship:

This was the first year that we combined our Spine fellowship with the Shriners Hospital of Philadelphia. Our complex spine deformity fellowship exposes the fellow to pediatric deformity for 6 months at Shriners and adult spine for another 6 months at Penn. Our two Spine fellows, Dr. Nissim Ackshota and Dr. Burhan Muhammad, are each in their second year of spine fellowship at Penn.

Sports Division

Brian Sennett, MD

Sports Medicine Faculty


Brian Sennett, MD


James Carey, MD, MPH


John Kelly, MD


Miltiadis Zgonis, MD


Kevin McHale, MD

The Division of Sports Medicine within the Department of Orthopaedic Surgery has continued to be at the forefront of collaborative medicine as it is comprised of faculty from Orthopaedic Surgery, Family Medicine, and Physical Medicine and Rehabilitation. With this collaborative approach, the Division has reached into the University with efforts focused on the Division of Recreation and Intercollegiate Athletics. Out of this initiative has sprung the Penn Sports Performance Program.

The Penn Sports Performance Program has become a cornerstone program for Penn Athletics. The development of this program has been an interdepartmental effort between Penn Athletics and Penn Sports Medicine. The Program focuses on the Penn athlete in the areas of Penn Medicine, Athletic Training, Strength and Conditioning, Nutrition, Mental Health and Wellness, and Sports Psychology. The focus is on optimization of the Penn athlete's experience through prevention of injuries, optimization of their medical care, and enhanced performance through nutrition, conditioning, and mental training. This initiative has been spearheaded by Dr. Brian Sennett. This is an exciting area of growth and development and will encompass all of Penn Medicine over the next year.

Athletic coverage has always been one of the cornerstones of Sports Medicine and this past year has not been any different. While the Division has always cared for Penn Athletics and the athletics program at the University of the Sciences, they now provide coverage for the entire City of Philadelphia's athletic programs with the addition of ten new certified athletic trainers. This coverage has expanded the coverage to their prior program, which included West Catholic and Bonner. In addition, Penn Sports Medicine provided exclusive care and coverage of the Philadelphia Freedom Professional Tennis Team in 2017. The Philadelphia Freedom is a tennis team currently competing in World Team Tennis and is comprised of international stars in tennis. The team is owned by Billie Jean King. The medical coverage was led by Drs. Kate Temme and James Carey.

The athletic community also continued to be served by the Penn Sports Medicine team. The running population was served by Penn Sports Medicine as John Vasudevan, MD served as medical director for the Tri-rock Philly Triathlon held in June, 2017. Rahul Kapur, MD continues to serve as the medical director for the Penn Relays and Dr. Alexis Tingan will serve as the medical director for this year's Philadelphia Love Run Half-Marathon in March, 2017. Dr. Sennett continues to serve as a medical advisor to the Philadelphia 76ers.

Education has also continued to be a main focus of the Division. In addition to continuous medical student, resident, and fellowship education, education forum has been held at the national level. The Penn Center for Advanced Cartilage Repair and Osteochondritis Dissecans Treatment has continued to grow annually. The Penn Cartilage Center (including members of CHOP and Penn) is now one of the highest volume autologous chondrocyte implantation centers in the world and one of the highest volume meniscus transplantation centers in the United States. The Penn Center for Cartilage Symposium has also continued to flourish. It has become an international course organized and run by Course Directors James L. Carey, MD, MPH and Robert L. Mauck, PhD. In 2017, Daniel Saris from the Netherlands served as international faculty at the 6th Annual Penn Cartilage Symposium. There were 200 participants. Dr. Carey concluded his two-year term as President of the Research in OsteoChondritis of the Knee (ROCK) group—an international professional and research society consisting of 36 surgeons from 24 sites in 7 countries.

The fifth annual Penn Medicine's Advances in Throwing Conference was held in January, 2018. The symposium was an exciting event featuring a multidisciplinary approach to the evaluation and treatment of pathologies related to the throwing athlete. The Co-Directors for the conference were Miltiadis Zgonis, MD and Kyle Schaefer, ATC. The symposium serves as one of the educational cornerstones of the Penn Throwing Clinic which is directed by John Kelly, MD. In 2017 and 2018, Drs. Kelly and Sennett taught Instructional Course Lectures at both the American Academy of Orthopaedic Surgeons and the Arthroscopy Association of North America annual meetings, focusing on Advances in the Thrower's Shoulder. These lectures have highlighted work performed at the Penn Throwing Clinic, located with the Penn Human Performance Center.

It has been an exciting past year at the Penn Sports Medicine Center with much more to follow in this upcoming year.

Hand Surgery Division

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

The hand and upper extremity service at Penn continues to expand and thrive. The service is developing into a more integrated program with the Department Plastic Surgery in addition to maintaining the close relationship with the pediatric hand section at Children's Hospital of Philadelphia and Shriner's Hospital of Philadelphia. The combined service provides better collaboration in research, clinical coverage and education.

Dr. Stephen Liu, MD returned home to Penn in September joining the hand surgery section. Dr. Liu completed his orthopaedic surgery residency at the University of Pennsylvania and hand surgery fellowship training at the University of Pittsburgh. His hand and upper extremity practice is based at Chester County Hospital.

As Director of Clinical Research for the Hand Surgery Section, Dr. Benjamin L. Gray oversees the continued expansion of research within the division. The program is supported by Annamarie Horan PhD, Director of Orthopedic Clinical Research and Andrew Diederich as research coordinator. The service currently participates in four externally funded studies and over 10 internally funded projects. This past year Dr. Gray was awarded the Bach fund grant to support the development of a low-cost motion capture device for the hand.

The hand transplant service has recently listed its fourth candidate for bilateral upper extremity allotransplantation. The team meets regularly to review candidates in addition to performing cadaveric rehearsals refining their surgical checklist.The three prior bilateral hand transplant patients are progressing well.

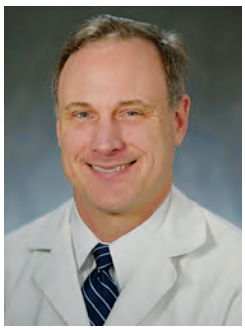
Dr. David R. Steinberg, Hand Fellowship Director, has led a very productive group of hand surgical fellows. Over the past year the group has authored 18 peer-reviewed journal articles, six book chapters and submitted six abstracts for presentation. Dr. Oded Ben-Amotz is completing his second year of fellowship and will be returning to practice at Rambam Medical Center, a level one trauma center in north Israel. Two new fellows were selected from over 140 applicants. Dr. Shaun Mendenhall completed his plastic surgical residency at Southern Illinois University School of Medicine. Dr. Mendenhall has accepted a position in the Department of Plastic Surgery at the University of Utah after his fellowship year. Dr. Joshua Mirrer completed his plastic surgical residency at NYU Langone Medical Center and has accepted a position at the Arizona Center for Hand Surgery in Phoenix. We look forward to great accomplishments from our fellows in the coming years in addition to the bright future for the hand surgery service at Penn.

Shoulder & 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 2017, the group performed over 11,000 visits and performed over 1000 surgical cases.

Now in its second year, and in collaboration with our French colleagues, we offer our fellow an opportunity to visit world leaders in shoulder surgery. Chad Myeroff (F'17), who is in academic practice in Minnesota, spent three weeks visiting academic centers in Monaco and France, while Josh Rogozinski (F'18) traveled to centers in Monaco, France and Spain. 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.

As director of research, Andy Kuntz is leading our research effort, with close collaboration with Louis Soslowsky, PhD and others in the McKay Research Laboratory. Together, we help form one of the largest shoulder research laboratories in the world. In addition to smaller grants, we now have three funded prospective clinical research studies in our division. One of the clinical research studies is a multi-center trial, which is the direct result and translational follow-up to basic science research performed in the McKay Lab. We have developed, in conjunction with Mike Hast, PhD in the Biedermann Lab, a new biomechanical testing apparatus and protocol currently to study reverse glenoid baseplate fixation.

Clinical studies include outcomes using multimodal pain control, transition to outpatient shoulder arthroplasty, and cost efficiency in delivering health care. The Penn shoulder and elbow faculty presented 16 abstracts at national meetings and gave 13 talks at international, national, regional and local meetings in 2017/18.

Arthroplasty Division

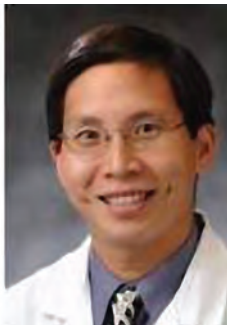
Charles Nelson, MD

Arthroplasty Faculty

Charles Nelson, MD

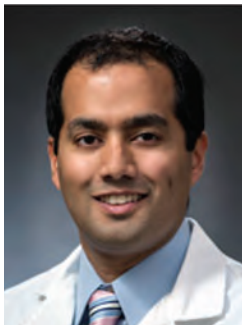
Craig Israelite, MD

Eric Hume, MD



Gwo-Chin Lee, MD

Neil Sheth, MD



Atul Kamath, MD

The 2017/2018 academic year has been an outstanding year for the 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 than150 participating hospitals.The annualized surgical volume this year for the total joint division was over 4000 surgical cases at the two down town 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 American Orthopaedic Association, the American Board of Orthopaedic Surgeons, the American Associaton of Hip and Knee Surgeons and the Knee Society. Our faculty where involved with more than 30 peer reviewed publications in 2017 and more than 60 scientific presentations and lectures by invitation.

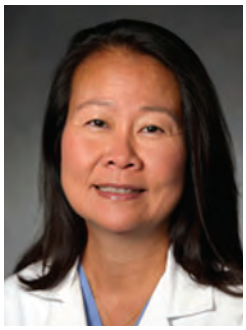
This past summer we had the honor of hosting the AOA Austrian-Swiss-German Traveling fellows in Philadelphia for four days in an outstanding exchange of information. This spring, Neil Sheth, MD will be one of the two American's visiting Austria, Switzerland and Germany as an AOA Austrian-Swiss-German Traveling Fellow and Atul Kamath, MD will be visiting Japan as one of the American Orthopaedic Association Japanese Traveling fellows.

Foot Ankle Division

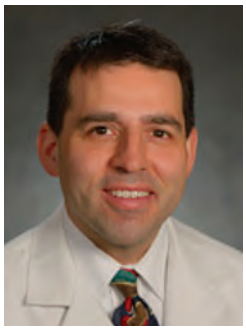
Daniel Farber, MD

Foot & Ankle Faculty

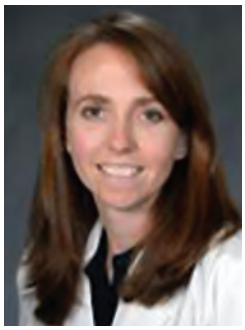
Keith Wapner, MD



Wen Chao, MD



Daniel Farber, MD



Kathryn O'Connor, MD, MSPT

The Foot and Ankle Division continues to serve the needs of Philadelphia and beyond. Our faculty includes Keith Wapner, Wen Chao, Kathryn O'Connor, and Daniel Farber and a team of physician assistants including Greg Ranalli, Kristen Storck, Lauren Sutcliffe, and Alyssa Meuthing. We serve Center City and beyond with locations at the Farm Journal Building, PMUC, Cherry Hill, Radnor, Valley Forge and Exton and perform surgical procedures at Pennsylvania Hospital, Penn Presbyterian Medical Center, the surgery center at PMUC, and at Chester County Hospital. Collectively, the division has had 22,000 patient visits and performed over 1,300 surgical procedures in the past year.

Dr. Keith Wapner continues to lead the division and represents Penn Orthopaedics with presentations around the world and in the United States. He also serves as a member of the managerial board of *Foot and Ankle International*. Dr. Daniel Farber is on the AOFAS Education committee and serves on the AAOS Resolutions Committee. He is still at work developing an accreditation pathway for foot and ankle fellowships in a cooperative venture between the AOFAS and AAOS. Dr. Farber is the also Associate Editor for Review Articles for *Foot and Ankle Orthopaedics,* the open access journal of the AOFAS. He continues to direct Penn's Foot and Ankle Fellowship. Dr. Wen Chao is an Orthopaedic Consultant to the Pennsylvania Ballet and serves on the AOFAS Public Relations committee. Dr. Kathryn O'Connor is running the foot and ankle education curriculum for the residents and serving on the AOFAS Evidence Based Medicine Committee in addition to receiving research grants from the McCabe Fund and the AOFAS.

The division has started enrolling patients in several national studies. These include an ongoing study of the STAR ankle replacement, a prospective study of a new bone graft substitute and an investigation of the use of bone stimulators for acute operatively treated ankle fractures. Other investigations include collaborations with Penn's Human Performance Laboratory exploring long term follow up of long harvest transfer of the flexor hallucis longus muscle for treatment of chronic Achilles pathology as well as a McCabe grant received by Dr. O'Connor and director Josh Baxter, PhD to examine nonoperative treatment of acute Achilles ruptures. We continue to explore insights gained from weight-bearing CT scanning in investigations of ankle and hindfoot arthritis as well as in bunion deformities. An ongoing study looks at the role Orthopaedic surgeons play in influencing patients' choice of footwear and another study surveys an international group of surgeons to determine the adequacy of radiographs in Foot and Ankle literature. We continue our collaboration with the Biedermann lab and Mike Hast, PhD to explore the compression properties of a new plate for fusions of the forefoot, midfoot and hindfoot.

Ongoing collaboration with the McKay Lab and Lou Soslowsky, PhD has led to multiple publications investigating early return to activity after repaired and non-repaired Achilles ruptures, as well as the effect of nicotine on tendon health. We hope to begin an investigation of treatment options for simulated chronic Achilles ruptures in a rat model this coming year.

Penn's Orthopaedic Foot and Ankle Division is poised for yet another exciting year of excellent patient care, resident and fellow education, service to the orthopaedic community and active research.

Orthopaedic Oncology Division

Kristy Weber, MD

Orthopaedic Oncology Faculty

Kristy Weber, MD, FACS

Robert Wilson II, MD

The Orthopaedic Oncology service at Penn is comprised of Dr. Kristy Weber and Dr. Robert Wilson who work as part of a multidisciplinary team of caregivers focused on 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 core team also includes Sarah Borgia, MHA, Administrative Coordinator, Kate Barrie, PA, and Laura Cappetti, RN. The overall footprint and access has improved with the addition of Dr. Wilson in September, 2017. Patients can now be seen 4 days per week with clinic locations at PCAM and Radnor. Surgeries are performed 2-3 days per week at HUP. Dr. Wilson also has a presence at the Philadelphia VA Hospital where he sees orthopaedic oncology patients in addition to patients needing hip or knee arthroplasty for non-oncologic reasons. Patients are also managed in the clinic and OR at CHOP along with Dr. Alex Arkader (Orthopaedic Oncology/Pediatric Orthopaedics) and Amy Rapino, CRNP. 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 2018 was Dr. Denis Clohisy, Chair of the Department of Orthopaedic Surgery at the University of Minnesota.

The multidisciplinary clinical team that treats patients with bone or soft tissue sarcomas meets 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.

Active marketing efforts are ongoing at both Penn and CHOP to expand the reach of the orthopaedic oncology program in the region. Dr. Wilson has done extensive outreach to orthopaedic and oncology physicians and groups throughout Pennsylvania and New Jersey. Furthermore, with the addition of Lancaster General and Princeton to the Penn Health Network, we have reached out to develop care pathways to collaboratively diagnose and treat patients with bone and soft tissue tumors.

One feature that stands out about the Penn Sarcoma program is the presence of a collaborative scientific team focused on new discoveries in sarcoma. The core sarcoma research team includes Karin Eisinger, PhD, Malay Haldar, MD, PhD, Celeste Simon, PhD, Margaret Chou, PhD (CHOP), and Nicola Mason, PhD, BVetMed. There is an ongoing search at CHOP to hire another sarcoma scientist in 2018. 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 its 4th year of organization and planning to support sarcoma research at Penn Med/Penn Vet/CHOP. In 2017, over $150,000 was raised and nearly 1000 people attended the annual Walk/Run. This year the event is June 10, 2018 at Wilson Farm Park in Wayne, PA. https://stepstocuresarcoma.com/

Children's Hospital of Philadelphia

Divya Talwar, BDS, MPH, PhD, John M. Flynn, MD

Pediatric Orthopaedics Faculty


John Flynn, MD


Alexandre Arkader, MD


Keith Baldwin, MD, MPH, MSPT

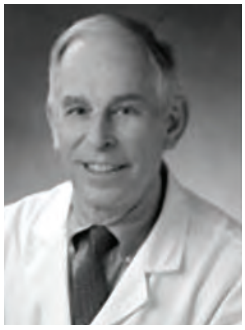

Patrick Cahill, MD


Robert Campbell, MD


Robert Carrigan, MD


Richard Davidson, MD


Theodore Ganley, MD


Malcolm Ecker, MD


David Horn, MD


John Lawrence, MD


Wudbhav Sankar, MD


Apurva Shah, MD, MBA


David Spiegel, MD


Lawrence Wells, 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 2017, *US News and World Report* ranked the Division of

Orthopaedic Surgery 2nd in the nation in pediatric orthopaedic surgery.

In 2017, CHOP Orthopaedics continued the Nicholson Visiting Professorship, hosted major conference meetings and Food and Drug Administration (FDA) reviewers, started a FDA investigational 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), National Science Foundation (NSF), renovated the Fellowship recruitment and interviewing process, and hired Quality Safety and Value advisors to improve efficiency and value initiatives in orthopaedic surgery.

Clinical Program

Our orthopaedic faculty continues to expand and is currently comprised of twenty-eight total providers, which consists of nineteen specially-trained pediatric orthopaedic surgeons (fourteen operative and five non-operative), four sports medicine-trained pediatricians, two active plastic surgeons, and three transition-to-adult care faculty.

Figure 1. Neeraj Patel, MD

Figure 2. Ariana Trionfo, MD

Figure 3. Amirhossein Misaghi, MD

Figure 4. Jason Anari, MD

Figure 5. Mahmoud El-Magd, MD

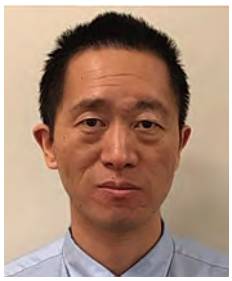


Figure 7. Dr. Dongliang Shi, MD

Education Program

CHOP Orthopaedics currently funds four one-year clinical fellowships and one one-year research fellowship. The 2017-2018 clinical fellows are Neeraj Patel, MD (Figure 1); Ariana Trionfo, MD (Figure 2); Amirhossein Misaghi, MD (Figure 3); and Jason Anari, MD (Figure 4). This year's research fellow is Mahmoud El-Magd, MD from Egypt (Figure 5) and Dr. Dongliang Shi, MD from China (Figure 6). While at CHOP Dr. El-Magd has focused his research efforts on trauma and lower limb deformities; Dr. Shi has concentrated on research projects related to sports injury.

To celebrate the graduation of the 2016-2017 clinical fellows, the Division hosted the Nicholson Visiting Professor Program and Fellows Graduation & Reunion in June 2017. This year's Visiting Professor was Dr. Dennis Wenger, who is the director of the International Center for Pediatric and Adolescent Hip Disorders at Rady Children's Hospital-San Diego and the Rady Children's/UC San Diego Pediatric Orthopedics and Scoliosis Fellowship. 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.

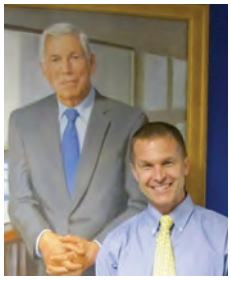


Figure 3. Dr. Jonathan G. Schoenecker,

We continued to hold our Drummond Rising Star Visiting Professorship in October 2017. Visiting professors are nominated by current CHOP staff. The 2017 Drummond Rising Star Visiting Professor was Jonathan G. Schoenecker, MD (Figure 7). Dr. Jonathan G. Schoenecker, Associate Professor of Orthopaedics, visited us from Vanderbilt University Medical Center. He is an orthopaedic surgeon-scientist dedicated to caring for children with orthopaedic trauma and hip conditions, educating future surgeon-scientists, and conducting high impact translational research.

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. Over the past year, the Division hosted Dr. Angela Shrestha from Nepal.

Research Program

This past year, our basic and translational medicine researchers (Figure 8) 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 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) and Temporo-mandibular Joint dysfunction.

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

Figure 8.

developing innovative projects in translational research. The CTIS program's mission is to advance care for patients with thoracic insufficiency syndrome (TIS) through basic science research, advanced imaging techniques, and clinical outcomes research.

The CTIS Basic Science Research Lab is developing a rabbit model of thoracic insufficiency syndrome. Dr. Casey Olson, a bioengineer, leads this lab to better understand the mechanisms of thoracic insufficiency syndrome and to provide biologic platforms for testing of new devices to treat thoracic insufficiency. To this end CTIS research lab has prepared for survival animal surgeries, pulmonary and electrophysiology evaluation, medical image processing, necropsy lab, pathology lab, and biomechanics lab.

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). To investigate further genetic characterizations of the EXT1/EXT2 mutations harbored by each exostosis and identify second hits across exostoses from the same patient, Dr. Arkader was awarded a competitive faculty award from Division of Orthopaedics. 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 was awarded grants by 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 167 IRB-approved clinical research projects. This includes 74 prospective and observational studies. CHOP Ortho faculty are also members of several multicenter study groups, including the Harms Study Group (HSG), Research in Osteochondritis Dissecans of the Knee (ROCK), The Fox Pediatric Spinal Deformity Study (Fox PSDS), Pediatric ACL: Understanding Treatment Operations (PLUTO), 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 2017, the Division published over 138 articles in major orthopaedic journals, including *JBJS, JAMA Pediatrics, JPO*, and *CORR*. Members across our division presented 122 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, Nakul Talathi (Perelman School of Medicine at the University of Pennsylvania), Alexander Adams (Thomas Jefferson University) and Jigar Gandhi (Rutgers Robert Wood Johnson Medical School), were awarded with the fellowship (Figure 9-11).

Figure 9. Nakul Talathi

Figure 10. Alexander Adams

Figure 11. Jigar Gandhi

Recognition and Achievements

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

Alexandre Arkader, MD co-directed the 5th Combined SLOATI/POSNA/EPOS/ meeting, Sao Paulo Brazil Oct 2017. He also served as an International Faculty at the Salzburg Medical Seminar in Pediatric Orthopedics in Salzburg, Austria. Dr. Arkader continues to serve as a reviewer for *Current Orthopaedic Practice, Journal of Bone and Joint Surgery, Clinical Orthopaedics and Related Research and Journal of Pediatric Orthopaedics*. He was invited as a lecturer for Grand Rounds at Louisiana State University, New Orleans LA.

Keith Baldwin, MD, MSPT, MPH is the current Director of Clinical Research and Associate Director of Orthopaedic Trauma in the Division of Orthopedic Surgery. Dr. Baldwin continued his term as president of the Orthopaedic Rehabilitation Association and served as course director for the 2017 Orthopaedic Rehabilitation Association Annual Meeting. He currently serves as a reviewer for several journals including the *BMC Medical Education, BMC Musculoskeletal Disorders, Journal of Bone and Joint Surgery—American*, and the *American Academy of Pediatrics*. He also serves as 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.

Patrick Cahill, MD continued his term as chair of the SRS research grants committee and is 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, Children's Spine Study Group, and Fox Pediatric Spine Deformity study group,

which are multi-center groups prospectively researching care improvements for complex pediatric spine deformities. He successfully started the FDA Investigational Device trial on Vertebral Body Tethering device.

Robert Campbell, MD continues to expand his multidisciplinary research center of Center for Thoracic Insufficiency at CHOP through the CHOP Frontier Grant. Dr. Campbell and Dr. Udupa (Perelman School of Medicine) continued their work on the NIH R21 Grant for their project, "Dynamic MRI Image Analysis for Studying Thoracic Insufficiency Syndrome". He continues to serve as a member of the Early Onset Scoliosis Task Force, FDA Grants for National Non-Profit Pediatric Device Consortia, and FDA Office of Orphan Product Development. Along with Drs. Cahill and Baldwin, he continues to develop and direct *Pediatric Spinal Surgery Symposium for FDA Reviewers.*

Robert Carrigan, MD continues to serve on the AAOS CAQH Test Validation 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.* Additionally, along with Dr. Apurva Shah and Shriners Hospitals for Children – Philadelphia, he co-hosted the 2017 Annual Pediatric Hand Study Group Meeting at CHOP.

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 Orthopaedic Surgery, continues to serve his 10-year term as Director of the American Board of Orthopaedic Surgery. Dr. Flynn is co-editor of *Lovell and Winter's Pediatric Orthopaedics, Rockwood's Fractures in Children, Operative Techniques in Pediatric Orthopaedics*. He is President of the Children's Spine Study Group and is active in the Harms Study Group, a multicenter collaboration of researchers studying care improvements for pediatric spine deformity surgery. In the past year, Dr. Flynn also was invited as the graduation speaker at Mayo Clinic and visiting professor at Harvard/Boston Children's Hospital, Brown University, St. Luke's Bethlehem, University of Utah, University of Florida, Medical University of South Carolina, Rady's Children Hospital, Temple University, Japanese Orthopaedic Association, and Northwestern University.

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*. Additionally, he was invited as a consultant and advisor for the International Olympics Committee to develop a consensus protocol for treatment of pediatric ACL injuries

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. He also served as an international faculty member at the Salzburg Medical Seminar in Pediatric Orthopedics in Salzburg, Austria. Dr. Lawrence is an active member of sports medicine multicenter research groups such as PLUTO and MEMO. He continues to serve as a reviewer for the *American Journal of Sports Medicine (AJSM)* and *Journal of Shoulder and Elbow Surgery (JSES)*.

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) and International Perthes Study Group. 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 awarded best eposter award at POSNA.

Apurva Shah, MD, MBA continued to serve as co-PI on the POSNA Directed Research Grant entitled, "Improving value delivery in pediatric distal radius fracture care."The grant aims to asses practice pattern variation and compare treatment costs across institutions and low- and high-volume centers. Dr. Shah also received a new grant as co-PI from Orthopaedic Trauma Association titled, "Opioid utilization after rotational ankle fractures". He continued to serve as team leader and traveled to Sigua Tepeque, Honduras for a pediatric hand surgery medical mission. Dr. Shah was invited as a visiting professor at Curtis National Hand Center, Baltimore, Saint Peter's University and MedStar Georgetown.

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). In collaboration with Dr. Bibek Banskota in Nepal, Dr. Spiegel is conducting the longest follow-up in the world's literature of patients treated by the Ponseti method in a low-middle income country. Dr. Spiegel continued to be an active academic internationally, giving lectures in Iraq, Nepal and Pakistan. In recognition of his dedication to improving the lives of children with orthopaedic conditions in underdeveloped countries, AAOS presented Dr. Spiegel with the prestigious 2017 Humanitarian Award.

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

Joshua Rozell, MD, Joshua Steere, MD, and Zachary Zimmer, MD

Another year has quickly come and gone, and we have been honored to serve as the academic chief residents for 2017-2018. Thankfully the hard work of our predecessors was an excellent springboard for further program development. This year, we sought to emphasize and enhance the intangibles of the program, namely culture, accountability, and professionalism. The orthopaedic surgery department continues to be one of the most well-regarded departments in the health system, and much of this recognition is due to the outstanding leadership of our chairman, Dr. Scott Levin. Dr. Levin's mentorship, coupled with the availability and guidance of our program directors, has allowed us to realize our goals.

From an educational standpoint, we have continued to refine our morning conference curriculum with both junior and senior-level readings to enrich discussion. The iTunes U app gives our residents mobile access to all readings, grand rounds lectures, and OITE review as well. Our robust grand rounds schedule is replete with sawbones, cadaver dissections, and now a series of business and leadership lectures for our residents to make the educational experience more well-rounded.

This year we created website for the residency program. The portal is a direct link from the Penn Orthopaedics webpage and has become a one-stop, comprehensive resource for our residents. The website is a collection of important documents, rotation information, FAQs, and general information that residents can access at any time from any location. Future applicants to the residency are also able to access parts of the website. The crown jewel of the website is our new surgical video library. Hours have been spent capturing high-quality videos of our faculty performing live surgery. Afterwards, faculty record step-by-step narration of the procedures. Residents can now view these videos when preparing for cases or starting a new service. We've also partnered with a leading publishing company to expand this educational endeavor.

Our visiting professor program continues to be one of the most robust in the country. More than twelve professors from institutions all over the country and the world have visited our program and lectured on their unique specialties. Guest speakers from within Penn such as Drs. Michael Useem, Ezekiel Emmanuel, and Rachel Kelz have also shared their expertise with the residency. Each visiting lecturer has enriched our department with their particular breadth of knowledge, and we are grateful for them. This year's professors have included: Frank Liporace (UMDNJ-Newark), Joseph Lane (HSS), Michael Leunig (Schulthess Klinik), Luis Scheker (University of Louisville), Scott Boden (Emory), Thomas Lee, Andy Eglesder (University of Maryland), Joel Matta (Steadman Clinic), Denis Clohisy (University of Minnesota), Thomas Sculco (HSS), James McCarthy (Cincinnati Children's Hospital), and Christopher Born (Brown). We also invited Seth Leopold, the editor in chief of *Clinical Orthopaedics and Related Research*, to discuss how to institute a residency-wide journal club curriculum.

Professionalism, accountability, teamwork, and pride in leadership are essential elements in the culture of Penn orthopaedics. We have worked hard to hone these tenets throughout the year, and these have been central to our program's many successes. The positive learning environment has enhanced mentorship between senior and junior residents. It has also enhanced real-time feedback between faculty and residents. We believe these pillars of our program will continue to be carried forward, year after year, and that each class will leave Penn just a little bit better than when they arrived.

We would personally like to thank all of the Penn orthopaedic surgery residents for their hard work and dedication this year. Our ultimate goal was to be your advocates and to make your time at Penn a fantastic, educational, and fulfilling experience. We would also like to express our gratitude for our faculty and program leadership who have been outstanding teachers and mentors throughout our time at Penn.

Recent Changes in the University Of Pennsylvania Orthopaedic Residency Program

Nicole A. Zelenski, MD and L. Scott Levin, MD

The University of Pennsylvania Orthopaedic Surgery Residency Program has seen many significant changes over the last several years, all which have focused on excellence in education and developing Orthopaedic surgeons that are committed to outstanding patient care.

In 2015, the program moved the majority of faculty offices and primary location from the Hospital of the University of Pennsylvania to Penn Medicine University City where musculoskeletal medicine was consolidated under one roof.At this location Musculoskeletal Radiology, Orthopaedic Surgery, Physical Therapy, Pain Management and Rheumatology provide integrative patient care as the flagship of the musculoskeletal and rheumatology service line. This same facility houses the Biedermann Biomechanics Laboratory and The Human Motion Lab where the department has contributed significant resources to Orthopaedic Research, many of which involve orthopaedic residents and fellows.

Faculty growth has expanded exponentially over the last several years with the addition of new faculty surgeons in hand, spine, tumor, joints, sports, foot & ankle and shoulder. This provides the residents with a diverse and comprehensive experience in every orthopaedic specialty. To meet this new need and allow residents to work with superb educators, the department has also expanded the midlevel providers significantly including the first inpatient PA in the department providing care for the arthroplasty service.This has streamlined patient care and improved the inpatient experience for both patient and providers alike.

The human tissue laboratory has become a foundation for Penn resident education and allows medial students, residents as well as attending physicians to receive advanced surgical training utilizing fresh tissue. The lab, in combination with an increase in endowed lectureships and visiting professors is an exceptional resource for resident education. In the lab, residents will routinely practice on fresh cadaveric tissue with procedures such as arthroscopy, arthroplasty, pedicle screw placement, dissections and approaches.

The residency has demonstrated a commitment to educating female residents and starting July 2018 will boast a 30% female resident rate-well above the national average of 14%. Strong female leadership in the department includes incumbent AAOS president Kristy Weber who demonstrates an excellence in leadership and patient care for not only women residents, but all residents in the program.

Along with a well-balanced morning conference schedule covering every Orthopaedic subspecialty in a bi-weekly rotation, the residency has allowed our residents be excused from clinical duties for 4 hours of Thursday AM curriculum. During these conferences, national as well as internationally known visiting professors lecture on a wide variety of topics.

The department has been committed to additional educational benefits for the residents. The department has supported a subscription to OrthoPass, a resource provided by Orthobullets that provides residents with daily reading assignments as well as self-assessment exam every month. Every incoming resident is provided with an iPad that allows access to hundreds of educational resources including a library of surgical videos from the faculty.A resident can now watch a complex surgical procedure performed by our own attending prior to entering the OR with that attending, optimizing the surgical experience.

When the ABOS mandated a dedicated rotation for Orthopaedic Interns, the department stepped up to the task, clearing a month free from clinical duties for all interns filled with more than 20 sessions taught by attendings, including 15 hands on sessions in the human tissue lab. The remaining sessions provide opportunities for peer-to-peer teaching and are resident run.

Orthopaedic Surgery education has changed drastically over the last 20 years and Penn Orthopaedic Surgery is adapting to these changes is on the forefront of Orthopaedic Education. Penn Orthopaedic surgery has demonstrated a commitment to education and devoted significant resources to training capable surgeons devoted to patient care. Continuous improvement in resident education is our watchword, and defining the future of training for the next generation of Orthopaedic leaders is our goal.

Visiting Professor Lecture Series

June 1st, 2017

Dean G. Sotereanos, MD

Clinical Professor of Orthopaedic Surgery, University of Pittsburgh School of Medicine, Department of Orthopaedic Surgery

Dr. Sotereanos is a graduate of the University of Pittsburgh and Hahnemann University School of Medicine. Following an

orthopaedic surgery residency at the University of Pittsburgh Medical Center, he completed a hand and microsurgery fellowship at Duke University Medical Center. Prior to joining UPMC, Dr. Sotereanos was a clinical professor of orthopaedic surgery at the Drexel University College of Medicine, West Penn Allegheny Health System campus.

In addition to his clinical practice, Dr. Sotereanos has authored numerous articles, book chapters and texts throughout his career. He is an active member in many societies including American Association for Hand Surgery, the Pennsylvania Orthopaedic Society, and the American Society for Surgery of the Shoulder and Elbow. He is actively involved in clinical research and is routinely invited as a guest lecturer throughout the United States and abroad.

His visit to Penn included updates on the most current treatment for contracted elbows and an overview of distal radioulnar joint arthritis. Notably, he also conducted a cadaveric lab demonstrating vascularized distal radius grafts for scaphoid nonunions, which the residents found particularly educational.

June 22nd, 2017—Jesse T. Nicholson Lectureship

Dennis R. Wenger, MD

Clinical Professor of Orthopaedic Surgery, Rady Children's Hospital San Diego

Dr. Dennis Wenger attended medical school at the University of Cincinnati followed by orthopedic residency at the University of Iowa. There, he was influenced by Dr. Ignacio Ponseti, a world renowned expert in childhood hip disorders, and went to the Hospital for Sick Children at the University of Toronto for his fellowship in scoliosis and children's orthopedics. His interest in the childhood hip continued in Toronto with his exposure to Robert Salter and others.

Dr. Wenger then joined the staff at the Texas Scottish Rite Hospital in Dallas where he worked for seven years with Tony Herring and others to expand scoliosis clinical care and develop a spine biomechanics laboratory. In 1984, he assumed a faculty position at Children's Hospital San Diego and shortly thereafter was named Director of the Children's Orthopedic Training Program.

As a result of his work, he has received multiple teaching and research awards including the Walter P. Blount Award from POSNA, the Hibbs Society award from the SRS and the 2016 POSNA distinguished achievement award for his career contributions to children's orthopedics.

During his visit to Penn, Dr. Wenger led lively case discussions with residents and fellows. He also served as the featured speaker later that day at the Children's Hospital of Philadelphia, where he discussed corrective instrumentation for scoliosis and led discussions on a variety of topics in pediatric orthopaedics.

September 28th, 2017

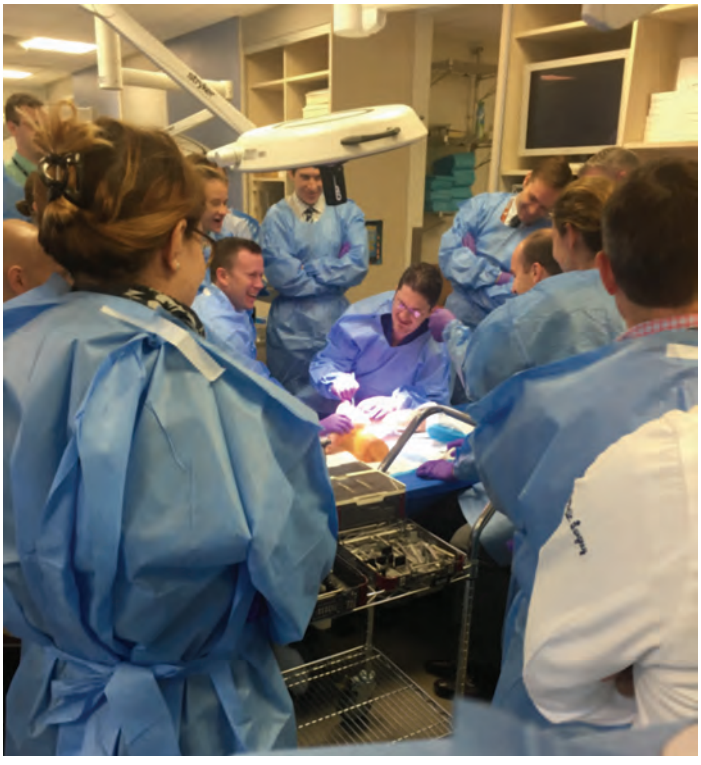
Frank A. Liporace, MD

Vice Chairman of the Department of Orthopaedics, Chief of Orthopaedic Trauma and Reconstruction, Jersey City Medical Center

Dr. Frank Liporace is a graduate of the State University of New York at Binghamton and New York Medical College. He completed his orthopaedic surgery residency at The Hospital for Joint Diseases, New York University followed by an orthopedic traumatology fellowship at Tampa General Hospital under the tutelage of Dr. Roy Sanders. His interests include pelvic and acetabular surgery, complex orthopaedic trauma reconstruction, hip and knee reconstruction, and treating complications associated with orthopaedic trauma. He is Director of the Orthopaedic Institute at Jersey Medical Center and Director of Orthopaedic Trauma Research at The Hospital for Joint Diseases, New York University.

Dr. Liporace has made multiple scientific presentations nationally and internationally and has over 70 publications in peer-reviewed journals and 10 chapters in orthopaedic textbooks. He has done over 300 invited lectures pertaining to orthopaedic trauma and joint reconstruction worldwide. He is currently a reviewer for the Journal of Orthopaedic Trauma as well as Clinical Orthopaedics and Related Research.

Dr. Liporace has won multiple teaching awards for his dedication to education, which was very evident during his visit to Penn. He presented strategies for internal fixation of femur and pilon fractures. He also guided residents through surgical approaches of the tibia during a cadaveric course, which has proven to be particularly useful for trauma rotations Cancer Center in New York, and Chairman of Orthopaedics at UCLA.



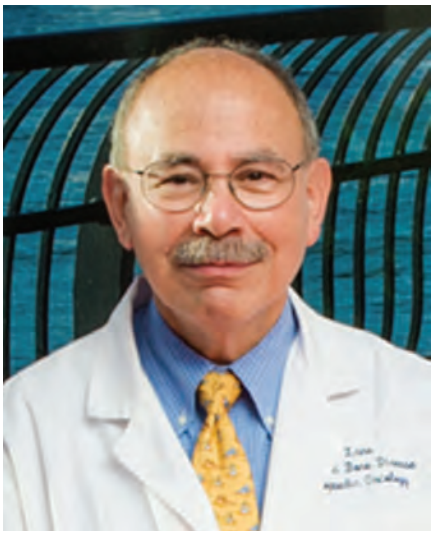
Dr. Lane has served as chairman of many medical organizations and committees, and was President of both the Orthopaedic Research Society and the Musculoskeletal Tumor Society. Dr. Lane has played a major role in developing diagnostic methodologies and treatment strategies for osteoporosis.

In a similar vein, Dr. Lane's lecture at Penn focused on recognizing and treating osteoporosis associated with fragility fractures. He emphasized the importance of the orthopedist playing a larger role in treating systemic bone health and commencing the osteoporotic evaluation as soon as the patient presents with a fracture in the inpatient setting.

October 12th, 2017— Annual R. Bruce Heppenstall Lectureship

Joseph M. Lane, MD

Chief, Metabolic Bone Disease Service, Hospital for Special Surgery, Professor of Orthopaedic Surgery, Weill Cornell Medical College, Assistant Dean, Weill Cornell Medical College



Dr. Lane trained at Columbia University (B.A.), Harvard University (M.D.), University of Pennsylvania (Orthopaedics), and the National In-stitutes of Health. He is renowned for pub-lications and lectures on bone biology, including osteopo-rosis, fracture repair, and bone cancer. He regularly serves on NIH study sections, awarding support for musculoskeletal research and training. He was a member of the Board of Directors of the American Academy of Orthopaedic Surgery, Chief of Bone Tumors at Memorial Sloan-Kettering Cancer Center in New York, and Chairman of Orthopaedics at UCLA.

Dr. Lane has served as chairman of many medical organizations and committees, and was President of both the Orthopaedic Research Society and the Musculoskeletal Tumor Society. Dr. Lane has played a major role in developing diagnostic methodologies and treatment strategies for osteoporosis.

In a similar vein, Dr. Lane's lecture at Penn focused on recognizing and treating osteoporosis associated with fragility fractures. He emphasized the importance of the orthopedist playing a larger role in treating systemic bone health and commencing the osteoporotic evaluation as soon as the patient presents with a fracture in the inpatient setting.

November 30th, 2017—Annual Hip Symposium

Michael Leunig, MD

Chairman, Department of Orthopaedic Surgery, Chief, Lower Limb Clinical Research Group, Schulthess Clinic, Zurich, Switzerland

Michael Leunig, MD is currently the Chairman of Orthopaedic Surgery at the Schulthess Clinic, the largest orthopaedic hospital in Switzerland and one of the largest centers in Europe. Academically Dr. Leunig has been affiliated with the University of Berne and the ETH in Zürich. His busy hip practice spans the entire spectrum from joint preservation to arthroplasty and revision surgery. He received his orthopaedic training under Professor Reinhold Ganz in Berne, Switzerland. In 2005, he was elected a member of the International Hip Society and currently serves on its board. He is also a member of several international research networks, as well as a board member of the Müller Foundation NorthAmerica and ISOT. His current research activities, inspired by his work with Professor Ganz, focus almost exclusively on the hip, particularly femoroacetabular impingement (FAI). He has described several surgical techniques for FAI and leads a research group focusing on the outcomes of FAI surgery.

In addition to serving as a reviewer for many orthopaedic journals, Dr. Leunig is the International Associated Editor of Clinical Orthopedics, Associate Editor of the Orthopaedic Journal of Sport Medicine, and Deputy Editor of the Journal of Hip Preservation Surgery. His research has been funded by national agencies such as the Swiss National Science Foundation for many years.

In his lecture at Penn, Dr. Leunig described the most cutting-edge techniques in pelvic osteotomies and cartilage repair of the hip. The residents particularly enjoyed his cadaveric course delineating the direct anterior approach to the hip and periacetabular osteotomies.

December 14th, 2017—Annual Leo Lung Lectureship

Luis R. Scheker, MD

Associate Clinical Professor of Surgery (Plastic and Reconstructive), University of Louisville, Assistant Consulting Professor of Surgery, Duke University

Dr. Scheker graduated from the University of Santo Domingo, Dominican Republic, and received his postgraduate training in Plastic and Reconstructive Surgery in London, England and the University of Glasgow in Scotland. He served as a Christine M. Kleinert Fellow in Hand Surgery in 1982 and then as a Research Fellow with the Louisville Institute for Hand and Microsurgery. Dr. Scheker's clinical interests include microvascular reconstruction, congenital deformities, the carpometacarpal joint, the distal radioulnar joint and the proximal radioulnar joint. He has developed several surgical techniques for arthroplasty about the wrist and elbow. In addition, he has developed arthroplasty implants for the radiocarpal/radioulnar joints, the proximal radioulnar joint, and the carpometacarpal joint of the thumb. In addition to his clinical practice, Dr. Scheker is actively involved in research. He has been studying forearm function for the last 30 years. He is the author of many original research articles and is co-editor of the book "The Growing Hand."

During his visit at Penn, Dr. Scheker discussed the role of emergency free flaps to the upper extremity. He also demonstrated insertion of the distal radioulnar joint replacement prosthesis that he pioneered.

January 18, 2018

Scott D. Boden, MD

Professor of Orthopaedic Surgery, Emory University School of Medicine, Vice-Chairman, Department of Orthopaedics; Director, Emory Orthopaedics & Spine Center, Chief Medical Officer/Chief Quality Officer, The Emory University Orthopaedics and Spine Hospital, Vice President of Business Innovation, Emory Healthcare

Dr. Scott Boden received his B.A. and M.D. from the University of Pennsylvania and completed his residency at The George Washington University Medical Center, followed by a spine fellowship at Case Western Reserve University Hospitals.

Dr. Boden's interests include innovative health care delivery strategies in a managed care environment and he is the founder and chairman of the National Spine Network, a collaboration of 25 Spine Centers of Excellence around the U.S. focusing on outcomes research and quality improvement. He has recently helped Emory open a free standing multidisciplinary Musculoskeletal Outpatient Center as well as an Orthopaedics & Spine Specialty Hospital. Dr. Boden's basic research focus has centered on gaining an understanding of the biology of spine fusion healing and bone graft substitutes, as well as the molecular control of bone formation and gene therapy applications for bone and intervertebral disc cartilage regeneration.

During his visit, Dr. Boden ran a discussion session with the residents exploring the nuances of diagnosing common spine disorders and developing clear algorithms for treatment based on focused questions and physical exam.

February 15th, 2018—June Wapner Lectureship

Thomas H. Lee, MD

President, American Orthopaedic Foot & Ankle Society

Dr. Thomas Lee earned his medical degree from Columbia University College of Physicians and Surgeons in New York City and completed his orthopaedic residency at the New York Orthopaedic Hospital at Columbia-Presbyterian Medical Center. He received his fellowship training in foot and ankle orthopaedic surgery at Thomas Jefferson University Hospital in Philadelphia.

Dr. Lee is in private practice in Pickerington, Ohio where his practice focuses on total ankle arthroplasty and sports medicine. He is active in humanitarian outreach, having volunteered as a surgeon for the AOFAS Overseas Outreach Project to Vietnam, as well as projects in Afghanistan, Pakistan, and Haiti. He is also a design surgeon for Wright Medical and Stryker Corporation. Dr. Lee was recently named the President of the AOFAS. Prior to his appointment, he had served on and chaired numerous AOFAS committees as well as served on the Board of Directors.

During his visit to Penn, Dr. Lee provided an intriguing history on the evolutionary biomechanics and anatomic adaptations that allow humans to run in the most energy efficient manner. He also lead discussions on resident and fellow case presentations, explorating in detail the subtle findings seen on foot and ankle radiographs.

Shoulder and Elbow UPenn-Princess Grace Traveling Fellowship

Chad Myeroff, MD

The relationship between Monaco and Philadelphia dates back to the marriage of our own Grace Kelly to Rainier, Prince of Monaco. She was revered by the citizens of Monaco. After her traumatic death, there was a re-prioritization of resources in Monaco. While climate change remains the prime initiative, healthcare was boosted to a close second. Starting in cardiology, and now orthopaedic surgery, The University of Pennsylvania became a natural partner in the pursuit of excellent care for the citizens of Monaco.

Relationships then forged among our orthopaedic chairman (Dr. Scott Levin), our shoulder and elbow service (Dr. David Glaser and Dr. Russell Huffman) and Tristan Lascar, Chief of Orthopaedics at Princess Grace Hospital. In an effort to increase academic collaboration, a traveling fellowship was spawned. As the shoulder and elbow fellow at Penn, and with the support by our department, I was given the opportunity to be the first UPenn-Princess Grace Traveling Fellow.

Dr. Lascar was gracious enough to host me and my family for these 2-weeks. Each day started with team rounds which included consult presentations by the orthopaedic resident as well as indications conference. Here, a multidisciplinary team included subspecialists in trauma, joint reconstruction, shoulder and elbow, spine, and arthroplasty. The team was diverse with members hailing from Portugal, Russia, Monaco, Italy, and France. Debate and planning mirrored that of American academic subspecialty teams. There were regional differences in treatment strategies and patient care which made for phenomenal debate and learning for all parties. This experience included time in the fracture clinic, shoulder clinic and operative theatre where I was able to learn and teach in a dynamic environment alongside Dr. Lascar and his resident. Cases focused on upper extremity trauma and elective shoulder and elbow surgery.

Regional differences in treatment algorithms were consistent throughout the traveling fellowship. Monaco sits in a geographical hotbed of shoulder excellence with regional thought leaders scattered in its vicinity, including Lorent Lafosse (Annecy, France), Giles Walsh (Lyon, France) and Pascal Boileau (Nice, France). Leveraging these opportunities, Dr. Lascar and I traveled to Nice where we joined Dr. Boileau for a day of complex shoulder reconstructions, including a bio-reverse shoulder arthroplasty which Dr. Boileau has developed and championed in the literature. Following a day of learning, Dr. Lascar hosted a debriefing dinner at his favorite restaurant overlooking the Mediterranean coastline.

After a brief respite, I traveled to the small town of Montbrison, where I visited a small rural hospital. Here, I teamed up with Dr. Grista, a master surgeon. I scrubbed alongside him for several unique cases including an endoscopic ulnar nerve decompression and stemless reverse shoulder arthroplasty, both of which are cutting edge techniques. Following a day in a rural French OR, I joined our industry partners (Fx Solutions) for an evening of French faire, followed by a day of didactics and a cadaver lab focused on stemless reverse shoulder and hemiarthroplasty for proximal humerus fractures.

After re-establishing roots in Monaco at Princess Grace Hospital, it was time to say goodbye to Dr. Lascar, his team and his gracious family. From there we traversed the the French alps on our way to beautiful Annecy, France. Here I joined hundreds of shoulder surgeons for a 3 days course lead by Dr. Lafosse, which was the perfect conclusion to my traveling fellowship and the capstone to my training at Penn. I am forever grateful for this educational opportunity and am privileged to wave the our flag high as we continue to build relationships and affect patient care worldwide.

Alumni Residents: Where are they now?

Sudheer Reddy

Fellowship: Sports Medicine at University of California – San Francisco, San Francisco, CA; Foot and Ankle at Oakland Bone and Joint with Roger Mann, Oakland, CA

Current Employment: Shady Grove Orthopaedics/Medical Faculty Associates George Washington University, Rockville, MD

How has training at Penn impacted your practice?

Coming from Penn, you will be well trained. Residency gives you the tools and the background to work.

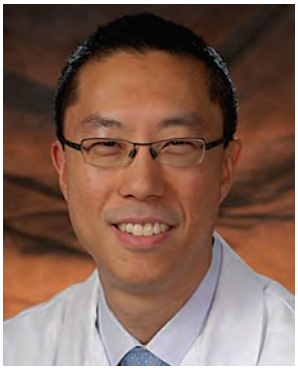
What have you learned in your first decade of practice?

Orthopaedics is a continually evolving field. What you end up doing in practice changes over time and will be far different from what you learned in residency.

What advice would you give residents?

Don't be afraid to change. Don't be afraid to ask for help either. Don't be afraid to admit your mistakes or complications. We all have them. It is how you handle them that matters.

Jamio Ahn



Fellowship: Orthopaedic Trauma at Hospital for Special Surgery/Cornell University with David Helfet, New York, NY.

Current Employment: University of Pennsylvania, Philadelphia, PA.

How has training at Penn impacted your practice?

In every way possible.

What have you learned in your first decade of practice?

That we have really awesome jobs as orthopaedic surgeons. The learning never stops, and while it also never really gets easier, you can always have fun.

What advice would you give residents?

Work hard, work smart, work happy. Take great care of your patients, yourself, your family, your friends, and your colleagues around you…every single day.

Gautam P. Yagnik

Fellowship: Sports Medicine at UHZ Sports Medicine Institute, Miami, FL

Current Employment: UHZ Sports Medicine Institute, Miami, FL

How has training at Penn impacted your practice?

Penn Ortho gave me a great foundation on which I have built my orthopaedic career. In addition, I have made lifelong friends that I still stay in touch with even though we are scattered throughout the country.

What have you learned in your first decade of practice?

The main thing that I have learned is that medicine is constantly changing.

What advice would you give residents?

As long as you always put your patients first and act in their best interest, you will be happy and successful.

John (Todd) R. Lawrence

Fellowship: Pediatrics at Children's Hospital of Philadelphia, Philadelphia, PA; Sports Medicine and Shoulder Surgery at Duke University Hospital, Durham, NC.

Current Employment: Children's Hospital of Philadelphia

How has training at Penn impacted your practice?

Training at Penn instilled in me the practice of being a lifelong learner and always questioning what I was doing and why.

What have you learned in your first decade of practice?

Be nice to all of the people that make it possible for you to do what you do. That includes people you can easily recognize, like your family, your assistant, the OR nurses, and your office assistants. More importantly though, it includes many people you rarely interact with, like the call center staff, the appointment schedulers, and the front desk and administrative people in the clinic and the OR. Get to know these people and thank them often for all that they do to make your practice work.

What advice would you give residents?

Learn the fundamentals. They never change. Have a reason for everything that you do and be willing to change how you do things when another better reason comes along.

Kristopher Downing

Fellowship: Joseph H. Boyes Hand and Microvascular Surgery at University of Southern California, Los Angeles, CA

Current Employment: Synergy Specialists Medical Group, San Diego, CA

How has training at Penn impacted your practice?

I am prepared to handle orthopaedic patients very well. The attending staff at Penn instilled in me the general principles that have lead me to be an effective, reputable orthopaedic surgeon in San Diego County.

What have you learned in your first decade of practice?

The logistics of private practice. Optimizing referral source relationships. Daily operations efficiency. What not to do. Forming strategic alliances/partnerships. Follow the relationships, not the money.

What advice would you give residents?

Work hard. Play hard. Strike a delicate balance that will keep you mentally and physically strong. Daily exercise, proper nutrition, mindfulness and meditation have all been instrumental to maintaining my ability to work long hours and to safely and effectively execute services that I offer.

Joshua Auerbach

Fellowship: Spine Surgery at Washington University, St. Louis, MO

Current Employment: Bronx-Lebanon Health System, Bronx, NY

Brian M. Vannozzi

Fellowship: Adult Reconstruction at Anderson Orthopaedic Clinic, Alexandria, VA

Current Employment: Princeton Orthopaedic Associates, Princeton, NJ

Rocco Bassora

Fellowship: Shoulder Surgery at University of Southern California, Los Angeles, CA

Current Employment: Crystal Run Healthcare, Middletown, NY

Current Residents

Clinical Year 5 Residents

Keith P. Connolly, MD

Undergraduate:
Michigan State University

Medical School:
University of Central Florida College of Medicine

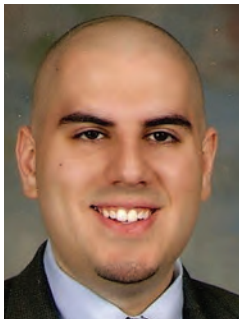
Fellowship:
Rothman Institute, Adult Reconstruction

Daniel P. Lim, MD

Undergraduate:
University of Southern California

Medical School:
Keck School of Medicine at USC

Fellowship:
Kerlan-Jobe Orthopaedic Clinic, Sports Medicine



Tyler R. Morris, MD*

Undergraduate:
The University of Pennsylvania

Medical School:
Drexel University College of Medicine

Fellowship:
Vanderbilt University, Orthopaedic Trauma

Alexander L. Neuwirth, MD*

Undergraduate:
Rutgers University

Medical School:
Robert Wood Johnson Medical School at Rutgers University (UMDNJ)

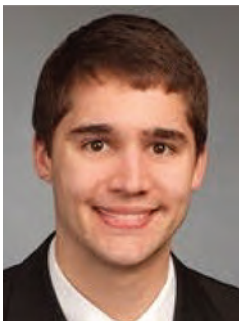
Fellowships:
Columbia University, Adult Reconstruction (2018-19)
Hospital for Special Surgery, Sports Medicine (2019-20)

Joshua C. Rozell, MD

Undergraduate:
Emory University

Medical School:
Drexel University College of Medicine

Fellowship:
The Steadman Clinic, Adult Reconstruction



Joshua T. Steere, MD

Undergraduate:
Creighton University

Medical School:
Stritch School of Medicine at Loyola University Chicago

Fellowship:
Stanford University Hospital, Adult Reconstruction

Chia H. Wu, MD, MBA

Undergraduate:
University of Pennsylvania

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

Fellowship:
Columbia University, Hand Surgery

Zachary R. Zimmer, MD

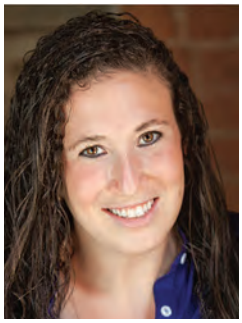
Undergraduate:
Colgate University

Medical School:
Stony Brook University School of Medicine

Fellowship:
Harvard University, Shoulder and Elbow Surgery

*Indicates Resident is in the 6-year Research Track

Clinical Year 4 Residents



Jenna A. Bernstein, MD

Undergraduate:
Cornell University

Medical School:
University of Connecticut School of Medicine

Kristin Buterbaugh, MD

Undergraduate:
Northwestern University

Medical School:
Icahn School of Medicine at Mount Sinai

Jose A. Canseco, MD, PhD

Undergraduate:
Rice University

Medical School:
Harvard Medical School / Massachusetts Institute of Technology

Jonathan R. Dattilo, MD

Undergraduate:
Northwestern University

Medical School:
Johns Hopkins University School of Medicine

James M. Friedman, MD*

Undergraduate:
Duke University

Medical School:
Duke University School of Medicine

Cody D. Hillin, MD, MS*

Undergraduate:
University of Rochester

Medical School:
Baylor College of Medicine

Luke A. Lopas, MD

Undergraduate:
University of Wisconsin-Madison

Medical School:
University of Wisconsin School of Medicine & Public Health

Nicole A. Zelenski, MD

Undergraduate:
Bryn Mawr College

Medical School:
Duke University School of Medicine

*Indicates Resident is in the 6-year Research Track

Clinical Year 3 Residents

Blair S. Ashley, MD*

Undergraduate:
The College of William and Mary

Medical School:
University of Pittsburgh School of Medicine

Ryan Charette, MD

Undergraduate:
University of Connecticut

Medical School:
University of Connecticut School of Medicine

Rikesh Gandhi, MD

Undergraduate:
Boston College

Medical School:
Duke University School of Medicine

Daniel Gittings, MD*

Undergraduate:
Providence College

Medical School:
Boston University School of Medicine

Mark Hasenauer, MD

Undergraduate:
Boston College

Medical School:
New York Medical College

Matthew Sloan, MD, MS

Undergraduate:
University of Massachusetts

Medical School:
University of Massachusetts Medical School

Andrew Tyler, MD, PhD

Undergraduate:
Harvard University

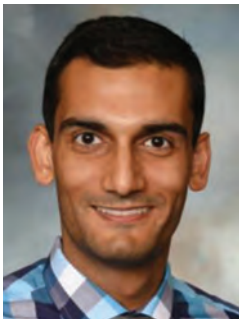
Medical School:
University of Texas at Dallas Southwestern Medical School

Matthew Winterton, MD

Undergraduate:
Brigham Young University

Medical School:
Perelman School of Medicine University of Pennsylvania

Research Year



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

*Indicates Resident is in the 6-year Research Track

Clinical Year 2 Residents

Gerald Andah, MD

Undergraduate:
University of Pennsylvania

Medical School:
Perelman School of Medicine University of Pennsylvania

Matthew Counihan, MD, MS*

Undergraduate:
Univ. of Richmond

Medical School:
Drexel University College of Medicine

Chelsea Hendow, MD, MS

Undergraduate:
Univ. of CA—Los Angeles

Medical School:
New York Medical College

Liane Miller, MD*

Undergraduate:
Univ. of CA—Santa Barbara

Medical School:
Univ. of CA—San Francisco School of Medicine

Christina Nypaver, MD

Undergraduate:
Univ. of Notre Dame

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

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 2 Residents

Perez Agaba, MD

Undergraduate:
Indiana University at Purdue University

Medical School:
Duke University

Sarah Blumenthal, MD

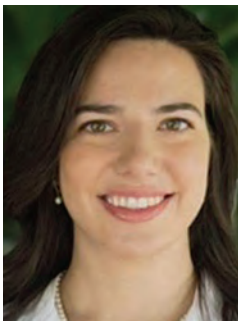
Undergraduate:
Harvard University

Medical School:
University of California–Los Angeles

Kelsey Bonilla, MD*

Undergraduate:
Rutgers University

Medical School:
Perelman School of Medicine at University of Pennsylvania



Agnes Dardas, MD, MSc

Undergraduate:
Harvard University

Medical School:
Washington University in St. Louis

George Fryhofer, MD, MTR*

Undergraduate:
Harvard University

Medical School:
Perelman School of Medicine at University of Pennsylvania

Brandon Haghverdian, MD

Undergraduate:
University of California–Irvine

Medical School:
University of California–Irvine

Eric Pridgen, MD, PhD

Undergraduate:
University of Delaware

Medical School:
Stanford University

Ivan Zapolsky, MD, MS

Undergraduate:
Tulane University

Medical School:
Tulane University

*Indicates Resident is in the 6-year Research Track

University of Pennsylvania Orthopaedic Surgery Fellows

Academic Year 2017-2018

Hand & Upper Limb Surgery

Oded Ben-Amotz, MD

Shaun Mendenhall, MD

Joshua Mirrer, MD

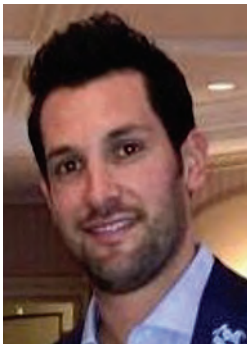
Adult Reconstruction

Jonathan Haw, MD

Christopher Travers, MD

Sports Medicine

Scott Doroshow, DO



Ryan Krochak, MD

Shoulder & Elbow

Joshua Rogozinski, MD

Spine

Nissim Ackshota, MD

Muhammad Janjua, MBBS

Foot & Ankle

Osama Elattar, MD

Adam Ferguson, DO

Corporal Michael J Crescenz VA Medical Center Update Update

Marlene DeMaio, MD

Chief and GME Site Director, Dept. of Orthopaedic Surgery, VAMC, Clinical Professor, Dept. of Orthopaedic Surgery, UPENN Perelman SOM, Captain, Medical Corps, U.S. Navy (retired)

Since last year we have had notable staff transitions and developments while continuing to support clinical care, research, and education. In August 2017, three pillars of UPENN Orthopaedics transitioned from the CPL Crescenz VAMC: Ernest J. Gentchos, Malcolm Ecker, and John D. Kelly, IV. Drs. Gentchos and Ecker are highlighted later. Dr. Kelly served seven years as shared faculty. His multiple contributions include compassion, insight, humor, and, unquestionably, surgical skill. His invaluable presence not only benefitted our patients and residents but also honored his U.S.M.C. father's legacy of virtue and respect. Dr. Kelly earned "America's Most Compassionate Doctors' Patient Choice" Award in 2011 and his most recent column in *Clinical Orthopaedics and Related Research* is "Forgiveness." He will continue to interface with the VA through the Leadership Lecture series he developed. Dr. Kelly remains active in multiple roles for UPENN Orthopaedics, including Director, Shoulder Surgery, Sports Medicine and Co-Director, Sports Medicine Fellowship.

We welcomed three new surgical staff and one research volunteer. Kathryn O'Connor, MD MSPT joined us in July 2017 as our Foot and Ankle Surgery subspecialist, adding another dimension for foot and ankle education to the residency program. Her fellowship was at Washington University School of Medicine. Drs. Andrew Milby and Robert J. Wilson, II joined our staff in September 2017 after completing specialty fellowships earlier in the year. Dr. Milby, a graduate of the UPENN Class of 2016 Orthopaedics Residency, returned after his Spine Fellowship at Emory University. His presence complements the Spine Clinic with Dr. Harvey Smith. Dr. Milby is organizing a multiple disciplinary Spine Conference. This will add to our regular Rounds with the Chairman, Dr. L. Scott Levin and safety (M&M) conference with Dr. Eric Hume. Dr. Wilson completed his Orthopaedic Oncology Fellowship at Vanderbilt University after residency there. Dr. Wilson is developing a needed Oncology Section and is very active with our total joint arthroplasty patients. Both Drs. Milby and Wilson are dedicated teachers who also provide essential subspecialty education. Annamarie Horan, MPA PhD joined us as a professional volunteer in June 2017. As Director of Clinical Research for the UPENN Departments of Orthopaedic Surgery, she will assist us with development and execution of clinical research. She brings expertise in development and implementation of clinical trials and studies. Dr. Horan's father served five years during World War II and her eldest daughter will be commissioned as an Ensign after graduating from the U.S. Naval Academy later this spring.

In the realm of basic science research, our staff shine with on-going VA funded studies. Drs. Joseph Bernstein, Andrew Kuntz, Harvey Smith, and David Steinberg continue to conduct their studies along with providing clinical and surgical care. Dr. Smith has the distinction of capturing both a Merit Grant and a Career Development Award. Jaimo Ahn, MD PhD has numerous research grants and was promoted to Associate Professor. Congratulations, Dr. Ahn!

From January 1 to December 31, 2017, 4897 visits were recorded for the outpatient Orthopaedic Surgery Clinic. In November 2017, our facility was named the "hub" for surgical integration for the eastern region of VISN 4. Clinics are structured around supervising staff and specialty, now increased to four days a week. A weekly Hand Clinic will start in April. Providing indispensable and knowledgeable support are two exceptional orthopaedic physician assistants, Mitchell "Chip" Staska, MPA-C and John Wheeler, PA-C. Mr. Staska is a regular instructor at the University of the Sciences Physicians' Assistant degree program. His expertise was on display for our new electronic orthopaedic "e-consult". Mr. Wheeler, a U.S. Navy retiree who served in the Gulf for one year for Operation Iraqi Freedom, is dedicated to the Spine Team.

In the arena of surgical care, we performed 386 operative procedures last year. A new operating room schedule includes four days of block time. Each of our three new surgeons has block time. The VA implemented a full time nursing position for pre-operative patient education and surgical scheduling. Kathleen Sweeney, RN, a highly experienced surgical nurse, is performing these duties and assisting us in development of this position. Her unwavering dedication to our patients is both genuine and personal as she has a son in the U.S.M.C. Catherine Linowski, RN MSN was recently named as the full time orthopaedic nurse. She is a retiree from the US Army Nurse Corps, having started her career as a medic. We welcome her vast experience from outside care coordination and surgical nursing.

We have made significant inroads managing special needs veterans, surgical timing, and out patient visit coding. To address the multiple disciplinary needs of the patient with osteoarthritis not requiring surgery, my vision of an OA clinic was realized. Carla Scanzello, MD PhD; Edna Schwab, MD; Adam Cooper, MD; Keith M. Robinson, MD; and Pat Mosko, CRNP participate weekly specialty clinic held under the direction of Rheumatology with Orthopaedic consultation. Dr. Scanzello submitted our first grant application to evaluate this coordinated care. Improved coordination of care outside

the VA is being developed with UPENN to include surgery for VA beneficiaries at UPENN surgical facilities. This approach has been very productive in federal medicine.

Academic, clinical, and research partnering is a VA hallmark. We have requested purchase of an arthroscopic simulator. Chief resident, Chia Wu, MD MBA spearheaded the implementation microvascular training in December 2017. The VA acquired loupes and materials to support a microvascular curriculum at the VA and the UPENN Simulation Center. The historical origin of such partnerships begins with a UPENN connection, Paul B. Magnuson, MD, Perelman School of Medicine Class of 1908. You may recognize Dr. Magnuson's name from the Magnuson Stack procedure for chronic recurrent shoulder instability. You should recognize his name as the endowed Professorship of UPENN Bone and Joint Surgery, established in 1974. This distinguished title is held by the Chair of Orthopaedics, L. Scott Levin, a U.S. Army veteran whose grandfather served in World War I as a UPENN trained otolaryngologist and whose Silver Star awardee father served in the U.S. Navy. Paul B. Magnuson, MD, then Professor of Surgery and Chair, Department of Bone and Joint Surgery at Northwestern University, was recruited as a consultant to the U.S. Army Surgeon General during World War II. Afterward, he remained as a consultant to develop prosthetic research at the VA. Ultimately his work resulted in major prosthetic advancements, congressionally funded research, and private sector-government collaborations. Importantly, he was responsible for implementing residencies in VA facilities close to medical schools in 1946. He structured his revolutionary program around physicians approved by a dean's committee to include professor consultants, VA staff, and resident physicians. This radical new structure, requiring many crusades, removed the oversight from politicians. Serving as Chief Medical Director of the VA from 1948-1951, this orthopaedic surgeon is responsible for the successful integration of VA resources to support medical schools for clinical care, research, and education. Currently, over 70% of U.S. physicians have trained at a VA. Over 120,000 trainees rotate through a VA annually. Each UPENN orthopaedic resident will join these ranks upon completion of training.

At our VA, UPENN residents had the distinction of learning from two noteworthy veterans whose lives are detailed in recent prior UPOJ editions dedicated to them. They are shared faculty, Dr. Gentchos and Dr. Ecker. Their genuine commitment to education and their patients define their careers. Dr. Gentchos's extraordinary personal history starts in Greece, surviving Word War II, immigrating to America, and becoming a doctor. He served in the U.S. Army Medical Corps with a 13-month tour of duty in Vietnam. His UPENN career began with his orthopaedic residency at the Graduate Hospital. Dr. Gentchos supported education ever since. He was the attending for our Friday general clinics for eight years, donating his VA salary for scholarships to students in high school, college, and medical school. Since 2000, UPENN honors him with Ernest J. Gentchos Lectureship, a yearly Grand Rounds focusing on shoulder and elbow. Dr. Gentchos has retired. He is now chronicling his experiences in essays, focusing on his teachers. Don't end your day unless you can answer his trademark question: "What have I learned today?"

Dr. Ecker's remarkable story starts right here in Philadelphia. He is an alumnus of Temple University and its Lewis Katz School of Medicine. After several years of training at Albert Einstein Medical Center and Boston City Hospital, he joined the U.S. Air Force Medical Corps for 10 years, serving for two years at Platsburgh Air Force Base as the only physician for 18,000. He completed his orthopaedic surgery residency at Hospital for Special Surgery, including 12 months at the Bronx VA. Dr. Ecker's roles at our VA encompassed surgery and clinical care. Most recently, he was a surgical coach for our chief residents. Dr. Ecker's 20-year affiliation with our VA is among the longest in any department. He remains a consultant at CHOP with a regular clinic there. His practice has been diverse, in children and adults, ranging from fractures, spine, and reconstruction. A prolific author and innovator, Dr. Ecker's contributions remain in the most recent edition of Campbell's Orthopaedics.

While very different people, both Dr. Gentchos and Dr. Ecker have much in common. They are true examples of shared faculty envisioned by Dr. Magnuson. Both worked successfully in the private and academic sectors, developing strong bonds to UPENN. Both are humble, industrious, inquisitive, and ethical people who always focused on the patient. Both steadfastly support resident education. Both are veterans with intense military service during Vietnam. Both dedicated their time, energy, and heart to our VA beneficiaries. Both value their families. We can learn from their example and follow it. Fair winds and following seas, Dr. Gentchos and Dr. Ecker.

Chia Wu (PGY5) in the new microsurgery simulation lab at the Philadelphia VAMC.

Pennsylvania Hospital Update

Neil Sheth, MD

Chief of Orthopaedic Surgery, Pennsylvania Hospital

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 four days per week, with dedicated clinic time in multiple sub-specialties. In addition, the foot and ankle resident and spine chief resident are at PAH hospital full time, while residents from the arthroplasty and sports medicine services spend part of their week operating and staffing clinic in the Cathcart building. In a continuing commitment to resident education, conferences are now video conferenced from PMUC. With a rigorous, structured curriculum, 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 residence. The hospital system has increased the number of physician extenders present, 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.

With the changes over the past year to the Orthopaedic department and an increase in faculty and overall volume, PAH has undergone a series of major changes. The Department of Orthopaedic Surgery at the University of Pennsylvania now staffs sixteen 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. Faculty from orthopaedic surgery run multiple rooms in the operating theater daily.

Notable this past year, Dr. Comron Saifi has joined Penn after completing a Spine Fellowship at Rush University. In addition, non-operative providers have been added to the complement of Penn Orthopaedics including Arsh Dhanota, Jasmine Zheng, Katherine Temme, and Christopher Fayock.

With the continued increase in operative volume, PAH continues to be staffed by a PGY-1, PGY-2, and a PGY-5 at all times, complemented by a team of nurse practitioners and physician extenders that assist with patient clinical care and floor work.

With the changes in healthcare that are being implemented, it is critical to be prepared in order to excel in this marketplace. As total knee arthroplasty has been removed from the inpatient only code, we are putting together a robust outpatient total joint arthroplasty program which started last year. The vision is to extend this service to the Tuttleman center which has experienced a significant increase in operative volume over the past two years. Pennsylvania Hospital is poised to be successful in the region as we continue to evolve.

Surgical Amphitheater at Pennsylvania Hospital (constructed in 1804).

McKay Orthopaedic Research Laboratory Update

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 just over 17,000 sq. ft. of newly renovated space on the Ground and 1st Floors of Stemmler Hall. There are over 120 full- and part-time staff and trainees now in the labs. McKay is an active, thriving research and educational environment.

The Mckay labs are in the midst of a transformation both in terms of physical space and faculty. Our home, Stemmler Hall, is undergoing a >$100 million dollar renovation, which will culminate in 2018 in a fully modernized and aesthetically pleasing facility in which to grow our laboratory space, faculty, and research and training endeavors. We will move from our current, temporary location to 3rd floor of the completed building in Fall/Winter 2018. In terms of recruitment, we were delighted to welcome Dr. Joel Boerckel, PhD, an expert in bone mechanobiology and Dr. Kyu Sang Joeng, an expert in disease models of bone and tendon, as our newest tenure track faculty members. We are also very excited that Dr. Sherry Liu was recently promoted to Associate Professor with tenure. We are also now actively recruiting for an endowed chair faculty position, and hope to grow our ranks further in the very near future.

Currently, the lab has an annual research budget from extramural grants, gifts, and endowments > $14,124,397 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 2016 ranking of #3. This past year has seen a very impressive and continued rise in new grant activity amongst the faculty.

We have had several new grants (>$25,000) awarded this year, representing the breadth and diversity of research undertaken by our faculty. These include:

- Dr. **Joel Boerckel**—"Mechanical Control of Therapeutic Vasculogenesis for Peripheral Ischemia"
- Dr. **George Dodge** and Dr. **Robert Mauck**—"Tunable Mechano-Activated Microcapsules for Therapeutic Delivery"
- Dr. **Nat Dyment**—"Defining the tendon lineage to improve tissue engineering strategies"
- Dr. Xiaowei **Sherry Liu**—"Roles of modeling- and remodeling-based bone formation in determining trabecular bone mechanics at multiple length scales"
- Dr. **Harvey Smith** and Dr. **Robert Mauck**—"Tissue Engineered Total Disc Replacement in a Large Animal Model"
- Dr. **Foteini Mourkioti**—"Cardiomyocyte telomere dysfunction in the progression of dystrophic cardiomyopathy"
- Dr. **Eileen Shore**—"Mechanisms regulating normal and ectopic endochondral ossification"
- Dr. **Lachlan Smith**—"Pathogenesis and Treatment of Bone Disease in the Mucopolysaccharidoses"
- Dr. **Louis Soslowsky**—"Training in musculoskeletal research"
- Dr. **Sarah Gullbrand**—"The Role of the Endplate in Intervertebral Disc Degeneration and Regeneration"

In addition, we are delighted to report that the NIH T32 grant supporting our training program in Orthopaedic Bioengineering, led by Dr. Lou Soslowsky, scored a '13' on its first submission, and will be renewed for another five years (extending this longest running T32 supported program)! This is as a testament to the excellent educational resources in McKay and the widespread impact of our department faculty on training the next generation of musculoskeletal scientists.

In addition to the above-mentioned new grants this year, each of the McKay Laboratory faculty remains well-funded through existing research grants not identified in this new grants list. Further, there were several new industry grants and clinical trials (>$25,000) initiated by both basic science and surgeon faculty this year. These include:

- Dr. **John Kelly**—"Operative versus Non-operative Treatment for Atraumatic Rotator Cuff Tears: A Multicenter Randomized Controlled Pragmatic Trial"—in collaboration with Vanderbilt University
- Dr. **Mona Al Mukaddam**, Dr. **Eileen Shore**, Dr. **Fred Kaplan**—"A Phase 3, Efficacy and Safety Study of Oral Palovarotene for the Treatment of Fibrodysplasia Ossificans Progressiva (FOP)"—from Clementia Pharmaceuticals
- Dr. **Andrew Kuntz**—"A Post-Market Clinical Follow-up Study of the TITAN (TM) Reverse Shoulder System used in Primary or Revision Total Shoulder Arthroplasty" – from Integra Life Sciences
- Dr. **Louis Soslowsky** – "MPT2 - pGlcNAc rotator cuff model study"—with Marine Polymer Technologies, Inc.

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. We look forward to another exciting year of continued growth and success.

What's New at the PVAMC Translational Musculoskeletal Research Center?

George R. Dodge, Ph.D. and Robert L. Mauck, Ph.D.

Aches and pains are a part of daily life and normal aging. However, musculoskeletal (MSK) conditions can also arise as a direct consequence of military service, with associated trauma and accidents. 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, as 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, with the goal of developing novel technologies to enhance tissue repair, regeneration, and ultimately function.

In keeping with this goal, 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 Corporal Michael Crescenz VA Medical Center (CMCVAMC) in Philadelphia. Physician investigators, basic scientists, and engineers at the CMCVAMC, together with colleagues from the University of Pennsylvania, are currently carrying out research projects focused on the injury and repair of MSK tissues, including tendons, ligaments, disc, bone, meniscus, and cartilage. Additional studies are underway to develop new technologies that may one day aid in the replacement of these tissues and ultimately improve function and quality of life. In keeping with this research focus, the CMCVAMC established the Translational Musculoskeletal Research Center (TMRC) in 2013. This Center brings together investigators from Orthopaedic Surgery, Rheumatology, Physical Medicine and Rehabilitation, Neurosurgery, and Bioengineering all under one roof, in >9,000 sq. ft. of newly renovated research space. Drs. George Dodge and Robert Mauck co-direct this enterprise with input, advice, and support from a joint PVAMC/Penn TMRC Advisory Committee.

The goal of the TMRC is to develop a focused, internationally recognized research center at the CMCVAMC and to emerge as a VA Center of Excellence, bringing new resources and regenerative technologies to all service members, past and present. To date, more than 30 VA-based physicians, scientists, bioengineers, and research staff have co-localized to the newly renovated, state-of-the-art research space at the CMCVAMC Medical Research Building. Current VA funding to these investigators has increased to >$2 million in direct costs per year (see table below). In addition, the VA has committed more than $5.5 million in equipment to outfit this new facility, including state-of-the-art devices such as vivo micro-CT, fluoroscopy, atomic force microscopy and nanomechnical cell/material testing, super-resolution, confocal, multiphoton, and light-sheet imaging. Over the past year, the TMRC has continued to grow, with TMRC postdoctoral fellow Dr. Sarah Gullbrand receiving a highly competitive Career Development Award (CDA 1) - a two year award that will fund her transition into an independent investigator. 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. The TMRC is committed to our goal of translating this research into life changing improvements in patient care and quality of life for both Veterans and the general population.

Current Funding at the TMRC

Type	PI	Amount & Duration	Title
Merit	J. Bernstein	$275,000 per year for four years (2013-18)	The Role of Local NSAID Administration and Inflammation on Tendon Healing
Merit	G. Dodge	$275,000 per year for four years (2014-19)	Cartilage Response to Compressive Injury: A Platform for Therapeutic Discovery
Merit	R. Mauck / L. Smith	$275,000 per year for four years (2014-19)	Bioactive Injectable Implants for Functional Intervertebral Disc Regeneration
Merit	J. Esterhai / R. Mauck	$275,000 per year for four years (2014-19)	Engineered Multi-Functional Nanofibrous Meniscus Implants
CDA-2	H. Smith	$400,000 per year for five years (2014-19)	Tissue-Engineered Constructs for Treatment of Intervertebral Disc Degeneration
SPiRE	C. Scanzello G Dodge	$100,000 per year for two years (2015-18)	The Impact of CC-Chemokine Receptor 7 (CCR7) on Synovitis and Osteoarthritis
SPiRE	A. Kuntz	$100,000 per year for two years (2015-18)	Effect of Scaffold-Delivered Growth Factors on Rotator Cuff Repair
Merit	H. Smith / R. Mauck	$275,000 per year for four years (2017-2021)	Tissue Engineered Total Disc Replacement in a Large Animal Model
CDA-1	S. Gullbrand	$84,000 per year for two years (2018-2020)	Engineered Constructs for Vertebral Endplate and Whole Disc Regeneration

Update on the Biedermann Lab for Orthopaedic Research

Michael W. Hast, Ph.D

Director, Biedermann Lab for Orthopaedic Research

Over the last year, the Biedermann Lab for Orthopaedic Research has been working on a variety of biomechanical research projects that focus on the biomechanical characterization of bone-implant behaviors. The portfolio of active projects in the Biedermann Lab contains experiments that are in various stages of development, execution, or publication, and include collaborations with DePuy Synthes, Integra LifeSciences, and Zimmer Biomet. The lab uses a wide spectrum of techniques to objectively measure implant performance, including *in silico* modeling, cyclic testing of implants, 3-D motion capture, measurement of articulating joint forces, and *in vitro* simulations of activities of daily living. So far in 2018, the Lab has had three peer reviewed manuscripts accepted for publication at *Injury, Orthopedics,* and *The Journal of Bone and Joint Surgery Reviews*.

In one of our more recent studies, the Lab conducted an experiment in collaboration with Dr. John Kelly and Dr. Josh Baxter. The team investigated superior capsule reconstruction- a technique that can be used to address 'irreparable' rotator cuff tears. In this study, we used a combination of *in vitro, in vivo,* and *in silico* experimental techniques to determine repair strategies that may maximize graft utility and minimize the likelihood of failure.

Additionally, the study was able to identify high-risk activities of daily living that may lead to premature graft failure immediately after surgery. At the time of writing this article, the findings from the superior capsule reconstruction study

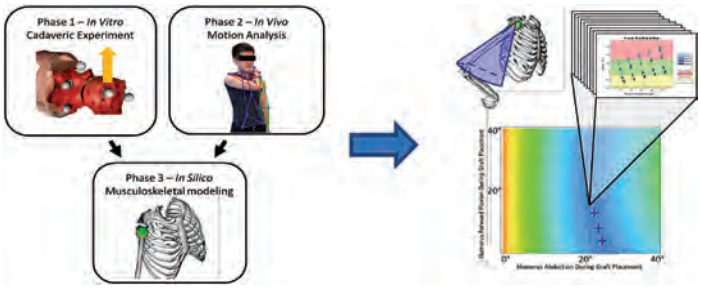


Figure 1: An overview of the techniques used to create an optimization capable of providing guidelines for both surgeons and patients involved with a superior capsule reconstruction.

were provisionally accepted as a full-length manuscript in the *Journal of Orthopaedic Research*. A copy of an abstract for this study can be found within this journal.

The continuous goal of the Biedermann Lab is to perform research that is relevant and translatable so that the standard of care and quality of life for patients can be improved. The Biedermann Lab will continue to pursue this goal by focusing its research on investigations of bone-implant behaviors. If you have a research interest that may be suitably addressed with the research competencies of the Biedermann Lab, you are encouraged to contact Michael Hast directly. For contact details and more information about the Biedermann Lab, please visit the Biedermann Lab's website: www.med.upenn.edu/biedermann/

Human Motion Lab Update

Josh Baxter, PhD

Director, Human Motion Lab

Patient movement biomechanics that were once challenging to characterize, can now be accurately quantified in the Human Motion Lab at Penn Medicine. Located within the clinics of the Department of Orthopaedic Surgery, the Human Motion Lab's mission is simple: support decision making with objective and quantitative measurements of patient biomechanics. The 1,200 square foot lab is fully instrumented with motion capture, strength testing, muscle analysis, and ultrasonography equipment to study a wide array of musculoskeletal pathologies. These resources allow our researchers to work closely with musculoskeletal providers to identify key indicators of injury and treatment outcomes.

The Human Motion Lab has active projects with promising young clinicians and researchers at Penn Medicine. In collaboration with the Human Motion Lab, several projects were developed into grant applications and have secured funds:

- Dr. Josh Baxter—'The effects of tendinopathy on Achilles tendon biomechanics'
- Dr. Josh Baxter—'Applying machine leaning algorithms to predict tendon health using ultrasound imaging'
- Dr. Kathryn O'Connor—'Correlating tendon diastasis with functional outcomes in acute Achilles tendon ruptures'
- Dr. Ben Gray—Feasibility of a low-cost motion capture device for clinical evaluation
- Dr. Ellen Casey—An *in vivo* longitudinal evaluation of the impact of oral contraceptives on connective tissue and neuromuscular control

Musculoskeletal models and cadaveric experiments are used in concert with measurements of human motion and tissue structure to more rigorously test research questions. Using simple computational models of the human body, we can perform virtual experiments to test the expected effects of changing musculoskeletal parameters on function. In close collaboration with Dr. Michael Hast, Director of the Biedermann Lab for Orthopaedic Research, we have also combined *in vitro* data with *in vivo* data capture in the Human Motion Lab. Having such a strong collaboration with an expert in cadaveric models of the musculoskeletal system has advanced the scope and rigor of many of our research projects.

In addition to researching musculoskeletal injuries and pathologies, the Human Motion Lab has been cultivating relationships with Penn Athletics and other organizations in the Philadelphia area to provide objective and quantitative assessments of player health and function. While most patients treated at Penn Medicine are not elite athletes, understanding how these athletes stay healthy can provide new and unique insights into musculoskeletal pathology and injuries. These pursuits dovetail with our research goals of linking function with tissue structure and movement patterns. A recent study on a group of Penn Athletics distance runners found that these runners have structurally different Achilles tendons when measured using ultrasound imaging, which may be a protective adaptation to the increased tendon loading experienced throughout the rigors of training. Fortunately, the tendon structure is stable throughout the season, suggesting that once habituated to training loads, tendon health is quite stable. These findings also suggest that deviations in ultrasound measurements may be a warning flag of tendon pathology.

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.

Clinical Research Update

Annamarie Horan, PhD

Director of Clinical Reseach, Orthopaedic Surgery and Anesthesia & Critical Care

Penn Orthopaedics Human Subjects Research (HSR) has evolved considerably in recent years. Dr. Samir Mehta assumed the role of Medical Director of Clinical Research in November 2016 and Fabian Marechal, Senior Director of Operations has also rolled Clinical Research under his many duties. Our collaboration with Anesthesiology and Critical Care (ACC) remains intact, and our financial, regulatory, and operational position in FY18 exceeds expectations. Figure 1 demonstrates the complex relationship between clinical research income and effort. The number of FTEs has risen from 1 in 2005 to ≥17 in 2018, with the majority of these staff dedicated exclusively to Orthopaedic Surgery. Further, since Orthopaedic Surgery projects often extend through multiple years of follow up, the turnover of projects is infrequent and the activity has tended to accumulate. As shown in the figure, the number of active funded clinical research projects from 2011to the first Quarter of 2018 (Q1-2018) has increased 20 fold.

The overall proportion of studies for each Division that are prospective and funded has shifted favorably in recent years and the current breakdown is shown in Table 1. Each Division has its own funding mix which may include sponsorship from grants, gifts, government and foundation grants, sub-awards through other academic institutions, and of course industry sponsorship. There are also several achievements of note relative to Table 1.

The Adult Reconstruction Division has, at this writing, 5 new sponsored studies pending activation in addition to those captured in Table 1. The Divisions of Foot & Ankle Surgery and Sports Medicine, both have at least 1 funded study per surgeon. Our Hand Division boasts 2 studies where Dr. Levin is the Global Principal Investigator (Axogen RECON, Dr. Bozentka is the local PI; and Polyganics PROTECT NEURO; Dr. Gray is the local PI). In Sports Medicine, the honor of being Global Principal Investigator has fallen to Dr. Kelly for the Trice Medical, mi-Eye study and will soon be bestowed upon Dr. Carey with the Vericel MACI trial in addition to his leadership of the now-funded, ROCK Registry. Dr. Mehta remains the Global PI for the Microbion MBN-101 (Dr. Donegan is the local PI) study and the Penn site is also the enrollment leader for this breakthrough work on the first new antibiotic in 50 years.

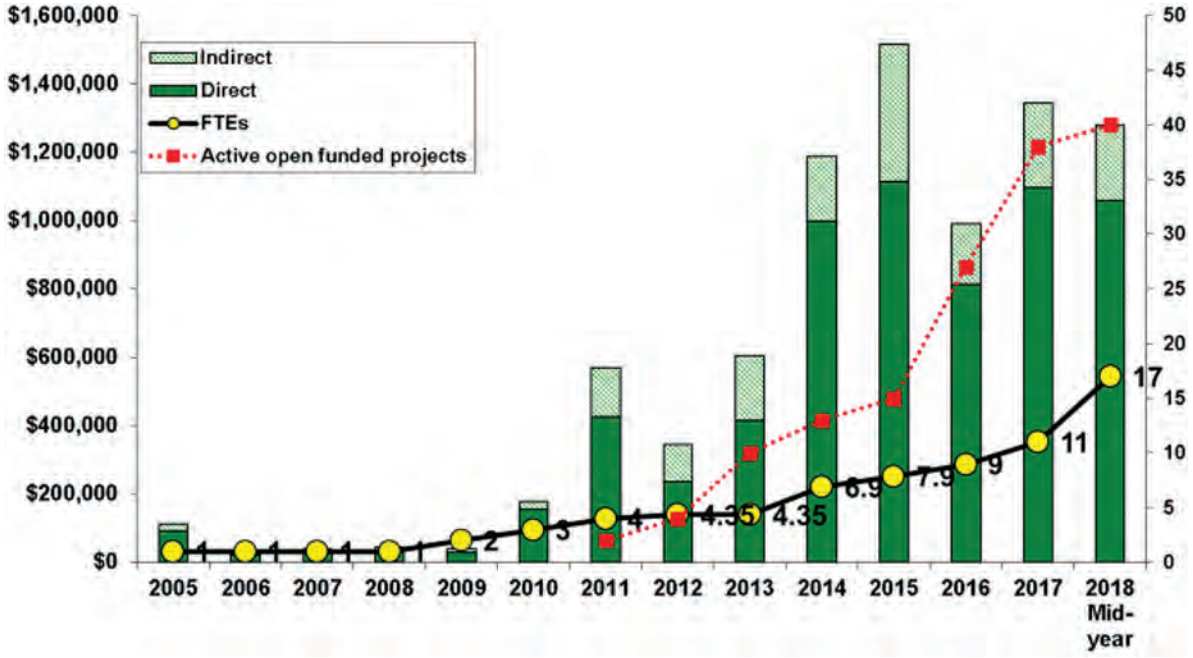


Figure 1. Orthopaedic Surgery Clinical Research Funding and Effort. Active open projects are captured from the time of study start up, and remain active as of FV18. (square symbols with dashed line). Funded studies closed in any year are not shown. Total funding for each year is reflected in the height of the column for that year. The proportion of indirect costs (patterned bars) *vs* direct costs (solid bars) is not uniform due to the differing indirect cost rates per funder in any given year. The total of FTEs (circles with solid lines) since 2014 includes those individuals paid by the Department of Anesthesiology & Critical Care, thus incorporating all the individuals on the team. Funding in FVII reflects an accumulated back-payment from Smith & Nephew, in addition to a double processed payment for the portion of Said Ibrahim's NIH grant (ends 2015). The funding for FOP clinical research studies has been added back into this scheme and gift funding for Mehta project # 809094 has also been appropriately added. Not all income is available for salary support. FV18 funding is reflected only through December 2017. An additional 17 new funded Orthopaedic Surgery projects are at various stages of pre-study activity (site selection, CTA negotiation, budget approval, IRB approval, and site initiation as of 22 Jan 2018).

Table 1. Clinical Research Studies by Division.

Division	Total Studies	Funded Studies	Prospective	Retrospective or Mixed	Proportion Funded
Adult Reconstruction	42	17	26	16	40%
Foot & Ankle	9	4	5	4	44%
FOP	4	4	4	0	10 0%
Hand	11	5	7	4	45 %
Shoulder & Elbow	13	3	6	7	23 %
Spine	6	1	1	5	17 %
Sports Medicine	30	6	18	12	20 %
Trauma	33	12	18	15	36 %
Total	148	52	85	63	35%

Figure 2. Clinical Research Staff. Pictured from L to R are our team of Clinical Research Coordinators serving Orthopaedic Surgery and Anesthesiology & Critical Care (ACC). **Front Row,** Samuel Oduwole (ACC), Aliaksei Basatski (Adult Recon), Thomas Rose (Ortho Trauma), Kamlesh Rai (FOP), Kim Lacy (ACC), Beth Howard (Sports Medicine) and Helena Moses (Adult Recon). **Back Row,** Renee Jurek (FOP), Vilair Feristin (ACC), Vance Doyle (formally FOP), Brandon Eilberg (Ortho Trauma), Matt Isenberg (formerly, Hand). *Not pictured* are Denise Knox (Project Manager), Melissa Redkar (Adult Recon), and new to the team, Bradly Fesi (Foot & Ankle), Rupa Chowdary (ACC), and temp Christine Branton-McMillon (Adult Recon), Robert Burgese (FOP), Evan Bannister (Shoulder & Elbow), Andrew Diederich (Hand), Shayla Awolusi (Spine) and Annamarie Horan, MPA, PhD (Director).

Drs. Kaplan and Al Mukaddam lead the FOP Division toward treatment interventions in FOP through the studies sponsored by Clementia Pharmaceuticals and in Q2-Q32018 will push forward the investigation of treatment options for this terrible disease by engaging with another sponsor, Regeneron Pharmaceuticals. As warranted, Dr. Kaplan will serve as the Global PI for the Regeneron study and with Dr. Al Mukaddam, should be commended for their unwavering commitment to not only new discovery, but to patient safety. The Regeneron study will also further strengthen our relationship with Anesthesiology & Critical Care by ensuring the highest possible on-site expertise at every patient treatment visit. Another special recognition goes out to Dr. Kuntz in Shoulder & Elbow for leading 3 new industry funded studies for his Division in the last year. Also breaking ground is Dr. Smith, who is leading the first industry study in Orthopaedic Spine Surgery (DePuy Vivigen) since at least 2008 with other studies in the wings.

The level of cooperation within Divisions and across service lines has been astounding and inspiring over the past 1 – 2 years and the rewards are evident as our successes continue to mount. We have multiple open studies that involve institutional operational and scientific collaboration involving Penn Radiology, and Penn Anesthesiology, as well as other institutions such as The Childrens' Hospital of Philadelphia, Medical University of South Carolina, Duke University, Vanderbilt University, McMaster University and Johns Hopkins University. These relationships may be study-specific or may be part of larger organizations such as the ROCK, MOON, or METRC consortia. The PCORI REGAIN study (PI: Mark Neuman, MD), an ongoing $12M 40-site multicenter trial to investigate the role of anesthesia delivery on functional outcomes after hip fracture surgery in the elderly. REGAIN incorporates a well-integrated team of Orthopaedic Surgery Faculty (Drs. Mehta, Donegan, and Ahn) with faculty from Anesthesiology & Critical Care (Drs. Neuman, Elkassabany, and others) and is poised to meet its enrollment goal of 1600 evaluable subjects; 800 subjects have been enrolled at mid-study. In every Division, the rewards of the 4 Cs, collaboration, cooperation, congeniality, and compliance are evident from the Office of the Chair, to the faculty, our residents, and all the way through to our staff of CRCs, and most importantly to the patients we serve.

Denise Knox, BS
Supervisor, Clinical Research.

At this time, it is important to recognize the individuals who tirelessly execute the daily operations of the clinical research program. Our team has grown, changed, and will continue to increase over the next few months. Shown in Figure 2 are most of the friendly and hard-working individuals on whom we depend to screen participants for studies, conduct research visits, capture data, and to ensure regulatory compliance and human subjects protections in our large and comprehensive program. Those unfamiliar with the execution of clinical research, express amazement at the quantity and quality of work that goes into even the "simplest" protocol. In the exceedingly busy clinics and ORs of our surgeons, these tireless staff members daily review the requirements of each active study against dozens of patients to ensure proper enrollment engage the prospective subjects and then follow them through to study completion. Every study is unique and brings its own challenges, that range from placing and ensuring the execution of study specific radiology and/or pharmacy orders to coordinating complex patient travel

Dexin Li, BS, Database Administrator.

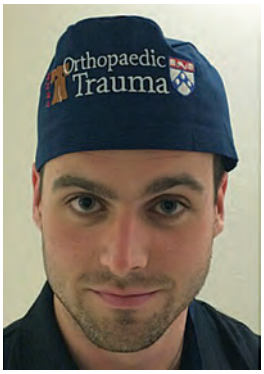
Team FOP, clockwise from L to R Lisa Gardo, BSN, Shannon Chester, BS, and Kamlesh Rai.

Shannon Marcoon, BS Clinical Research Coordinator, Sports Medicine and Ava Marie Marcoon, CRC in training.

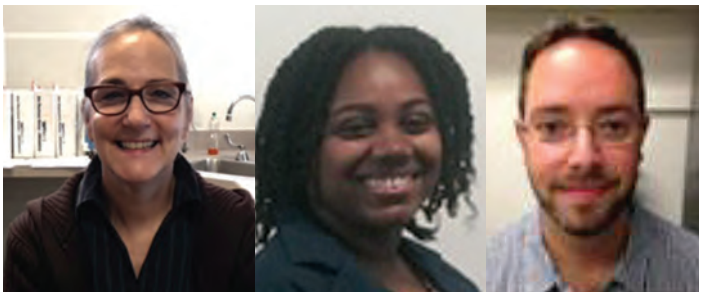
Kara Napolitano, BS serves Upper Extremity, Foot & Ankle, Oncology research.

schedules, resolving research billing issues, ensuring patient payments, diligently capturing and reporting adverse events, submitting all study activity for IRB and other committee review, and of course data capture. The work of our staff is routinely scrutinized by outside monitors and, to date, our team, with the cooperation of our faculty, continues to represent our Department(s) very well to outside parties, thus contributing to the likelihood of future site selections.

At this time, we heartily congratulate both Brandon Eilberg and Samuel Oduwole on their acceptance to Medical School (starting Fall of 2018).



Patrick Hesketh, BS and Evan Bannister, BS, aka OrthoTraumaTeamSix.



Kim Lacy, BSN and Rebekah Williams, BS and Marlon Schwarz, MD, Anesthesiology & Critical Care CRCs.

Additional congratulations go out to both Katherine Todor and Renee Jurek of the FOP team who have, at this writing passed the Clinical Research Coordinator Certification exam from the Association of Clinical Research Professionals and merit the designation of CCRC. This 3rd party certification validates the knowledge and commitment of these two individuals. Five others on our team are slated to sit for this exam in the spring of 2018. We also extend a loving welcome the newest member of the team, Murdock Hoagey-Howard (pictured but not visible in Fig. 2). We also wish to recognize other support staff throughout our institution without whom the proper conduct of clinical research would be nearly impossible. These individuals include but are not limited to the teams at the Institutional Review Board (IRB), the Office of Clinical Research (OCR), the Clinical Trials Contracting Unit (CTCU), the Center for Human Phenomic Science (CHPS), the Investigational Drug Service (IDS), the perioperative services teams, and countless Departmental clinical and other support staff.

Annamarie Horan, PhD, Director of Clinical Resarch, Orthopaedic Surgery and Anesthesiology & Critical Care.

Samir Mehta, Chief, Division of Orthopaedic Trauma, Medical Director, Orthopaedic Clinical Research.

Thank you to all the named staff above as well as the leadership of Penn Orthopaedics and Anesthesiology & Critical Care for their ongoing support of our team. Briefly, these include 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.

Penn Orthopaedics: Advancing Care Through Network Development

Rachel Kleinman, MHSA

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

While health systems and hospitals have been merging and consolidating for many years, the post-Affordable Care Act world has seen significant activity. From 2010-2015, 561 hospital mergers and acquisitions deals were announced, affecting over 1,200 hospitals[1]. Moreover, physician practices across specialties are not immune to the trend.

Many physician groups either merge together or with a health system to better compete in value-based payment models, improve financial standing, or protect from uncertainty in the health care market; though, there are a multitude of other reasons groups are merging, including notably, a shift in practice preferences among providers. However, physician practice consolidation does not guarantee higher quality of care and more efficient use of resources, and it may indeed limit some amount of flexibility and innovation found in smaller organizations.

Recognizing that quality improvement can and should happen regardless of outright ownership, Penn Orthopaedics, as a part of the Musculoskeletal & Rheumatology Service Line, has worked to create a network of physician practices and hospitals to share in goals around improving the standards of care for all orthopaedic patients.

Strategically, the Penn Orthopaedics Network most directly supports the ever-growing footprint of Penn Medicine. In January 2018, Penn Medicine merged with Princeton HealthCare System, in Plainsboro, NJ. Subsequently, Penn Orthopaedics and Princeton Orthopedic Associates formed a strategic alliance, which builds formal channels for surgeons to share patient management protocols that enable seamless care coordination in the community and at the downtown campuses. It also enables the collection and benchmarking of patient outcomes data from both groups to enhance research, practice approaches and treatment options.

Similarly, for almost six years now, Bayhealth Medical Center has been an affiliate of Penn Orthopaedics. The cornerstone of the relationship with Bayhealth is the Penn Orthopaedic Surgery Residency Rotation. Through this relationship, Penn residents are offered the opportunity to learn about health care delivery in a community hospital and independent practice setting.

Additionally, Penn Orthopaedics has a community presence in Cape May Court House, NJ with two Penn surgeons, Dr. Kevin McHale and Dr. Stanley Michael practicing at Cape Regional Medical Center (CRMC). Here, there is ongoing work with CRMC to share proven hospital-based programming and best practices.

Finally, Lancaster General Health (LGH) in Lancaster, PA and Chester County Hospital (CCH) in West Chester, PA are home to multiple well-established Penn-employed and private orthopaedic groups. Thus, the partnership with both hospitals is a collaboration on patient care pathways, post-acute protocols, and program development. Although located in different geographic markets, we develop programs synchronously, not only discovering best practices sooner, but also reducing duplicative efforts in collaboratively solving similar problems.

In conclusion, although various types of relationships have been developed with partners across the region, they are approached with the same goal in mind: *how can we deliver the highest quality of care to patients regardless of geography?* In doing that, meaningful partnerships have been forged that focus the clinical teams on improving care at the delivery level. When success is realized in one hospital or practice, there is a nimble ability to spread that success across the region. As such, we have created a network that recognizes our quest for quality care does not occur simply upon joining forces; rather, this is just the beginning of a dynamic Penn Orthopaedic Network that will work tirelessly to stay at the vanguard of continuously improving orthopaedic care.

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Continued Growth and Expansion

Neil Ravitz, MBA

Chief Operating Officer, Chief Administrative Officer, Musculoskeletal Service Line

I began my role as the COO for Orthopaedics in June of 2017 after replacing Lori Gustave. It has been a true honor getting to know the faculty, advanced practice providers, and administrative support team that make Penn's Department of Orthopaedics one of the finest in the country. Their drive to deliver the highest level of patient care, pioneer research in their fields, and educate the next generation of physicians is inspiring. In order to continue to meet the needs of our patients in our growing healthcare system, we have made some significant expansions to our faculty over the last year.

Our Orthopaedic Spine Division saw the largest growth this past year, adding three new physicians to the section. Under the leadership of Dr. Vincent Arlet, the section now has five busy surgeons practicing across three Penn Medicine Hospitals. Additionally, we added a faculty member to both our Hand Division and our Oncology Division, respectively. Paralleling the growth of our patient population outside Philadelphia, all of our new faculty are spending a portion of their time offering clinic hours in suburban locations.

Dr. Andrew Milby, a former Penn Resident, returned home to the Philadelphia Region after completing a fellowship in Spine at Emory University. We were excited to have him return and build his practice at Penn Presbyterian Medical Center alongside his colleague Dr. Harvey Smith. Dr Milby has quickly grown his clinical volume, while also providing valuable insights to the department about the residency, the care of patients, and the processes from his previous time here at Penn and his experience at Emory.

Dr. Comron Saifi joined the section in September of 2017 after completing a residency at New York-Presbyterian/ Columbia University and then a fellowship in Spine at Rush University Medical Center. His practice is focused on spinal deformities, and he is based at Pennsylvania Hospital with Dr. Arlet.

Dr. Michael Murray joined the Spine Division in August of 2017. He completed his residency at Northwestern University and a fellowship in Spine at Emory University. Following his training, he served as a spine surgeon and clinical instructor at Union Memorial Hospital in Baltimore, Maryland. While in Maryland, Dr. Murray was part of the official medical team of the NFL Baltimore Ravens. Dr. Murray is focusing his practice on minimally invasive approaches; he is based at Chester County Hospital.

In 2017, we also welcomed back Dr Stephen Liu. Dr Liu completed his residency with the Department before going to University of Pittsburgh to complete a Fellowship in Hand and Upper Extremity. The Hand division recruited Dr Liu to be at Chester County Hospital, growing further the subspecialized orthopaedic care that Penn offers in that market. While building his practice, Dr. Liu is staying active in Department activities and taking Trauma Call.

Finally, in 2017, we also expanded our Orthopaedic Oncology Division with the recruitment of Dr. Robert Wilson. He completed his residency and fellowship training at Vanderbilt University before joining the Department in September. Dr. Wilson is practicing with Dr. Kristy Weber at the Perelman Center for Advanced Medicine and operating at the Hospital of the University of Pennsylvania.

We are thrilled about the maturation and expansion of the Department in these clinical areas as a part of our greater growth strategy in the Southeastern Pennsylvania and Southern New Jersey Region. Each of these new members of the Department come to us with distinguished experiences and backgrounds, highlighting the future of Penn Orthopaedics in patient care, research and academics. We look forward to offering them a place to continue to advanced orthopaedic surgery, and together, we hope for many accomplishments and successes ahead.

University of Pennsylvania Orthopaedic Journal

2018 Clinical and Basic Science Research

The following sections highlight clinical and basic science research conducted at the University of Pennsylvania in the field of Orthopaedics. This includes research from the Department of Orthropaedic Surgery,The McKay Laboratory for Orthopaedic Research, Children's Hospital of Philadelphia, the Philadelphia Veterans Affairs Translational Musculoskeletal Research Center, The Biederman Lab for Orthopaedic Research and the Human Motion Lab, in addition to investigators from around the world who collaborate with these departments. In addition to research, technique articles and case report articles are included for education and to display the distinctive breadth of musculoskeletal disease seen and treated in our hospital system.

This year, we are excited to announce the inclusion of a new 'Orthoplastics' section which will highlight the unique multidisciplinary approach undertaken to deliver care to patients with highly complex musculoskeletal diagnoses.

Clinical Research Sections:

Orthoplastics
Arthroplasty
Foot & Ankle
Hand Surgery
Oncology
Pediatrics
Shoulder & Elbow
Spine
Sports
Trauma

Basic Science Research Sections:

Bone
Cartilage
Tendon

Tips & Tricks: Soft Tissue Reconstruction of the Complicated Knee Arthroplasty: Principles and Predictors of Salvage

David Colen, MD[1]
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Valeriy Shubinets, MD[1]
Michael Lanni, MD[1]
Tiffany Liu, BS[1]
L. Scott Levin, MD[1,2]
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Introduction

Nearly 700,000 knee joints are replaced annually, making total knee arthroplasty (TKA) one of the most common procedures performed in the United States (US)[1]. TKA is effective, safe, and significantly improves quality of life in patients suffering from end stage joint disease[2,3]. However, the procedure is not without complications. These typically arise from loosening of implants, mechanical failure, infection, or compromise of the surrounding soft tissues[4,5]. These complications can be devastating, resulting in failure of the prosthesis, knee fusion, or even amputation[6,7]. While several authors have shown that plastic surgeons can help improve outcomes in TKA's compromised by soft-tissue deficits[8-12], the optimal timing and position of the reconstructive surgeon within the stages of revision TKA has not been firmly defined. In this study, we aimed to: 1) elucidate the ideal role of soft-tissue reconstruction within the time course of knee salvage after a compromised TKA, and 2) identify key factors that affect outcomes, primarily long term retention of a knee prosthesis.

Materials and Methods

A retrospective review of all patients who underwent total knee arthroplasty and subsequent soft tissue reconstructive surgery by the senior author (S.J.K) was performed from 2008 to 2016. Relevant clinical and operative data was collected including medical comorbidities, surgical history, culture data, and follow-up.

The primary outcome of interest was TKA salvage, defined as retention of the prosthesis at last follow up; secondary outcomes included subsequent knee fusion and above knee amputation. Patients were subdivided based on the status of their knee at the time of presentation to our institution: Group 1 patients did not have an open knee wound upon presenting to our hospital, receiving all orthopedic care within the institutional health system, Group 2 had an active wound that was referred from outside of our institution. We hypothesized that patients were referred to our tertiary care center from outside hospitals would have a more complex surgical history and would be at higher risk for ultimate prosthesis failure.

Results

Initially, 77 patients with 79 compromised TKAs were identified. Five patients were excluded for inadequate records, leaving 71 patients with 73 reconstructed knees.

Salvage

Forty-five knee prostheses (61.6%) included in our study were successfully salvaged. Patients who were referred from outside hospitals and presented with active wounds or infected prostheses (Group 2) suffered a higher rate of adverse outcomes, including a significantly higher rate of prosthesis failure (Table 1). Success of salvage was negatively correlated with the total number of knee surgeries prior to plastic surgery intervention (OR = 0.68, p = 0.011). There was a trend toward decreased likelihood of salvage with increasing time (days) from diagnosis of soft-tissue compromise to index plastic surgery procedure (OR = 0.99, p = 0.09) and increasing debridements between diagnosis of wound complication and definitive soft-tissue reconstruction (OR=0.765, p = 0.093). In Group 1 patients, each additional trip to the OR after wound complication significantly decreased the likelihood of salvage (OR = 0.43, p = 0.03). Similarly, each additional day between diagnosis of complication and index plastic surgery operation decreased likelihood of salvage (OR = 0.98, p = 0.09) (Table 2).

Culture data also proved to be a significant determinant of prosthesis salvage. Nearly all (93.3%) patients who had negative cultures were able to achieve TKA salvage, whereas only 52.6% of patients with positive cultures were salvaged (p = 0.006). The lowest rate of TKA salvage occurred in the presence of gram-negative organisms (47.1%, p = 0.029), with gram-positive infections having a slightly higher rate of success (52.7%, p = 0.01). Patients with positive wound cultures at the time of the definitive soft tissue reconstruction had a significantly lower rate of salvage (40% vs 71%, p = 0.028) (Table 3).

Knee fusion and Amputation

Risk of knee fusion was significantly increased in the setting of a gram-negative infection (20.6% vs 2.9%, p = 0.05). The risk of amputation was significantly increased with each additional

Table 1. Operative Outcomes

	All		Group 1 (n = 31)		Group 2 (n = 42)		
	n	%	n	%	n	%	
Salvage	45	61.6	23	74.2	22	53.7	$p < 0.05$
Failure	28	38.4	8	25.8	20	46.3	$p < 0.05$
Fusion	8	11.0	3	9.7	5	11.9	
Amputation	18	24.6	6	19.4	12	28.6	

Table 2: Temporal factors affecting outcomes

All patients	Effect	p value
Each additional knee surgery prior to definitive reconstruction	Decreased risk of salvage (OR = 0.68)	0.011
	Increased risk of amputation (OR = 1.42)	0.02
Number of knee washouts prior to definitive reconstruction	Decreased rate of salvage for each additional washout (OR = 0.77)	0.093
Time (days) from diagnosis to index PRS procedure	Decreased salvage rate (OR = 0.99)	0.09
Group 1	Effect	p value
Each additional knee surgery prior to definitive reconstruction	Decreased salvage rate (OR = 0.58)	0.03
	Increased risk of amputation (OR = 1.63)	0.05
Each additional knee washout prior to definitive reconstruction	Decreased salvage rate (OR = 0.43)	0.03
	Increased risk of amputation (OR = 2.25)	0.06
Time (days) from first orthopedic washout to index PRS procedure	Decreased salvage rate (OR = 0.98)	0.09

operation prior to attempt at definitive reconstruction (OR = 1.42, p = 0.02), especially in Group 1 (Amputation OR = 1.63, p = 0.05). Group 1 patients who had more serial debridements also had a higher rate of amputation (OR = 2.25, p=0.06). Positive wound cultures at the time of definitive reconstruction tended to increase the risk of amputation (45% vs. 19% p = 0.06). (Table 3)

Discussion

Soft-tissue complications after primary TKA are relatively rare[13] and more common in patients with history of multiple knee surgeries or medical comorbidities [4,8,11,12,14]. In the setting of compromised prostheses, staged revision arthroplasty has shown to be successful in up to 93% of cases[15]. However, in the remaining knees who fail a revision arthroplasty, likelihood of successful knee salvage is astonishingly low. Maheshwari et al. showed that in patients who require a secondary treatment cycle after reinfection of their revised knee replacement, the likelihood of success is as low as 32.2%, with a 16% risk of amputation[16]. Thus, every effort should be made to achieve a successful outcome at the initial revision attempt. Based on our results, there is an important benefit to early, proactive soft-tissue management, immediate plastic surgery involvement upon suspected infection, and minimizing the amount of procedures prior to reconstruction, and the value of an orthoplastic approach to limb salvage. Furthermore, patients who are referred from outside institutions with active wounds and/or infections had a significantly higher risk ultimate prosthesis failure and therefore must be treated aggressively and without delay (Table 1).

Table 3: Microbiology factors affecting outcome

Joint Space Culture (any timepoint)	Positive: 40% salvage Negative: 73.7% salvage	p = 0.006
GNR culture:	GNR +: 47.1% salvage GNR −: 73.7% salvage	p = 0.029
GPC culture:	GPC +: 52.7% salvage GPC −: 88.2% salvage	p = 0.01
Culture (at definitive reconstruction)	Positive: 40% salvage Negative: 71% salvage	p = 0.028
	Positive: 45% amputation Negative: 19% amputation	p = 0.06

We suggest three simple but important reconstructive principles when approaching the challenge of a compromised TKA: 1) obtain adequate soft-tissue coverage of a clean and aseptic knee joint with the least operations and in the timeliest fashion possible: "time is tissue" 2) employ an orthoplastic approach[17-19] for complex patients and carefully consider prophylactic soft tissue coverage in patients who require TKA and have tenuous soft tissues. The former relies on prompt operative intervention and only after the joint space is completely free of contamination should definitive soft-tissue reconstruction occur. Soft tissue reconstruction follows the reconstructive ladder with local fasciocutanous flap coverage preferred as a first line, followed by local muscle flaps, and lastly, free tissue transfer (Figure 1). Patients in need of a joint replacement but with fragile soft tissues or multiple scars around the knee should be referred to a plastic surgeon prior to joint replacement for consideration of prophylactic soft tissue coverage either in advance or at the same time as arthroplasty.

The timing of reconstructive efforts relative to the diagnosis of the soft-tissue complication proved an important factor in determining ultimate success. Our data support that earlier intervention by a plastic surgeon and fewer procedures leading up to definitive soft tissue reconstruction of the knee improve long term salvage. Choosing a method of soft tissue reconstruction is done on a patient to patient basis and depends on the past surgical history, local tissue quality and availability, and orthopedic requirements. With this in mind, the tenets of the reconstructive ladder remain the basis of the technical decision-making algorithm[4]. The most common definitive soft tissue reconstruction in our cohort was the medial gastrocnemius flap (MGF), a local muscle flap that is our workhorse for coverage of the knee. This flap provides abundant muscle tissue on a reliable vascular pedicle (medial sural artery) and can be re-elevated at a later time for access to the knee joint. Harvest of the gastrocnemius muscle, however, does confer functional consequences. Daigeler et al. showed that harvest of the gastrocnemius muscle results in decreased force of ankle plantar flexion by approximately 23.8% [20]. Nevertheless, this functional deficit is a minor sacrifice for patients with compromised knee joints who are in danger of losing ambulation or worse, amputation. When the soft tissue deficit is so great that the MGF is deemed inadequate to provide a supple soft tissue envelope around the knee joint, the surgeon must consider free tissue transfer. Our group prefers the use of a free fasciocutaneous flaps, particularly the anterolateral thigh (ALT) flaps, because they provide abundant pliable soft tissue without functional morbidity of muscle flaps.

Culture data also had significant impact on the likelihood of success, with any positive operative culture decreasing rate of salvage by 33.7% (p = 0.006). Although the presence of gram negative organisms portended a lower overall salvage rate (47.1% vs 73.7% without GNRs, p = 0.029) the presence of gram positive organisms reduced the rate of salvage to a greater degree (by 35.5%). (Table 2) Finally, the presence of positive cultures at the time of definitive reconstruction both decreased salvage (-31%, p = 0.028) and increased the rate of amputation (+26%, p = 0.06). This is in contrast to the recent data published by Leckenby et al who showed that the presence of infection did not influence outcomes [21]. This may be due to their institutional protocol which includes specialists in orthopedic infectious disease as an integral component of the treatment team, a prospect now being considered at our own institution.

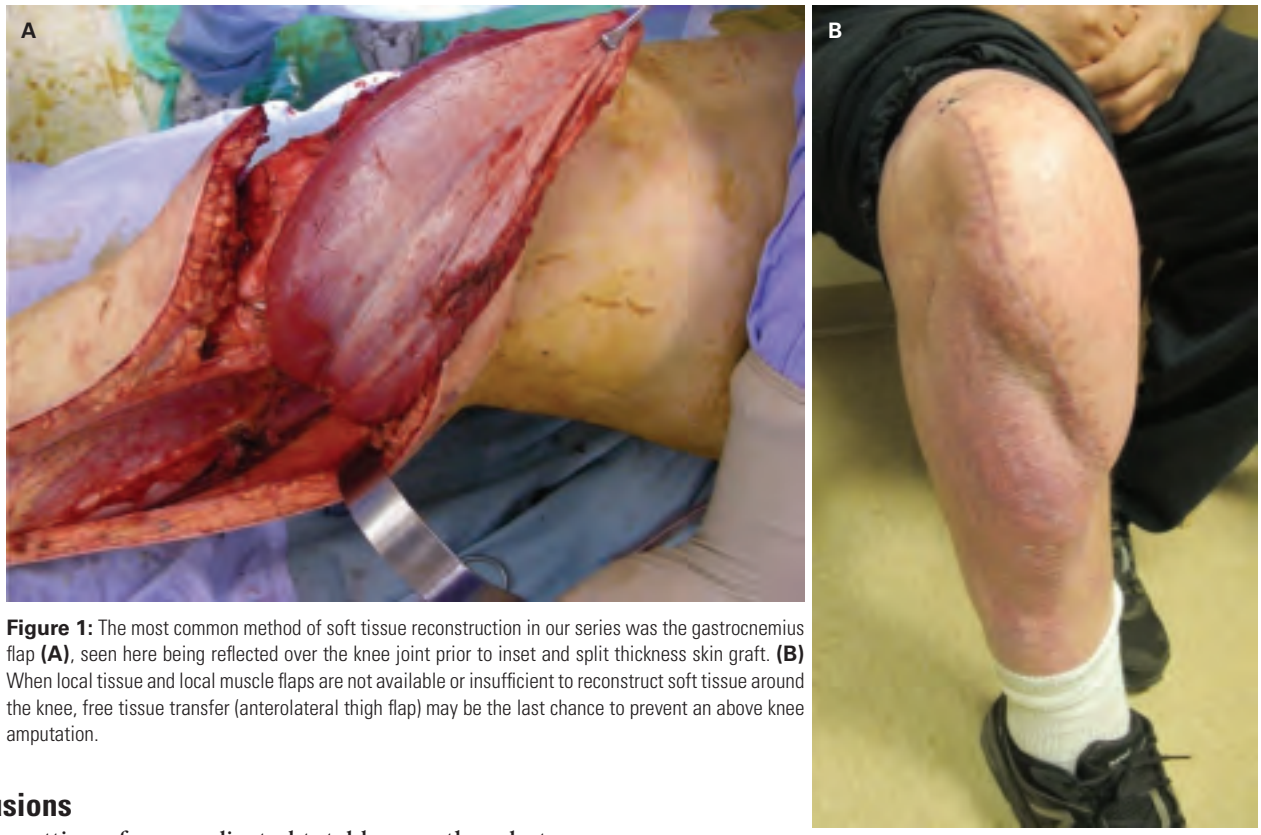

Figure 1: The most common method of soft tissue reconstruction in our series was the gastrocnemius flap **(A)**, seen here being reflected over the knee joint prior to inset and split thickness skin graft. **(B)** When local tissue and local muscle flaps are not available or insufficient to reconstruct soft tissue around the knee, free tissue transfer (anterolateral thigh flap) may be the last chance to prevent an above knee amputation.

Conclusions

In the setting of a complicated total knee arthroplasty, our data supports prompt intervention by the reconstructive surgeon in order to optimize genicular soft tissues and maximize prosthesis salvage. Operative goals include achieving negative joint cultures in the fewest possible procedures prior to definitive soft tissue closure. In patients with tenuous soft tissues and a need for future knee arthroplasty, careful consideration should be given to prophylactic soft tissue coverage about the knee. Timely intervention is the key to success in salvage of TKA.

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All Hope is Not Lost: Saving Limbs with the Orthoplastic Approach

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Introduction

The Penn Orthoplastic Limb Salvage Program provides hope for many individuals who thought they were out of options. Whether they suffered upper or lower extremity mutilating injuries, limb threatening infections, or aggressive bone or soft tissue tumors, the Orthoplastic approach to limb salvage gives patients one last chance at preserving function and a sense of wholeness prior to undergoing amputation. Orthoplastic surgery combines the strengths of orthopaedic and plastic surgery[1] and can be defined as:

"The principles and practices of both specialties applied to clinical problems simultaneously, either by a single provider, or team of providers working in concert for the benefit of the patient."[2,3]

This combined Orthoplastic approach to severe injuries of the extremities provides us as individual surgeons with an expanded view of what is possible in terms of limb salvage and can greatly benefit patients who are on the brink of limb loss.

This article reflects on a few memorable cases of Orthoplastic limb salvage over the last year during our time as hand, micro, and orthoplastic surgery fellows at Penn. No Institutional Review Board approval is necessary at this institution for case series involving 3 or fewer patients. Written, informed consent was obtained from each patient prior to surgery.

Case 1

A 55-year-old female was involved in a motor vehicle rollover after being struck by a semi-truck. Among her injuries was an open both bone forearm fracture with significant bone loss of the distal radius and ulna (Figure 1A). She was initially treated at an outside hospital with irrigation, debridement, and external fixator placement. She was then transferred to Penn for definitive treatment of her fractures and upper extremity orthoplastic limb salvage. The patient was taken to the OR with the orthoplastic team for reconstruction of the 8 cm bone defect in the distal radius with an osteocutaneous free

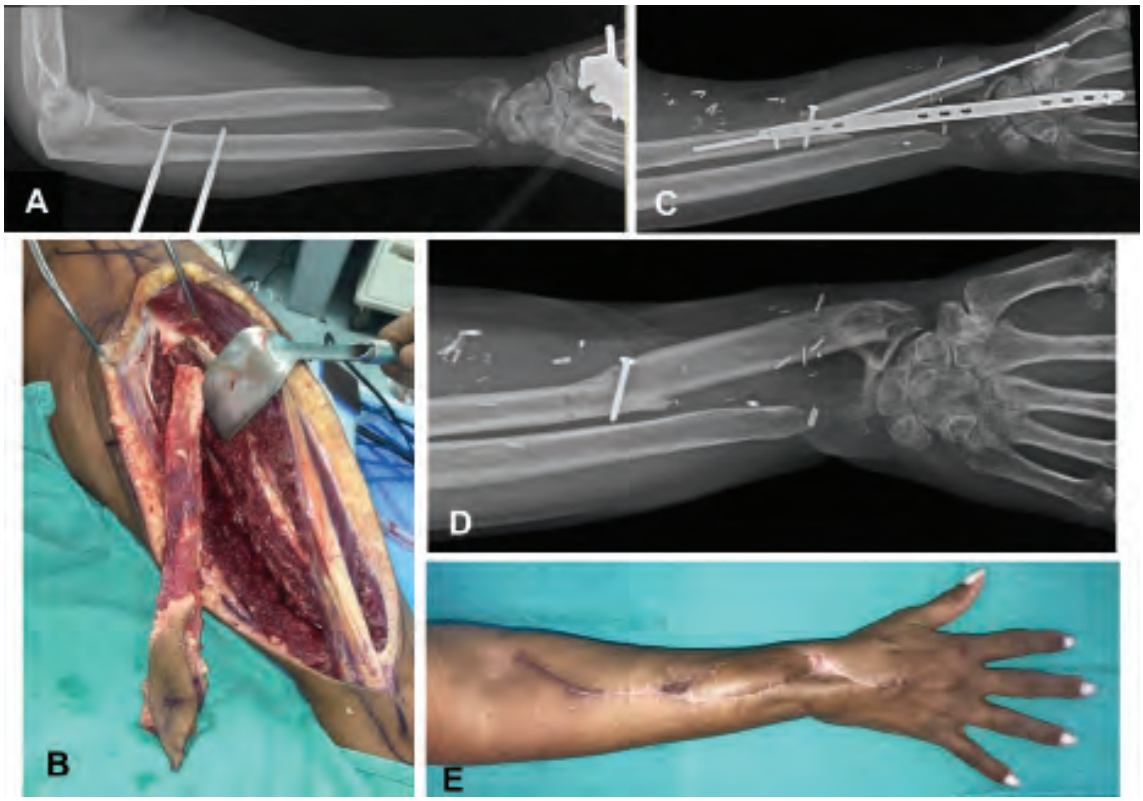

Figure 1. Case 1, Orthoplastic reconstruction of the forearm after an open both bone forearm fracture with an 8 cm defect of the radius **(A)**. This was reconstructed with an osteocutaneous fibula free flap **(B)** and **(C)**. Postoperative radiograph at 7 months showing bone union and a preserved radiocarpal joint **(D)**. Post operative photograph at 5 months **(E)**.

fibula flap (Figure 1B). Upon exploration of her volar ulnar laceration from her open fracture, the ulnar artery was noted to be tied off so the proximal ulnar artery was selected as the recipient vessel for the free flap. The flap was raised and transferred to the defect, fixating the fibula with a Steinmann pin, a dorsal bridging plate, and minimal screws to prevent vascular compromise of the bone flap. The fibula was impacted distally into the remnant of the distal radius to preserve the radiocarpal joint (Figure 1C). After the arterial anastomosis, there was poor egress from the veins, so the decision was made to abort the ulnar artery and use the radial artery in an end-to-side fashion as the recipient vessel which perfused the flap robustly. Two veins were then anastomosed. The patient did well post op and had evidence of partial bone union by 2 months, and complete union by 6 months post-operative. Her hardware was removed at 7 months (Figure 1D). Her wrist has remained stable with approximately 30 degrees of flexion and extension (Figure 1E). If her wrist collapses ulnarly in the future, a total wrist arthodesis to the fibula will be performed.

Case 2

A 38-year-old male was involved in a head-on collision motor vehicle accident and suffered severe bilateral lower extremity trauma. On the right leg, he had a Gustilo IIIA open fracture of the tibia with 15 cm of bone loss (Figure 2A). His fractures were treated at an outside hospital which consisted of an external fixator and a large antibiotic spacer for the tibial defect. One month after the accident he was referred to Penn for limb salvage. He was then taken to the operating room for free fibula flap to reconstruction of the tibial defect. Although fractured, the ipsilateral fibula was used because the contralateral fibula also had a fracture and previous ORIF. There was some difficulty raising the fibula flap because of the significant trauma to the area, but the pedicle and proximal bone was well preserved. The fibula was slid down into the bone spacer cavity using the same approach from the fibula harvest. The proximal fibula flap was placed into a slot in the tibia and secured with a Steinmann pin, a small spring plate, and the external fixator was replaced (Figure 2B). The peroneal pedicle of the fibula was anastomosed to the anterior tibial vessels in an end-to-side fashion. The patient did well post-operatively and was taken back to the OR 6 weeks later for placement of a Taylor Spatial Frame (TSF) and arthrodesis of the fibula to the talus (Figure 2C). He was then transitioned to toe touch weight bearing 2 weeks later, and weight bearing as tolerated 4 weeks after that. Once the fibula hypertrophies sufficiently, the TSF will be removed. He has had one pin site infection postoperatively that was treated successfully with IV antibiotics.

Case 3

A 63-year-old right hand dominant diabetic woman presented who 2 years prior fell and fractured her proximal humerus which was treated at an outside hospital with ORIF. She subsequently developed a severe staphylococcal infection that required 8 more surgeries and removal of all hardware and nearly the entire humerus except the distal portion just above the elbow (Figure 3A) resulting in a flail arm (Figure 3B). After living for some time without a humerus and with very poor dominant hand function she presented to the Penn shoulder and elbow clinic and the Orthoplastic clinic for evaluation. She had been infection free for 11 months. After very thorough informed consent, the decision was made to proceed with a combined humerus allograft, hemi-shoulder arthroplasty, and free vascularized fibula onlay reconstruction. A two-team approach was utilized with the shoulder/elbow team preparing the rotator cuff, hemi-arthroplasty, and humerus allograft, and the orthoplastic team preparing the recipient bed and raising the free fibula flap (Figures 3C-3E). Once the recipient bed and implant were prepared, the allograft was plated to the distal humerus remnant, and sutured in proximally to the rotator cuff. The free fibula was placed into a channel created in the allograft with a bur, and secured with 2 screws (Figures 3F). An end-to-side arterial anastomosis was performed to the brachial artery followed by 2 vein anastomoses. The skin paddle was inset and the incisions closed (Figures 3G and 3H). Because the patient had a history of PE, she was started on a heparin drip immediately after surgery. Her postoperative course has been complicated by a hematoma that required evacuation and delayed wound healing. At 3 months post-operative, the patient is currently in a skilled rehabilitation center.

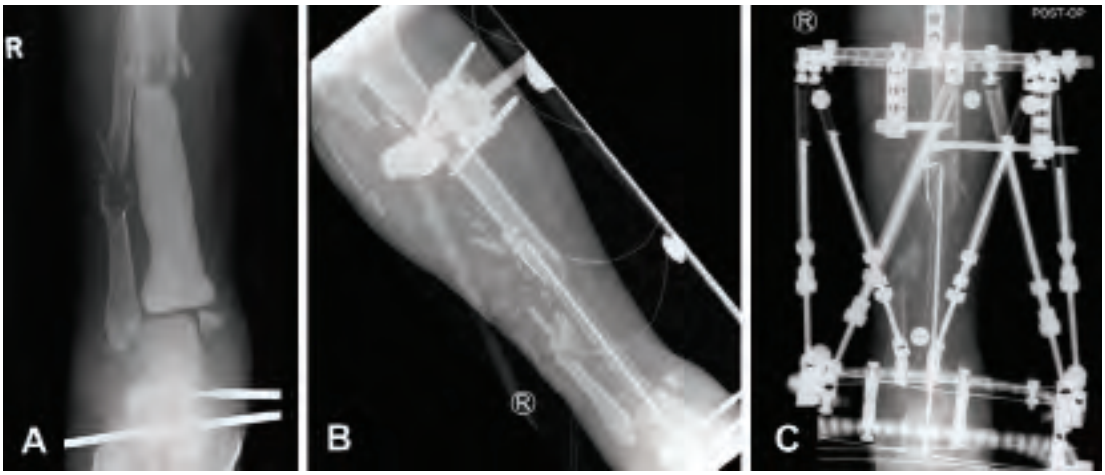

Figure 2. Case 2, Orthoplastic reconstruction of a 15 cm tibial defect after a Gustilo 3A tib/fib fracture **(A)**. Ipsilateral free fibula reconstruction was performed for limb salvage **(B)**. A Taylor Spatial Frame was placed to allow gradual weight bearing and hypertrophy of the free fibula **(C)**.

Discussion

The concept of the Orthoplastic approach brings together the strengths of orthopaedic surgery of stable bone reconstruction and

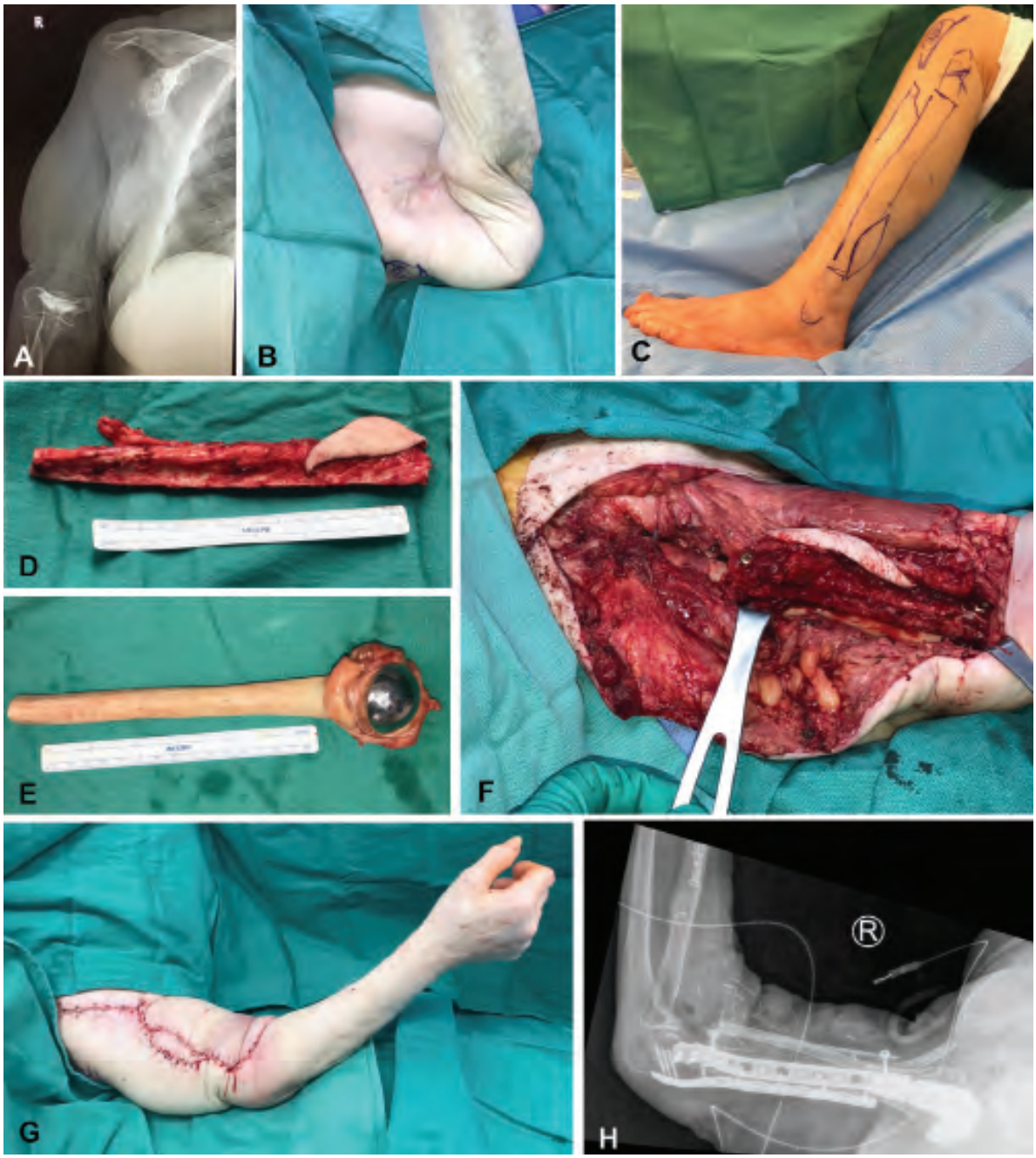

Figure 3. Case 3, Orthoplastic reconstruction of the upper extremity after resection of most of the humerus due to osteomyelitis. Image **(A)** shows an AP radiograph of the arm missing most of the humerus and **(B)** shows a clinical photograph of the flail arm. This was reconstructed with a free fibula osteocutaneous flap **(C)** and **(D)**, combined with a humerus allograft with a hemiarthroplasty **(E)**. Image **(F)** shows the allograft with the fibula onlay after insetting and the immediate post-operative result **(G)** and radiograph **(H)**.

rehabilitation with the microvascular soft tissue and aesthetic principles of plastic surgery simultaneously to maximize outcomes in extremity salvage and reconstruction. When both perspectives are clearly understood and applied, outcomes in reconstruction are maximized. Limb salvage procedures are often demanding but with careful preoperative planning, intraoperative technique, and postoperative care, this approach can lead to successful preservation of the limb and function. Early and late complications can arise, but an experienced microsurgical team can offer complex reconstruction with high rates of success.

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U·P·O·J

Hand Transplantation in the Rat: Technical Refinements of the Rat Forelimb Vascularized Composite Allotransplantation Model

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Introduction

The worldwide experience in upper limb transplantation has now reached nearly 150 limbs in 100 patients with overall promising mid-term results[1]. Until recently, most limb transplant research done on rats consisted of either orthotopic or heterotopic hind limb transplantation[2]. This approach, based on anastomosis of the femoral vessels, has been technically achievable since at least the 1970s[3]. With the improvement of microsurgical techniques over the years and the need for a better functional model of limb transplantation, our team was the first to report successful orthotopic forelimb vascularized composite allotransplantation in a rat model[4]. Since this publication, we have developed technical refinements of the model which we hypothesize will lead to better allograft and animal survival rates, allowing for better study of immunologic and functional outcomes.

Methods

After IACUC approval, we performed 60 orthotopic forelimb transplants from Brown Norway rats to Lewis rats. Transplantation was performed at the mid-humeral level on rats 8-10 weeks old weighing an average of 250g. For the donor operation, under deep Isoflurane inhalational anesthesia, the brachial vessels, radial, median, and ulnar nerves were dissected and the nerves were divided with as much length as possible (Figure 1). The muscle was cut with bipolar cautery and the bone sectioned with a rotary saw. The vessels were then divided and the limb was stored in moist gauze on ice. The recipient operation was similar to the donor, except the lateral thoracic vein was also dissected and transposed into the field as a larger recipient vein (instead of the external jugular vein as in our previous work). In addition, instead of using the common carotid artery for the recipient artery as done previously, we used the axillary artery. Transplantation was then performed with a 25gauge needle for humerus fixation as an intramedullary rod (Figure 2), followed by muscle repair, microvascular arterial, vein, and nerve repairs (Figure 3). The skin was then closed (Figure 4). The animals were treated

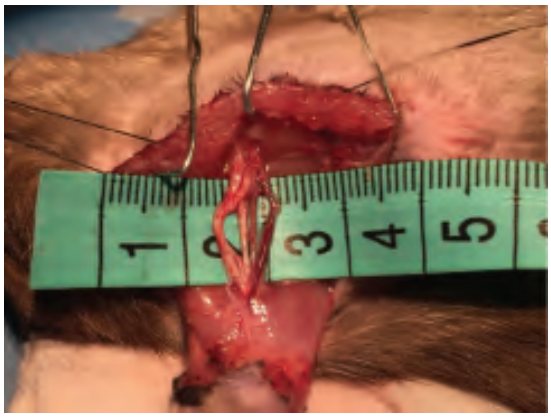

Figure 1. Donor limb neurovascular bundle of the right forelimb with head to the left. The median, ulnar, and radial nerves are to the left and the brachial artery and vein to the right.

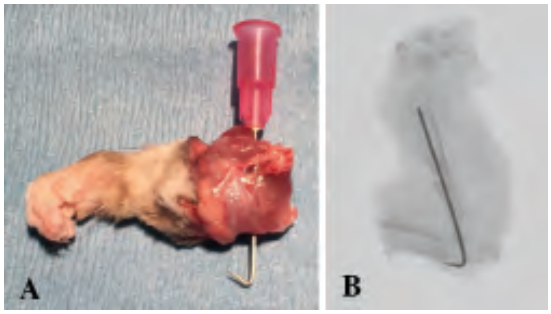

Figure 2. Bone fixation in the rat forelimb transplant. **(A)** Donor limb with a 25 g needle through the distal humerus as an IM rod. **(B)** X-ray of the rat forelimb transplant with the needle IM rod showing adequate bone contact between donor and recipient. This is reinforced by the surrounding muscle repairs.

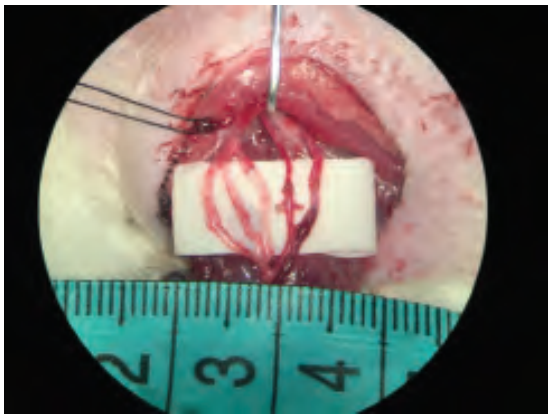

Figure 3. Demonstration of anastomosis of brachial artery to brachial artery and brachial vein to lateral thoracic vein with 11-0 suture. And approximation of the median, ulnar and radial nerves with 10-0 nylon interrupted epineurial sutures.

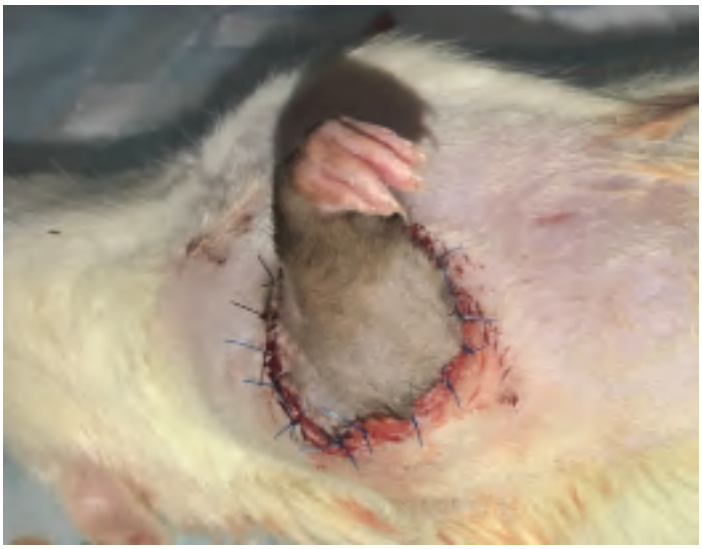

Figure 4. Immediate postoperative photo of the rat forelimb transplant from Brown Norway rat (donor) to a Lewis rat (recipient).

with analgesics, and some with an implantable capsule for sustained release of rapamycin 1mg/kg/day. Allograft and animal survival rates were recorded.

Results

Surgery time was 2.79 ± 0.58 hours with an ischemia time of 1.98 ± 0.48 hours. One animal died during surgery making for 98.3% survival. The allograft survival rate was 91.7% with 5 vascular complications including venous thrombosis in 2, arterial thrombosis in 2, and 1 animal death. The average artery size was 0.72 ± 0.17 mm and the vein size was 1.22 ± 0.24 mm. The allograft survived less than 13 days without rapamycin and up to 35 days with rapamycin.

Conclusions

Although technically demanding, rat orthotopic forelimb transplantation is feasible with standard microsurgical techniques leading to high allograft survival rates. We were able to improve on our previous work by using the lateral thoracic vein for outflow instead of the external jugular vein, and the axillary artery for inflow instead of the common carotid artery. This saves time by preventing dissection in the neck and mitigates risk of brain injury in the animals. This model may prove to be good for studying functional outcomes after forelimb transplantation and the impact of immunomodulation/immunosuppression on nerve regeneration.

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Tips & Tricks: Preoperative Planning and Templating for Total Hip Arthroplasty

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Introduction

The total hip arthroplasty is one of the most successful surgical procedures invented over the past century. It has revolutionized treatment of arthritic conditions of the hip and allowed improved quality of life for the majority of patients with acceptable risk and morbidity. Improvements in surgical technique, implants, peri-operative pain and blood management in many cases have led to less blood loss, increased implant survivorship, more rapid rehabilitation and reduced complications. However, optimal outcome of a total hip arthroplasty remains predicated on a detailed pre-operative evaluation, templating and surgical plan. Here, we discuss the critical components to evaluate when planning for a total hip procedure. Clinical examination and diagnosis are critical components to preoperative planning, but are outside the scope of this article.

Radiographic Evaluation

Radiographs

Standard imaging of the arthritic hip includes anteroposterior (AP) view of the pelvis centered over the pubic symphysis, as well as AP and lateral of the affected hip. In anticipation of surgical templating, it is best to perform these studies with a standardized scale marker ball at the level of the greater trochanter for later calibration and accurate sizing. When possible it is best to internally rotate the hip 10-15 degrees to correct for femoral anteversion and allow more accurate assessment of femoral offset. Prominence or lack of the standard profile of the lesser trochanter may indicate external or internal rotation of the limb. The film should be examined for signs of rotation, as evidenced by the symphysis not lying directly below the sacrum or asymmetry between the obturator foramina. Additionally, evaluate the lumbosacral region for signs of scoliosis or degenerative spine disease, which could confound the diagnosis of hip arthritis.[1] In some cases, dynamic spine imaging sitting and standing is helpful to evaluate pelvic tilt and assess spino-pelvic mobility.[2]

Evaluation of the hip should include assessment of the grade of arthritis. Standard radiographic signs of arthritis include joint space narrowing, subchondral cysts, and osteophyte formation. Especially in younger patients, it is important to assess for signs of acetabular dysplasia, such as increased inclination of the acetabular sourcil and/or decreased lateral coverage on the AP view. In subtle cases there may only be decreased anterior coverage on a false profile view. Signs of Pincer femoral acetabular impingement and acetabular retroversion include the prominence of the ischial spine and the crossover sign of the anterior and posterior walls. Make note of any hardware from prior hip surgery. This may require full-length femur imaging to determine whether the femoral implant will fit, assess the need to remove prior hardware, bypass stress risers or perform a concurrent osteotomy to allow placement of an appropriate femoral hip prosthesis.

Landmarks

Begin by marking the horizontal inter-teardrop line, passing through the base of the teardrops on both sides of the pelvis. Identify the ilioischial line, which marks the medial border of the true acetabulum.[1]

Acetabular Templating

Manual templates or computer templating software may be utilized. For manual templates confirm magnification by comparing the marker ball with the reference scale on the template. Alternatively, the marker ball in the computer templating program may be used for image calibration. Assessment of any length discrepancy is performed by comparing a fixed point on the lesser or greater trochanter with a perpendicular to the inter-teardrop line. If the teardrop is obscured by arthritic changes, the inter-teardrop horizontal can be replaced by the horizontal connecting the ischial tuberosities or a horizontal line across the top of the obturator foramen. The radiographic leg length difference should be compared with the assessed clinical difference to determine the planned center of rotation for the cup and stem to restore the desired change in leg length and off-set. In some cases it is helpful to template the normal hip to allow restoration of equal radiographic length and off-set when indicated. Beware that flexion contracture may cause compensatory lumbar lordosis that makes the AP radiograph appear more like an inlet view.[1] Flexion contractures may cause limb lengths to appear significantly

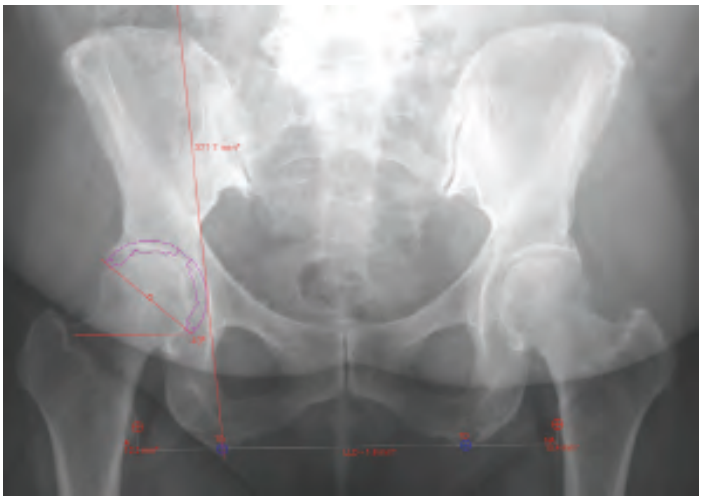

Figure 1. Limb length discrepancy using horizontal line drawn across the bilateral ischial tuberosities. Vertical measurements made perpendicularly to equivalent prominence of the lesser trochanters. Medialization of the cup to Kohler's line (oblique vertical red line), with inferomedial cup placed at level of teardrop. Hip center of rotation marked with red circle in middle of acetabular cup template. Note is made of superolateral osteophytes.

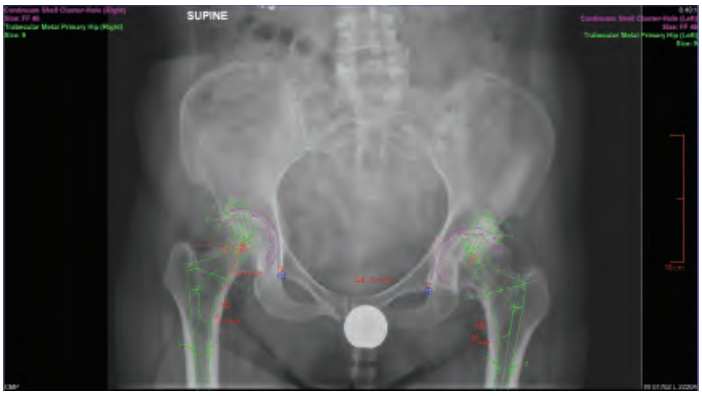

Figure 2. Templating using the operative (left) and non-operative (right) hips. Goal is to restore operative hip to same muscle tension as normal side. A neck resection at the level of the green line (templated here) can be measured intraoperatively. By templating the normal side, we can visualize where our resection is. The patient below has a 5.3 mm leg length discrepancy. The cup is medialized to the teardrop and abducted between 40-45 degrees. The stem will be limited by the shape of the stem hitting the calcar.

different. Before adjusting the preoperative plan to fix a large limb length discrepancy (anything greater than 1 cm), review carefully the physical exam and imaging for indications of a flexion contracture that may confound the measurements. Figure 1 demonstrates how to assess limb length discrepancy and template the acetabular cup on the AP pelvis radiograph.

Femoral Templating

Once satisfied with the acetabular templating process and planned center of rotation, then we proceed to femoral templating. It is important to understand the stem geometry and the method by which the planned stem achieves fixation. Begin with sizing the stem, independent of acetabular component. Choose the implant that will provide appropriate fit along the medial cortex and calcar in addition to allow restoration of leg length. Different implants will have a variety of metaphyseal shapes to best fit the patient's native contour. Depending on the femoral canal size and Dorr classification, size options may be limited by diaphyseal inner diameter. (Figure 2) Sequentially check femoral stems of increasing size until the appropriate implant body is selected. (Figure 3) When the desired restoration of leg length and offset is not possible using a cementless stem, cemented stems can be at a more distal or proximal level without optimal stability prior to placement of bone cement, but with markedly improved stability as well as excellent long term results following polymerization of bone cement.

With the femoral stem size chosen, move to evaluate neck offset. The lateral or extended offset neck designs offer either a more varus neck angle or a medially translated neck at the same neck angle. Points along the standard or extended offset line represent the head length. In order to correct for limb length discrepancies and restore native offset, select the neck offset and head-neck offset point in the vertical plane of the center of rotation of the acetabulum. If limb lengths are equal, the femoral point should overlie the center of rotation. If the limb length is short compared to the unaffected side, the point should lie proximal to the center of rotation to gain length when the hip is reduced. Conversely, if the limb length is long compared to the unaffected side, the point should lie distal to the center of rotation to decrease length when the hip is reduced. However, we would caution against planned reduction in length or offset due to the risk of instability.

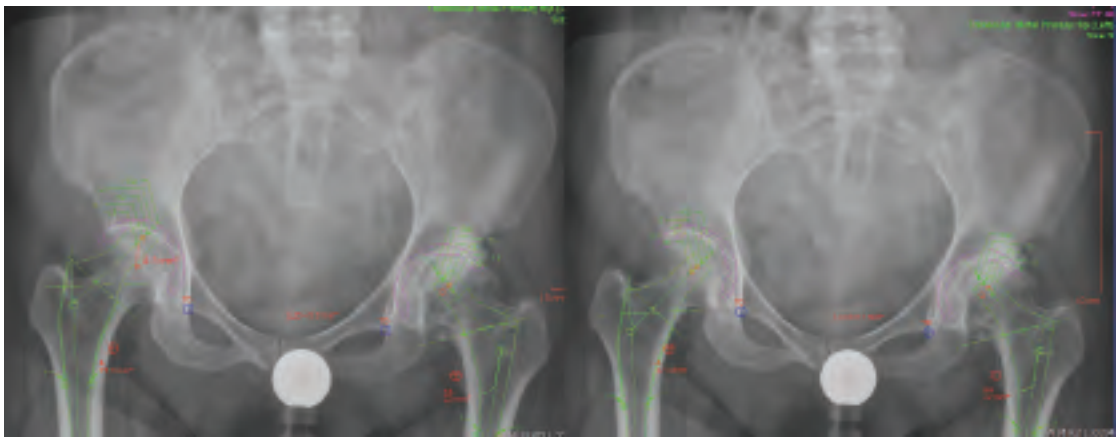

Figure 3. The appropriate geometry stem for this patient is changed to a different geometry stem (Left, Zimmer ML taper). Even with downsizing to the smallest available size, it would not be possible to sink the stem past the calcar. With the -3.5 mm head and the shortest neck available, this patient would be lengthened by 14 mm. Demonstration of attempt to sink the inappropriate geometry stem to achieve equal leg lengths. Here, the stem perforates through the calcar. Without templating this could lead to intraoperative fracture (Right).

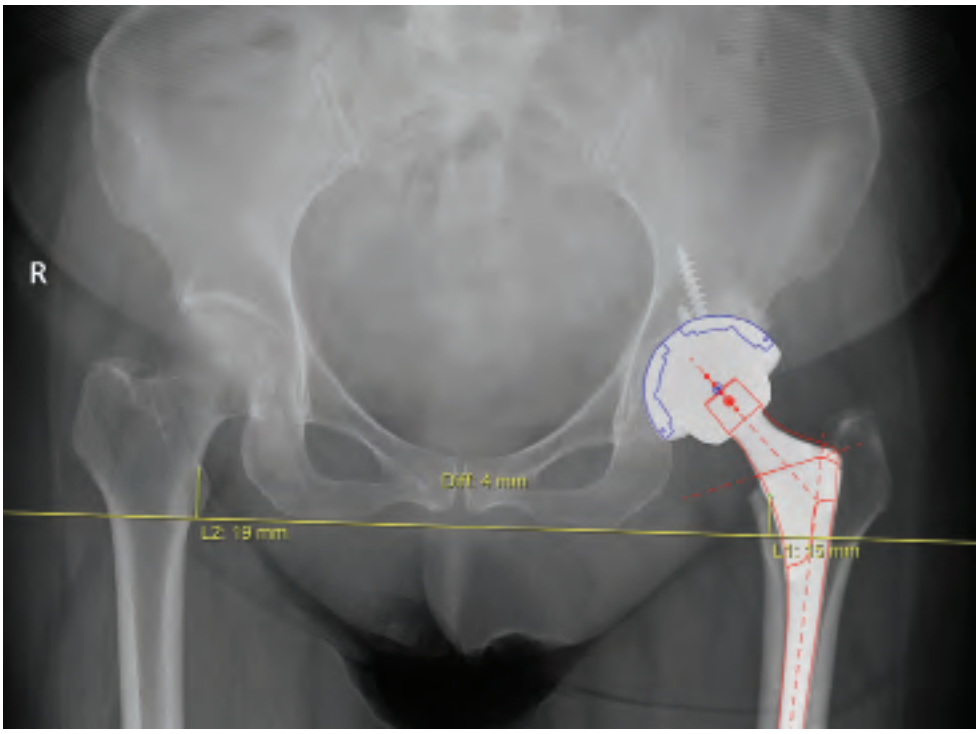

Figure 4. Postoperative x-ray with template demonstrating the actual implant and size selected. Leg length discrepancy improved to within 4 mm.

Surgical Execution

Once the template has been completed, evaluate carefully for challenges such as large medial or superolateral osteophytes. Review the template in detail to confirm the center of rotation has been restored, particularly in cases of protrusion, dysplasia, or hypertrophic arthritis.

With this complete, the surgeon is prepared to efficiently execute their plan in the operating room. Intraoperatively, the surgeon now has an idea of expected cup and femoral stem size, which can aid in minimizing time and beginning preparation closer to the templated sizes. In addition, when planned size is much larger than the size achieved, there should be strong suspicion that the femoral implant may be in excessive varus alignment. While templating is important, the intra-operative fit and implant stability ultimately will dictate implant sizes. An example postoperative radiograph is demonstrated in Figure 4. The ability to successfully plan for hip arthroplasty preoperatively improves with experience. Senior orthopaedists have demonstrated accuracy to within one size compared with their template 94.6% of the time, while resident estimates were within one size only 82.4% of the time.[3] Pre-operative planning allows the surgeon to confirm their diagnosis, become familiar with the details of the patient's anatomy, avoid potential hazards, and move expediently in the operating room.

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Increasing Rates of Obesity, Diabetes, and Depression Prevalence Among Primary and Revision Total Joint Arthroplasty from 2002-2014

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Introduction

Total joint arthroplasty (TJA) procedures have increased in volume continuously over recent decades. Previous studies have evaluated expected future growth for primary and revision TJA procedures. There has been little discussion of the changes in the comorbidity prevalence amongst the TJA population since 2002 and how it can be expected to influence the total joint arthroplasty population in the future. This paper seeks to evaluate the recent changes in trends in diabetes mellitus, obesity, and depression among patients undergoing primary and revision TJA procedures in comparison to trends in the general United States population.

Background

Primary and revision TJA are common procedures that are expected to continue to rise in the coming years.[1] These procedures are associated with a significant cost to the health system, and in the era of bundled care, understanding and preventing potential complications and readmissions is paramount. Clinicians and hospital systems need to continue to look for ways to improve delivered care and potentially reduce these complications and readmissions. Diabetes mellitus, depression, and obesity are three common comorbidities that have seen a significant increase in prevalence in general United States population over the last two decades. Outcomes of patients with these comorbidities has been studied, but little has been studied regarding these trends in the TJA population. Understanding these trends and how they may affect future patients is critical in optimizing outcomes and care.

Diabetes mellitus (DM) is a common and increasingly prevalent comorbidity in the United States. Diabetes has important clinical effects on the musculoskeletal system, and has been shown to be an independent predictor of development of severe osteoarthritis.[2] Similarly, patients with DM have been shown to be at an increased risk to undergo primary and revision TJA.[3] Notably, the prevalence of DM has increased from 9.3% of adults in the general United States in 2002 to 11.7% in 2014.[4] Diabetes is not only associated with risk for undergoing joint replacement, but has been associated with increased rates of stiffness, prosthetic joint infection, revision arthroplasty and cost of care.[5,6] Taken together, it can be expected that more patients undergoing TJA will have diabetes and understanding these risk factors and management is critical to sustaining good outcomes.

Comparably, obesity has seen a rise through the United States and the globe, becoming an epidemic. The rate of obesity (classified as BMI > 30 kg/m^2) has risen from 30.5% in 2002 to 37.7% in 2014.[7] Obese patients have been shown to have significantly increased rates of cardiopulmonary complications, wound and implant complications and readmissions.[8-10] These rates of complications are also directly related to the degree of obesity, as patients with BMI > 40kg/m^2 have been shown to have higher rates of these complications.[8-10] Unfortunately, this trend continues to increase.

Lastly, mental health is an area of medicine that has been gaining increased attention in term of diagnosis, treatment, and surgical outcomes. In 2016 alone, 14% of adults in the United States were diagnosed with a mental illness, and 4.2% were diagnosed with a mental illness that interfered with life activities.[11] The prevalence of depression has risen significantly, from 7.1% in adults in 2002 to 8.1% in 2014.[12,13] Recent studies have demonstrated that depression is associated with a significantly higher risk of readmission following TJA, even when controlled for other chronic conditions.[14] Additionally, depression is an independent predictor of increased cost of stay and post-operative complications.[15]

Taken together, three common comorbidities (diabetes mellitus, obesity, depression) have been shown to be increasing in frequency in the general United States and have been associated with increased rates of complications, worse clinical outcomes, and readmissions. What is not known, is how these rates have changed in the TJA population during this time frame. This paper seeks to identify these trends in the primary and revision TJA population from 2000-2014.

Methods

The National Inpatient Sample (NIS) database was queried. This database contains a 20% sample

of all public United States hospital discharges annually. The database is built as a representative sample of all inpatients in the United States in order to simulate national trends. Patients undergoing primary total hip arthroplasty (THA), primary total knee arthroplasty (TKA), revision THA, and revision TKA were identified by ICD-9 procedure code. ICD-9 diagnosis code at time of discharge was used to identify the annual prevalence of obesity, diabetes, and depression among the TJA population.

Sampling weights provided by NIS were used to estimate national comorbidity rates. Proportional changes from 2002 to 2014 were compared using a Chi-square test. Linear regression was performed to assess trends in comorbidity prevalence over time. Data from the Centers for Disease Control and Prevention were used to compare comorbidity prevalence in the TJA population with the general United States population over the same time period.

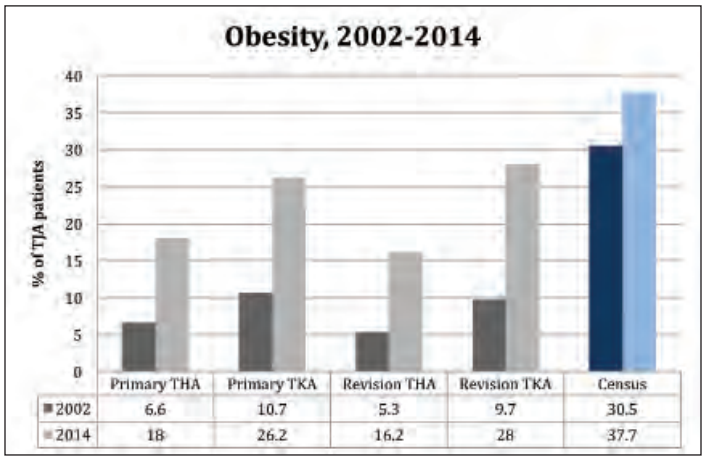

Figure 1. Percentage of Obesity in TJA patients in 2002 and 2014.

Results

In 2002, volume of procedures for each TJA category was 339,686 for primary TKA, 194,998 for primary THA, 30,007 for revision TKA, and 37,049 for revision THA. In 2014, volume of procedures for each TJA category was 680,886 for primary TKA, 371,605 for primary THA, 63,205 for revision TKA, and 50,425 for revision THA.

From 2002-2014, the TJA population comorbidity prevalence changed significantly. Obesity, diabetes, and depression all significantly increased from 2002-2014 in both primary TJA and revision TJA categories. (Table 1)

Obesity was noted to increase significantly ($p < 0.01$) at all times points for all groups. (Figure 1) Primary THA (6.6% to 18%), Primary TKA (10.7 to 26.2%), Revision THA (5.3 to 16.2%), and Revision TKA (9.7 to 28%). Notably, while obesity increased in every group, at all time points obesity is below that of the general population (30.5% and 37.7% in 2002 and 2014 respectively).

Diabetes was shown to increase significantly ($p < 0.01$) at both time points in all groups. (Figure 2) Primary THA (9.7 % to 13.5%), Primary TKA (15% to 19.8%), Revision THA (10.5% to 15%), and Revision TKA (16.2% to 22.9%). For all groups in 2002 and 2014, the prevalence in the primary and revision TJA groups is above that of the general population.

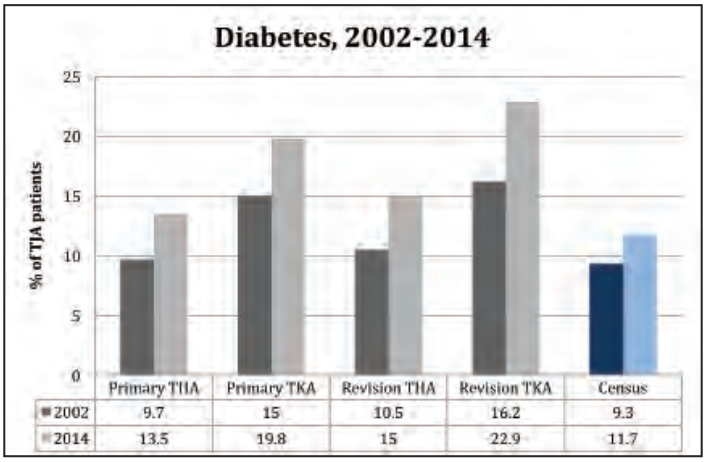

Figure 2. Percentage of Diabetes in TJA patients in 2002 and 2014.

The prevalence of depression increased significantly ($p < 0.01$) at both time points in all groups. (Figure 3) Primary THA (4.9 to 12.6%), Primary TKA (5.7% to 14.4%), Revision THA (6.7% to 17%), and Revision TKA (6.9% to 18.8%). In 2002,

Table 1. Prevalence of Obesity, Diabetes, Depression in Primary THA, TKA and Revision THA, TKA in 2002 and 2014.

	Primary THA Trend (p)	Primary TKA Trend (p)	Revision THA Trend (p)	Revision TKA Trend (p)
Obesity				
2002 Prevalence, % (SE)	6.6 (0.0012)	10.7 (0.0012)	5.3 (0.0025)	9.7 (0.0038)
2014 Prevalence, % (SE)	18.0 (0.0014) +0.0102 (<0.01)	26.2 (0.0012) +0.0132 (<0.01)	16.2 (0.0037) +0.0099 (<0.01)	28.0 (0.0040) +0.0159 (<0.01)
Diabetes				
2002 Prevalence, % (SE)	9.7 (0.0015)	15.0 (0.0014)	10.5(0.0035)	16.2 (0.0047)
2014 Prevalence, % (SE)	13.5 (0.0013) +0.0037 (<0.01)	19.8 (0.0011) +0.0041 (<0.01)	15.0 (0.0036) +0.0040 (<0.01)	22.9 (0.0037) +0.0056 (<0.01)
Depression				
2002 Prevalence, % (SE)	**4.9 (0.0011)**	**5.7 (0.0009)**	**6.7 (0.0028)**	**6.9 (0.0032)**
2014 Prevalence, % (SE)	**12.6 (0.0012) +o.0066 (<0.01)**	**14.4 (0.0010) +o.0073 (<0.01)**	**17.0 (0.0037) +0.0088 (<0.01)**	**18.8 (0.0035) +0.0097 (<0.01)**

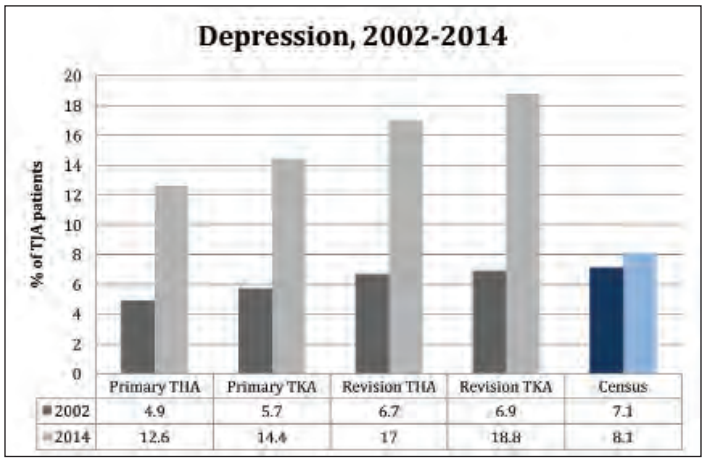

Figure 3. Percentage of Depression in TJA patients in 2002 and 2014.

depression was noted to be of a lower prevalence than the general United States population in all groups, while found to be higher as compared to the census in all groups at 2014.

Discussion

Analysis of the National Inpatient Sample database demonstrated that the prevalence of obesity, diabetes mellitus, and depression all significantly increased ($p < 0.01$) in the primary and revision TJA groups from 2002 to 2014. The prevalence of depression and diabetes were both higher than that of the United States population as a whole for both the primary and revision groups at all time points. However, the recorded prevalence of obesity was below that of general population in all groups in both 2002 and 2014. There are several key takeaways from these findings discussed below.

Obesity, diabetes, and depression are all significantly associated with post-operative complications, worse outcomes, and unplanned readmissions.[2, 6, 8, 9, 14, 15] All three comorbities significantly increased in prevalence from 2002 to 2014 in both the primary and revision TJA groups. The current trends of these comorbidities in the general population suggest that this increase in prevalence can be expected to continue in the near term. Long term trends are uncertain. This has important implications for clinicians and health systems alike. Hospitals are financially incentivized by Medicare, Medicaid and insurance companies to encourage efficient care coordination and reduce hospital readmissions. This database demonstrated a significant increase in known risk factors for complications and unplanned readmissions. In order to provide efficient cost effective care, hospital systems and clinicians need to address these issues pre-operatively via collaborative management with primary care and mental health providers. In the era of bundled care, addressing known risk factors such as obesity, diabetes, and depression in an organized fashion is paramount to prevent poor outcomes and increased costs. Further studies are needed to address specific controllable variables including the influence of hemoglobin A_{1c}, perioperative hyperglycemia, preoperative psychosomatic interventions and evaluations, and obesity interventions.

This study's limitations are related to the dataset and the retrospective nature of the study. As noted above, the diagnosis of obesity is below that of the general population at all time points in this database review, contrary to prior studies.[8, 9] Administrative databases have known issues when coding-based data is utilized, specifically when related to obesity.[16] This is again highlighted in this study, as a relative increase in coding frequency will overestimate the true trend of the variable of interest. At the root of this study is reimbursement, as hospitals and physicians are not reimbursed for an ICD-9 diagnosis of obesity following TJA at the current time. Thus, there is no incentive to properly code this data, and thus the specific proportions reported here are likely underestimates, based only on the coded rates of these comorbidities. Understanding and interpreting retrospective database sets with caution is important in order to draw accurate conclusions.

In summary, this retrospective review demonstrates a total joint arthroplasty population that has an increasing prevalence of obesity, diabetes and depression, in parallel with the general population. The overall United States general population demonstrates increasing prevalence of diabetes, obesity, and depression with trends that do not look to be decreasing in the near future. Understanding these trends and their implications for patient care and outcomes is critical in providing cost effective care.

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Prophylactic Tibial Stem Fixation in the Obese: Comparative Early Results in Primary Total Knee Arthroplasty

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Introduction

Obesity is a risk factor for aseptic loosening after total knee arthroplasty (TKA). The prophylactic use of a tibial stem may enhance proximal tibia fixation in obese patients. Our aim was to review whether a tibial stem extension decreases early rates of failure in obese patients.

Methods

This retrospective cohort study included 178 consecutive primary TKAs (143 patients) with a body mass index (BMI) $\geq$ 35 kg/m^2. Fifty TKAs (42 patients) were performed with the use of a 30mm tibial stem extension, and 128 TKAs (101 patients) were performed with a standard tibial component alone. Patients with two year clinical follow up were included. The primary outcome was revision for aseptic loosening. Secondary outcomes were all-cause revision and radiolucent lines (RLL).

Results

The average follow up was 34 months (range, 24-46 months). No failures for aseptic loosening occurred, and the occurrence of secondary procedures was not significantly different between groups. Quantification of RLL found no difference between groups.

Conclusion

In this small sample size at early follow-up, no difference was measured in revision rates, need for subsequent procedures, or quantity of RLL between groups. While the results call into question the effectiveness of tibial stems in improving tibial fixation in TKA, longer-term data is needed to determine whether the use of tibial stems improves fixation in obese patients.

Funding

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A Computational Modeling Approach to Optimize Cup Coverage and Minimize Impingement Risk using Subject-specific Activities of Daily Living

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Introduction

Total hip arthroplasty (THA) is a highly effective surgery for treating end-stage hip osteoarthritis. However, impingement between the femoral and acetabular components has been linked to poor outcomes, dislocations, and implant failures. Classic work by Lewinnek et al.[1]identified an acetabular cup 'safe zone' as a critical factor for reducing dislocation risk, which has been challenged by recent clinical studies leveraging larger cohorts.[2,3] Activities of daily living associated with THA dislocation vary amongst individuals,[4,5] highlight the need for implant positioning recommendations based on patient-specific motions.

The objective of this study was to establish a simulation framework for optimizing THA acetabular cup positioning based on patient-specific biomechanics. Development of this simulation tool using an open-source musculoskeletal modeling platform for determining implant geometry and surgical placement based on patient-specific motions, provides potential for future technique implementation in the orthopaedic community.

Methods

A healthy-young male (22 years, BMI 20.8) performed activities of daily living that are considered to increase the risk of implant dislocation in total hip arthroplasty patients.[4] Sit to stand motions from low and normal-height chairs, shoe tying, bending at the waist to pick up an object from the floor, and pivoting at the waist, performed ten times each, were measured using a 12-camera motion capture system (Raptor Series, Motion Analysis Corp, Santa Rosa, CA), while ground reaction forces were acquired from three embedded force plates (BP600900, AMTI, Watertown, MA). Written-informed consent was provided in this IRB approved study.

Component impingement and cup coverage were calculated using a musculoskeletal modeling paradigm (Figure 1A).[6] The musculoskeletal model was initially scaled to fit anatomical landmarks of the healthy-young male. Model motions were subsequently calculated to match the experimentally-collected motion data, using an inverse kinematics paradigm. In order

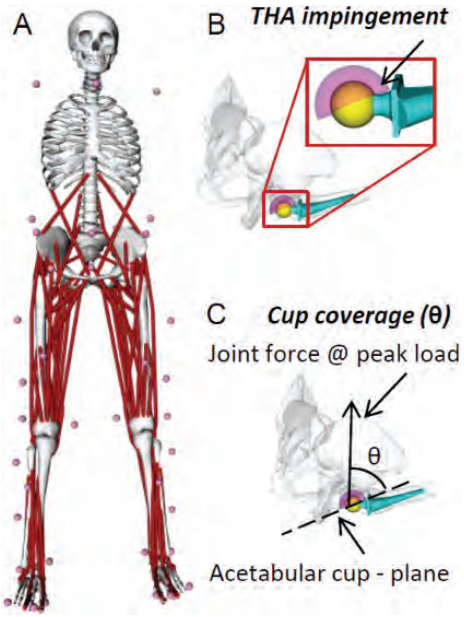

Figure 1. **(A)** Subject-specific anatomy was used to scale a musculoskeletal model that was used to calculate **(B)** THA impingement and **(C)** cup coverage during the high-risk activities performed in this study.

to calculate the joint reaction force magnitude and direction at the hip joint for determination of cup coverage angle, static optimization was performed next. Lastly, an elastic foundation model detected contact between the acetabular cup and femoral neck, providing instances of collision between the two THA components.[7]

The effects of cup positioning on cup coverage and component impingement were tested by simulating all combinations of inclination [20 – 60°] and version [0 – 40°] values in two-degree increments, resulting in a total of 441 possible cup positions. The angle between the joint reaction force and the plane of the cup at peak joint loading (Figure 1B) defined cup coverage for each simulation. Hip impingement was defined to occur in any simulation in which the contact forces between the acetabular cup and femoral components were non-zero (Figure 1C). These analyses were repeated for all ten trials of each of the five high-risk motions. Heat maps were generated for each activity to provide visualization of 1) the cup coverage angle at peak joint load and 2) the odds of movement completion without impingement. The resultant heat maps were further combined

to demonstrate optimal cup positioning based on the observed patient-specific motions.

Results

Component impingement and cup coverage proved sensitive to both cup position and movement type. Activities requiring a large degree of hip flexion are prone to reduced cup coverage and impingement when cup version angles are reduced and inclination is increased (Figure 2). This relationship is more pronounced in component impingement than cup coverage. Pivoting at the waist, which causes external rotation of the THA, produces the opposite effect on cup coverage and component impingement with respects to cup positioning: increased version and decreased inclination appear to be risk factors for suboptimal biomechanics.

Lowest risk of impingement was observed when the cup positioning was between 10 to 30 degrees version and 20 to 40 degrees inclination. Cup coverage was greater than 30 degrees in a small linear-range of cup positions, from 10 degrees version and 20 degrees to 30 degrees and 60 degrees inclination. These two factors were used to establish the patient-specific 'safe zone' that mitigated the risk of poor cup coverage and impingement (Figure 3)

Discussion

A computational modeling framework was developed to identify patient-specific 'safe zone' that is sensitive to both cup positioning and patient-specific motions (Figures 2 and 3). Current efforts are focused on optimizing implant positioning to minimize the amount of loading near the rim of the acetabular cup, which affects both wear and dislocation rates.[8] Motion data from a healthy-young control confirmed that THA cup coverage and component impingement detected using this framework were sensitive to both cup positioning and subject biomechanics. While this specific data set does not have immediate clinical relevance, it has demonstrated a viable simulation framework for surgeons, that could be leveraged to optimize THA cup coverage and minimize impingement in patient populations.

Clinical studies have debated the 'safe zone' for patients with total hip arthroplasty.[1-3] In a series of 300 total hip replacements, nine (3 per cent In addition to studying the implications of cup positioning and patient-specific motions

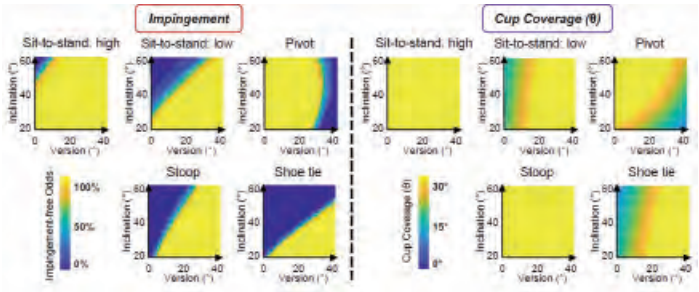

Figure 2. Component impingement cup coverage were established for each 'high-risk' activity throughout a range of cup positions and visualized in heat maps. Cup positions that did not impingement and maintained at least 30 degrees of cup coverage were yellow, while cup positions with impingement events and poor cup coverage were blue.

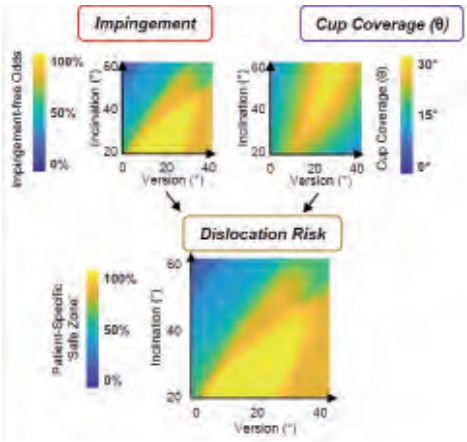

Figure 3. Component impingement and cup coverage heat maps were combined to establish an overall dislocation risk. Cup positions that avoided impingement events and maintained at least 15 degrees of cup coverage were considered to be the patient-specific 'safe zone'.

on cup coverage and impingement, this modeling framework can test a myriad of other factors; varying implant geometry, femoral anatomy and positioning, pelvic bony geometry, and lumbosacral spinal deformities among many others. Linking these surgical and patient factors with cup coverage and impingement may highlight numerous mechanisms of dislocation and implant wear.

Conclusions

Our results that cup coverage and impingement are unlikely to be the drivers of THA dislocations in commonly implanted cup positions—for example, 15 degrees version and 30 degrees inclination—suggest that other patient and surgical factors, such as altered movement patterns or soft-tissue constraints, may be important to consider when discussing total hip arthroplasty.

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Clinically Relevant Knee Motion is Accurately Measured with a Self-calibrated Wearable Sensor

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Introduction

Total knee arthroplasty is an effective treatment for many patients suffering from end-stage osteoarthritis. However, post-operative knee stiffness often leads to flexion contracture deformities that require aggressive therapies and revision surgery. Restoring knee motion within three months following joint replacement surgery mitigates the risk of flexion contracture and poor outcomes[1]. While motion analysis accurately characterizes knee motion, such measurements are financially and logistically impractical for continuously monitoring post-operative patient progress. Recently, our group developed a wearable sensor paradigm that utilizes a low-cost motion sensor and magnet to quantify knee angle during activity[2].The purpose of this study is to develop a self-calibration procedure that (1) is simple to perform, (2) generates accurate knee flexion data, and (3) does not require any external measurements.

Methods

Seven healthy young adults (4 males, 3 females; 26 ± 4 years; BMI 23.8 ± 3.7) participated in this IRB approved study. Subjects wore standard lab attire, a low-cost wearable sensor on the knee, and retro-reflective markers. The wearable sensor[2] was based on a strong earth magnet and a 9-degree- of-freedom motion sensor (LSM9DS0, FLORA 9-DOF, Adafruit) that was secured on the distal-lateral thigh and the proximal-lateral shank of the right leg, respectively, with fabric-backed tape and self-adhesive wrap. The wearable sensor was calibrated from a series of five static knee poses between 0 and 90 degrees knee flexion while the subject sat on a treatment table (Fix 1A).A 3rd order polynomial was fit to the pitch of the shank with respect to gravity—calculated via the accelerometer—and the magnetic field strength captured throughout this calibration motion (Figure Y). Subjects then performed clinically relevant motions—seated knee extension and sit to stand—and walked on a treadmill at three different speeds (0.9, 1.2, and 1.5 m/s) and up a 10% grade (1.2 m/s). Motion capture and wearable sensor data were synchronously collected and cross-correlations and peak knee angles were calculated for all trials.

Results

Peak knee extension values during the seated-knee extension exercises were accurate within 5 degrees across all subjects (p = 0.29, RMS Error: 2.6 degrees). Peak knee extension measurements were less accurate during the sit to stand exercises, consistently under-approximating extension values (p = 0.48; RMS Error: 16.6 degrees). Peak knee flexion during both of these movements reached sensor saturation at approximately 65 degrees knee flexion (Figure 1B). Knee angles during walking strongly correlated with motion capture measurements ($0.84 \leq rxy \leq 0.99$). Despite these strong similarities in waveform pattern, the wearable sensor showed an RMS Error of 10.3 degrees peak knee flexion when considering all walking conditions. Walking faster and up an incline generated smaller errors (p = 0.47; RMS Errors: 7.9 and 7.4 degrees, respectively) compared to

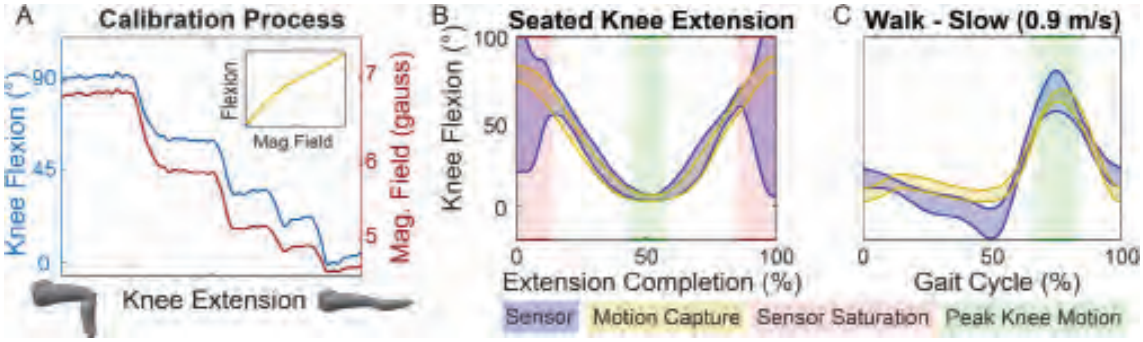

Figure 1. (A) Knee flexion and magnetic field strength are taken at 5 points and used to develop a 3rd order polynomial (inset) **(B)** Knee flexion measured by the device and motion capture throughout a seated knee extension exercise, green highlights show when peak knee extension occurs, red highlights show where sensor saturation produced non-real angle predictions by the sensor **(C)** Knee flexion plotted across a gait cycle from heel strike to heel strike, the sensor predicts a similar waveform as motion capture but exact values are much less accurate due to soft tissue artifact.

walking at slow and medium speeds generated ($p = 0.64$; RMS Errors: 12.8 and 13.2 degrees, respectively) compared to motion capture.

Discussion

This study presents a new calibration paradigm that accurately measures clinically relevant joint motions using a single low-cost sensor. Our results support the feasibility of this sensor paradigm for measuring knee extension during clinical exams. However, more functional motions—for example, walking and rising from a chair—appear to be affected by soft tissue artifact [3] and produce less accurate predictions of knee angle. Many of the issues caused by soft tissue artifact could be lessened by integrating the device into a brace and reducing its overall size, but a major limitation of the device lies in the nature of magnetic fields: the farther a magnet is from the sensor, the smaller the changes in magnetic field strength will be with respect to distance. This means that calibrating for accurate measurements at full extension will make measurements at deep flexion more prone to saturation errors. While this study focused on measuring knee motion, this paradigm can be adapted to work with other planar joints such as the elbow or ankle. Monitoring knee motion using a low-cost sensor provides new opportunities for clinicians to monitor patient progress and function outside of clinical visits, especially during the first three months following joint replacement when restoring motion is the most critical [1]. Current work is focused on developing educational material and a smartphone app to monitor patient knee motion during in-home rehabilitation protocols.

Significance

Knee extension can be accurately measured within 5 degrees using a low-cost and self-calibrating sensor, which may be used to identify patients at risk of developing knee flexion contractures.

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Tips & Tricks: The Scandinavian Total Ankle Replacement (STAR): Design Evolution and Clinical Results

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Introduction

Total ankle replacement (TAR) was introduced for end-stage arthritis of ankle in the 1970s. The Scandinavian Total Ankle Replacement (STAR, Waldemar Link, Germany) was originally designed in 1978 by Hakon Kofoed as a two-component, anatomic, fixed bearing, unconstrained resurfacing ankle prosthesis covering the medial and lateral facet joints. The 12-year survival rate for this prosthesis in terms of retention of both components was quoted at 70%[1, 2]. Most other first-generation ankle replacement designs had less successful outcomes[2-8]. Bolton-Maggs et al[6] reported at 5 year follow up of 41 ankle arthroplasties that 13 of them had been removed and converted to arthrodesis. Kitaoka et al[5] reported on the Mayo total ankle arthroplasty and observed a 42% survival rate at ten years. The first generation of TAR were a two-component design with a concave polyethylene tibial component and a convex metal talar component. Constrained and unconstrained designs were available, with constrained designs most often failing due to increased stress at the implant-bone interface leading to loosening. Unconstrained designs suffered instability due to increased stresses on the surrounding soft tissues[9]. The failure of some early prosthesis designs were also attributed to aggressive bony resections, improper balancing of the prosthesis and soft-tissue envelopes and non-congruent designs[10].

To aid in decreasing rotational stresses seen with a two-component design, the STAR was modified to a three-component design with a mobile-bearing polyethylene (PE) meniscus in the late 80's. The purpose of the PE meniscus between the tibial and talar components is to allow only compressive forces at the implant-bone interface and to avoid rotational stresses. This review will focus on the current implant design, fixation strategies and outcome data present in the literature.

Implant Design

The ankle joint is made up by the articulation of the tibia, talus and fibula. It is a highly congruent, reported as high as 96% during the arc of motion[2, 11], joint with nearly cylindrical motion between the talus and tibia[12]. The STAR prosthesis is a 3-part press-fit design. Notably, it is the only design which is approved for press-fit fixation by the FDA in the United States. The STAR incorporates a flat tibial component which is wider anteriorly. It carries two parallel bars on the superior surface which are inserted into solid subchondral bone during implant impaction. Holes for these bars are created with a drill and punch system[13]. Importantly, there is a stop on the drill system to prevent perforation of the posterior cortex of the distal tibia, therefore limiting communication between the ankle joint and distal tibia. This, along with proper sizing to match the tibial cortical surfaces, prevents joint fluid under high hydrostatic pressure from leeching into the distal tibia and causing cyst formation[14-16], leading to possible implant failure and need for revision[17-23]. Additionally, after impaction of the final tibial implant, the anterior drill holes are filled with bone graft to prevent this same complication.

The talus cap component is anatomically shaped with wings to replace the medial and lateral facets. A superior flat talar bony resection is made along with anterior and posterior chamfer resections with multiple cutting guides to accommodate the prosthesis. There is a crest along the dome of the prosthesis which corresponds to a groove on the PE insert. The talus component has a longitudinal stem on its undersurface for fixation into a groove created on the talus with a drill and punch[13].

The PE insert is square shaped and congruent with both the tibial and talar components. The groove on the undersurface limits rotation on the talus component, however it is free to rotate on the tibial component. The PE meniscus is made from ultra-high molecular weight PE and comes in different heights from 6-10 millimeters(mm).

The tibial and talus components are made of cobalt-chromium alloy and are available in different sizes (5 tibial sizes, 4 talar sizes), which are interchangeable. The talus component is available in right and left[13].

Evolution of STAR Implant Design

There have been four generations of the STAR to date. The first design by Kofoed was a two-component, fixed bearing cemented prosthesis (Figure 1). It consisted of a polyethylene tibial component and a cobalt chrome (CoCr) talar component. In 1986 the STAR was converted

Figure 1. First-generation fixed bearing cemented prosthesis. *Gilbert et al. 2016*[24]

from a two-component device to a Second Generation three-component mobile bearing device (Figure 2). This included CoCr tibial and talar components with a PE meniscus in between. Kofoed reported a 70% survival rate at 12 years with both of these devices[1, 2]. The Third Generation device was introduced in 1989 and implemented a hydroxyapatite (HA) coating over smooth CoCr and use cementless fixation. This is also referred to as the single-coated prosthesis. Kofoed reported a 95.4% survival rate 12-year survivorship of the third generation prosthesis. The base coating of the STAR was changed in 1998 to a rough Titanium (Fourth Generation Ti) plasma spray (Figure 3), and one year later a calcium phosphate coating was added on top of the titanium plasma spray (Fourth Generation Ti + CaP)[24]. The latter is also referred to as the double-coated prosthesis. It is important to note when reviewing the literature that only the Fourth Generation Ti is available in North America, while the Fourth Generation Ti + CaP is used in the European literature.

Clinical Outcomes

Early short-term outcome studies on total ankle arthroplasty showed encouraging results[25-28], however medium and long-

Figure 2. Second-generation mobile bearing cemented prosthesis. *Gilbert et al. 2016*[24]

Figure 3. Fourth-generation uncemented Ti plasma spray prosthesis. *Gilbert et al. 2016*[24]

term results revealed significant complications, including ankle pain, painful malleolar impingement, tibial component loosening and talar component subsidence[6, 8, 28-31]. The major factors implicated in loosening were highly constrained or incongruent designs, high soft tissue stress and aggressive bony resections with cement fixation[32]. The STAR implant was designed as a cementless, three component device that implements low constraint. Early medium term studies showed promising results, and more recently there has been 10-to-20-year data published.

European Data

Kofoed et al.[2] reported on 58 patients undergoing either cementless (HA coated) or cemented STAR with mean follow up 9.4 years. There were significantly higher failures in the cemented (9/33) over the cementless (1/25) group. Twelve-year survival rate for the cemented prosthesis was 70% while the cementless group showed a 95% survival rate.

Brunner et al.[22] reported on 77 third generation STAR with average follow up 12.4 years. The primary outcome was revision of one or both of the metallic components. They reported a survivorship of 70.7% at 10 years and 45.6% at 14 years. The main reasons for revision were aseptic loosening, subsidence of the talar component and progressive cyst formation. There were also 11 PE fractures.

Wood et al.[33] conducted a reported on 100 STAR Forth Generation Ti+CaP. At an average follow-up of 54 months there were only 4 failures; two patients required PE exchange due to PE fracture, one patient was converted to fusion due to early infection, and one patient was converted to fusion for aseptic loosening.

Henricson et al.[34] reported on 10-year follow up of uncemented 3-component TAR from the Swedish Ankle Register. In this study they analyzed data on both the third generation single-coat and fourth generation double-coat prosthesis. They found a lower rate of all-cause revision for the double-coat compared to the single-coat; 49 of 205 versus 56 of 117, respectively. Henricson and Carlsson[35] conducted a follow-up study of the Swedish Ankle Register. They reported a 53% revision rate at 14 years for the single-coated prosthesis

and a 36% revision rate at 12 years for the double-coated prosthesis.

More recently, Frigg et al.[36] reported on 50 STAR procedures over a ten year period by one surgeon. The primary endpoint was exchange of the whole prosthesis or conversion to arthrodesis. They reported a 94% survival rate at ten years and a 91% survival rate at nineteen years. There were both single and double-coated prostheses used in this study and they mentioned that the coating did not influence the outcomes, however they did not provide a breakdown of results by prosthesis.

North American Data

Daniels et al.[37] looked at 111 consecutive STAR over a four year period and reported a 29% revision rate at 9 years, although the survival rate of the metallic components was 88%. Twenty (18%) of the patients underwent PE bearing exchange, with the majority being for PE fracture. The combined rate of metal and PE bearing revision was greater for the first twenty ankles (38%) compared with the subsequent ankles (24%).

Haytmanek et al.[38] reported on 79 ankles undergoing TAR with fourth generation Ti done over a 9 year period. At average follow-up of 8 years they observed a metallic component survival of 89.9%. They reported that 27.8% of the patients required revision of at least one component, with 63.6% of them requiring PE exchange only.

Mann et al.[39] reported a 91% metallic component survival rate at 10 years of the fourth generation Ti component, and a follow-up study with 15 year follow up reported a 73% survival rate[40]. Jastifer and Coughlin[41] reported a 94.4% implant survival rate at 12.6 years in 18 patients.

Summary

End-stage ankle osteoarthritis is a debilitating condition with substantial impact on quality of life. Main surgical treatment options are arthrodesis or joint replacement. Total ankle replacement offers patients a motion sparing option, however its success has not been to the same level as total hip or total knee arthroplasty[36]. Early implant designs showed high rate of failure due to high constraint, creating increased rotation stresses at the impant-bone interface. The STAR implant is a three-component implant with a tibial and talar metal component with a PE bearing surface in between. This design allows a small degree of rotational freedom, thereby reducing the stress at the metal-bone interface. Overall, North American clinical results with the STAR show high intermediate and long-term survival rates, with ten-year survival rates as high as 95%, although other studies continue to show lower rates of survival . While the long term survival rate of the STAR prosthesis are reported as high, patients should be aware that their chance for reoperation is also high, most often due to aseptic loosening of the prosthesis.

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Chronic Nicotine Exposure Alters Tendon Vascularity and Viscoelasticity

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Introduction

Tendon injuries are common and lead to significant disability. Smoking is a modifiable risk factor that has numerous adverse health effects, including association with tendon injuries. However, the effect of nicotine and smoking on tendon morphology and function is not well understood.[1] Therefore, the purpose of this study was to investigate the effect of chronic nicotine exposure on Achilles tendon (AT) and supraspinatus tendon (SS) structural and mechanical properties in a rat model. We hypothesized that chronic nicotine exposure would lead to tendinopathic changes as evidenced by altered tendon vascularity, tenocyte and extra-cellular matrix histology consistent with degeneration, and diminished mechanical properties.

Methods

Study Design

Twenty male Sprague-Dawley rats (398±16g) were randomly allocated to groups exposed to either 0.9% saline (n=10) or 36mg/mL of nicotine (n=10) at a rate of 2.5 µL/hr through osmotic pumps for 12 weeks before being euthanized (IACUC approved). Timing for nicotine exposure was based on previous experiments and the nicotine concentration was based on the average tobacco user in the United States (14 cigarettes per day).[2,3] Serum levels of cotinine, the predominant metabolite of nicotine, was measured every 4 weeks with an enzyme-linked immunosorbent assay at 450 nm to monitor the systemic release of nicotine. Osmotic pumps were exchanged after measurement of serum cotinine levels. In vivo assays: At 12 weeks, AT was imaged with contrast enhanced ultrasound (CE-US) to assess for vascularity (n=4/group). CE-US of AT was visualized in B-mode in the sagittal plane with a 21MHz center frequency ultrasound transducer and then video data was converted into echo-power data (linearization). Perfusion parameters were derived from this model including peak enhancement, rise time, time to peak, wash-in rate, wash-in area under the curve, and wash-in perfusion index as described.[4]

Ex vivo assays

Bilateral AT and SS were then harvested for ex vivo histologic structural (n=5/group) and biomechanical analysis (n=8-10/group) as described.[5,6] Briefly, stain lines were used to track optical strain and cross-sectional area was measured using a custom laser device. Tensile testing was performed as follows: preload to 0.08 N, preconditioning (10 cycles of 0.1-0.5 N at a rate of 1% strain/s), stress relaxation at 5% strain for 600 seconds, and ramp to failure at 0.1% strain/s for AT and 0.3% strain/s for SS.

Analysis

Statistical analysis was performed using Student's t-tests and Mann- Whitney U tests to compare parametric and non-parametric variables respectively. Significance was set at $p<0.05$ and trends at $p<0.1$.

Results

AT CE-US demonstrated an increase in contrast wash-in rate and trend to decrease in rise time and time to peak in the nicotine group compared to the saline group, indicating an increase in tissue perfusion rate (Fig 1.). No differences were found in the other amplitude-based CE-US measures.

Nicotine did not alter AT or SS histologic parameters (Figure 2). AT percent relaxation, a measure of tendon viscoelasticity, was significantly increased with nicotine exposure compared to saline (Figure 3a). Similarly, SS percent relaxation had an increased trend with nicotine exposure compared to the saline group (Figure 3b). No differences in maximum load, maximum stress, stiffness, or modulus were observed with nicotine exposure in either AT or SS (n=6-10/group). DISCUSSION: After chronic nicotine exposure at a clinically relevant dose modeling the average US smoker, AT perfusion rate increased and both AT and SS viscoelasticity were altered in this rat model. In a previous clinical study, CE-US detected a significant increase in vascularity in tendinopathic AT when compared to healthy human patients.[7] Furthermore, nicotine has been shown to have pro-angiogenic effects that may represent a compensatory mechanism for nicotine's vasoconstricting effect.[8] In our study, the changes in AT vascularity may suggest early tendinopathic changes to the tendon's structure following chronic nicotine exposure. Despite the changes in vascularity, we did not detect structural changes in cell shape

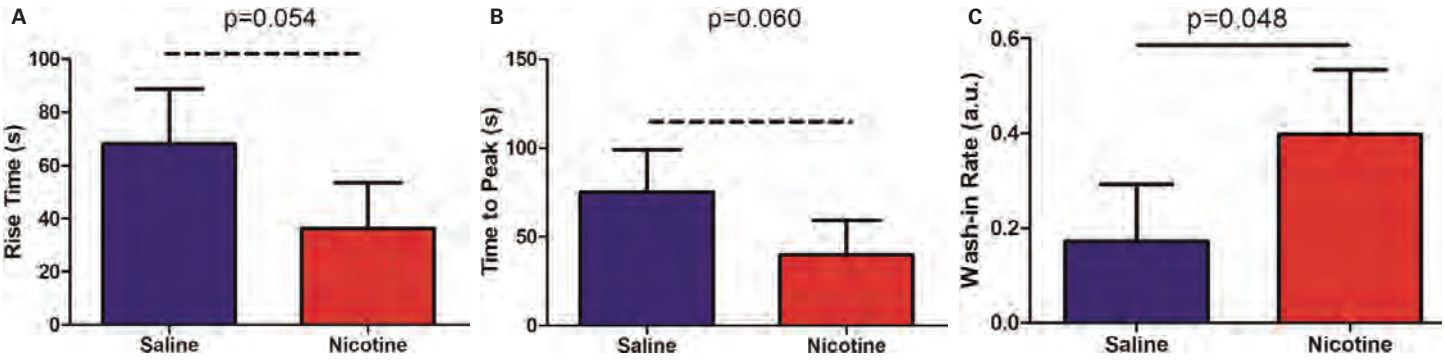

Figure 1. CE-US results of AT. **(A)** Rise Time **(B)** Time to Peak **(C)** Wash-in Rate. Graphs represent mean +/− standard deviation, solid lines denote statistical significance ($p<0.05$), and dashed lines denote trends ($p<0.01$).

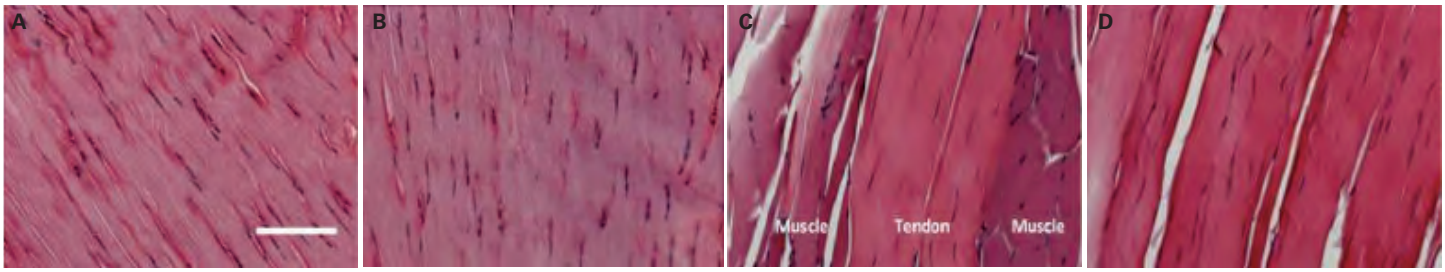

Figure 2. Representative H&E images of saline exposed and nicotine exposed AT **(A,B)** and SS **(C,D)** respectively. All images are at 200x magnification with scale bar representing 100mm. (no scale bar)

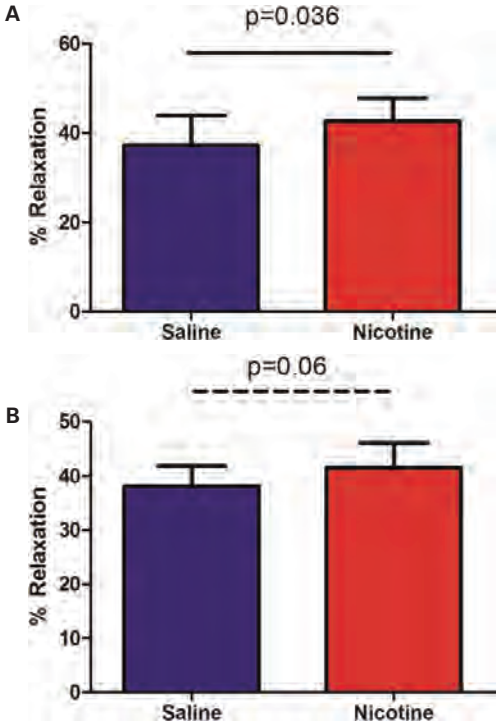

Figure 3. (A) % Relaxation of AT **(B)** % Relaxation of SS. Graphs denote mean +/− standard deviation, solid lines denote statistical significance ($p<0.05$), and dashed lines denote trends ($p<0.01$).

or density. A previous study of porcine tenocytes exposed to nicotine found that alterations in matrix metalloproteinase (MMP) expression were dependent upon exposure to cyclic stretch.[9] Throughout our study, animals were housed in cages and thus were not exposed to a high level of repetitive stimuli. Nicotine exposed tendons also had an increase in percent relaxation, a viscoelastic property, similar to changes seen in fibrotic tendon tissue post-injury. The addition of exercise or overuse as a physical stimulus to these nicotine exposed animals may manifest more dramatic changes to the tendon structure and composition. Further studies are also needed to assess the effect of nicotine dose on tendon properties and on healing of injured tissue.

Significance

Chronic nicotine exposure alters tendon vascularity and viscoelasticity, which may predispose tendons to degeneration and injury.

Acknowledgements

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Effect of Pulsed Electromagnetic Field Therapy on Healing in a Rat Achilles Tendon Partial Tear Model

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Introduction

Partial tears of the Achilles tendon are relatively common and are typically treated conservatively[1]. To this end, a variety of nonoperative, noninvasive therapies exist for the treatment of these tears. It has been previously shown that Pulsed Electromagnetic Field (PEMF) therapy improves supraspinatus tendon-to-bone healing as well as full-thickness Achilles tendon healing in rat models[2, 3]. However, the effects of an FDA- approved PEMF therapy (Physio-Stim®, Orthofix Inc., Lewisville, TX, USA) on in vivo joint function and ex vivo tendon fatigue properties after a partial Achilles injury remain unknown. Therefore, the objective of this study was to quantify the effects of this FDA-approved PEMF therapy on joint and tendon level properties after a partial width, full thickness injury. We hypothesized that PEMF treatment would improve Achilles tendon healing compared to a non- PEMF group.

Methods

This IACUC-approved study consisted of 160 adult male Sprague-Dawley rats. Anesthetized with isoflurane, 144 animals underwent a unilateral, full thickness, partial width (1.5mm) Achilles tendon injury. All animals were cast immobilized in plantarflexion for 1 week following injury. These animals were then placed into 3 groups (n=48/group): 1 group received no PEMF treatment (NP) while the other 2 groups received 1 and 3 hours of PEMF treatment daily (Physio-Stim®, 1HP and 3HP, respectively). The final 16 rats were not injured, received no PEMF treatment, and were sacrificed at 3 weeks, following 1 week of initial cast immobilization. PEMF treatment was administered systemically via custom modules surrounding the rat cages. At 2, 3, and 6 weeks post injury, animals were evaluated for ankle joint function using a joint range of motion measuring device[4]. Ambulatory measurements were collected at 3 and 6 weeks post injury using an instrumented walkway[5]. Animals were sacrificed at 1, 3, or 6 weeks. For histology, the injured Achilles tendon and gastrocnemius/soleus muscle complex was dissected at time of sacrifice (n=6 per group). Specimens were sectioned and stained with hematoxylin and eosin and graded for cellularity and cell shape[2]. Circular standard deviation was measured to ascertain collagen alignment. For mechanical testing, the Achilles tendon and foot complex were dissected at time of sacrifice (n=10 per group) 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[6]. For all outcome measures, the two treatment groups (1HP and 3HP) were compared to the control (NP) group at each time point using two-tailed, Student t-tests after checking for normality. Bonferroni post-hoc corrections were applied to account for multiple comparisons.

Results

Joint Range of Motion: After 6 weeks, both PEMF treatment groups exhibited decreased joint range of motion compared to the NP group (Fig 1A). *Ambulatory Assessment:* No differences were observed between the PEMF treatment groups and the NP group at any time point (not shown). *Histology:* Decreased cellularity was observed in the 1HP group 3 weeks post injury compared to the NP control group (not shown). *Mechanical Testing:* At 3 weeks post injury, 1HP specimens exhibited increased stiffness and modulus compared to the NP tendons making them behave more like the uninjured control tendons (Fig 1B, Fig 1C). At 1 week post injury, 3HP tendons demonstrated the same increases (Fig 1B, Fig 1C). During fatigue testing, the 1 week, 3HP tendons and 3 week, 1HP tendons survived more cycles than the NP controls (Fig 2A). Throughout the fatigue life, 1 week, 3HP tendons and 3 week, 1HP tendons exhibited increased stiffness compared to NP tendons (not shown). At 6 weeks after injury, 3HP tendons exhibited decreased laxity and decreased peak strain compared to NP tendons (Fig 2B). Finally, K2, a measure of how quickly tendons exhibit increased strain during fatigue testing, was decreased in the 3HP tendons 6 weeks post-injury (not shown).

Discussion

The aim of this study was to determine the effects of non-invasive PEMF treatment on rat

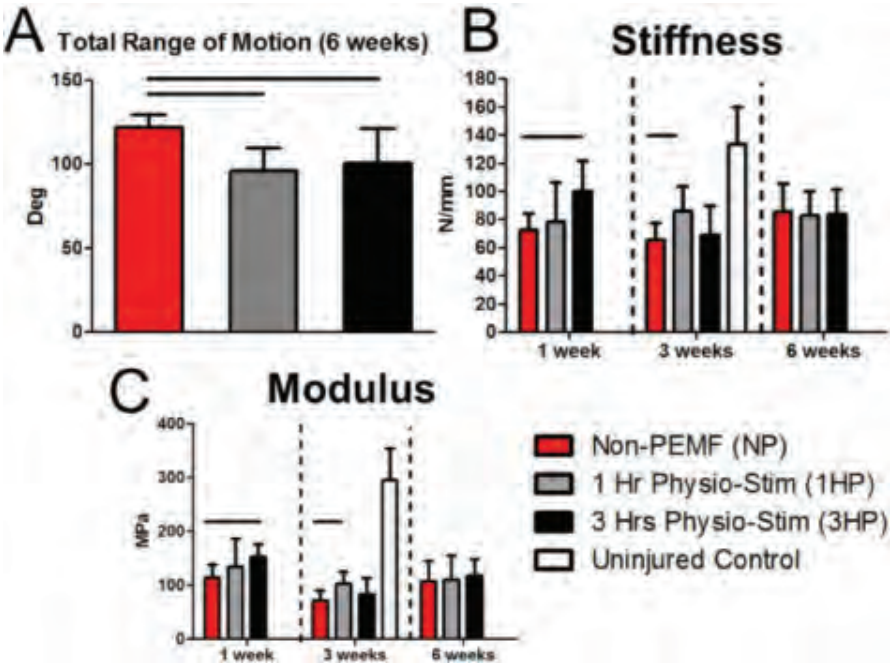

Figure 1. (A) Total ankle joint range of motion was decreased in PEMF treated animals compared to non-PEMF animals at 6 weeks. **(B)** Stiffness during mechanical testing was increased in 1 week, 3HP tendons and 3 week, 1HP tendons. **(C)** Modulus was increased in 1 week 3 HP tendons and 3 week, 1 HP tendons. Data are mean + SD. Markers indicate $p < 0.025$.

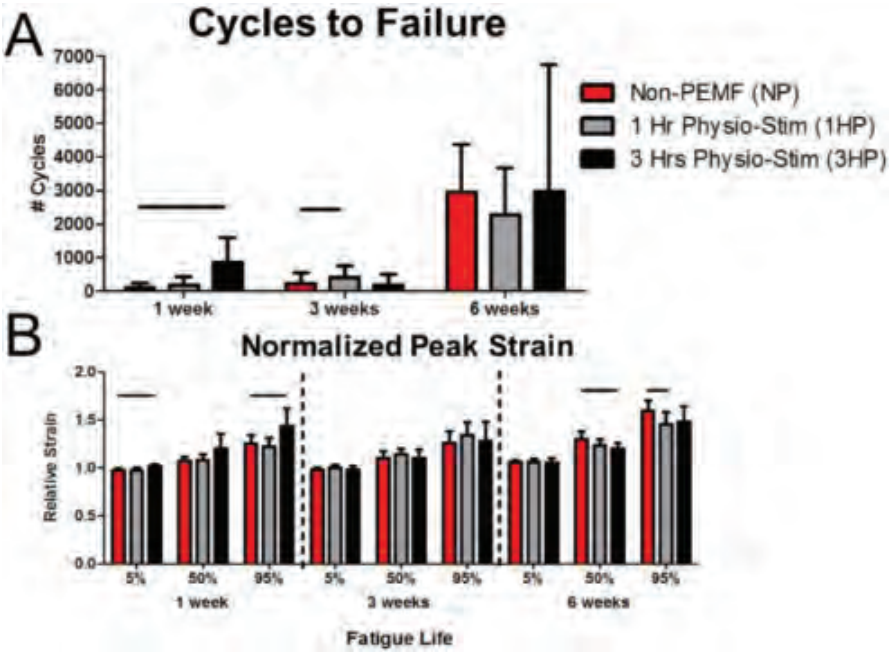

Figure 2. (A) Cycles to failure were increased in 1 week, 3HP tendons and 3 week, 1 HP tendons than non-PEMF control tendons at the same respective time points. **(B)** Normalized peak strain was increased in 3 HP tendons at 1 week compared to non-PEMF tendons. At 6 weeks, both PEMF treatment groups resulted in decreased strain. Data are mean + SD. Markers indicate $p < 0.025$.

Achilles tendons following partial tendon injury. We hypothesized that PEMF treatment would result in improved healing compared to control tendons. Although no differences in joint function were observed via ambulatory assessment, PEMF-treated joints exhibited decreased range of motion 6 weeks post injury. This observation was corroborated by the findings of decreased peak strain and increased K2 in the 6 week tendons during mechanical testing. In general, PEMF-treated tendons exhibited increased stiffness and decreased laxity during this fatigue protocol. It is unclear if this increase in both tendon and joint level stiffness is beneficial for healing. However, uninjured control tendons exhibit greater stiffness than the PEMF tendons at 3 weeks post injury suggesting that this increased stiffness may be beneficial (Fig 1B). Ultimately, while no change was detected in several measured parameters, it appears that PEMF treatment may aide in early tendon healing following partial width, full thickness Achilles injury in rats. Additional study is underway to understand the role of immobilization in tendon properties in this model. Further study may be necessary to understand the long-term effect of the decreased ankle joint range of motion and decreased tendon strain observed at our final time point.

Significance

This study shows that early tendon healing in a rat model may be improved by the use of PEMF treatment. This study is the first to investigate this nonoperative, noninvasive therapy to accelerate tendon healing in an Achilles tendon partial tear model.

Acknowledgements

Funding was provided by Orthofix, Inc. The authors wish to thank Stephanie Weiss, Mengcun Chen, and Daniel Gittings for their assistance with surgical procedures and Jasmine Wang for assistance with data processing.

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Modulation of Vascular Response after Injury in the Rat Achilles Tendon Alters Healing Capacity

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Introduction

Although vascular ingrowth is necessary for tendon healing, hypervascularization following tendon injury is not always considered beneficial[1] as, for example, degenerated tendons are also highly vascularized. We demonstrated that delivery of VEGF and anti-VEGF antibody locally to tendons can increase and decrease the vascular response after injury, respectively[2]. However, the effect of altering the vascular response after healing in the tendon is unknown. Therefore, the objective of this study was to define the alterations to tendon healing following injection of angiogenic factors. We hypothesize that reducing the vascular response will result in reduced scar tissue formation and reduced failure properties while increasing the vascular response will result in the opposite. Further, we hypothesize that in vivo gait and joint functional measures will not be significantly impacted by vascularity changes.

Methods

Study Design: 90 Fischer 344 rats (4 months old, IACUC approved) underwent a bilateral Achilles incisional injury, followed by local injections of vascular endothelial growth factor (VEGF) (Peprotech), anti-VEGF antibody (B20.4-1-1, Genentech), or saline (SAL). In vivo functional measures and ultrasound imaging were performed, and animals were sacrificed at 7, 14, and 28 days after injury. *Injury:* A 1.5mm incisional injury in the Achilles tendon mid-substance was created without repair. *Injections:* On days 4-6 after surgery, each animal received either 5μg VEGF or 250μg anti-VEGF antibody (B20) in 20μl saline, or 20μl saline only, injected bilaterally intratendinously. *Imaging:* Imaging was performed on days 7, 14, 21, and 28 (n=12/group) after injury using a Vevo LAZR ultrasound system (MS550D and MS250 transducers, VisualSonics). Animals were anesthetized and positioned with the transducer parallel to the tendon long axis. For contrast-enhanced ultrasound imaging, a 200 sec ultrasound clip was initiated at the start of a bolus injection of 100μl Definity (Lantheus Medical Imaging) microbubble contrast agent. The echo-power vs. time data was fit to a perfusion model[3]. Color Doppler images were taken to quantify percent area of signal and blood flow velocity measures[4]. Photoacoustic images were taken at wavelengths of 750 and 850 nm based on the absorption spectrum of oxygenated and deoxygenated hemoglobin, respectively[5]. *In Vivo Measures:* Gait, passive ankle joint range of motion (ROM), and stiffness measures were evaluated on days 7, 10, and 14 (n=12/group). *Histology:* Tendon sections from 7, 14, and 28 days after injury (n=6/group) were stained with hematoxylin-eosin (H&E) and graded for cell shape (1=spindle to 3=round) and cellularity (1=less cells to 3=more cells), and stained for CD34 and graded for vessel density (1=less to 4=more dense) and vessel size (1=small to 4=large diameter). *Mechanics:* Tendons from 14 and 28 days after injury (n=12/group) were prepared for tensile testing with preconditioning, stress-relaxation, frequency sweeps at 0.1, 1, 5, and 10 Hz, and a ramp to failure at 0.1% strain/sec. *Statistics:* Ultrasound, mechanical, and functional measures were analyzed using Student's t-tests, and histology analyzed using Mann-Whitney t- tests, all with Bonferroni corrections. Significance was set at $p<0.05$ and trends at $p<0.1$, and all comparisons were made to saline control.

Results

Ultrasound: The B20 group demonstrated a decrease in contrast peak enhancement, wash-in rate, and wash-in perfusion index at day 14. When evaluating only the injury area, this group also had a decreased wash-in area under the curve at day 14 and decreased rise time at day 28 (Fig1A,B). The VEGF group showed no changes when evaluating the whole tendon, but an increase in rise time (Fig1A) at days 7 and 14 and a decrease in wash-in rate at day 7 in the injury region. There was a decrease in the Doppler mean color level at day 14 (Fig1C), corresponding to blood flow velocity, but an increase at day 21 in this group. Similarly, there was a decrease in Doppler fractional area (Fig1D) and color weighted fractional area in the B20 group in both the whole tendon and at the injury site at 7 and 14 days, but an increase in these properties at day 21 in the whole tendon. Finally, mean color level and fractional area increased in the VEGF group in the whole tendon at day 21 (Fig1C,D). Photoacoustics imaging (data not shown) revealed an increase in blood oxygenation in the B20 group at day

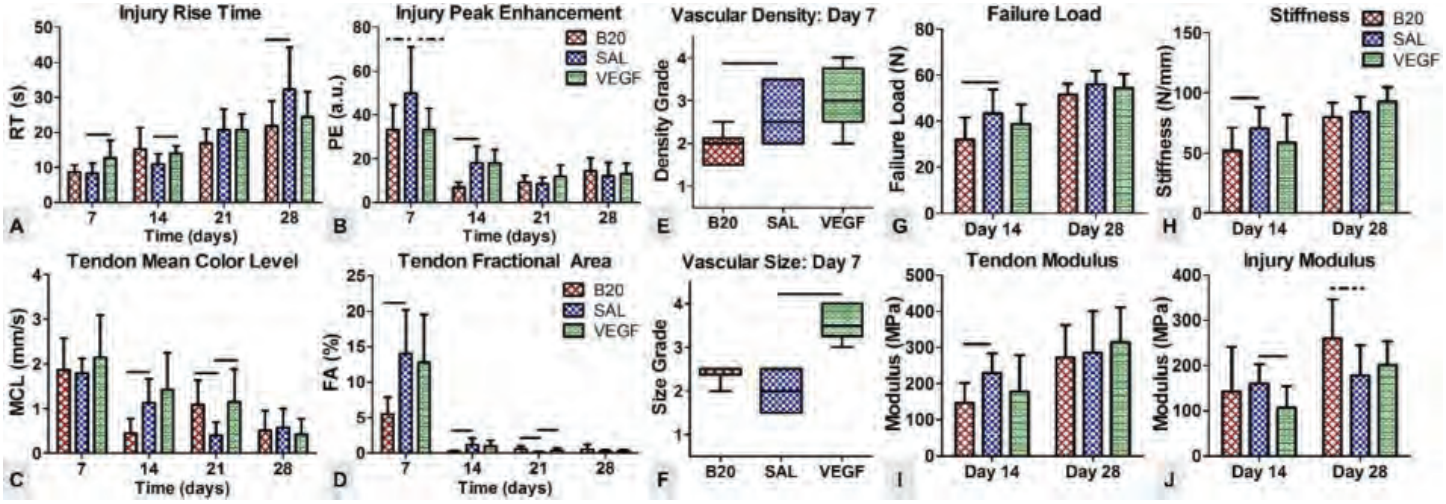

Figure 1: Contrast-enhanced ultrasound showing **(A)** rise time increased with VEGF and **(B)** peak enhancement decreased with B20. Doppler ultrasound **(C)** mean color level and **(D)** fractional area. Histological measures of CD34 showing **(E)** decreased vascular density with B20 and increased vascular size with VEGF. Mechanical measures of **(G)** failure load, **(H)** stiffness, **(I)** tendon modulus, and **(J)** injury modulus showing overall changes at early time points.

21. There was an increase in tendon tissue oxygenation level at day 28 in the B20 group, but no other differences. *In Vivo Measures:* There were no changes in the passive joint stiffness, range of motion, or gait analyses between groups (data not shown). *Histology:* CD34 staining for vascular endothelial cells demonstrated a decrease in vascular density in the B20 group at days 7 (Fig1E) and 14. Additionally, there was an increase in vascular size in the VEGF group at day 7 (Fig1F). There were no significant changes in H&E histology. *Mechanics:* The B20 group demonstrated a decrease in failure load (Fig1G), max stress, stiffness (Fig1H), and tendon modulus (Fig1I) at day 14. The VEGF group had decreased modulus at the site of injury (Fig1J) and % relaxation, but no changes in tendon quasi-static properties. There were no differences in cross-sectional area, dynamic modulus, or Tan(δ) in either group. At day 28 after injury, there were no differences for either group in any parameter compared to saline.

Discussion

Alterations in vascular response after injury impacted healing outcome in the rat Achilles tendon. Decreases in all ultrasound measures of vascularity with the delivery of the anti-VEGF antibody were supported by a decrease in histological measures of vessel density at early time points. The decrease in vascularity caused a reduction in mechanical properties 14 days after injury. However, all negative mechanical changes returned to control levels by day 28. Additionally, tissue oxygenation, as well as the Doppler fractional area and blood flow velocity, were increased in this group at late time points, which could explain the improvements in mechanics. Surprisingly, we found only mild changes in our ultrasound and mechanics data with the delivery of VEGF. We found an increase in vessel size, but no change in vessel density from our histology. While we previously demonstrated that VEGF increased the vascular response after injury, these smaller changes could be due to the use of younger animals, potentially with an already robust vascular response to injury. It is also possible that our ultrasound measures are more sensitive to changes in vessel density than vessel size. Ongoing work includes implementing these vascular modifications on aged animals, which could yield larger changes in the case of VEGF delivery.

Significance

A decrease in vascular response after injury reduced mechanical outcome in early healing, which recovered over time. Future studies will evaluate the effect of vascular modulation after injury with aging to potentially determine therapeutics for improved tendon healing in this population.

Acknowledgements

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Achilles Tendon Structure in Distance Runners does not Change Following a Competitive Season

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Introduction

Achilles tendinopathy is a painful degeneration of the tendon that is ten-times more common in running athletes compared to age-matched peers.[1] Tendon loads in excess of twelve body weights are cyclically applied during running, which may be the driving factor in tendinopathy development in these athletes.[2] However, the progression of asymptomatic and symptomatic tendinopathies is not well understood.[3] Structural changes associated with symptomatic tendinopathy such as decreased collagen alignment—or 'organization'—and increased tendon thickness have both been reported in athletic populations. Previous work by our group has demonstrated that competitive collegiate distance runners have thicker and less organized tendons than their recreationally active peers even in the absence of signs or symptoms of tendinopathy.[4] Similarly, hypertrophy of the Achilles tendon has been observed in elite and recreational athletes[5,6] indicating a relationship between structural differences and the cyclic loading experienced during running.

These differences in tendon structure have been linked to decreased mechanical properties in both humans[7] and small animals[8] in response to tendinopathy and acute injury, respectively. In contrast, the mechanical properties of healthy endurance runners' tendons have been shown to be similar to non-runners[9] despite being structurally different. Our prior work has demonstrated that trained runners have structurally different tendon prior to the rigors of a competitive running season. However, it is unclear how tendon structure in highly-trained runners changes in response to prolonged bouts of training.

Therefore, the aim of this study was to prospectively quantify Achilles tendon structure of competitive distance runners at the beginning and completion of a cross country season. We hypothesized that, in the absence of injury, there would be no significant changes in tendon thickness, organization, or echogenicity for a runner with a habituated tendon. Should signs or symptoms of tendinopathy develop, there should be detectable changes in thickness, organization, and echogenicity as a result. Understanding how a tendon responds to the continued demands of high risk activities such as running is crucial to understanding how tendon disorders progress.

Methods

Nineteen collegiate cross country runners (9 females; Age: 19 ± 1.5 years; Height: 172 ± 7 cm; Weight: 60.4 ± 8 kg) provided written consent in this IRB approved study. All participants had no signs or symptoms of Achilles tendinopathy before or after participation. Subjects were seen a week prior to and a week following competing in a Division I NCAA Cross Country season. Each study visit consisted of a self-reported assessment of tendon health and a quantitative ultrasound assessment. Subjects were asked to fill out a clinical outcome questionnaire (VISA-A)[10] to determine the level of health and function. The structure of the tendon was determined by measuring the level of organization present in its collagen fascicles through ultrasonography.

Longitudinal B-mode ultrasound images of the of the mid-substance of the right Achilles tendon were acquired while subjects lay prone on a treatment table with ankles placed in the resting position off the end of the table. Images were acquired using an 18 MHz transducer (L18-10L30H-4, SmartUs, TELEMED) with a scanning width of 3 cm (scan parameters: Dynamic Range: 72dB; frequency: 18 MHz; gain: 47 dB). Collagen organization was quantified in the ultrasound images using custom-written software.[11] This image processing algorithm is a computational analog to crossed polarizer imaging, which assesses collagen fascicle alignment and quantifies tendon 'organization' as the circular standard deviation (CSD) of these collagen structures and has been shown to be reliable in Achilles tendon.[12] These images were also used to quantify the longitudinal thickness and mean echogenicity of the tendon.

Tendon organization, thickness, and echogenicity as well as VISA-A scores were compared between the two study visits using two-way paired t-tests. Additionally, effect sizes were determined for any differences found to be statistically significant ($P < 0.05$). Effect sizes were reported using Cohen's d, calculated as the mean difference divided by the pooled standard deviation.[13]

Table 1. Mean and standard deviation values for VISA-A as well as tendon thickness, organization, and mean echogenicity for measurement sessions 1 and 2 are shown. The percent changes between these measurements is also reported as well as their statistical significance. Thickness was found to increase significantly but the effect size of this increase was small.

	Session I (Mean ± STD)	Session II (Mean ± STD)	Percent Change	Significance
VISA-A (out of 100)	93 ± 8.1	94 ± 6.9	1%	$P > 0.05$
Thickness (cm)	0.54 ± 0.1	0.56 ± 0.1	7%	$P < 0.05$
Organization (CSD)	9.4 ± 0.7	9.2 ± 0.4	2.50%	$P > 0.05$
Mean Echogenicity (%)	14 ± 3.5	15 ± 5.8	4.50%	$P > 0.05$

Results

Achilles tendon symptoms did not develop in any of the runners, which were confirmed by no change in VISA-A scores between the pre- and post-season sessions ($P > 0.1$, Table 1). Similarly, tendon organization and echogenicity did not change over the course of the competitive season between the two sessions ($P > 0.05$, Table 1). Tendon thickness increased by 7% ($P < 0.001$, Table 1) but the effect size of this change was small ($d = 0.36$).

Discussion

We confirmed our hypothesis that competitive distance runners have Achilles tendon structure that is habituated to prolonged cyclic loading and does not change over a competitive season. These findings agree with previous work that showed that collegiate distance runners do not undergo Achilles tendon hypertrophy throughout a competitive season.[14] This habituated tendon appears to be a protective adaptation, allowing trained runners to cyclically load their tendons without injury. Mechanically, the thicker-habituated tendon should undergo the same amount of strain observed in a naïve tendon at lower levels of stress. This would result in similar maximal ankle torque generation potential while decreasing the impact of the rapid loading experienced during distance running.

The processes by which tendon remodels from a naïve to a habituated—and from a healthy to a pathologic state—are still not well understood. Exercise has been shown to increase levels of collagen synthesis in humans[15,16] but the effects of this increase has not been directly linked to tendon remodeling. Additionally, different types of running demands appear to have different effects on tendon remodeling. Sprinters, for example, have stiffer Achilles tendons than distance runners and non-runners, (9) though these findings have not been linked to tendon structure. As a result, there is a need to link the structural differences of habituated tendon with function to better understand the remodeling process and to elucidate the mechanisms that drive pathology.

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Tips & Tricks: Local Anesthetic Techniques for the Hand

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There are several techniques for providing anesthesia for hand procedures. While systemic administration of general anesthesia has long been the gold standard and a reliable option, it can lead to derangements of other organ systems. Regional and local anesthetic techniques are preferred for the management of upper extremity conditions[1]. Local anesthesia is especially well-suited for use in the emergency department setting for the management of acute hand injuries or infections as well as in the operating room setting for minor operations. Although regional anesthesia is typically administered by a trained anesthesiologist, local anesthetics can be administered by the surgeon.

Advantages of local anesthesia include less time spent during recovery, improved pain control, lower opiate consumption, less postoperative nausea and vomiting, and lower costs[1, 2]. There are few absolute contraindications, which include patient refusal or active infection at the needle insertion site. Relative contraindications include the need for assessing postoperative nerve status or compartment syndrome and use in anticoagulated patients.

Choice of anesthetic:

Lidocaine and bupivacaine are the two most common local anesthetics used. The effects of lidocaine typically lasts 1.5-3 hours in duration, while bupivacaine is longer acting and can last from 3-10 hours making it preferable for operations lasting more than 2.5-3 hours (Table 1). It is important to note the pain block provided by bupivacaine lasts about half as long (10 hours) as the return to normal sensation (20 hours) so it is worthwhile to inform patients pain sensation will return much sooner than numbness will resolve. With lidocaine, pain and sensation return simultaneously[3].

Epinephrine in the finger:

Epinephrine use for the finger and hand is now regarded to be safe when there is minimal concern for digital ischemia[4, 5]. The typical dose is 1mg (1:100,000) in 10 mL of 1% lidocaine. The maximal time to vasoconstriction after injection has been shown to occur 25 minutes after injection[6]. It is recommended that waiting approximately 30 minutes before incision will provide maximal hemostasis; thus, patients should ideally be blocked in the preoperative area prior to entering the operating room theatre.

Wide awake local anesthesia no tourniquet technique (WALANT)

WALANT uses a combination of a local anesthetic such as lidocaine or bupivacaine and epinephrine to induce anesthesia and hemostasis in the area of the surgical procedure. The primary advantage is to avoid the use of a tourniquet subsequently reducing patient discomfort and avoiding the risk nerve and skin injury from the tourniquet. Intravenous access for sedation is typically not required as pain from tourniquet is obsolete and preoperative testing is typically not required. There is a high patient satisfaction and recovery is quick, with more >90% patients stating they would choose this anesthetic option again[7].

Specific intraoperative use for WALANT includes tendon transfers to allow for appropriate tensioning and observation of the tendon transfer in action before definitive fixation. Soft tissue releases for trigger finger and De Quervain tenosynovitis can be confirmed intraoperatively with active motion. Flexor and extensor tendon repair can be immediately visualized to ensure that the tendon glides appropriately. Patient education and rehabilitation can begin immediately after surgery because active total motion is observed in the operating room[7].

Authors preferred method:

- For standard procedures with MAC anesthesia, we typically use 5 mL of 1% lidocaine and 5 mL of 0.5% bupivacaine in a 10 mL syringe.

Table 1. Duration and maximal doses of common anesthetics used for hand procedures

Anesthetic	Duration of Effect	Maximal Dose
Lidocaine	1.5-3 hours	7 mg/kg (50 mL in 150 lbs. patient)
Bupivacaine	3-10 hours	2.5 mg/kg (20 mL in 150 lbs. patient)

- For local procedures without tourniquet, we utilize 1% lidocaine with 1:100,000 epinephrine.

Tips for administration

There are certain techniques that can be used to diminish pain during administration. We recommend use of a 27-gauge needle or smaller. Buffering the solution of lidocaine also helps relieve the burning sensation during administration. 1% with 1:100,000 epinephrine has a pH 4.2. Adding a 1:20 ratio of 8.4% sodium bicarbonate to lidocaine 1% with 1:100,000 epinephrine has a more physiologic pH 7.4 and will lead to less pain when administering[8]. Warming the solution also decreases pain at the injection site.

Choosing the correct angle for needle insertion is critical. Needles oriented at 90 degrees to the skin are shown to be significantly less painful than those with needles oriented at 45 degrees[8]. Injecting the solution under the dermis (subdermal) produces less pain than intradermal injections. There should always be at least 5 mm of firm palpable local anesthesia in the skin ahead of the needle tip so the needle tip never penetrates an area that is not anesthetized except for the first poke of the first needle penetration. Injecting slowly also allows the lidocaine to work ahead of the needle tip.

Types of Local Blocks

Median nerve wrist block

Anesthetic is injected between the palmaris longus and flexor carpi radialis (FCR) tendons. The needle is inserted at the level of the proximal wrist crease (Figure 1). The needle is advanced through the flexor retinaculum at a depth of approximately 1 cm and 5 mL of local anesthetic is injected. Injecting 1 mL of local anesthetic above the retinaculum as the needle is withdrawn can block the superficial palmar branch supplying the skin over the thenar eminence.

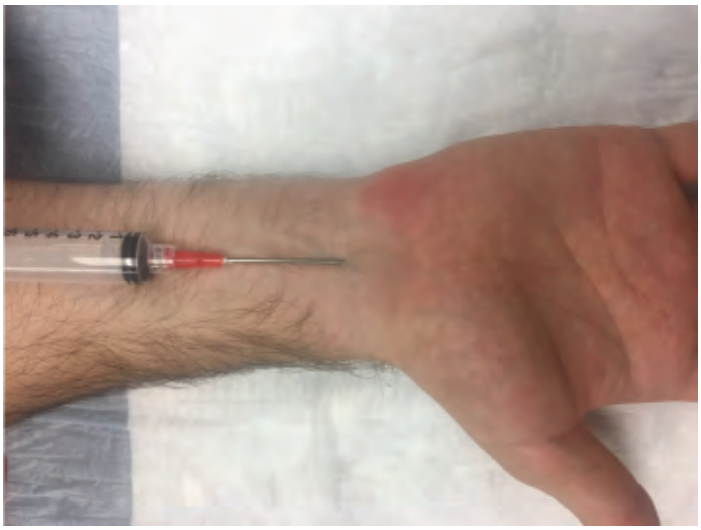

Figure 1. Median nerve block being performed with needle entry ulnar to the FCR tendon at the level of the distal wrist crease.

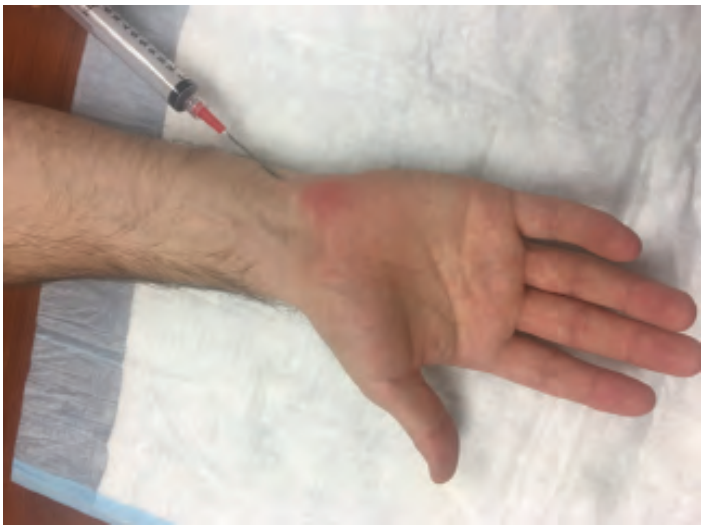

Figure 2. Ulnar nerve block being performed with needle entry ulnar to the FCU tendon at the level of the distal ulna.

Ulnar nerve wrist block

Anesthetic is injected on either the radial or ulnar side of the flexor carpi ulnaris (FCU) tendon. The ulnar approach is preferred so as to avoid intravascular injection, given the location of the ulnar artery on the radial side of the tendon. At the level of the distal ulna, the needle is introduced on the dorsal ulnar side of the FCU (Figure 2). 5 mL of local anesthetic is injected under the FCU**.** Additional subcutaneous infiltration of the dorsal ulnar area of the wrist ensures adequate blockade of the dorsal cutaneous branch of the ulnar nerve.

Radial nerve wrist block

The radial nerve is superficial and divided into branches running in the subcutaneous fat at the level of the radial styloid. 5-10 mL of local anesthetic is injected in a subcutaneous field block at the level of the radial styloid. Initial injection is made using 2-3 mL of local anesthetic just lateral to the radial artery at the level of the proximal wrist crease. Needle can then be redirected and advanced with subcutaneous injection across the proximal border of the snuffbox to the midpoint of the dorsal wrist.

Digital nerve block

There are three main approaches for performing a digital nerve block—transthecal, transmetacarpal, and subcutaneous. The transthecal digital nerve block uses the flexor tendon sheath for anesthetic infusion. While effective, we recommend against this technique as it may lead to rupture of sheath and continued pain along the tendon sheath[9]. A subcutaneous block is typically preferred and accomplished with injection just distal to the distal palmar crease. The needle is inserted superficially and perpendicular to the direction of the digit (Figure 3). A wheal is created superficial to the flexor tendon sheath using 1-2 mL to block the volar digital nerve as they enter the digit. This process is repeated on the dorsal aspect of the hand. It is unnecessary to guide the needle toward the web space as this can lead to iatrogenic nerve penetration. A

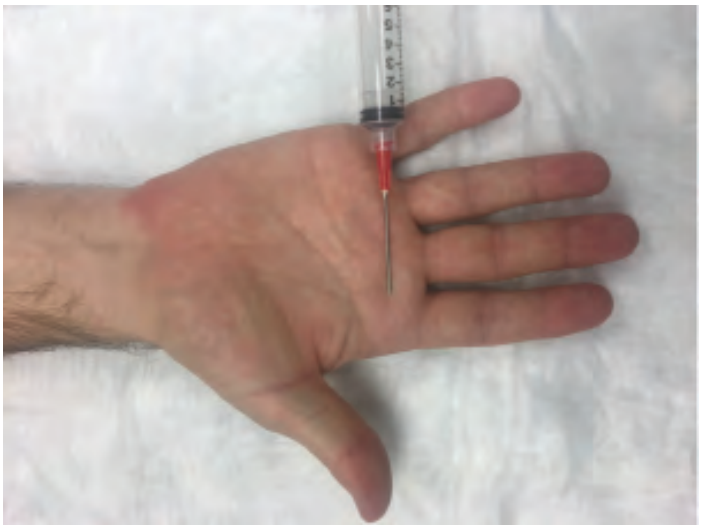

Figure 3. Index finger digital nerve block being performed with a subcutaneous technique showing needle entry superficial to the flexor tendon sheath.

circumferential ring block along the base of the digit is also not recommended because the subsequent pressure can result in gangrene. An additional option includes the transmetacarpal digital nerve block, which is accomplished at the level of the distal palmar crease with the injection site being 1 cm proximal to the MCP joint on the volar aspect of the hand. 2 mL are injected on either side of the metacarpal neck to block the common digital nerve.

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CT Scans Oriented Along the Longitudinal Scaphoid Axis Do Not Change Surgical Management of Scaphoid Fractures

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Introduction

It is imperative that the correct patients with scaphoid fractures to offer surgery to be identified, as some scaphoid fractures can be managed non-operatively.[1] CT scans can be useful because they allow surgeons to make precise measurements. For example, CT scans can be used to measure whether >1mm of displacement is present, which is often a surgical indcation.[2,3] CT scans are more accurate than plain radiographs in determining the degree of fracture displacement[4,5]but operative treatment is being offered with greater frequency to active patients as an approach to reduce the period of cast immobilization. Computed tomography is more useful for evaluating displacement than standard radiography. Displaced fractures are at greater risk for nonunion and malunion-both of which have been associated with the development of radiocarpal arthritis in long-term studies–and should therefore be treated operatively. Surgical treatment is also recommended for complex fractures (open fractures, perilunate fracture-dislocations, and scaphoid fractures associated with fracture of the distal radius and can also be used to make more specialized measurements such as height-to-length ratios and intra-scaphoid angles[3,6]

Reformatting CT scans along the long axis of the scaphoid improves the detection of scaphoid fractures.[7] However, it is unclear whether these reformats affect the clinical decision to perform open reduction internal fixation (ORIF). Our null hypothesis was that assessing scaphoid fractures in the longitudinal scaphoid axis would not lead to different surgical recommendations than those from those made from the wrist axis.

Methods

After obtaining IRB-approval, we retrospectively identified 30 patients using an online database (Montage Healthcare Solutions, Nuance Communications Inc.) of radiology reports with acute scaphoid fractures. All enrolled patients were identified from one institution. All identified CT scans were removed of patient identifiers. Each CT scan was then re-formatted along the longitudinal axis of the scaphoid using the TeraRecon™ software system. These reformats were then compared against the wrist axis CT scans.

The anonymized scaphoid axis and wrist axis CT scans were evaluated by two musculoskeletal radiologists and two board certified orthopedic hand surgeons. Each specialist independently read the CT scans in a random, blinded fashion. On each CT scan, the following measurements were made: fracture gap, displacement of articular surface, intrascaphoid angle, and height-to-length ratio.[8,9] To assess our null hypothesis, each scaphoid CT was assigned a designation of "Requires Surgery" if any one of the following cutoffs was met: fracture gap >1mm, articular displacement >1mm, intrascaphoid angle >35, or height-to-length ratio >0.65.[9,10] The determination of surgery based on wrist versus scaphoid axes was then compared using McNemar's test and a p value was calculated.

Results

87% of the fractures evaluated resulted in the same surgical recommendations on both the scaphoid and wrist axis, while 13% resulted in discordant surgical recommendations. To determine whether these differences were statistically significant, the McNemar's test was used. A two-tailed p value of 0.21 was obtained, demonstrating no statistical significance.

Discussion

We failed to reject our null hypothesis that reformatting CT scans along the scaphoid axis would lead to different surgical recommendations. We used very specific cutoffs to determine which patients would be offered surgery and we acknowledge that not all hand surgeons would ascribe to these exact parameters. However, demonstrating that measurements of scaphoid fracture displacement and deformity do not differ depending on CT formatting is important. While exact cutoffs for individual surgeons may differ, our study indicates that the measurements are not affected.

There are several limitations to this study. Chief among these limitations is that we analyzed only thirty scaphoid fractures, which makes our study prone to a type II error, especially given that no differences were found.

Additionally, making the above measurements of displacement and deformity are also subject to variability based on the clinician making the

Table 1. Surgical Assignments Based on Wrist and Scaphoid Axes for all Fractures

	Requires Surgery based on Wrist Axis	Does not Require Surgery based on Wrist Axis
Requires Surgery based on Scaphoid Axis	103 (86%)	5 (4%)
Does not Require Surgery based on Scaphoid Axis	11 (9%)	1 (1%)

measurements and which specific CT slice they choose. More studies are needed to determine the best technique or CT slice for making these measurements.

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The Porcine Accessory Carpal as a Model for Biologic Joint Replacement for Trapeziometacarpal Osteoarthritis

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Introduction

Trapeziometacarpal (TMC) osteoarthritis (OA) is one of the most common conditions affecting middle and older aged adults[1]. Given that the opposable thumb is central to all activities of daily living, loss of function has a significant impact on quality of life. Patients with TMC OA are initially managed with activity modification, non-steroidal anti-inflammatory drugs, splinting, and occasionally corticosteroid injections[2]. These conservative treatments often fail in the long term, and many patients will eventually require surgical intervention. However, most of these procedures are destructive, involving removal of all or part of the trapezium, and replacement with tendon, fascia, or an artificial substrate or 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 this study, we explored the porcine accessory carpal (AC) bone as a model for TMC OA, with the goal of using this to evaluate a tissue-engineered biologic joint replacement.

Methods

The forelimbs of skeletally mature Yucatan minipigs under general anesthesia were imaged with a portable 8-slice CT scanner (CereTom, Neurologica). DICOM files were exported and opened in ITK-SNAP[5], where the bones were individually segmented. Using this information, a 3D model was generated in OpenSim, and the relative motion of the AC and normal and shear contact forces were evaluated through a range of flexion angles. Next, five AC bones were isolated from the right forelimbs of adult Yucatan minipigs from an unrelated study. A custom indentation testing setup was used to evaluate cartilage mechanics along the midline of the AC articular surface via stress relaxation tests. The saddle-shaped articular cartilage surface was indented with a 2 mm diameter spherical indenter in three locations (superior, middle, and inferior). Four compressive ramps (10% strain each) were applied, with a 600s relaxation between each step. The equilibrium modulus was calculated from the second step. Samples were then fixed in formalin and imaged via μCT (VivaCT 75, Scanco medical), before and after immersion in Lugol's solution (5% I2, 10% KI in water) to enhance cartilage contrast. DICOMs from the initial scan were imported into ITK-SNAP and the bone was segmented. 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 in order to compute the bone volume and surface features. Scans post Lugol's treatment were manually registered with the bone scan and processed similarly, with the cartilage layer segmented in a semi-automated manner. Cartilage thickness was determined across the 3D object with a grid spacing of 1.25 mm. After imaging, samples were decalcified, processed into paraffin, sectioned, and stained with Safranin O and fast green to visualize cartilage, bone, and fibrous tissue. Statistical analysis was by one-way ANOVA with Tukey's posthoc testing, and Pearson correlation of animal weight against cartilage volume and surface area.

Results

The cartilage surface of the pig AC consists of a main saddle-shape that articulates with the ulnar carpal bone and a secondary facet that interacts with the ulna (Fig 1A-B). The remainder of the bone is embedded in fibrous tissue (Fig 1F). When the unloaded hoof extends, this fibrous tissue sheath goes into tension and causes the AC to articulate slightly distally, resulting in estimated contact forces in the range of 138N compression and 21N shear (Fig 1C). Across five donors, the AC had the same basic shape and geometry, but showed a high degree of inter-subject variation in both shape (Fig 2) and in size (Fig 3B). AC volume (Pearson $r = -0.1065$) did not correlate with animal weight, while cartilage surface area was negatively correlated (Pearson $r = -0.6507$). The average thickness of the AC articular cartilage ranged from 310-420 microns within the contour of the main articulating surface. There was a trend towards greater thickness on the superior and

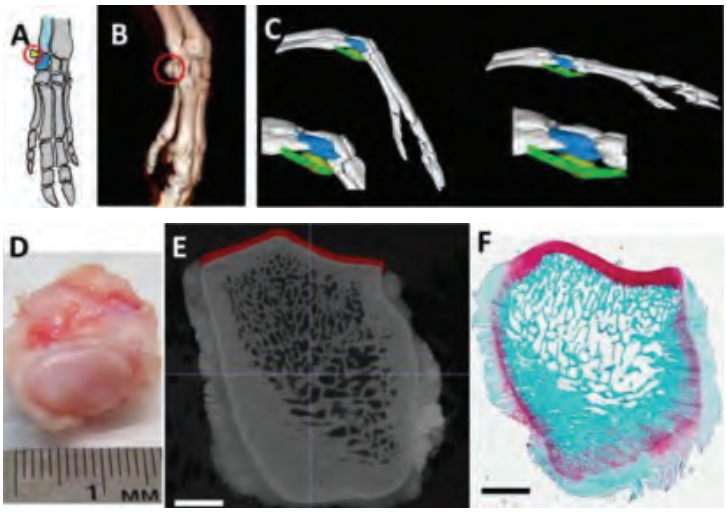

Figure 1. (A) Position of the AC (yellow) with respect to the ulnar carpal (blue) and ulna (light blue); **(B)** CT visualization with the AC identified (red circle); **(C)** OpenSim model showing position of the AC (yellow) relative to the ulnar carpal (blue) in flexion (left) and extension (right); **(D)** Gross view of cartilage surface of the AC; **(E)** μCT slice in ITK-SNAP showing segmented cartilage in red. Scale = 3mm; **(F)** Safranin O/Fast Green stained section of AC. Scale = 3mm.

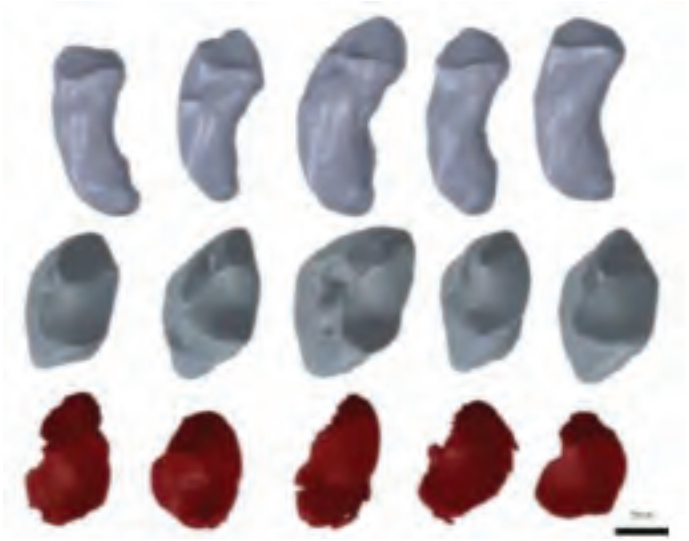

Figure 2. Solidworks models of five AC bones and the corresponding cartilage surfaces (in red). Scale = 5mm.

middle regions compared to the inferior region (Fig 3A). Interestingly, there was more variation in the size and shape of the cartilage surface than there was in the thickness. The equilibrium modulus in the superior, middle, and inferior regions was 1.17 +/− 0.20, 1.63 +/− 0.16, and 1.54 +/− 0.12 MPa, respectively (Fig 3C), with the superior region trending softer than the middle and inferior regions (p=0.14).

Discussion

We evaluated the geometric, histologic, and mechanical properties of the accessory carpal bone and cartilage in a Yucatan minipig model. This bone and articulating surface bears anatomic similarities to the human TMC in terms of its saddle-shaped cartilage surface as well as its load bearing function. While there was variation in geometry between subjects, several trends emerged. Specifically, the superior aspect was thicker and softer, while the inferior aspect was thinner and stiffer. These data provide benchmarks for the generation of anatomic models and living engineered replacements for the AC cartilage and bone[4]. The consistency in cartilage thickness suggests that CT rendering, using a clinical scanner, may provide sufficient resolution for implant generation, a priori, without the need for high resolution scanning of isolated tissue. This will enable ex vivo production and maturation of engineered constructs on an individualized basis. Having established these principles, future studies will focus on the creation of anatomic molds to create engineered bone coupled to an engineered articular cartilage surface. Ultimately, these engineered osteochondral units will be used for biologic joint resurfacing of the AC in a large animal model, advancing the state of the art in the treatment of TMC osteoarthritis

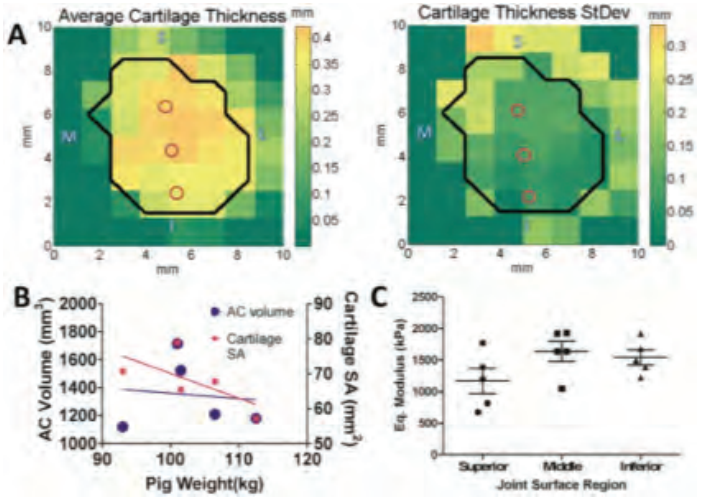

Figure 3. (A) Average (left) and standard deviation (right) thickness maps of the main articulating surface overlaid on top of a profile indicating the average cartilage perimeter (black line). Indentation test location indicated by red circles; **(B)** Correlation analysis of animal weight and cartilage volume and surface area; **(C)** Equilibrium modulus at three locations along the midline of the AC articular cartilage. N = 5, p = 0.14.

Significance

This study defined the anatomic and mechanical features of the porcine AC bone and cartilage, a first step in the development of a large animal model to rigorously evaluate biologic resurfacing strategies for the treatment of TMC osteoarthritis.

Acknowledgements

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Tips & Tricks: Determinant and Indeterminate Lesions: When is Biopsy Necessary?

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Case 1

A 23 year old female patient presents with a 5cm x 5cm painful mass in her posterior calf after a collision playing college soccer. It is diagnosed as a resolving hematoma by clinical examination only. She followed up several months later with a persistent soft tissue mass that had slowly increased in size. She then had an excisional biopsy of the lesion through a transverse incision without wide margins. The pathology results were consistent with a myxoid liposarcoma. There was extensive ecchymosis noted after the surgery, so it is presumed that the wound bed and surrounding area is likely contaminated with residual tumor cells.

Presentation

Although approximately 99% of soft tissue masses are benign (Papp 2007), misdiagnosis of a malignant lesion can lead to potential loss of limb or life. A high suspicion and algorithmic approach must be used to prevent a delay in diagnosis that may affect survival. A patient's history is not enough to confirm the diagnosis in many cases and may be misleading. Many lesions are identified after a traumatic event, although only about half of soft tissue sarcomas are painful (Papp 2007). Additionally, slow growing lesions may be benign, however many malignant lesions are slow growing as well, such as synovial sarcoma. Advanced imaging is required when there is any question of the diagnosis on clinical examination.

Imaging

XR can be helpful in a small number of soft tissue sarcomas. For example, 30% of synovial sarcomas demonstrate intralesional calcifications. However MRI with and without contrast is the gold standard for workup of soft tissue masses. Determinant lesions are those that can be diagnosed definitively based on MRI characteristics and do not need a biopsy for confirmation. Indeterminate lesions require a biopsy for diagnosis. All soft tissue sarcomas are indeterminate lesions. Examples of determinant and indeterminate lesions are demonstrated in Table 1.

Biopsy

A biopsy is required for all indeterminate lesions. In a core needle biopsy, a large bore needle is inserted into the mass and multiple samples are obtained for pathology. Core needle biopsy is the most common method of establishing a diagnosis of indeterminate soft tissue masses. It creates a small tract that may or may not be excised if the definitive pathology is malignant. In general, if an indeterminate soft tissue mass is to be biopsied, it should be ideally done in coordination with the treating orthopaedic oncologist. An open incisional biopsy can be performed if the core needle biopsy fails to obtain adequate tissue or a diagnosis. In this case, a longitudinal biopsy tract is designed that will be excised at the time of definitive resection if malignant. In the case of an incisional biopsy, hemostasis is critical as any local hematoma is considered contaminated.

An excisional biopsy should not be performed for indeterminate lesions. The local recurrence rate is over four times higher in patients after unplanned excisions of sarcomas compared with patients who underwent a planned excision (Potter 2008). Re-resection for residual disease and additional therapy is often needed after unplanned excision of a sarcoma. Additionally, patients with unplanned excisions often require

Table 1: Determinant vs. Indeterminate lesions

Determinant Lesion	Indeterminate Lesion
Heterotopic Ossification	Benign solitary fibrous tumor
Lipoma	Intramuscular myxoma
Ganglion cyst	Giant cell tumor of tendon sheath
Hemangioma	Soft tissue sarcoma (Figure 2: C-D)
Neurofibroma	
Muscle tear	
PVNS	

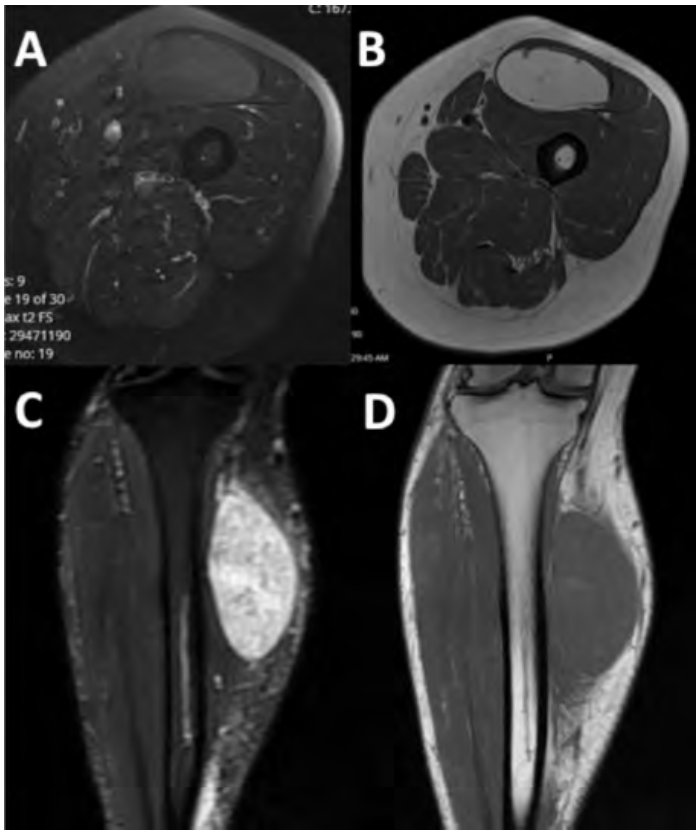

Figure 1. A: Axial T2 FS and B: Axial T1 of intramuscular lipoma in anterior thigh. Note homogenious structure that is isointense to fat on both T1 and T2 FS sequences. Compare to C: Coronal STIR and D. Coronal T1 of myxoid liposarcoma in posteromedial calf. Note heterogeneous consistency isointense to adjacent muscle on T1 imaging (images courtesy of Kristy Weber).

more extensive soft tissue reconstruction in the setting of limb salvage surgery (Potter 2008). Although long-term outcomes appear similar in patients with unplanned excisions, it is with potentially greater morbidity to the patient as more extensive therapy and reconstruction are often needed (Smolle 2017).

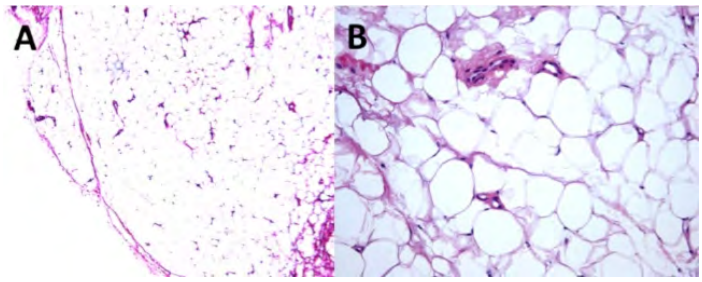

Figure 2. A: Low and B: High power H&E staining of lipoma. Note that sample is comprised almost entirely of fat cells (histology courtesy of Kristy Weber).

Case 2

A 40 male presents with a well-defined soft tissue mass on the dorsal aspect of his forearm. It has enlarged over the last 3 years and was evaluated for possible excision. Although soft and compressible, an MRI was obtained that demonstrates an intramuscular mass with features isointense to subcutaneous fat on all sequences (Figure 1: A-B). There are no septations or nodularity. A diagnosis of a lipomatous lesion is made and the patient proceeds with an excisional biopsy without complications. The final pathology confirms the diagnosis of a simple intramuscular lipoma (Figure 2).

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Tips & Tricks: Atraumatic Foot Drop, A Case Report of an Intraneural Peroneal Ganglion Cyst

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Introduction

Intraneural ganglion cysts are mucinous, fluid-filled formations that collect within the epineurium of peripheral nerves.[1] These cysts have been reported in peripheral nerves of the upper and lower extremity, but most frequently occur within the common peroneal nerve. [2,3] Accumulation of cystic fluid within the nerve can cause direct pressure leading to a compressive neuropathy presenting with motor or sensory deficits, most notably a foot drop, or with pain about a palpable mass.[4-6]

Intraneural ganglion cysts in the lower extremity are rare, particularly in the pediatric population.[5] With prompt diagnosis and surgical decompression of the nerve and cystic fluid, prognosis is good with near full recovery of motor strength reported in all cases. However, intraneural ganglion cysts can also be difficult to diagnose as they can be overlooked or misdiagnosed on imaging. Here, we report a case of a rapidly progressive atraumatic foot drop in a 13 year old boy who was initially diagnosed with a nerve sheath tumor based on MRI imaging, but intraoperatively was found to have an intraneural ganglion cyst of the common peroneal nerve.

Case Report

History

The patient presented to clinic at the age of 13 with approximately four months of left leg and ankle pain. He played football as a lineman and reported pain worse with activities such as running The pain had been preceded by paraesthesias in the left foot, however he did not seek medical evaluation at that time. One month prior his clinic visit, he was participating in a football game when he suddenly developed an atraumatic foot drop in his left foot. He was pulled from the game and evaluated by the team's athletic trainer. He was then referred to physical therapy and completed two sessions, however there was a concern for peroneal nerve dysfunction and was referred for orthopeadic evaluation.

Examination

On exam, he had a palpable, cord-like, and non-compressible mass proximal to the fibular head extending to the popliteal fossa with associated tenderness. There was no erythema or concomitant swelling. There was full range of motion at the knee without pain. On motor examination, he had profound weakness in foot dorsiflexion and eversion with 1out of 5 strength in the tibialis anterior (TA), extensor hallucis longus (EHL), extensor digitorum longus (EDL), and peroneal muscles. He exhibited full muscle strength in gastrocnemius-soleus complex, flexor hallucis longus, flexor digitorum longus, and posterior tibialis muscles. He had decreased sensation in the peroneal distribution to the first webspace and dorsal foot. Tibial and saphenous nerve distributions intact. There was no clonus or hyperreflexia.

Imaging

Given the palpable mass, neurologic deficit, and normal xrays, he underwent MRI examination of the left lower extremity including a modified combination of tumor and neurography protocols. The MRI revealed a T2-weighted hyperintense lesion along the course of the left common peroneal nerve extending into the lower sciatic nerve measuring up to 11.6 cm in length, extending from the level of the distal femoral diaphysis to the proximal fibular metaphysis (Figure 1A). The lesion appeared to course around the head of the fibula and to involve the lateral sural cutaneous nerve (Figure 1B, D). The lesion was fusiform in character and demonstrated mild peripheral enhancement concerning for a soft tissue mass involving the common peroneal nerve and was diagnosed as a nerve sheath tumor.

Management

Given concern for a lesion compressing the common peroneal nerve, the decision was made to proceed with open biopsy followed by possible surgical excision. With the patient in the prone position, a posteriolateral approach to the left knee was performed. The common peroneal nerve was identified just over the lateral condyle of the femur and appeared significantly enlarged. An epineurotomy was performed, draining a gelatinous-type material similar to a ganglion cyst. A small portion of the surrounding epineurium was resected for pathology review and frozen section confirmed the clinical diagnosis of an intraneural ganglion cyst. The nerve was then

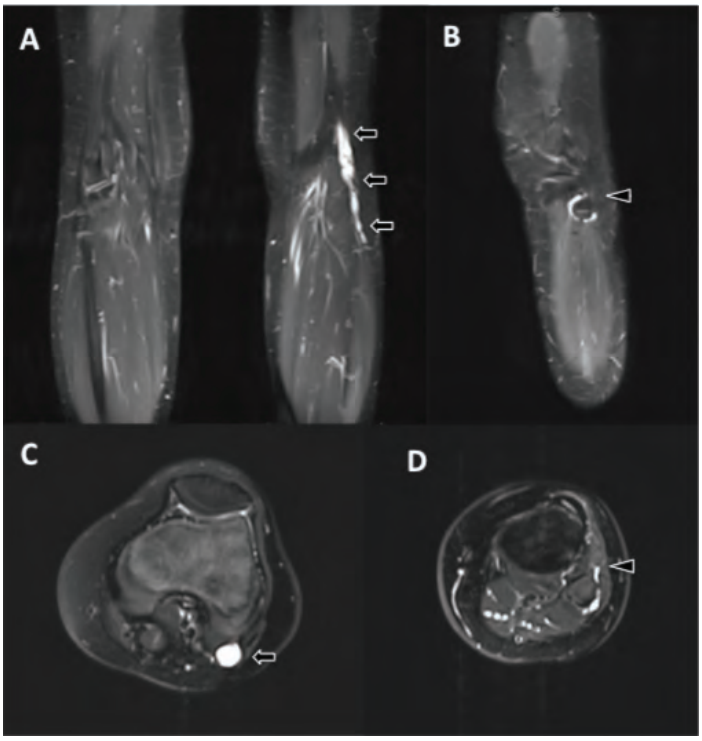

Figure 1. MRI images of left knee. **(A)** Coronal, **(B)** sagittal, and axial **(C, D)** T2-weighted imaging showing cystic appearing lesion in the region of the common peroneal nerve (arrows) with connection to the proximal tibial-fibular joint "tail sign" (arrow head).

completely exposed, extending all the way to the bifurcation of the common peroneal nerve distally, and to the bifurcation of sciatic nerve proximally, and a neurolysis was performed for mobilization (Figure 2A). The epineural incision was further extended to decompress the entire intraneural ganglion. The articular branch of the peroneal nerve was identified and then followed to the proximal tibial-fibular joint where it was ligated (Figure 2B). This branch was enlarged throughout its course and the epineurium was thickened. Given the epineural defects from the ganglion decompression, a 6.5cm synthetic conduit was used to wrap the nerve to allow for axonal regrowth though the common peroneal nerve. Finally, extensive irrigation was performed and hemostasis was obtained. The wound was closed in anatomic layers and the patient was placed in a CAM boot.

Postoperative Course

His postoperative course was uncomplicated and he was discharged from the hospital on postoperative day one. The patient was seen at two weeks postoperatively for a wound check and suture removal. At that time, he continued to have residual weakness in TA, EHL, EDL, and peroneals with 2 out of 5 muscle strength as well as decreased sensation in the common peroneal nerve distribution. He was transitioned to a custom made AFO and physical therapy for ankle and knee stretching and strengthening was initiated. By 5 weeks postoperatively, he had significant recovery of motor function and was able to discontinue use of the AFO. At 7 weeks postoperatively, he had almost full motor strength of his left lower extremity with 4 out of 5 strength in TA, and 3 out of 5 strength in EHL, EDL, and

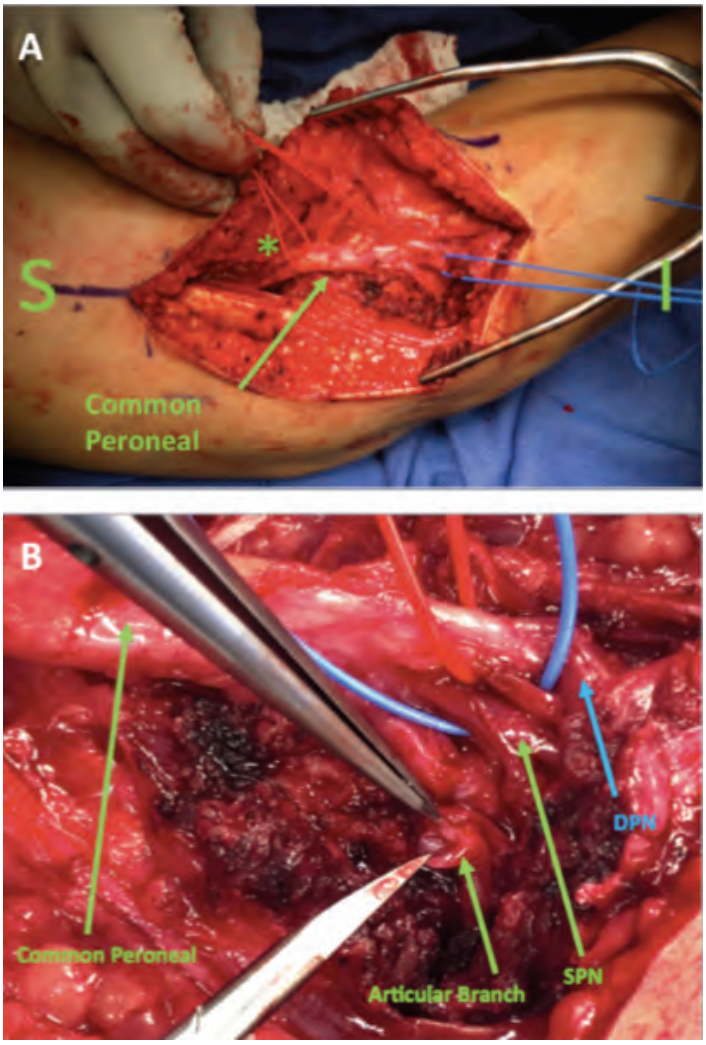

Figure 2. Intraoperative clinical photographs. **(A)** Decompression of common peroneal nerve (*) and isolation of the DPN and SPN **(B)** The common peroneal nerve was identified and followed distally to identify the articular branch that was ligated. S= superior, I= inferior, DPN= deep peroneal nerve, SPN=superficial peroneal nerve.

peroneal muscles. He continued to have diminished sensation to light touch within the common peroneal nerve distribution and reported some paraesthesias in the first webspace, but overall felt that it was improving. He was most recently seen four months postoperatively and had near complete motor strength recovery with 4 out of 5 strength in EHL and EDL and 5 out of 5 TA. Sensation remained decreased in the first web space but continues to improve. He has returned to full activities and sports without restrictions.

Discussion

Intraneural ganglion cysts are uncommon, typically occurring in adult men and involving the common peroneal nerve at the level of the fibular neck.[7,8] The pathogenesis of these cystic formations remains controversial, but the prevailing unified articular theory proposed by Spinner et al [9] describes a one way communication between the anterior proximal tibial-fibular joint and the articular branch of the common peroneal nerve. Synovial fluid from the joint dissects

along the articular branch through the path of least resistance, ascending proximally to the common peroneal nerve. With increasing pressure, the fluid can tract to the sciatic bifurcation of the common peroneal and the tibial nerve and can either ascend proximally along the sciatic nerve or descend distally along the tibial nerve.[10]

Patients typically present with a palpable mass about the lateral knee with associated pain, and motor/sensory deficits in the common peroneal nerve distribution. Electromyography and nerve conduction testing, if performed, often show decrease in distal motor amplitudes in the muscles innervated by the deep peroneal nerve.[11] Standard radiographs are typically normal. Magnetic resonance imaging is the next imaging study of choice, and often shows a cystic-appearing, homogeneous, T2 hyperintense mass in the region of the common peroneal nerve at the level of the knee. Diagnostic of an intraneural ganglion of the common peroneal nerve is the "tail sign" which represents the connection of the proximal tibial-fibular joint and the dilated articular branch.[12]

Timely surgical treatment is recommended for consistent recovery of motor and sensory function, and should involve complete decompression of the nerve and exploration and resection of the articular branch communication with the proximal tibial-fibular joint. In a clinical series of 24 patients with intraneural ganglion cysts of the common peroneal nerve that were surgically treated as described above, there were no reported recurrences at 1 year follow up. This was contrasted with 3 patients who only underwent decompression of the nerve, with all experiencing recurrence of the intraneural ganglion at 1 year.[9]

There have been 8 case reports of intraneural ganglion cysts involving the common peroneal nerve in the pediatric population.[5] In the reported cases, all those that underwent surgical decompression of the lesion and ligation of the articular branch showed excellent neurologic outcomes with full motor recovery recorded between 2 weeks and 14 months postoperatively.[3, 5] Additionally, these cases all showed timely diagnosis of the intraneural ganglion via MRI or alternative imaging. Residual motor deficits could be devastating in his age group, making proper and rapid diagnosis paramount.

Here, we report a case of an intraneural ganglion cyst of the common peroneal nerve in a 13-year-old boy. He presented with many weeks of lateral knee pain with a palpable mass, and ultimately, developed an atraumatic foot drop, prompting him to seek orthopaedic evaluation. MRI imaging showed a fusiform, T2-weighted hyperintense lesion along the course of the common peroneal nerve and wrapping around the head of the fibula, however intraneural ganglion was not considered as a potential diagnosis. Instead, he was thought to have a nerve sheath tumor and was planned for resection and reconstruction of the nerve. Intraoperatively, the common peroneal nerve appeared dilated and cystic, with viscous, clear fluid released upon epineurotomy, and was found on frozen pathology to be an intraneural ganglion cyst. He underwent decompression of the nerve and ligation of the articular branch, but did not require extensive resection of the common peroneal nerve, and has recovered nearly full strength and function at 4 months postoperatively. This case highlights the importance of considering intraneural ganglion cysts as a potential diagnosis and recognizing its characteristic features on imaging as patients can reliably recover motor strength with appropriate surgical decompression.

Conclusion

Intraneural ganglia are uncommon in the pediatric age group. Although any nerve can be affected, intraneural ganglia of the common peroneal nerve are believed to arise from the articulating branch at the proximal tibial-fibular joint, and present with foot drop, pain, sensory deficits, or simply the presence of a palpable mass. This case highlights the importance of including intraneural ganglion cyst in the differential diagnosis of new onset peripheral neurologic deficit in the pediatric population. Early recognition and surgical decompression of intraneural ganglia within the common peroneal nerve with exploration and ligation of the articular branch is paramount for improved functional recovery.

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U·P·O·J

Preliminary Mechanical and Ultrastructural Characterization of Pediatric Anterior Cruciate Ligaments and Tendons Used for Reconstruction

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Introduction

A large amount of cadaveric research has been devoted to the biomechanical characterization of knee tendons and ligaments in adults; however, relatively little is known about the pediatric population due to the rarity of these specimens. Extrapolating data back to pre-pubescent ages is inadequate, and the clinical need for this data has grown along with the recent increase in diagnosed anterior cruciate ligament (ACL) tears in skeletally immature patients.[1] Ideally, surrogate grafts should closely parallel the native pediatric ACL in both its biologic properties and mechanical durability. Thorough characterization of the ACL and potential autograft options will help to further improve surgical outcomes in pediatric patients. The purpose of this study was to characterize the mechanical properties and ultrastructure of ACLs and the most common tendons used for reconstruction in the pediatric knee. Our goal was to gain a better understanding of the structure and function of these tissues to improve surgical outcomes.

Methods

Mechanical Testing

Five fresh-frozen knee specimens from separate donors were used in this study; three male, two female specimens with average age of 9.2 years. ACLs, patellar ligaments, quadriceps tendons, and semitendinosus tendons were fine dissected free from the knee and subsequently cut into dog-bone shapes at the mid substance (ACL, patellar ligament) or distal third substance (quadriceps and semitendinosus tendon) with a custom-built jig. Cross-sectional areas of the prepared specimens were measured with a noncontact laser-based measurement system.[2] Specimen ends were placed in custom aluminum clamps and attached to a 4500N load cell on a universal testing frame (TA Instruments ElectroForce 3550, Eden Prairie, MN) to perform uniaxial tensile testing. Specimens were subjected to a standard preload, cyclic preconditioning, and stress-relaxation protocol before a ramp to failure at a constant quasistatic strain rate of 0.03% per second. Ultimate strain and ultimate stress were recorded while Young's modulus and stiffness were calculated as the slope of the stress-strain curve and load-displacement curve, respectively. Strain energy density was calculated as the area under the stress-strain curve.

Histology and Transmission Electron Microscopy

A patellar tendon from the contralateral knee of a specimen (age 9, F) was selected as a pilot sample for histology and transmission electron microscopy (TEM) analysis. The specimen was fixed in 10% formalin, dehydrated, embedded in paraffin, sectioned, and stained with hematoxylin & eosin (H&E) for viewing under a standard light microscope. The TEM sample was fixed, embedded in resin, cut orthogonal to the axis, and stained with uranyl acetate for examination with a JEOL 1010 electron microscope. Ten micrographs were obtained at 60,000x magnification for each specimen. Micrographs were analyzed using a semi-automated threshold and segmentation protocol in Image-J/Fiji software (NIH, Bethesda, Maryland). Cross-sectional areas of collagen fibrils was determined using the minor fibril diameter and the distribution of fibril areas was fitted using a kernel density estimation (Figure 2C).

Results

Mechanical properties for the pediatric ACLs and anterior cruciate ligament reconstruction (ACLR) candidate grafts are summarized in Table 1 and Figure 1. The patellar ligament exhibited mechanical properties that were most similar to that of the ACL, particularly for ultimate stress, ultimate strain, Young's modulus, and strain energy density. The same structural properties in the adult populations seem to exist in the pediatric condition, despite considerably weaker mechanical properties. This was expected based on previous studies in immature animal models.[3,4] In adults, hamstrings tendons have previously been shown to exhibit significantly higher elastic modulus (1036±312 MPa) and ultimate stress values (120.1±30.0 MPa) than other graft candidates, including the patellar ligament (417±107 MPa, 76.2±25.1 MPa).[5]

Table 1. Mechanical Properties of Pediatric ACLs and Tendons used for Reconstruction

Tissue	n	Age Group	Ultimate Stress (MPa)	Ultimate Strain(%)	Young's Modulus (MPa)	Stiffness (N/mm)	Strain Energy Density (MPa)
ACL	4	9-11	5.24 (2.20)	46.43 (5.71)	24.32 (15.63)	40.48 (18.83)	0.84 (0.43)
Patellar Ligament	5	7-11	5.23 (3.07)	44.58 (8.38)	27.00 (6.86)	20.25 (5.34)	1.17 (0.86)
Quadriceps Tendon	5	7-11	12.09 (8.26)	51.02 (21.91)	64.61 (68.78)	42.71 (35.84)	2.54 (1.91)
Semitendinosus Tendon	5	7-11	27.87 (12.88)	31.5 (9.17)	194.34 (28.54)	98.81 (15.57)	3.05 (1.90)

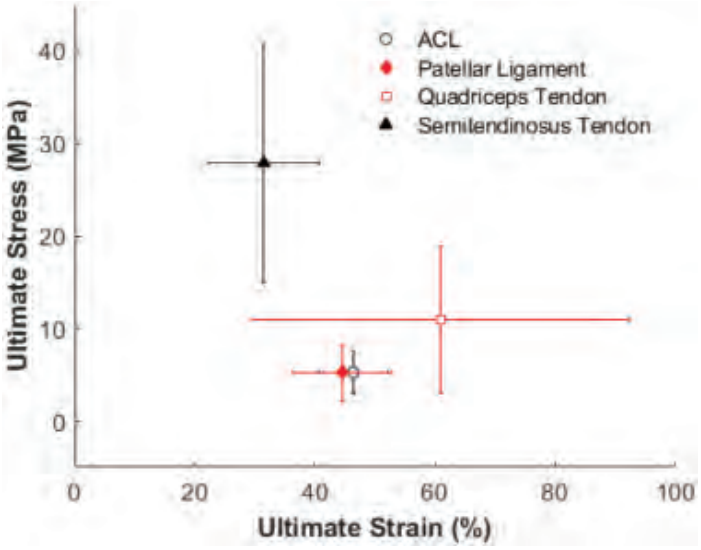

Figure 1. Ultimate stress-strain plot for the ACL, patellar ligament, quadriceps tendon, and semitendinosus tendon. Points represent the average ultimate stress and ultimate strain and the error bars indicate the standard deviation.

Histology of the single patellar ligament tested appeared to have the typical characteristics of a healthy tendon: organized and anisotropic in structure with collagen fibers closely packed along the fascicle's longitudinal axis (Figure 2A). Fibroblasts were located within and between the fascicles, in parallel with the collagen fibers. The characteristic crimp patterning of the collagen fibers was also visible. Approximately 5,000 fibrils were analyzed over 10 TEM micrographs of the patellar tendon (Figure 2B). Average fibril area fraction was 61.6±2.6% and average fibril concentration was 67±7/μm^2. Fibril areas were bimodally distributed between 508.6 nm^2 and 27,442.0 nm^2, with smaller area fibrils exhibiting higher frequency (57.4%) than larger area fibrils (42.6%) (Figure 2C).

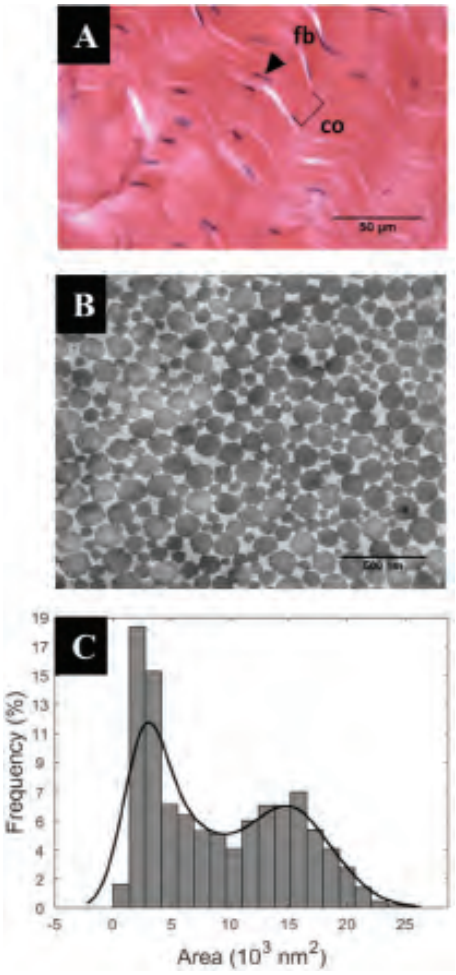

Figure 2. Representative histologic staining for a longitudinal section of patellar tendon **(A)**, showing fibroblasts (fb) and collagen fibers (co) (H&E, original magnification 300x) and representative TEM micrograph for a cross section of patellar tendon **(B)** (original magnification 60,000x). The distribution of collagen fibril areas over 10 separate micrographs was fitted with a kernel density estimation **(C)**.

Discussion

The methods and results from different studies on the mechanical properties of adult knee tendons and ligaments vary markedly, making comparisons difficult. This is in agreement with our data for a pediatric population, which showed that the semitendinosus tendons are stronger and less compliant than the quadriceps or patellar tendons. The histomorphometry of the pediatric patellar ligament did not appear qualitatively different than what has been documented in the literature for healthy, adult humans.[6,7] Previous studies conducted with TEM have reported collagen fibril area fractions and densities from adult cadaveric patellar tendon specimens that are comparable to ours.[7,8]

Based on the similarities of their material properties alone, the patellar ligament may be the better graft candidate for pediatric ACLR. However, it is important to take into consideration that the mechanical properties of ACLR grafts have been demonstrated to decrease during the remodeling

process in adults and never return to normal.[9] Therefore, it may be more appropriate to utilize a hamstrings tendon graft, which is significantly stronger than the patellar ligament and could resist the loads that make the ACL prone to reinjury or caused the injury in the first place.

Conclusion

More work is needed to explore the full implications of this preliminary study. We intend to complete a comprehensive ultrastructural examination for the ACL, quadriceps tendon, and semitendinosus tendon, including examination with polarized light microscopy. This suite of data can be used to inform the design and selection of grafts for reconstruction and also to develop constitutive computational models that can be applied to clinically relevant loading conditions that are difficult to test with bench-top experiments alone.

Acknowledgements

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Trends in the Surgical Management of Osteochondritis Dissecans of the Knee at a High-Volume Pediatric Hospital Network

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Introduction

Osteochondritis dissecans (OCD) in the skeletally immature patient has remained a challenging condition within the orthopedic community since its first description well over a century ago.[1] The etiology of OCD has yet to be fully elucidated, though several mechanisms have been proposed.[2-14] The disease has become an increasingly common cause of knee pain and dysfunction amongst adolescents,[15-17] thus necessitating treatment modalities that are effective in reducing symptoms and altering the progression of the degenerative process.[18,19] In general, operative treatment is indicated for stable lesions upon failure of conservative management and for detached or unstable lesions.

No universal consensus exists for the specific surgical method used as only limited high-quality clinical studies investigate the comparative effectiveness of different treatments. Therefore, many different surgical techniques are currently utilized by orthopedic surgeons in practice.[20] In this study, we aim to characterize the practice patterns of a single, high-volume cartilage surgeon treating exclusively pediatric patients at a single center over time. Specifically, we are interested in trends related to the specific drilling techniques for stable lesions and fixation methods for unstable lesions. We expect that this data may be helpful by 1) revealing the techniques utilized by a high-volume OCD surgeon, which may aid in treatment selection in the absence of high-quality clinical data to guide decision-making and 2) observing trends in operative technique over time, which may help identify factors in the primary literature that have contributed to observed changes.

Methods

Under the approval of the Institutional Review Board, a retrospective chart review was performed to analyze patients with a diagnosis of OCD who underwent surgical treatment from 2008 through 2015. These patients were identified by querying surgical logs using the surgical OCD Current Procedural Terminology (CPT) code, which yielded 419 patients. Exclusion criteria included non-knee OCD, an unclear OCD diagnosis and unclear operative reports with respect to surgical technique.

After applying exclusion criteria, 214 procedures were evaluated. Patient demographics, OCD lesion characteristics and specific surgical technique(s) were recorded using Research Electronic Data Capture Network (REDCap). One hundred and one subchondral bone drilling procedures were performed for stable, intact lesions on 93 patients (75 males, 18 females; mean age 13.87 +/− 2.11 years). Trends in internal fixation were similarly determined by identifying fixation procedures for unstable lesions. 16 procedures performed on 16 patients met these criteria (9 males, 7 females; mean age 14.88 +/− 1.09). These procedures for drilling and fixation were sorted by year and analyzed for the drilling technique or fixation method used.

Results

Drilling

Of the 101 procedures that were analyzed from 2008 through 2015, there was substantial variation in the drilling technique used to treat stable, intact OCD lesions of the knee (Figure 1). For drilling procedures that occurred during 2008 and 2009, 83.3% were treated with transarticular-only drilling while 10% were treated with transarticular/notch combined drilling (Figure 1B). Retroarticular and transarticular/retroarticular combined drilling were less common. In 2010 and 2011, transarticular/notch combined drilling became the most commonly performed technique at 79.5%. From 2012 through 2015, there was a slight rise in the proportion of lesions treated with transarticular-only drilling, but transarticular/notch drilling remained the most common technique (53.85%).

Internal Fixation

Compared to drilling procedures, there were significantly fewer total internal fixation procedures performed (Figure 2A). Throughout 2008 and 2009, all of the fixation procedures were performed with bioabsorbable headless compression screws (Arthrex) (Figure 2B). After 2009, bioabsorbable headless compression screws were not used for any of the fixation procedures that were performed. Instead, from 2010 through 2013, metal headless compression screws and suture fixation were the chosen

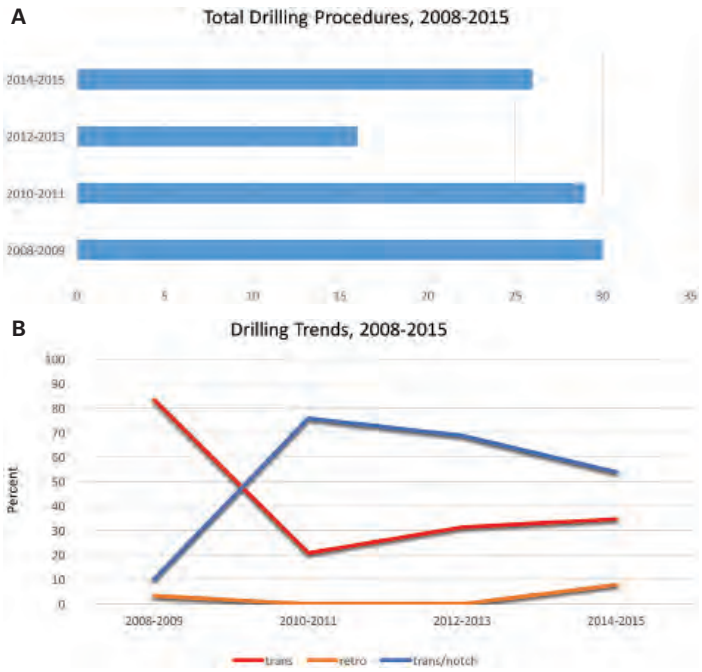

Figure 1. Total procedures performed **(A)** and trends in surgical technique by two-year period **(B)** from 2008 through 2015.

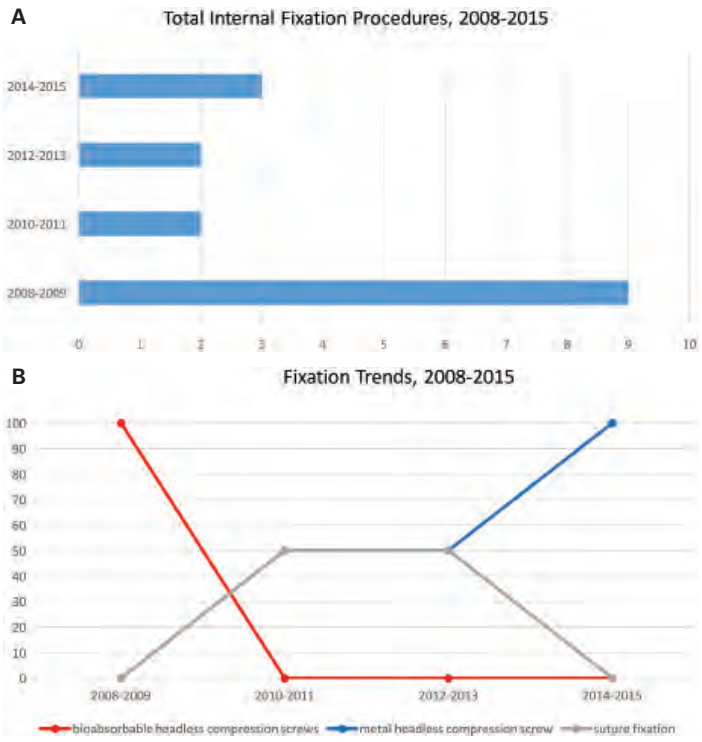

Figure 2. Total fixation procedures performed **(A)** and trends in fixation method **(B)** from 2008 through 2015.

methods, each accounting for 50% of the cases requiring fixation. By 2014-2015, 100% of the cases requiring fixation were achieved with metal headless compression screws.

Discussion

The most notable change in drilling technique from 2008 through 2015 was the sudden change in preference from transarticular-only drilling (83.3% in 2008-2009) to transarticular/notch combined drilling (75.9% in 2010-2011), which held until combined drilling became the preferred method in 2015 (53.85%) (Figure 1). With regard to internal fixation, the most significant change was the sudden switch from 100% of fixations achieved with bioabsorbable screws in 2008-2009 to 0% in 2010-2011 (Figure 2B). This trend continued through 2015, at which point the metal headless compression screws were the only method utilized to achieve fixation.

While it is difficult to predict what accounts for these changes in practice patterns, the formation of the Research in OsteoChondritis Dissecans of the Knee (ROCK) study group in 2009 resulted in a surge in collaborative work investigating the treatment of OCD of the knee,20-24 most notably the first AAOS Clinical Practice Guideline in 2010.18 The surgeon whose practice patterns have been analyzed in this study serves as an active participant and consumer of ROCK publications and meetings, which may have played a role in the difference in surgical management between 2008 (prior to the founding of the ROCK group) and 2015.

Limitations to the study include the small sample size, especially for internal fixation of unstable lesions. In addition, we were not able to account for specific contributing factors to operative technique, including exact lesion size, location, etc., given the limited sample size for each characteristic.

Conclusion

We have provided an analysis of surgical practice patterns in the management of osteochondritis dissecans (OCD) of the knee from a single, high-volume cartilage surgeon treating exclusively pediatric patients at a single center. The surgeon's preferred techniques shifted between 2008 and 2015, which may reflect his participation in the ROCK study group and the group's collaborative effort to improve OCD research and standardize optimal care. As of 2015, the most common drilling methods were transarticular/notch combined drilling and transarticular-only drilling for stable lesions and the most common internal fixation method for unstable lesions was with headless metal compression screws. However, the persistence of considerable variability in treatment highlights the need for further collaborative high-quality clinical studies.

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U·P·O·J

Type IV Tibial Spine Fractures Revisited: Arthroscopic Treatment and Outcomes for an Uncommon Injury

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Introduction

Tibial spine fractures are most commonly seen in children aged 8 to 14 years and occasionally seen in adults.[1-4] While only occurring in 3 per 100,000 children annually, they are associated with 2-5% of pediatric knee injuries with effusions, and complications including ACL deficiency, arthrofibrosis, and concomitant soft tissue injury.[5-7] Given the ACL's insertion on the tibial spine, injury mechanisms are similar to ACL rupture, involving forced knee flexion with tibial external rotation or hyperextension and lateral movement.[2,8] Although historically caused by bicycle accidents, the rise in competitive youth sports has brought increased public attention to this injury.

Tibial spine fractures were first described by Poncet in 1875,[9] and then fully classified in 1959 by Meyers and McKeever.[8] They described a three-tier classification based on fracture pattern and displacement seen radiographically. Type I fractures are nondisplaced, Type II are displaced anteriorly with an intact posterior hinge, Type III fractures are completely displaced and sub-divided into IIIA (involving only the ACL insertion) or IIIB (involving the entire intercondylar notch).[10] Zaricznyj first described the Type IV fracture as defined by comminuted fragments.[11] Literature focusing specifically on Type IV tibial spine fractures is greatly lacking, despite its status as rare and the most technically difficult to surgically fix with poorer long-term outcomes. Thus, the aim of this retrospective study is to report on the treatment and outcomes of patients treated for Type IV tibial spine fractures at our center.

Methods

After IRB approval, we retrospectively reviewed all patients between 0 and 18 years old who presented with Type IV tibial spine fracture between 2011-2017 at our single level 1 pediatric trauma center, with classification confirmed by a musculoskeletal radiologist. Demographics, injury and surgical characteristics, and follow-up outcomes were recorded for descriptive analysis.

Results

Eighteen patients were available for our study. Patient demographics and preoperative injury characteristics are detailed in Table 1. Activities during injury included basketball (3), football (3), skiing (2), trauma (2), trampoline (1), lacrosse (1), bicycle (1), soccer (1), and other activities (4). Soft tissue entrapment and loose bodies were present in 6 of the 18 patients. All patients underwent arthroscopic reduction internal fixation (ARIF). Operative details and follow-up outcomes are detailed in Table 2. Bone bridge technique was utilized in 5/18 patients. There were no malunions or nonunions. Five patients developed arthrofibrosis.

Discussion

Surgical Technique

Fractures were first visualized via traditional anteromedial and anterolateral arthroscopy portals. Then, lateral and medial mid-patellar portals were placed to allow soft tissue debridement and/or concomitant injury repair. The techniques for Type IV fractures that were performed included the following: sutures placed through drill holes in the proximal tibia that were tied over the anterior proximal tibia, screw and washer fixation, and arthroscopic anchor fixation. Because of the complexity of comminuted Type IV fractures, there were times when a combination of sutures, screws, and anchors were used. For Type IV fractures we then recommend a similar technique to arthroscopic shoulder labral repair using a shoulder anchor.[12] Via the mid-patellar portals, two limbs of high-strength suture were passed through the ACL base and then through the anchors, which are secured in an anterior-to-posterior angle. Intraoperative photographs depicting key steps are included in Figure 1.

Outcomes

Comminuted Type IV fractures are technically difficult to repair and subject to poor outcomes, where May et al found an association between Type IV fractures and decreased Tegner score at 7 years postoperatively.[13] Despite this, most studies combine Type III and Type IV fractures together and have not examined the treatment and outcomes of Type IV fractures specifically.[14,15] In this regard, our goal was to study only the Type IV tibial spine fractures treated at our center between 2011-2017.

Our patients' demographics demonstrate

Table 1: Patient Demographics and Preoperative Injury Characteristics

A) Patient Demographics	
Age (Mean ± Standard Deviation)	13.3 ± 2.6 years
Sex (Male:Female Ratio)	2.6:1.0
BMI (Mean ± Standard Deviation)	21.9 ± 4.9
Laterality (Right:Left)	1.3:1.0
B) Preoperative Characteristics	
Mechanism of Injury	
Twisting Non-Contact	8 / 18 (44%)
Contact	4 / 18 (22%)
Hyperextension	5 / 18 (28%)
Not Recorded	1 / 18 (6%)
Preoperative Range of Motion (Mean ± St. Dev.)	
Flexion (Degrees)	104.5 ± 37.6
Extension (Degrees)	11.4 ± 13.2
Total (Degrees)	85.5 ± 47.2
Preoperative Physical Exam Findings	
Anterior Drawer, Lachman, & Pivot Shift	1 / 18 (6%)
Lachman	3 / 18 (17%)
Pivot Shift	1 / 18 (6%)
No Laxity	14 / 18(78%)
Concomitant Injuries	
Meniscal	5 / 18 (28%)
Chondral	6 / 18 (33%)
Ligamentous	1 / 18 (6%)
Ligamentous and Meniscal	1 / 18 (6%)
Chondral and Meniscal	2 / 18 (11%)
Intraarticular Fracture and Chondral	1 / 18 (6%)
None	2 / 18 (11%)
Days Until Treatment (Mean ± St. Dev.)	9.1 ± 8.1

more males of slightly older age than commonly seen with most tibial spine fractures. Activities and injury mechanisms are consistent with literature, with sports quickly becoming the most common cause versus bicycle falls previously.[1] Concomitant meniscus and/or cartilage injuries were most common in our cohort (13/18), consistent with other literature.[16]

Time to treatment represents an area for future focus given its significant length and variability in our study. Watt et al found that patients with prolonged surgical delay and operative duration had increased risk of arthrofibrosis.[17] Others theorize that patients presenting with severe joint stiffness (excluding mechanical obstruction) should improve preoperative range of motion before surgery for better outcomes, similar to prehabilitation goals with ACL rupture.[18] Type IV fractures are almost universally treated operatively and with sutures versus screws, generally consistent with our results although many of our patients underwent combined techniques and may represent more complicated cases referred to our specialists.[14,19]

Patients' restricted preoperative range of motion (ROM) significantly improved by final follow-up ($p=0.0107$). Total ROM at follow-up was still less than normal; however, this is consistent with literature that has shown 27.8% of Type III and IV have loss of ROM.[15] One method of prevention is ROM rehabilitation within 4 weeks of treatment, which leads to lower rates of arthrofibrosis (0% vs. 36%; $p=0.04$) and earlier return to full activity (103 days vs. 217.5 days; $P=0.02$).[20] In a 2017 survey of Pediatric Orthopaedic Society of North America members, surgeons who treat more than 3 tibial eminence fractures per year were more likely to immobilize fractures for under 2 weeks ($p=0.018$).[21] This is reflected in our results.

Most patients undergo formal physical therapy for multiple months, advancing their activity on a case-by-case basis.

Table 2: Operative, Postoperative, and Follow-up Results

A) Operative Details	
Mean ± St. Dev. Operative Time (Min)	174.7 ± 81.8
Fixation Techniques	
Suture(s), Screw(s), & Suture Anchor Fixation	8 / 18 (44%)
Screw(s) & Suture Anchor Fixation	2 / 18 (11%)
Suture(s) & Suture Anchor Fixation	4 / 18 (22%)
Suture(s) & Screw(s)	1 / 18 (6%)
Suture(s)	1 / 18 (6%)
Screw(s)	1 / 18 (6%)
No Internal Fixation	1 / 18 (6%)
B) Postoperative Details	
Immobilization Technique	
Cast	4 / 18 (22%)
Brace	1 / 18 (6%)
Knee Immobilizer	3 / 18 (17%)
No Immobilization	10 / 18 (56%)
Postoperative Protocol	
Physical Therapy, Home Exercise, & CPM	8 / 18 (44%)
Physical Therapy & CPM	3 / 18 (17%)
Physical Therapy & Home Exercise	5 / 18 (28%)
Physical Therapy Only	1 / 18 (6%)
Home Exercise & CPM	1 / 18 (6%)
Mean Time Until Knee Mobilization (Days)	7.6 ± 11.5
Mean Time Until Return to Full Activity (Months)	9.5 ± 4.5
Follow-up Outcomes	
Mean Follow-up with Surgeon (Months)	14.8± 12.2
Mean Length of Physical Therapy (Months)	20.6 ± 14.8
Mean Range of Motion at Final Follow-up (Degrees)	
Flexion	127.2 ± 10.3
Extension	−0.4 ± 4.6
Total	127.7 ± 13.6
Reoperation Incidence	8 / 18 (44%)
Removal of Hardware	3 / 8 (38%)
New Injury	5 / 8 (63%)
Cartilage	1 / 5 (20%)
Meniscus	2 / 5 (40%)
ACL	2 / 5 (40%)
Arthrofibrosis Incidence	4 / 18 (22%)

Reoperation rates for hardware removal were low in our cohort, as rates have been reported as high as 65% screw-based fixation and 4% for suture-based fixation.[14] Arthrofibrosis rates for combined groups of Type III and IV have been described as 14.2%,[15] but studies examining this rate in Type IV fractures alone are very limited or non-existent, thus future multi-center retrospective and prospective trials are needed to confirm this rate.

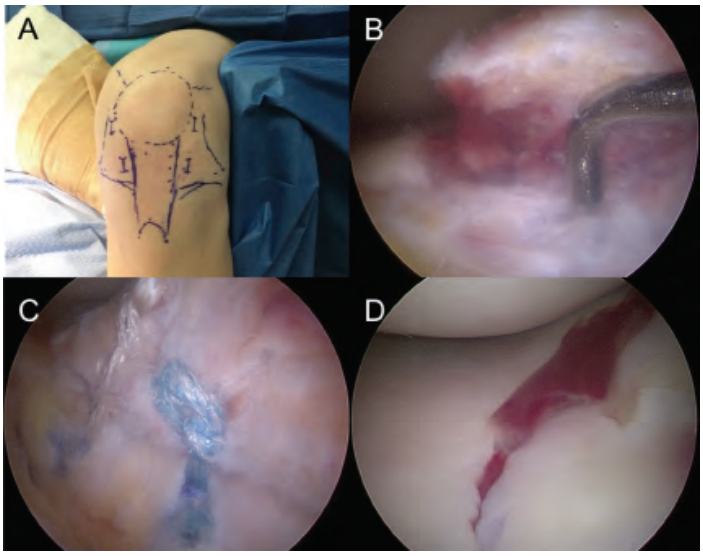

Figure 1. Intraoperative photographs of ARIF of tibial spine fracture. **(A)** Preoperative anatomic marking and port placement; **(B)** Displaced tibial spine fracture fragment; **(C)** Fixation of fracture fragments using suture and suture anchors; **(D)** Reduced tibial spine fracture secured with sutures and suture anchors showing anatomic alignment.

Conclusions

This paper demonstrates the inherent high complication risks and technical difficulty of surgery for Type IV tibial spine fractures, the importance of expeditious treatment, and the need for effective communication and rehabilitation with patients and families.

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U·P·O·J

Evidence-Based Orthopaedics: Current Concepts, Principles, and Practice

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Since its introduction in 1995 by Sackett et al, evidence-based medicine (EBM) has become a cornerstone of the clinical decision-making process.[1] Conceptually, there are 3 fundamental principles of EBM: (1) optimal clinical decision-making requires awareness of the best available evidence; (2) EBM provides guidance to decide whether evidence is more or less trustworthy; and (3) evidence alone is never sufficient to make a clinical decision. Subspecialties within orthopaedics have adopted these key principles of EMB in order to provide treatment recommendations based on the available evidence to assist their members in providing optimal patient care. For clinicians, however, it is challenging to integrate these principles without an understanding of what constitutes high-quality and low-quality evidence. An EBM hierarchy of evidence thus becomes an important factor for evaluating the strength of evidence as it takes into account the study design in order to determine the quality of evidence it provides.[2] According to this hierarchy, the confidence in study results should increase when it is less likely to be affected by bias or systematic errors. In order to assimilate the principles of EBM into their practice, all clinicians must be able to perform a literature search for the clinical question at hand and critically appraise all types of relevant literature.

Generally speaking, the hierarchy of evidence should be followed when dealing with various types of studies such as case-control studies, cohort studies and interventional studies. Just as it is important to recognize that meta-analyses and randomized controlled trials are not all inherently level I studies (meta-analyses fall under the same level as the level of articles they include, and randomized controlled trials with poor follow-up can be dropped to level II), it is equally important to recognize that lower level of evidence studies do serve a purpose. In fact, not all clinical questions can be feasibly (or even ethically) answered through randomized controlled trials. Certain types of questions may be better answered though particular study designs. For example, if we want to learn more about natural history of the diseases, observational studies, more specifically, prognostic studies, are appropriate, while randomized control trials and systematic reviews are the best suited for comparing two or more interventions. Once we identify a study that can potentially provide an answer to the clinical question at hand, we must appraise the study.

Using critical appraisal skills, one can assess the quality of research and then be able to make an informed decision to clinically accept or contest its results. An appraisal of clinical study should be performed by asking three crucial questions: (1) What are the results of the study? (2) Are the results valid? (3) Are these results relevant to the clinical scenario at hand? The abstract can reveal the credibility of the authors and reputation of the peer-reviewed journal, as well as the breadth of research topic and hypothesis being tested. Next the appropriateness of the study design, pertinence for testing the hypothesis, and both the internal and external validity of the study should be assessed. Internal validity refers to how well a study is performed, especially whether it avoids confounding. The less chance for confounding in a study, the higher its internal validity is. External validity is the extent to which an internally valid effect measured in a study sample reliably reflects the effect in a population of interest – also described as the target population.[3] For a study that is both internally valid and relevant, it is important to determine whether the results are applicable to the patient or patient population before implementing the evidence. Table 2 outlines some of the critical questions to test for validity of the study.

Although our attempt to provide evidenced-based care can be best served by following the aforementioned principles, the usefulness of applying EBM to individual patients is limited. This is primarily because there are significant variations in individual circumstances and values. Additionally, the uncommon diseases and variants pose a further challenge in designing higher quality studies in order to produce higher quality evidence.[4,5]

In conclusion, EBM can serve as an effective tool in providing care that is based on evidence. However, individual patient needs must be taken into account before implementing treatment options derived by following the aforementioned steps.

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IM Nails vs. Plate and Screws in Radial/Ulnar Fractures

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Introduction

Pediatric diaphyseal fractures of the radius/ulna are the third most common fractures in the pediatric population.[1-3] The goal of treatment for distal radius fractures is obtaining sufficient pain-free motion and allowing return to activities.[4] Here we provide a brief description of the evolution and use of intramedullary (IM) nails and plate fixation in these fractures.

Plate and screw fixation was first introduced by Carl Hansmann in 1886 and later evolved rapidly in the 20th century with the introduction of the x-ray and other surgical technique advancements[5]. Plate fixation by nature necessitates extensive surgical exposure, soft tissue stripping, and risk of hardware problems, which may require later removal of the implant.[6-8] IM nailing in the forearm was first reported in 1913. At that time, unacceptable non-union rates and a high degree of pronation/supination deficit at the proximal and distal radioulnar joints was noted.[9-11] The cause of this deficit was that restoration of proper rotational alignment, length, and anatomic bow of the radius are required for full pronosupination.[9]

Fracture fixation with flexible nails has gained popularity in recent years with proponents arguing that nailing results in decreased surgical dissection.[3,12,13] IM nail implementation for radial/ulnar fracture fixation should be considered over open fixation with plate and screws within the pediatric population for providing a less surgically invasive approach with outcomes that can be as safe and effective.

Case Description

A 13-year-old male athlete initially seen at an outside institution presented to our Emergency Department with x-rays that showed dorsally displaced radius and ulna fractures with a 3cm overriding fragment. They were taken to the OR for open reduction and intramedullary nailing of left radius and ulna fractures. After identifying the growth plate, a skin incision was made over the dorsum of the wrist and carried down to Lister's tubercle. An entry point was made dorsally in the distal radius, and a 2mm contoured titanium elastic nail was passed down the radius to the fracture site. Next, an incision was made over the distal ulna. After making an ulnar entry point, a second 2mm contoured nail was placed down the ulna to the fracture site. The fractures were reduced, and the nails were passed across the fracture sites proximally. Flouroscopy confirmed satisfactory position and anatomic alignment. The nails were retracted approximately 5mm for cutting, then advanced back with end caps on both. After capping, fluoroscopy was used to show normal pronation and supination as well as the interosseous space (Figure 1). At 6 weeks post nail fixation, they were transitioned to a volar splint and sling with continued activity restrictions and a plan for advanced range of motion (ROM) exercises (Figure 2). The patient returned at the 4-month post-op mark with full ROM and had both nails removed. The nails and end caps were localized with fluoroscopy and an incision was made over the end cap and dissection was carried down to the radial end cap. A second incision was made over the ulnar end cap. Both end caps and nails were removed without issue. By 6 weeks post-op the patient was cleared to return to all activities (Figure 3).

Discussion

Intramedullary nail fixation is best indicated for extra-articular distal radius fractures that are unstable and cannot be maintained with closed reduction. It provides a rigid construct and disperses loading forces through the distal radius via load-sharing as opposed to load-bearing.[14] Plate and screw constructs are subject to tremendous loads that can lead to implant failure and secondary displacement during the several months it can take for cortical defects of fractures to reintegrate.[15] In addition, IM nails require smaller incisions and avoid soft

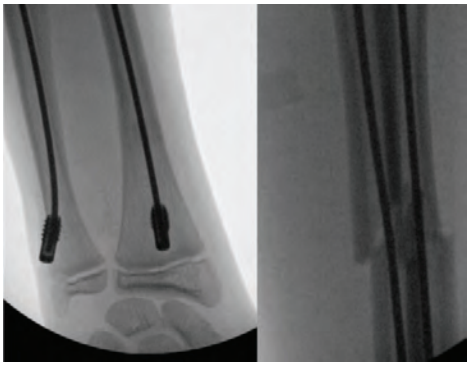

Figure 1. Intraoperative radiographs of radial and ulnar IM nails in appropriate placement across the fracture site (right) and with endcaps (left).

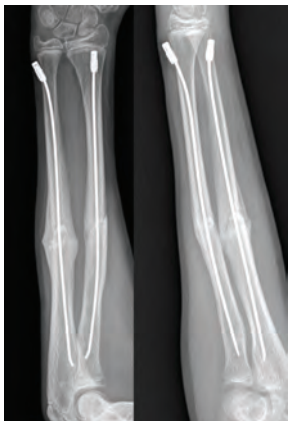

Figure 2. AP and Lateral radiographs 6 weeks s/p IM nail fixation of displaced radius and ulna fractures.

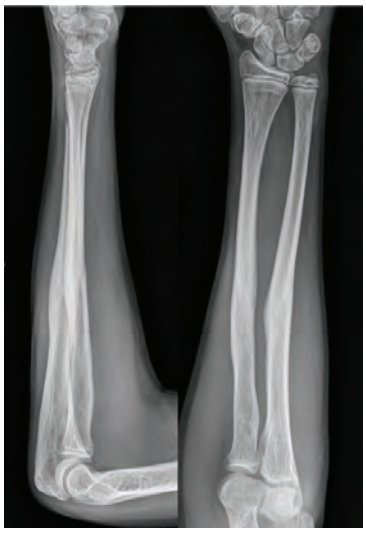

Figure 3. AP and Lateral radiographs 5 weeks s/p IM nail removal with appropriate radius and ulna alignment.

tissue injuries such as tendon irritation/rupture and carpal tunnel syndrome. Most complications of the ESIN technique are consequences of surgical unfamiliarity, therefore it is important to highlight proper technique. Penetration of the physis in pediatric patients should be avoided at all costs. Nail size is determined by measuring the canal diameter at the isthmus. Two nails of the same diameter will occupy 80% of the measured diameter. Radius nailing can be done in a retrograde approach to avoid the risk of damage to the deep branch of the radial nerve.[16] The ulna can be inserted with a retrograde approach or an anterograde approach depending on surgical preference. Contour of the nails should be done incrementally such that the ends occupy the metaphysis of the bone. Corkscrewing of nails can be avoided by rotating the tip in an arc of 180 degrees and opposite each other at the ends. TEN caps benefit by preventing soft tissue/tendon irritation, countering nail migration, and aiding in extraction of the nail. Protruding nail lengths should not exceed 5-7 mm, otherwise TEN caps will not adequately screw into the bone.

There is ongoing debate about plate removal vs. plate retention with at least one study finding that rates of complication in patients with retained plates were similar to those in patients who had their plates removed.[17] It's important to note that Peterson *et al.* advised plate removal in those involved in contact sports due to concern for refracture at the areas of stress generated by the retained plate, and that refracture rates in pediatric populations are influenced by plate characteristics, early removal, and lack of post-removal protection.[17, 18]

Conclusion

Internal fixation of radial/ulnar fractures with intramedullary nails in pediatric patients has advantages over ORIF with plate and screws. Surgical techniques involving IM nail placement are less invasive and require smaller incisions. In addition to more cosmetically appealing scars IM nails decrease risks of soft tissue/tendon irritation which, in the case of plate fixation, require an additional surgery for plate removal. Lastly many will argue that IM nails are less likely to be complicated by refracture than plate and screw fixation.

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Tips & Tricks: The Saline Load Test is Effective in Detecting Traumatic Arthrotomies of the Shoulder

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Introduction:

Penetrating injuries about the shoulder girdle may be challenging to discern intra-articular involvement, yet these injuries are common, as 9% of gunshot wounds involve the shoulder girdle[1]. Early diagnosis of a traumatic arthrotomy is paramount, and surgical debridement is the standard of care to prevent morbidity. The saline load test is a frequently-used diagnostic tool to assess for traumatic arthrotomies in the knee, ankle, and elbow.[2-4] However, there is a paucity of information in the current literature in regard to the amount of fluid infusion required to reliably detect a traumatic glenohumeral arthrotomy. The purpose of this study was to investigate the amount of fluid required during a saline load test to detect intra-articular glenohumeral involvement of traumatic wounds about the shoulder girdle with high sensitivity.

Methods:

A cadaveric study was conducted using 18 thawed, fresh-frozen forequarter amputations from 10 different donors (2M, 8F). Specimen age (mean 75.5 years, range 56-93 years), laterality (8 right, 10 left), body weight (mean 134.6 lbs, range 77-187lbs), and glenohumeral range of motion (ROM) was assessed prior to testing. The glenohumeral capsule was punctured with an 11-blade scalpel through the posterior portal site under fluoroscopic guidance to ensure the injury was intra-articular (Fig 1). A 19G needle was then placed through the anterior portal site and confirmed with fluoroscopy to ensure intra-articular placement (Fig 2). Normal saline was then injected until frank extravasation from the posterior portal site was observed. The volume of saline required to detect the arthrotomy was recorded, a histogram of saline volumes (by percentile) was created, and a logarithmic distribution was calculated.

Results:

The average amount of saline that resulted in extravasation was 34 mL (range 8-105mL). In order to identify 75%, 90%, 95% and 99% of the simulated glenohumeral arthrotomies, 42 [95% CI: 28-59] mL, 68 [42-106] mL, 90 [53-151] mL and 156 [80-289] mL were required, respectively (Figure 3). Pre-test ROM did not correlate with saline volume.

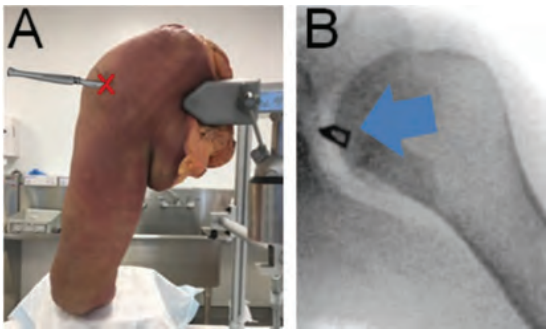

Figure 1. (**A**) Photograph of the experimental setup from a posterior view. The cartoon scalpel and "X" indicates the anatomic location where the traumatic athrotomy was created. (**B**) A fluoroscopic image confirming the 11-blade scalpel position for creation of traumatic arthrotomy. The location of the blade is highlighted by a blue arrow.

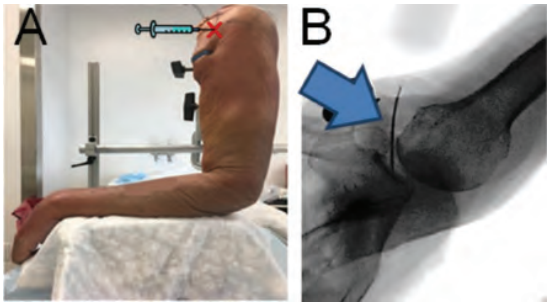

Figure 2. (**A**) Photograph of the experimental setup from a lateral view. The cartoon of a syringe and "X" indicates the anatomic location where the saline was injected. (**B**) A fluoroscopic image confirming the 19G needle was in the glenohumeral joint space. The location of the needle is highlighted by a blue arrow.

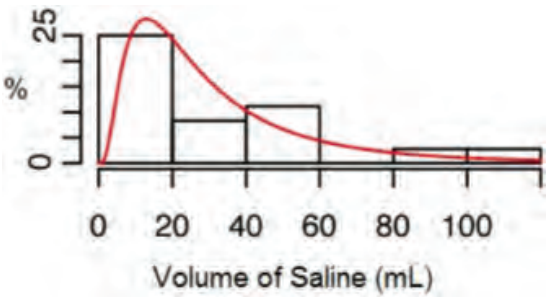

Figure 3. Logarithmic transformation showing distribution of saline volumes required to detect traumatic arthrotomy.

Discussion:

The saline load test has previously been shown to be an effective tool to diagnose traumatic arthrotomies.[2-4] This study demonstrates the efficacy of the saline load test in detecting traumatic arthrotomies of the glenohumeral joint with high sensitivity. Penetrating injuries involving joints must be treated aggressively. Gunshot wounds are

common in urban environments and may cause devastating sequelae with significant morbidity. Retained intra-articular bullets may lead to arthropathy. Furthermore, synovial fluid may dissolve bullets and lead to arthrofibrosis, chondrolysis, and hypertrophic arthropathy. Other foreign bodies may also be entrapped in the joint and must be debrided to prevent septic arthritis. Consequently, prompt and accurate diagnosis of traumatic arthrotomies is paramount to guide management and optimize post-injury outcomes.

Significance:

Glenohumeral joint traumatic arthrotomies may be detected with high sensitivity with the saline load test when injecting at least 68 mL of fluid.

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Rotator Cuff Repair: An Opportunity for Improved Efficiency, Cost-Effectiveness and Ultimately, Cost Savings

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Purpose

To identify factors associated with increased overall cost and decreased operative time during rotator cuff repair at one academic institution's university hospital system and ambulatory surgery center.

Introduction

Rotator cuff repair is one of the most common orthopaedic procedures performed in the United States each year. However, just as the number of rotator cuff repairs increases each year, so do the overall national health care costs. Due to the unsustainability of the current health care model, surgeons and hospitals are increasingly urged to improve the value of health care delivery by offering more cost-effective and efficient patient care while maintaining superior patient results. In order to adequately develop and implement cost-saving measures, factors associated with increased cost and decreased efficiency must be clearly identified. We hypothesized that surgeon experience and an outpatient surgical setting would be associated with decreased overall cost of rotator cuff repairs at an academic institution.

Methods

In the first part of our study, we retrospectively reviewed all rotator cuff repairs performed by 7 fellowship-trained surgeons at our institution between July 1, 2014 and May 31, 2015. All procedures were performed at either one of two university hospitals or a university-owned ambulatory surgery center, which utilizes similar nursing and anesthesia staff. Data collected included direct costs associated with each procedure such as disposable equipment, surgical time, performing surgeon post-graduate surgical experience, and surgical location. This data was then analyzed to determine any differences in cost, operative time, surgeon experience and location of surgery. In the second part of the study, all rotator cuff repairs performed by the same surgeons were reviewed from July 1, 2015 to September 30, 2015. In addition to overall costs of each procedure, additional data collected included tear size, which tendons were torn, number of anchors used for each repair, concomitant procedures and location of surgery. This data was analyzed to identify cost differences associated with tear size, number of anchors used, surgeon experience, and location of surgery.

Results

Between July 1, 2014 and May 31, 2015, a total of 441 rotator cuff repairs were performed. The average direct cost per procedure was \$1532.15, with a range of \$1167.55-\$1953.00. Surgeons with greater than 10 years of post-training surgical experience had overall shorter surgical times (134 minutes vs 170 minutes; $p < 0.001$) and lower surgical costs (\$1341 vs \$1841; $p=0.03$). Amongst surgeons, there were wide variations in the amount spent on specific equipment as a percentage of overall supply costs, including cannulas (1.4-8.9%), suture (1.3-7.6%), sterilized packs (4.5-10.6%), and sterilized equipment (6.0-18.7%). Between July 1, 2015 and September 30, 2015, a total of 84 rotator cuff repairs were performed and 68 repairs when excluding concomitant biceps tenodesis. The average direct cost per procedure was \$1411.47, with a range of \$451.50-\$3,269.25. Multiple tendon tears were associated with higher overall costs when compared to single tendon tears (\$1565.54 vs \$1278.61, $p = 0.019$). There was a trend toward greater number of anchors used with a greater number of tendons torn, although this difference was not statistically significant (2.08 vs 2.55, $p = 0.082$). Surgeons with greater than 10 years of post-training surgical experience had overall lower surgical costs when compared to those surgeons with less experience (\$1320.15 vs \$1871.99, $p = 0.001$). There was a trend toward rotator cuff repairs being more expensive in a hospital setting compared to an ambulatory setting, although this difference was not statistically significant (\$1364.99 vs \$1508.84, $p = 0.17$). The most-expensive single-tendon repairs had significantly higher costs associated with implants (\$397.51 vs \$253.68, $p = 0.017$), burrs (\$74.45 vs \$22.89, $p<0.001$), surgical tools (\$364.04 vs \$89.81, $p<0.001$), suture (\$142.09 vs \$43.34, $p = 0.003$), cannulas (\$48.07 vs \$20.62, $p = 0.003$), surgical sets/drape packs (\$174.67 vs \$117.14, $p = 0.013$), and arthroscopy fluid (\$28.55 vs \$12.17, $p = 0.024$).

Conclusion:

Increased costs of rotator cuff repairs are associated with multi-tendon tears and less post-training surgical experience. There is a trend toward higher costs associated with rotator cuff tears in university hospital setting. Costs of specific equipment as a percentage of overall costs vary greatly amongst individual surgeons. In addition, there are significant differences in direct costs on specific equipment such as implants, sutures, cannulas, and surgical tools between the most expensive and least expensive single-tendon rotator cuff tears. These results suggest an opportunity to lower overall supply costs by reducing the use of specific equipment amongst some surgeons.

Significance:

With increased pressures to decrease health care costs, hospital systems are seeking to improve the value of health care delivery by identifying more efficient and cost-effect ways of providing patient care. Understanding actual costs and the predictors of expenses are critical to improving the value of health care. Encouraging surgeons to be conservative in their use of surgical equipment and efficient in the operating room can provide significant opportunities for cost savings in rotator cuff repairs.

Assessing the Contribution of the Central Screw to Glenoid Baseplate Fixation in the Presence of Osteopenic Bone

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Introduction:

Reverse total shoulder arthroplasty (rTSA) has become a widely accepted solution for patients with various shoulder pathologies. Despite its popularity, complications are prevalent in the elderly population due to a limited amount of bone stock that may also be of poor quality.[1] Previous studies on glenoid loosening have extensively followed the established ASTM Standard for Dynamic Evaluation of Glenoid Loosening.[2] Although this approach effectively evaluates glenoid loosening, implants tested in this method are not loaded in clinically relevant positions commonly seen during activities of daily living. In addition, most studies utilize synthetic bones to model implant stability and osteopenic cadaveric specimens are seldom used.[1,3,4] This study introduces a novel cadaveric testing method that simulates physiologically relevant cyclic loads to create implant loosening. The primary goal of the current study was to utilize this model to investigate how the inclusion or exclusion of a central screw changes micromotion, subfailures, and catastrophic failure. We hypothesized that there would be no difference in fixation between implants that utilize the central screws and those without it.

Methods:

Eight matched pairs of cadaveric shoulders from 3 males and 5 females (average age: 80.6 years, range: 73 to 88 years) were confirmed for osteopenia with DEXA scan T-scores that were lower than -1.Scapulae were disarticulated from the shoulder and skeletonized of all soft tissues. Specimens were implanted with Integra Titan rTSA systems and divided into two groups that had a central screw (CS+) and did not have a central screw (CS−).The left and right scapulae of matched pairs were randomly assigned into one of the two test groups. CS+ underwent normal baseplate implantation following manufacturer guidelines, which included the use of the 5.5 mm diameter, 20 mm long central screw. CS- underwent the same procedure but with the exclusion of the central screw. All specimens used 4.5 mm diameter, 25 mm long superior/inferior locking screws and 4.5 mm diameter, 40 mm long anterior/posterior non-locking screws for baseplate fixation. After implantation, each specimen was osteotomized and potted in polycarbonate cylinders with poly methyl methacrylate.To prevent cementing screw tips, beads of dental wax were used to cover screw tips that were protruding from the bone.

Each specimen was tested using a novel custom testing apparatus (Figure 1). In this setup, bi-axial loading was applied by the testing frame actuator and a pneumatic air cylinder to simulate shoulder compressive loads. An adjustable angled vise was used to hold the specimen in a position that represented 30 degrees abduction, similar to that of someone rising from a chair or ambulating with a walker. In addition, each specimen was kept at body temperature via the temperature controlled water bath. 3-D motion tracking was implemented to calculate relative displacement between the scapula and glenosphere. Cyclic fatigue loads were imparted onto each specimen with a monotonically increasing 1 Hz sinusoidal waveform. Specifically, the waveform had a minimum compressive load of 100 N and a first peak of 150 N. The upper limit of the load was increased at a rate of 0.2 N/cycle until failure. To simulate the compressive forces of the muscles squeezing the joint and to prevent the joint from disarticulating, a constant 100 N medial-lateral load was imparted to the horizontal slider through the pneumatic cylinder. The vertical testing frame actuator applied cyclic compressive loads along the axis of the humerus in the superior-inferior direction until catastrophic failure.

Subfailure was defined as permanent creep between the bone-baseplate interface exceeding 1 mm, as determined by actuator displacement and 3-D motion tracking. Groups were

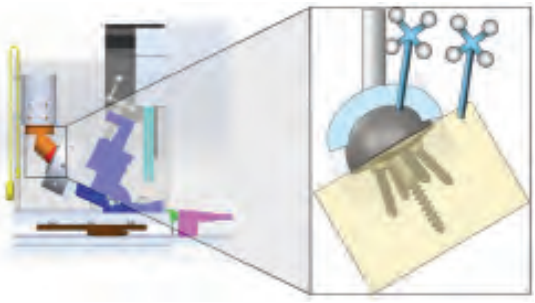

Figure 1. Computer-aided drawing of the testing setup. Horizontal and vertical loads (red arrows) are applied to the implant (orange) in a temperature controlled water bath to simulate physiological loading in the human shoulder.

Figure 2. Photograph of a specimen after catastrophic failure. Implant is separated from the scapula at the bone-baseplate interface.

subsequently compared with 1-tailed paired student t-tests. Axial stiffness, deformation, ultimate load, and survived cycles were measured.

Results:

Use of the central screw improved fatigue life before catastrophic failure, as the average maximum number of cycles survived for CS+ and CS− groups were 7281.88 ± 2517.32 and 5911.63 ± 2686.38 cycles ($p = 0.026$), respectively. The CS+ group sustained 1451.49 ± 465.55 N of compressive load on average, while the CS− group survived an average maximum compressive load of 1213 ± 480.11 N ($p = 0.026$). There were no significant differences found between groups for subfailure, defined as permanent bone-implant construct deformation exceeding 1mm. An analysis of cycle numbers survived as a function of DEXA T-score indicated no strong correlation, with R-squared values of 0.19 and 0.12 for the CS+ and CS- groups, respectively.

Discussion:

This study introduces a novel testing paradigm that effectively elucidated the role the central screw plays in fixation of the glenoid component in rTSA. The screw improved the long-term fatigue life of the implant but did not improve the implant's resistance to 1 mm of creep during monotonically increasing cyclic loading.

Both actuator and 3-D motion capture measurements were used for subfailure analysis in this study, which both have advantages and drawbacks. Actuator-based measurements were recorded for the duration of the test at higher resolutions at 10 microns, however, measurements can only be collected in one dimension. On the other hand, 3-D motion-based measurements have the capacity of three dimensional analysis, but were only recorded every 100 cycles at a lower resolution, about 200 microns.

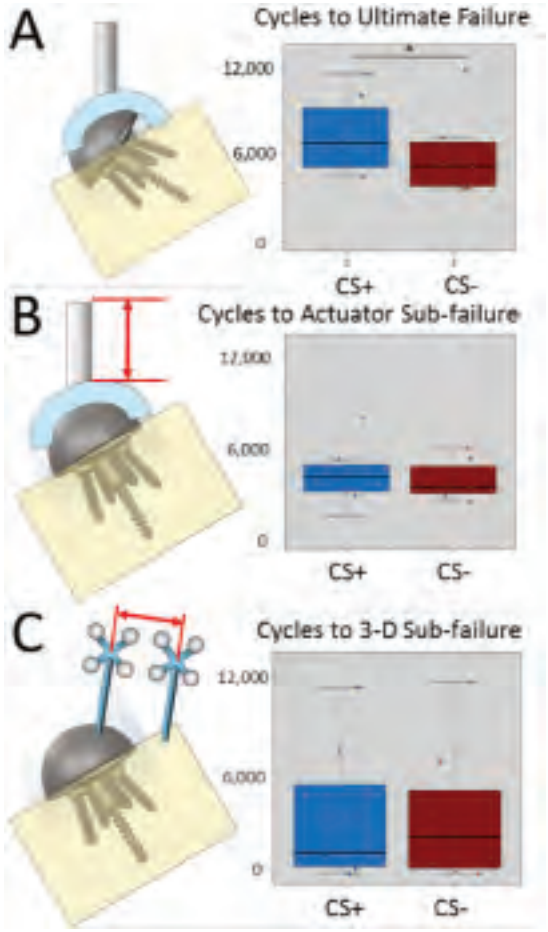

Figure 3. (A) Screw omission significantly decreased the number of cycles to ultimate failure. No significant differences in either subfailure analyses **(B)** measured by actuator movement or **(C)** measured by 3-D motion marker cluster displacement.

Conclusion:

Optimizing screw fixation in poor quality bone is an important clinical issue that requires further research. It is evident the rTSA implants can adequately restore shoulder joint function, but preservation of the already limited bone in the scapula may be beneficial if revision surgery were to be required in the future. Our study suggests that omission of the central screw may provide a reasonable tactic to preserve this bone, but only in a casewhere small external forces are exclusively applied to the joint.

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Aging Related Degenerative Mechanical Changes Manifest Earlier in Supraspinatus Tendons

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Introduction:

Rotator cuff tendinopathy is a common condition affecting a large portion of the population and can result in pain and joint dysfunction.Advancing age is directly correlated with increased incidence of rotator cuff pathology,with over 90% involving injury to the supraspinatus tendon specifically.[1-4] However,the mechanism(s) by which tendon-specific changes with aging may predispose the supraspinatus to injury relative to the other rotator cuff tendons is unclear.[5] Therefore, the objective of this study was to define the age-related mechanical alterations in all four rotator cuff tendons to determine whether the supraspinatus is more susceptible to injury due to aging than the other rotator cuff tendons.We hypothesized that aging would preferentially affect supraspinatus tendon mechanics when compared to the subscapularis, infraspinatus and teres minor.

Methods:

Experimental design and sample preparation: 7-month juvenile (n = 7-10), 18-month adult (n = 7-10), and 27-month old (n = 7-10) male F344XBN rats were obtained from the National Institute of Aging (IACUC approved). After 3 weeks of facility acclimation, all animals were sacrificed. Lower and upper subscapularis (LS & US, respectively), supraspinatus(SS), infraspinatus(IS), and teres minor (TM), muscle-tendon complexes were then each carefully dissected from the scapula of the right shoulder and removed with the proximal humerus for mechanical testing.[7] Muscle, along with extraneous tissue was removed from each tendon and cross-sectional area of each tendon was measured using a custom laser device.[8] Each humerus was potted in a custom acrylic cylinder secured with polymethyl-methacrylate, leaving the proximal humerus exposed. The head of the humerus was secured using a self-tapping screw to prevent failure at the growth plate. Mechanicaltesting: The LS, US, SS, IS,and TM from each animal were mechanically tested independently on an InstronElectroPuls E3000.The testing protocol consisted of a 0.1N preload, preconditioning (30 cycles, 0.125% to 0.375% strain, 0.25 Hz), stress relaxation at 3% strain magnitude for 600s, frequency sweep at 3% strain(+/−0.1875% strain at 0.1Hz, 1.0Hz, 2.0Hz, and 10.0Hz),stress relaxation at 6% strain magnitude for 600s, frequency sweep at 6% strain(+/− 0.1875% strain at 0.1Hz, 1.0Hz, 2.0Hz, and 10.0Hz), 300s rest at 0% strain, and a ramp to failure at 0.15% strain/second.Tendon toe and linear stiffness was calculated using a bilinear fit. Insertion site linear modulus was determined via optical tracking of stain lines at the insertion site. A 1-way ANOVA with Bonferroni post-hoc tests was used to compare the different ages for each tendon with significance set to $p < 0.05$.

Results:

There were no significant differences in cross-sectional area between any tendons across all age groups(data not shown). There was a significant decrease in percent relaxation at 3% strain between SS juvenile and adult groups, as well as IS juvenile to adult, and juvenile to old

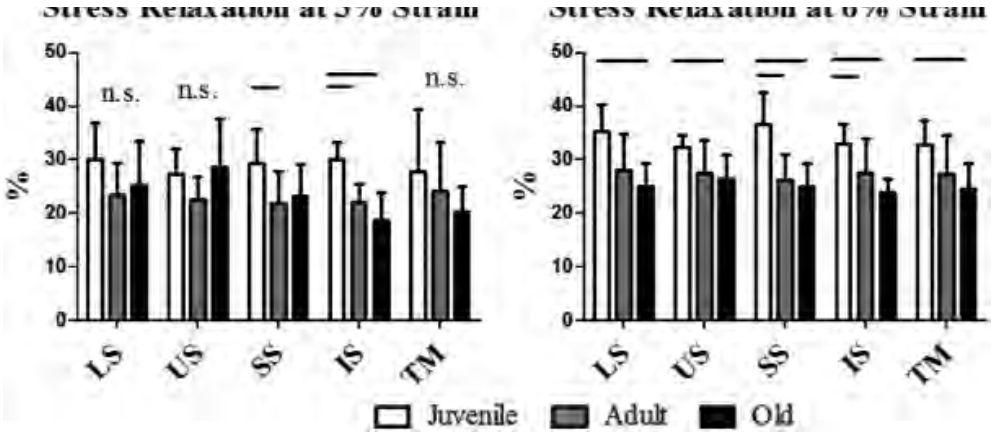

Figure 1. Percent relaxation of SS and IS is decreased at (**A**) 3% and (**B**) 6% strain between juvenile and adult. Percent relaxation of all tendons is decreased at (**B**) 6% strain from juvenile to old.

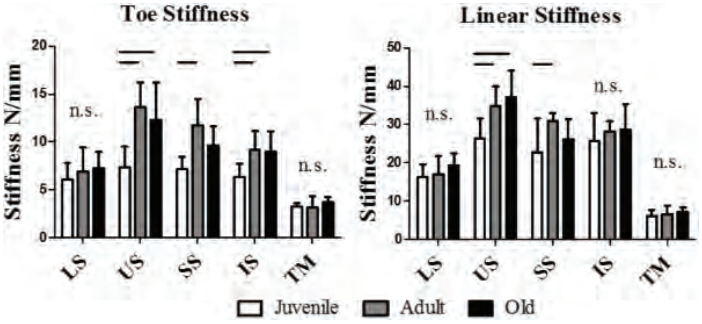

Figure 2. Toe **(A)** region stiffness increased in US, SS, and IS with age. Linear (**B**) stiffness also increased in US and SS with age.

(Figure 1). A significant decrease in percent relaxation at 6% strain was detected in all tendons between juvenile and old animals, and the SS and IS from juvenile to adult as well (Figure 1). Toe stiffness of the US, SS, and IS was increased from juvenile to adult animals, and from juvenile to old animals in the US and IS (Figure 2). Linear stiffness also increased in US and SS juvenile to adult, and US juvenile to old (Figure 2). No differences in insertion site modulus were observed for any of the tendons across age (Figure 3).

Discussion:

This study defines the effect of aging on the mechanical properties of the subscapularis, supraspinatus, infraspinatus, and teres minor tendons of the rotator cuff in a rat model. Supraspinatus structural properties (toe and linear stiffness) and its viscoelastic response (stress relaxation) displayed degenerative changes earlier in the aging process with consistent differences between juvenile and adult ages. These earlier changes were also observed in the upper subscapularis and infraspinatus, but not as consistently across properties. Surprisingly, these changes were not exacerbated further into old age, with no differences between the adult and old group in any of the tendons for any of the properties examined. Previous studies reported a steady and dramatic increase in supraspinatus tears in the aging human population.[1-4] Results from the animal model presented here demonstrate that supraspinatus tendon health is consistently affected earlier in the aging cycle, which may predispose the supraspinatus to injury due to other factors not present in this study such as overuse, high cholesterol, and diabetes.[9-11] Future studies will investigate the effect of aging on the healing response of the supraspinatus compared to the other rotator cuff tendons.

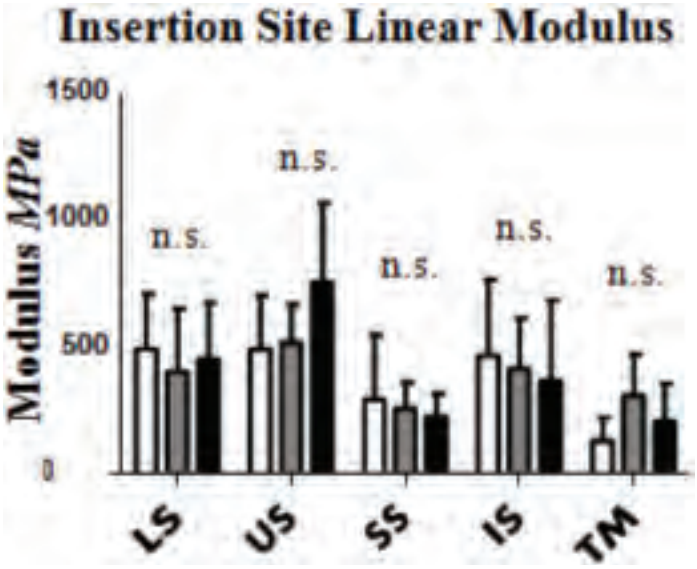

Figure 3. Insertion site linear modulus showed no changes.

Significance:

This study highlights that supraspinatus degeneration initiates early in the aging cycle. These findings could potentially guide timely preventative therapeutic interventions to arrest the continued degeneration of this important rotator cuff tendon.

Acknowledgement:

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Biceps Detachment Alters Joint Function and Tendon Mechanical Properties in a Chronic Massive Rotator Cuff Tear Rat Model

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Introduction:

Lesions of the long head of the biceps tendon are often associated with massive rotator cuff tears (MRCT) and may be responsible for shoulder pain and dysfunction.[1] As a palliative treatment, biceps tenotomy is sometimes recommended for pain relief and improvement in joint function.[2] Our previous study indicated that simultaneous detachment of the long head of the biceps tendon in the presence of a MRCT resulted in improved shoulder function and reduced damage to the joint.[3] However, the effect of biceps tenotomy on the surrounding tissues in a chronic condition remains unknown. Therefore, the objective of this study was to define the impact of surgical detachment of the biceps tendon as a potential treatment in a chronic MRCT rat model. We hypothesized that biceps tenotomy would result in improved mechanical and histological properties of the intact subscapularis tendon and improved in vivo shoulder function.

Methods:

Study Design: In 25 male Sprague-Dawley rats (464 ± 24 g; IACUC approved), the supraspinatus and infraspinatus tendons were detached to create a MRCT followed by 4 weeks of cage activity. Animals were then randomly divided into groups that received a surgical biceps tenotomy (BT, n = 11) or a sham surgery (SS, n = 14).

Mechanics: Upper and lower bands of the subscapularis tendon were mechanically tested independently, 4 weeks after the second surgery.[4] Stain lines were used to track optical strain. Cross-sectional area was measured using a custom laser device.[5] Stiffness was calculated as the slope of the linear region of the load-displacement curve during a ramp to failure at 0.3%/s. Modulus was calculated as slope of the linear region of the stress-strain curve. Stress relaxation (%) was calculated from a 300s stress-relaxation test at 6% strain.

Histology: Subscapularis tendon sections were stained with hematoxylin and eosin and images were graded for cell density and cell shape.[7]

Quantitative ambulation: To assess in vivo shoulder joint function, forelimb gait and ground reaction forces were recorded using an instrumented walkway 1 day before the first detachment surgery (baseline), as well as 1 day before, and 3, 7, 10, 14, and 28 days after the second biceps tenotomy/sham surgery.[6]

Statistics: Ambulation data was assessed using a two- way ANOVA with multiple imputations (for ~13% of missing data). Tendon mechanical properties were compared using t-tests. Histology grades were compared using a Mann-Whitney test. Significance was set at $p < 0.05$ and trends at $p \leq 0.1$.

Results:

Decreased stress relaxation and increased tendon stiffness, along with a decrease in insertion site modulus, were exhibited in the lower band of the subscapularis tendon in the BT group. A trend of decreased stress relaxation was observed in the upper band in the BT group with no changes in any other mechanical parameters (Figure 1). A trend of increased

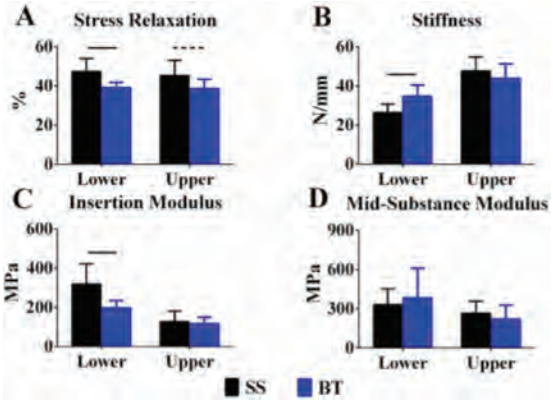

Figure 1. Mechanical properties. Lower subscapularis tendon in the BT group showed **(A)** decreased percent stress relaxation and **(B)** increased stiffness, but **(C)** insertion site modulus was decreased. **(A)** Upper subscapularis tendon in the BT group showed a trend of decreased percent stress relaxation.

cellularity was noted in the insertion area of the lower band in the BT group with no differences in the upper band (Figure 2). Consistently decreased lateral stride width following the second surgery was observed in rats in the BT group (Figure 3). Increased vertical force and rate of loading in the operated limb and increased speed of the contralateral limb were noted in animals with biceps tenotomy.

Discussion:

This study investigated the role of biceps tenotomy in the presence of a chronic massive rotator cuff tear. The resulting increase in overall lower band tendon stiffness and decrease in both upper and lower bands stress relaxation can be attributed to a rebalance of the transverse force couple as previously reported.[7] In the absence of biceps tenotomy, the unbalanced anteriorly directed force of the biceps tendon on the humeral head could decrease loading to the subscapularis tendon, resulting in reduced stiffness of the lower band. This is supported by an increased stride width in the SS group at later time points, as the intact biceps may prevent internal rotation in that group. Furthermore, the decrease in insertion site modulus of the lower band in the BT group indicates a return toward baseline subscapularis material properties (unpublished data). The increases in cellularity in the lower band of the BT group could indicate remodeling in response to biceps detachment and support these mechanical differences. Further studies will investigate the effects of biceps tenotomy on other joint tissues such as articular cartilage to more thoroughly quantify joint health. Overall, results suggest biceps tenotomy in the presence of chronic massive rotator cuff tears partially preserves in vivo shoulder function and potentially restores subscapularis tendon health, consistent with our previous study and supported by clinical outcomes.[3,8]

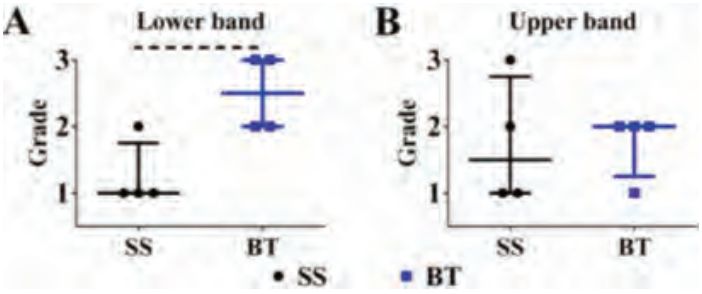

Figure 2. Histology. **(A)** Lower subscapularis tendons in the BT group showed a trend of increased cellularity in the insertion area. **(B)** No difference was noted in the upper subscapularis tendons.

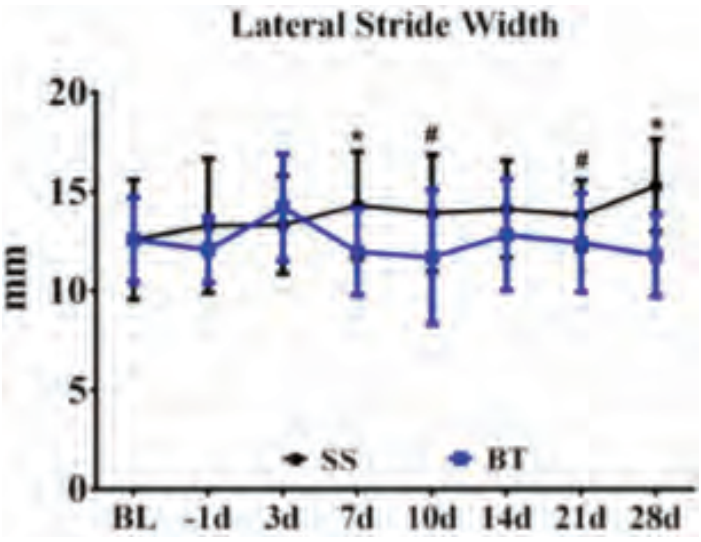

Figure 3. Ambulation. Rats in the BT group showed decreased lateral stride width from 7 days after the biceps tenotomy / sham surgery. (* $p < 0.05$, # $p < 0.10$)

Significance:

This study demonstrates that biceps tenotomy results in largely protective effects to various parts of the shoulder joint in chronic massive rotator cuff tears in a rat model. Further investigation of the role of biceps tenotomy on overall shoulder joint health is needed.

Acknowledgements:

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Indirect Decompression Progresses Substantially after Immediate Postoperative Period following Lateral Lumbar Interbody Fusion

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Introduction

Lateral lumbar interbody fusion (LLIF) is a useful technique for the treatment of lumbar spinal stenosis combined with spinal instability. LLIF is discectomy and interbody fusion via a lateral transpsoas approach to the lumbar spine.[1] Compared to posterior techniques, this approach allows a thorough discectomy and disc space preparation and placement of a large interbody device on the lateral apophyseal rings of the vertebral body.[2] In the setting of a preserved anterior longitudinal ligament, ligamentotaxis and tensioning of the annulus and the hypertrophic ligamentum flavum allows restoration of disc height and subsequent reduction of spondylolisthesis. These unique technical aspects allow for the phenomenon of indirect decompression. This reduction of spondylolisthesis and tensioning of the ligametum flavum has been shown radiographically to enlarge the area of the neural foramina and central canal post-operatively.[3] Indirect decompression via LLIF can obviate the need for a posterior decompression in the form of laminectomy, laminotomy, facetectomy, or foraminotomy.[4,5] The complications germane to open decompression procedures such as epidural hematoma, postoperative anemia, nerve root injury, CSF leak, epidural fibrosis, and additional muscle disruption may be avoided if indirect decompression via LLIF is successful.[6]

Radiographs and MRI have been used to quantify the indirect decompression that occurs in the 2 week immediate post-operative period with a documented average 41.9% increase in disc height, 13.5% increase in foraminal height, 24.7% increase in foraminal area, and 33% increase in central canal area.[3] There has not yet, however, been a study noting continued progression of the indirect decompression achieved by LLIF after the immediate post-operative period.

Materials and Methods

A 63 year old female presented with 6 months of mechanical back pain and neurogenic claudication in the setting of a previous L2-L3 LLIF with lateral plate and interspinous process plate by an outside surgeon 8 years prior. MRI demonstrated adjacent segment degeneration and severe spinal stenosis and degenerative spondylolisthesis at L3-L4. The patient failed conservative treatment and was a candidate for surgical intervention. An L3-L4 LLIF with percutaneous bilateral pedicle screw instrumentation was performed. A direct posterior decompression was not performed (CoRoent XL, NuVasive Inc, San Diego, CA). There was complete resolution of neurogenic claudication on post-operative day (POD) one. On POD two, a lumbar spine MRI was obtained incidentally. At 19 months post-operatively the patient had another MRI for symptoms of lumbar radiculopathy unrelated to the surgical level. This series of MRIs provided the opportunity to compare the amount of indirect decompression achieved long term with the immediate post-operative decompression.

Results

The pre-operative axial images demonstrate severe central canal and lateral recess stenosis at L3-L4 (Figure 1). Despite the immediate post-operative resolution of symptomatic neurogenic claudication, the MRI that was performed on POD two continues to demonstrate severe spinal stenosis in the central canal and lateral recess of the L3-L4 segment (Figure 2). At 19 months, images demonstrate nearly full resolution of spinal stenosis in the central canal and lateral recess, with significant attenuation of the facet joints, annulus, and ligamentum flavum (Figure 3).

Discussion

In this case, there was not only successful immediate resolution of the patient's neurogenic claudication but also an improvement in the radiographic degree of stenosis at the surgical level that continued to improve beyond the immediate post-operative period following LLIF. LLIF has been shown to indirectly decompress the neural elements immediately following surgery, but this case suggests that decompression may continue to progress well after the immediate post-operative period. This is the first report that suggests long term progression of indirect decompression of

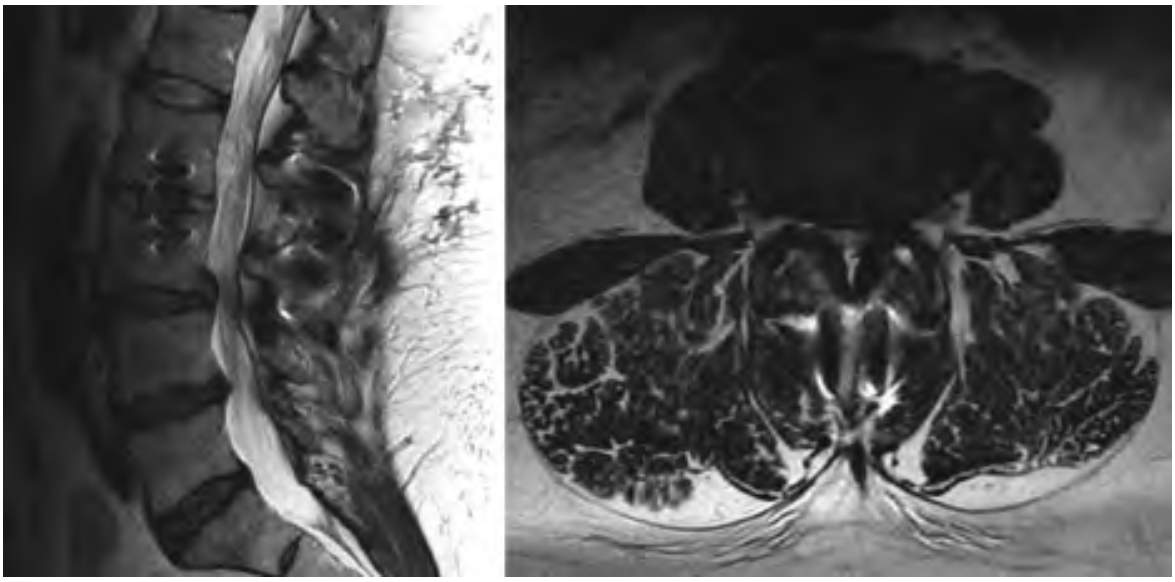

Figure 1. Preoperative T2 mid-sagittal and axial images of the L3-L4 level.

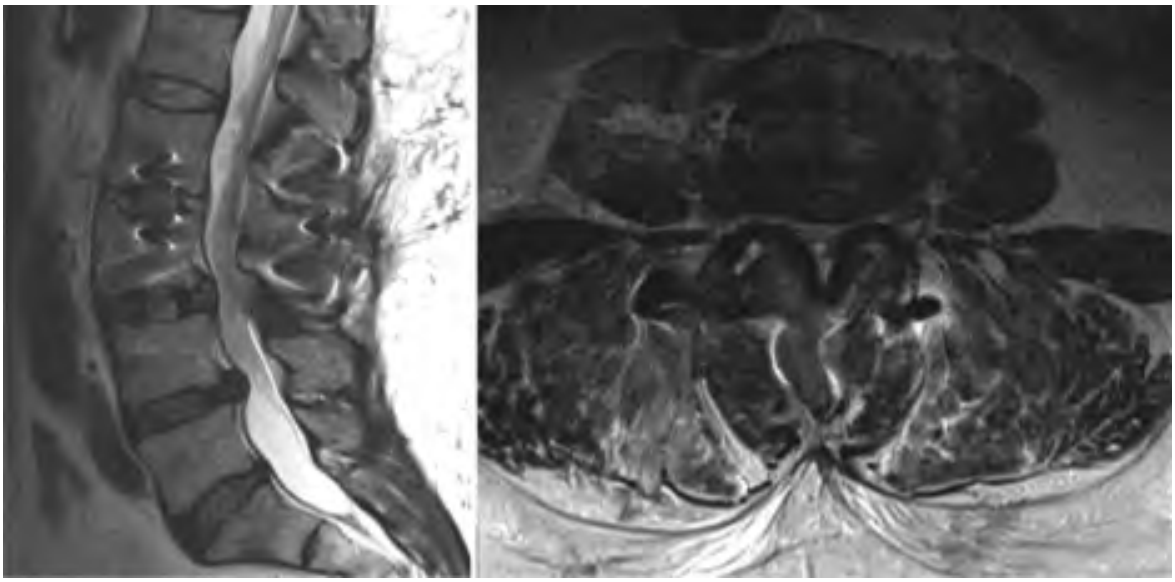

Figure 2. Post-operative day 2 T2 mid-sagittal and axial images of the L3-L4 (operative) level.

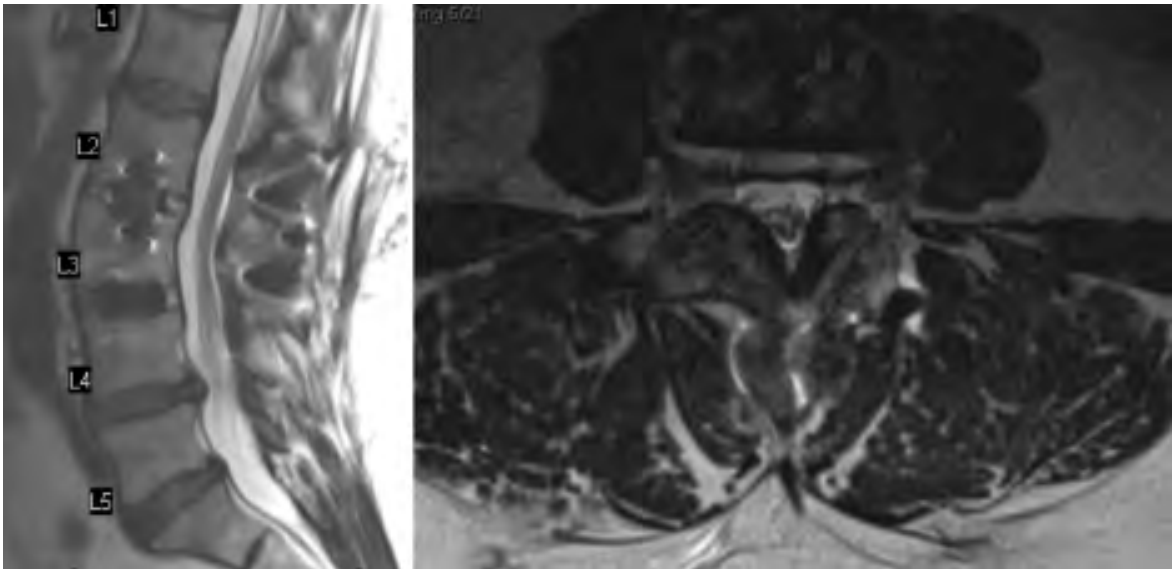

Figure 3. 19 months post-operative T2 mid-sagittal and axial images of the L3-L4 (operative level).

the lumbar spine with comparison to the immediate post-operative period. The attenuation of not only the bony facet joints but also the posterior soft tissues including the posterior annulus and ligamentum flavum is of particular interest.

Further research may include retrospective or prospective imaging studies of cases of LLIF that involved indirect decompression for symptomatic central and/or lateral lumbar stenosis to validate what this case study suggests. Furthermore, the extent of decompression could be quantified and the time-course of progressive indirect decompression established. Such information could be useful for patient counseling, pre-operative planning, and post-operative expectations.

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U·P·O·J

Risk Factors for Surgical Site Infections after Posterior Spinal Fusion in Neuromuscular and Cerebral Palsy Scoliosis Patients: A Retrospective ACS NSQIP Pediatric Database Analysis

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Introduction

Surgical site infections (SSI) after pediatric spinal deformity surgery greatly increase postoperative morbidity and rates of readmission. In addition, these complications drastically increase healthcare costs with mean hospitalization of 29 days and hospital charges of $154,000, respectively. In some cases, a deep SSI may result in hardware removal, deformity progression, and failure to cure.[1-4] Incidence greatly varies depending on scoliosis etiology, ranging from 0.5% with adolescent idiopathic scoliosis to ≥ 25% for neuromuscular scoliosis. Despite unique patient population-specific infection rates and risk factors, multiple etiologies are often combined as single cohorts in the literature.[1]

Studies have shown higher SSI incidence in neuromuscular scoliosis patients, with associated risk factors including incontinence, inappropriate antibiotics, obesity, malnutrition, pelvic fixation, operative time, blood transfusion, prolonged hospitalization, and others.[3] Existing studies analyzing SSI risk factors are generally small, single-center studies, and research of risk factors on subtypes of neuromuscular scoliosis such as cerebral palsy (CP) is very limited.[2,5-7] Thus, the purpose of our study was to identify perioperative risk factors for wound complications in neuromuscular and CP scoliosis patients using the American College of Surgeons (ACS) National Surgical Quality Improvement Program Pediatric (NSQIP-P) database.

Methods

Data Collection

The NSQIP-P databases for available years 2012 and 2013, containing 51,008 and 63,387 cases at 50 and 56 participating sites respectively, were retrospectively queried. CPT codes for posterior spinal fusion (PSF) as a main, other, or concurrent procedure of >7 segments were used. Other etiologies of scoliosis or spinal pathology were excluded by ICD-9 codes (Figure 1), confining our cohort to neuromuscular scoliosis patients with or without CP (NMS) (n = 702), and neuromuscular scoliosis patients with CP (CPS) (n = 411). SSI was classified according to CDC National Healthcare Safety Network criteria.[8] We collectively grouped all SSI types as one outcome, wound complications, which included superficial and deep incisional SSI, organ/space SSI, and deep and superficial wound disruption. We evaluated individual and perioperative factors as risk factors for that outcome.

Statistical Analysis

Statistical analysis was completed with. Univariate analysis was conducted to identify appropriate regressors for multivariate analysis. We performed binary logistic regression using regressors which were significant on univariate at the 0.10 level or less. Finally, we used Receiver Operating Characteristic (ROC) curves on significant continuous variables to select thresholds that optimize sensitivity and specificity, and then recoded the variables so that the continuous variables were the new binary variables discovered in the ROC analysis. A new regression model including odds ratios (OR) was created based upon binary variables created in the previous step. All analysis was completed with SPSS v.20.

Results

Demographics, perioperative factors, and comorbidities are detailed in Table 1. Postoperative adverse events including wound complications and unplanned reoperation details are listed in Table 2.

Neuromuscular Scoliosis

Wound complication and unplanned reoperation related to index procedure rates were 57/702 (8.1%) and 42/702 (6.0%), respectively. Logistic regression showed ASA classes 3&4 ($p = 0.043$, OR = 3.0), pelvic fixation ($p = 0.047$, OR = 1.9), and operative time ($p = 0.011$), where exceeding 6.5 hours resulted in even higher risk ($p = 0.007$, OR = 2.1), to be risk factors for wound complications. Congenital heart disease (CHD) approached statistical significance as a risk factor ($p = 0.052$, OR = 2.3).

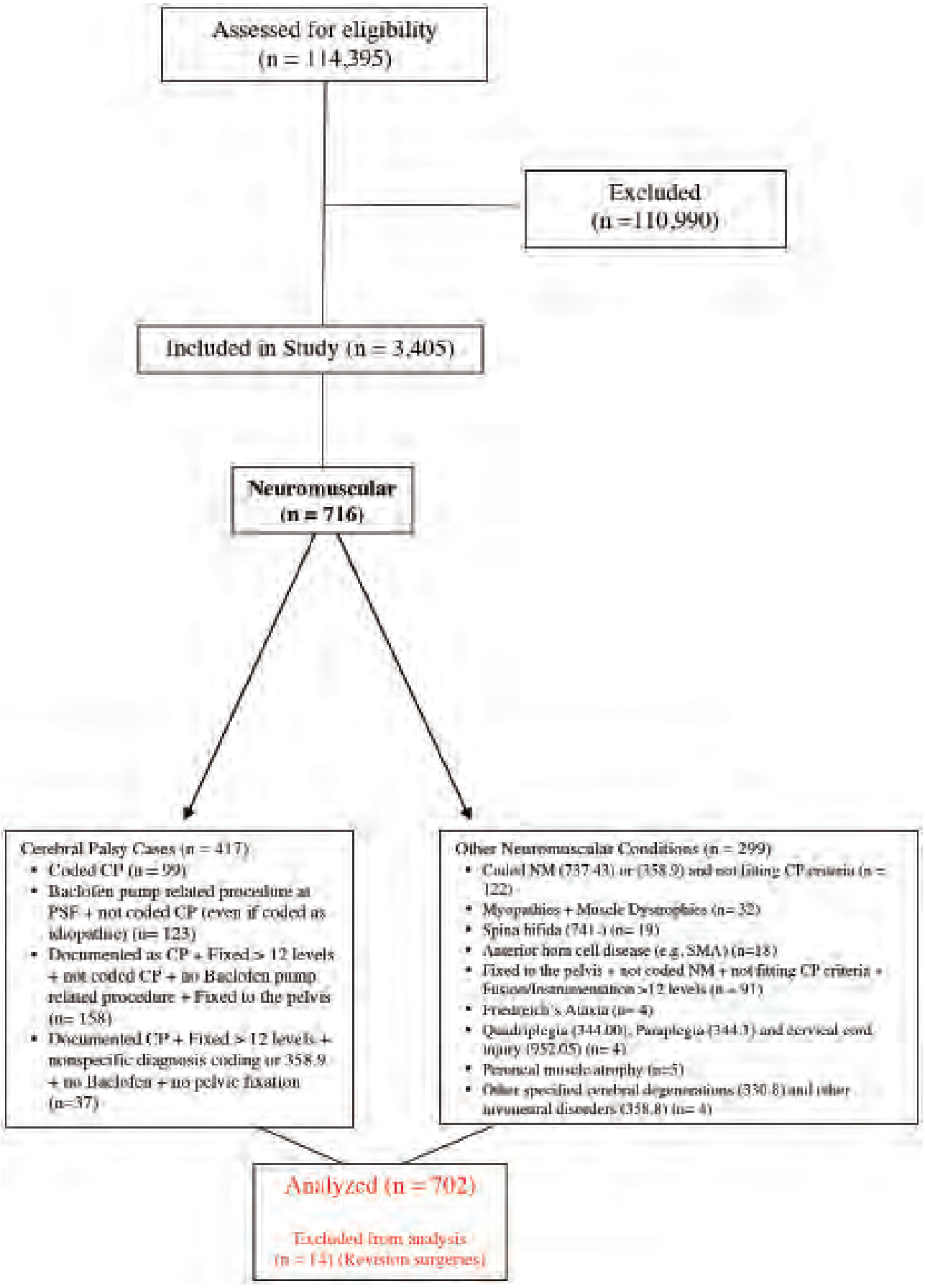

Figure 1. Consort diagram showing patients included and excluded for analysis.

Table 1. Demographics and perioperative comorbidities documented for Idiopathic, Neuromuscular and CP patients in NSQIP Ped database for 2012 & 2013

		All Neuromuscular Cases (n = 702)	CP Cases (n = 411)	All patients (N = 3362)
Preoperative				
Age at surgery in years		13.2±3	13.5±2.8	14±2.4
Gender	M (%)	316 (45%)	177 (43.1%)	927 (27.6%)
F (%)	386 (55%)	234 (56.9%)	2435 (72.4%)	
Weight at surgery in kg		39.5±17.1	38.9±16.2	50.8±17.5
Body Mass Index (BMI) in kg/m2		18.2±10.3	17.7±9.8	20.5±8.1
Diabetes		0	0	11 (0.3%)
Seizure Disorder		267 (38%)	205 (49.9%)	367 (10.9%)
Asthma		116 (16.5%)	71 (17.3%)	303 (9%)
O2 Support preoperatively		59 (8.4%)	27 (6.6%)	77 (2.3%)
Tracheostomy		41 (5.8%)	20 (4.9%)	50 (1.5%)
Congenital Heart Disease		54 (7.7%)	22 (5.4%)	163 (4.8%)
Previous Cardiac Surgery		31 (4.4%)	17 (4.1%)	114 (3.4%)
Cardiac Risk	None	617 (87.9%)	379 (92.2%)	3121 (92.8%)
Minor	52 (7.4%)	22 (5.4%)	150 (4.5%)	
Major	28 (4%)	8 (1.9%)	74 (2.2%)	
Severe	5 (0.7%)	2 (0.5%)	17 (0.5%)	
Steroid Use within 30 days		21 (3%)	6 (1.5%)	44 (1.3%)
Prior Operation within 30 days		19 (2.7%)	5 (1.2%)	31 (0.9%)
Open Wounds (with or without infection)		12 (1.7%)	5 (1.2%)	18 (0.5%)
Weight Loss/ Failure to Thrive		29 (4.1%)	18 (4.4%)	47 (1.4%)
Nutritional support		247 (35.2%)	181 (44%)	314 (9.3%)
Bleeding Disorders		14 (2%)	9 (2.2%)	32 (1%)
Preoperative Serum Albumin (gm/dL)		4.3±0.5	4.3±0.6	4.4±0.4
Preoperative WBCs		7.2±2.6	6.9±2.6	6.9±2.6/dL
Preoperative HCT		40.7±4.7	41±4.9	39.7±4.1%
ASA Class.	ASA 1	29 (4.1%)	25 (6.1%)	679 (20.2%)
	ASA 2	128 (18.2%)	79 (19.2%)	1680 (50%)
	ASA 3	490 (69.8%)	286 (69.6%)	924 (27.5%)
	ASA 4	54 (7.7%)	20 (4.9%)	71 (2.1%)
	None assigned	1	1	8
Intraoperative				
Anaesthesia Time in Hours		8.2±2.4	8.2±2.1	6.8±2.1
Operative Time		6±2.2	6.1±1.9	5±1.9
Spinal Osteotomy		227 (32.3%)	149 (36.3%)	1034 (30.8%)
13-level instrumentation or more		586 (83.5%)	338 (82.2%)	1418 (42.2%)
Pelvic Fixation		399 (56.8%)	243 (59.1%)	402 (12%)
Concomitant Anterior Spinal Fusion		19 (2.7%)	9 (2.2%)	53 (1.6%)
Baclofen Pump-Related Procedure		134 (19.1%)	134 (32.6%)	134 (4%)
Inotropic Support intraoperatively		16 (2.3%)	8 (1.9%)	119 (3.5%)
Cases with Blood Transfusion		568 (80.9%)	337 (82%)	2376 (70.7%)
Days until Transfusion		0.1±0.5	0.1±0.5	0.1±0.5 days
Total Amount Transfused in ml		913.8±756.4	955.2±761.7	444.2±603

Table 2. Postoperative adverse events documented for Idiopathic, Neuromuscular and CP patients in NSQIP Ped database for 2012 & 2013

Postoperative Adverse Event	All Neuromuscular Cases (n = 702)	CP Cases (n = 411)	All patients (N = 3362)
Postoperative Wound Problems	57 (8.1%)	36 (8.8%)	120 (3.6%)
Superficial Incisional SSI	11 (1.6%)	5 (1.2%)	34 (1%)
Deep Incisional SSI	15 (2.1%)	11 (2.7%)	44 (1.3%)
Organ/Space SSI	5 (0.7%)	4 (1%)	12 (0.4%)
Superficial Wound Disruption	21 (3%)	14 (3.4%)	58 (1.7%)
Deep Wound Disruption	16 (2.3%)	10 (2.4%)	36 (1.1%)
Unplanned Reoperation	50 (7.1%)	37 (9%)	151 (4.5%)
Related to the index surgery	42	32	136
Second Unplanned Reoperation	16 (2.3%)	12 (2.9%)	42 (1.2%)
Third Unplanned Reoperation	9 (1.3%)	7 (1.7%)	21 (0.6%)
Unplanned Readmission	59 (8.4%)	43 (10.5%)	171 (5.1%)
Related to the index surgery	42	29	121
Death within 30 days of index surgery	3 (0.4%)	2 (0.5%)	7 (0.2%)

Cerebral Palsy Scoliosis

Wound complication and unplanned reoperation related to index procedure rates were 36/411 (8.8%) and 32/411 (7.8%), respectively. Logistic regression showed CHD ($p = 0.024$, OR = 3.0), inotropic support at time of surgery ($p = 0.003$, OR = 11.0), and pelvic fixation ($p = 0.006$, OR = 3.5) to be predictors of wound complications.

Discussion

Wound problems are clinically and financially devastating to patients and their families after spine deformity surgery, particularly in patients with neuromuscular etiologies. Our rates of wound complications are consistent with multiple independent studies,[9-11] and NSQIP database studies specifically have reported SSI rates for neuromuscular patients of 4.67%, 1.52%, and 4.5%.[12-14] Variation between studies is largely due to different patient inclusion/exclusion and dependent outcome criteria, for example our study combines wound disruptions with SSI.

ASA classes 3&4 and pelvic fixation were shared risk factors in NMS and CPS patients, which has been observed in other literature.[12-16] Previous NSQIP studies have identified complication risk factors for spine deformity surgery using multivariate analysis, including cardiac and hepatobiliary disease, obesity, cognitive impairment, ASA classes 3&4, and prolonged operative time; however, they did not separate patients with CP as done here.[12,13]

Basques et al analyzed neuromuscular scoliosis patients in NSQIP using multivariate analysis, and they found that BMI-for-age $\geq 95^{th}$ percentile, ASA classes 3&4, and pelvic fixation were risk factors for infection. Our study uniquely found operative time as a wound complication risk factors for neuromuscular patients, and CHD and inotropic support as specific risk factors for CPS patients. In a systematic review on outcomes of scoliosis surgery in CP patients, Toovey et al found insufficient evidence to make clinical recommendations on complication risk factors.[17] Minhas et al found that underweight status was a risk factor for 30-day complications in CP patients undergoing various orthopedic surgeries; however, their sample was not limited to spine procedures.[15]

Limitations of this study include the relatively small sizes of our study samples in comparison to other studies utilizing NSQIP, as well as only 2 years of available data, which limits the statistical power of identifying other wound complication risk factors even though they are likely clinically irrelevant. Furthermore, NSQIP does not record important operative details including implant types, exact number of instrumented segments, and technique variability, nor does it include follow-up past 30 days postoperatively.

Conclusions

Newly identified risk factors unique to the two patient populations in this study may assist surgical candidacy assessment and offer areas for preoperative and intraoperative improvement in wound complication prevention.[1,18] For example, McLeod et al found that broad-spectrum antimicrobial prophylaxis for PSF varied amongst national hospitals, and new studies are needed to compare prophylaxis effectiveness amongst specific high-risk subgroups such as CP patients identified here.[19] Furthermore, this study will allow more effective preoperative counseling of patients and families on the risks of surgery, and illustrates unique risk factors for cerebral palsy scoliosis patients using a large multi-center national database.

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Development of Disc-Like Angle Ply Structures for Total Disc Replacement at Clinically Relevant Size Scales

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Introduction

Replacement of the disc with a viable, tissue-engineered construct that mimics native disc structure and function is an attractive alternative to fusion or mechanical arthroplasty for the treatment of disc pathology. Towards this end, our group has developed disc-like angle ply structures (DAPS) sized for the rat caudal disc space that achieve near native composition and mechanical function with *in vitro* culture.[1] Composite tissue-engineered discs have also been developed by several other groups; however, the average size of constructs reported in the literature remains a fraction of the size of human discs.[2-3] In order to translate tissue-engineered disc replacement towards clinical use, successful fabrication and *in vivo* evaluation of these constructs at larger size scales is critically important. The purpose of this study was to evaluate the maturation of medium (rabbit lumbar disc equivalent) and large (goat/human cervical disc equivalent) sized DAPS constructs over 15 weeks of *in vitro* culture and after 5 weeks of subcutaneous implantation.

Methods

DAPS Fabrication, Culture and Subcutaneous Implantation

DAPS were fabricated in two sizes—medium (3 mm height × 10 mm diameter, NP diameter = 5 mm) and large (6 mm height x 20 mm diameter, NP diameter = 10 mm). The AF region of the DAPS was fabricated by electrospinning aligned sheets of 250-300 μm thick poly(ε-caprolactone) (PCL), and cutting the sheets into strips at a 30 degree angle. The strips were hydrated, coated with fibronectin and seeded with bovine AF cells (3,333 cells/mm^2). Following 1 week of culture in chemically defined media with TGF-β3 (CM+), strips were coupled at opposing fiber angles (+/− 30°), and wound in a custom mold to form the circular AF region. The NP region of the DAPS was fabricated by seeding bovine NP cells in a 2% agarose hydrogel (20 million cells/mL), and culturing for 2 weeks in CM+ prior to combining with the AF region. The combined DAPS were cultured for either 5, 10 or 15 weeks in CM+ on an orbital shaker. After 5 weeks of pre-culture, DAPS of both size scales (n = 6 per size) were implanted subcutaneously (SQ) in athymic rats for 5 weeks.

Viability, Metabolic Activity and Biochemistry

At each *in vitro* and *in vivo* time point (n=4-6 per group), DAPS of each size were bisected. From one half-DAPS, GAG and collagen content were quantified via the DMMB assay and the OHP assay, respectively. From the remaining half DAPS, cell viability of the NP region was assessed via live-dead staining, and metabolic activity of the AF region was assessed via the MTT assay. *MRI and Mechanical Testing:* At each *in vitro* time point (n = 3 per group), sagittal MRI T2 maps of the DAPS were obtained. Mechanical properties of the DAPS in unconfined compression (20 cycles compression, 0.24 MPa) were determined via a bi-linear fit of the stress-strain curve.

Histology

DAPS (n = 2 per group) were processed through paraffin, sectioned in the sagittal plane, and stained with Alcian blue (GAG) or picrosirius red (collagen).

Statistics and Correlation Analysis

Significant differences in quantitative outcome measures were assessed via two- way ANOVA with Tukey's post-hoc test. Correlations between DAPS T2 values, biochemistry and mechanical properties were assessed using the *corr.test* function in R (r-project.org) for each size scale.

Results

In general, medium DAPS outperformed large DAPS with respect to AF and NP cell viability during *in vitro* culture and following subcutaneous implantation (Figure 1A, B). Subcutaneous implantation of the DAPS significantly increased AF cell metabolic activity in the medium DAPS, while NP cell viability was significantly reduced at both size scales compared to pre- implantation values. Analysis of compressive mechanical properties (Figure 1C, D), illustrated that medium DAPS matured more rapidly than large DAPS, as characterized by increases in toe modulus and reductions in transition strain at 10 weeks. AF T2 values significantly decreased from 5 to 15 weeks culture in both medium and large DAPS; NP T2 values were not affected by culture duration. NP and AF GAG and collagen content were significantly higher in medium DAPS compared

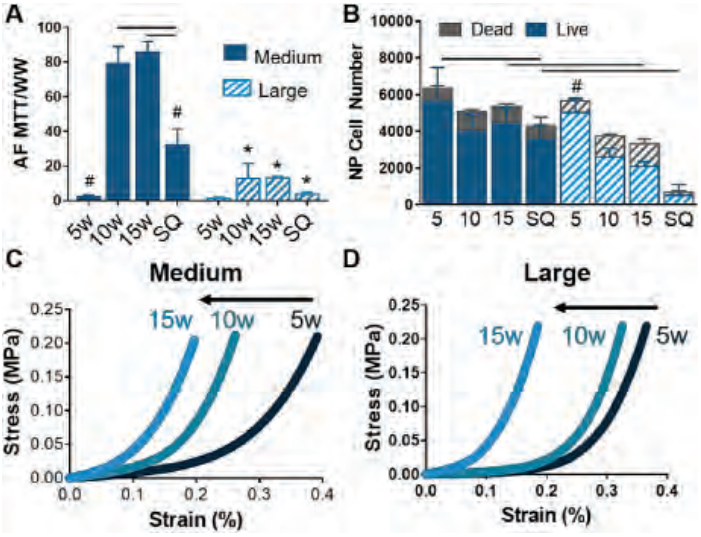

Figure 1. DAPS **(A)** AF cell metabolic activity, **(B)** NP cell viability for all experimental groups, and representative compressive stress- strain curves of **(C)** medium and (D) large DAPS. Bars denote significance, * = $p < 0.05$ compared to medium at the same time point. # = $p < 0.05$ compared to all other time points within a size.

to large DAPS, and reached maximal values after 15 weeks of culture at both size scales (Medium: NP GAG = 3.0%ww, AF GAG = 2.4%ww, NP collagen = 2.0%ww, AF collagen = 1.4%ww; Large: NP GAG = 1.5%ww, AF GAG = 1.2%ww, NP collagen = 1.1%ww,AF collagen = 1.0%ww). NP GAG content was significantly reduced compared to pre-implantation values in both medium and large DAPS following SQ implantation. SQ implantation significantly increased NP collagen content in the medium DAPS, but did not affect AF collagen or GAG content at either size scale. Histology (Figure 2) confirmed quantitative biochemical analyses and further demonstrated the heterogeneity of matrix distribution present in the DAPS, particularly at the large size scale. Correlation analyses illustrated stronger correlations between MRI, biochemistry and mechanical properties in the medium DAPS than in large DAPS.

Discussion

Medium DAPS outperformed large DAPS, maturing more rapidly with more homogenous matrix distribution compared to large DAPS. Subcutaneous implantation was detrimental to

Figure 2. Alcian blue (top) and picrosirius red (bottom) stained sagittal histology section of DAPS in each experimental group (scale = 2 mm).

cell viability and GAG content in the NP region independent of DAPS size, as we have previously observed in small DAPS sized for the rat caudal disc space.[4] In contrast, AF matrix content was maintained at pre-implantation values at both size scales following subcutaneous implantation, potentially due to infiltration of host cells into the outer layers of the AF. *In vitro* matrix distribution and *in vivo* performance of large DAPS could be further improved via the inclusion of nutrient channels, as has been utilized for cartilage tissue engineering, or via culture in a bioreactor.[5-6] Future work will evaluate the DAPS in a large animal model to further the translation of these constructs for the treatment of end stage disc degeneration.

Significance

We have demonstrated the feasibility of scaling up DAPS for total disc replacement to clinically relevant size scales. Clinical translation of tissue-engineered discs will offer an alternative to mechanical disc arthroplasty and fusion procedures, and may change the paradigm of clinical care for patients with disc pathology and associated axial spine and neurogenic extremity pain.

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The Effect of Remobilization on the In Vivo Function of an Endplate-Modified Engineered Disc

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Introduction

A promising alternative to fusion surgery for intervertebral disc pathology is total disc replacement with a cellular, engineered whole disc construct that restores normal structure and mechanical function to the spine. To this end, our group developed endplate-modified disc-like angle-ply structures (eDAPS) that mimic the structure and function of the native disc. Our previous work showed that, over a 5 week period of implantation in the rat tail disc space, eDAPS outperformed DAPS implanted without endplates with respect to construct composition and integration.[1] However, this previous work utilized an external fixator to immobilize the segment post-implantation. Chronic immobilization is known to be detrimental to disc health,[2] and thus the eventual restoration of physiologic loading to the implanted eDAPS will be essential for integration and long term viability.The purpose of this study was therefore to elucidate the impact of remobilization (via fixator removal) on eDAPS structure, composition and mechanics.

Methods

eDAPS Fabrication and Culture

eDAPS sized for the rat caudal disc space were fabricated by concentrically wrapping aligned, angled strips of electrospun PCL nanofibers to form the AF region, and filling the center with a hyaluronic acid hydrogel to form the NP region [3]. Both regions were seeded with bovine disc cells (2×10^6cells/AF and 6×10^5 cells/NP), and combined after two weeks culture with acellular porous PCL endplates to form the eDAPS. eDAPS were pre-cultured for 5 weeks in chemically defined media with TGF-β3.

Implantation

32 athymic, male, retired breeder rats were anesthetized, and Kirschner wires were passed through the C8 and C9 caudal vertebral bodies, allowing for external fixator placement.[4] eDAPS were implanted following removal of the C8-C9 disc and a partial corpectomy of the adjacent vertebral bodies. The effects of remobilization (R) via external fixator removal were investigated after 5 weeks or 10 weeks of implantation, with endpoints of 10 weeks (10W R, n = 6) and 20 weeks (20W R, n = 10), respectively. Control groups included animals with external fixators left in place for 10 (10W F, n = 5) and 20 weeks (20W F, n = 11). *MRI:* T2 mapping of the eDAPS was performed at 4.7T (16 echoes,TE/TR = 7.84 ms/2,000 ms, FOV = 15x15 mm^2). Average T2 maps were generated for each time point using a custom MATLAB code.

μCT Imaging and Radiographs

In the 20W R and 20W F groups, the PCL endplates were rendered radiopaque via the inclusion of zirconia nanoparticles.[5] Implanted motion segments were subjected to μCT scanning at 3μm resolution before and after application of 3N compressive loading (Scanco μCT50 Compression Device) to identify functional boney integration of the constructs. Lateral tail radiographs were taken immediately post-operative (PO), and at 10, 15, and 20 weeks PO. The angulation of the vertebral bodies (VB) of the implanted motion segment was quantified in MATLAB.

Mechanical Testing

3-4 vertebra-eDAPS-vertebra segments in each experimental group, and 4 native rat tail vertebra-disc-vertebra segments were subjected to compression testing (20 cycles, 0 to 3N, 0.05 Hx), followed by tension to failure for eDAPS samples. Mechanical properties were quantified via a bilinear fit to the 20^{th} cycle. Sugnificant differences in quantitative outcomes were assessed via a one-way ANOVA with Tukey's post-hoc test.

Results

NP T2 values (Figure 1) were maintained at native levels for up to 20 weeks *in vivo*; there were no significant differences in NP T2 across experimental groups. The toe and linear region moduli (Figure 2A) of eDAPS implanted motion segments were not significantly different from native rat tail motion segments, and there were no significant differences between experimental groups. Maximum strain was significantly greater in the 10W R group compared to the native rat tail disc; no other significant differences between groups or compared to native discs were found for transition and maximum strains (not shown). Tensile load to failure after 10 weeks implantation ranged from 4-8 N. Radiographic analysis

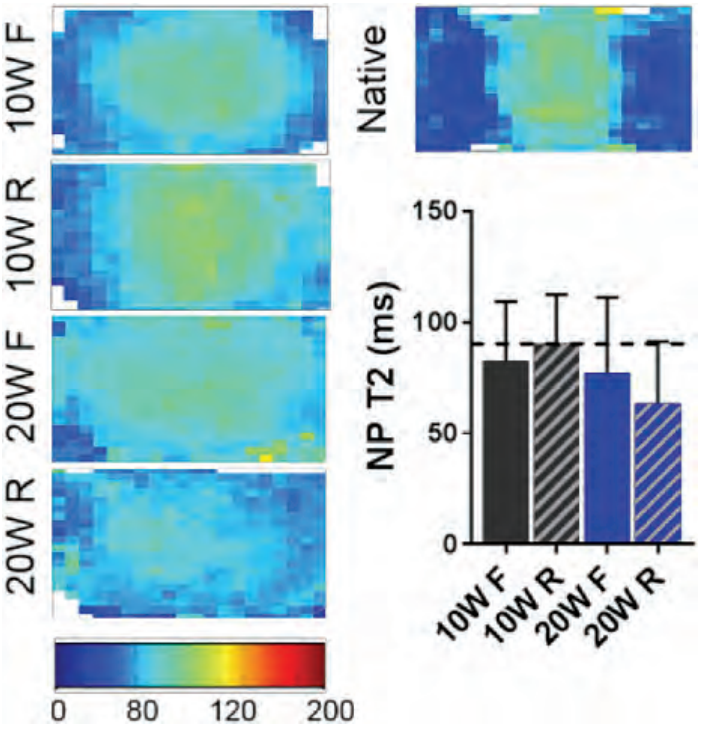

Figure 1. Average T2 maps for each experimental group, and quantification of NP T2. Dashed line = native rat tail NP.

revealed a progressive increase in vertebral body angle in eDAPS implanted motion Segments following remobilization. Vertebral body angle (Figure 2B) also increased from PO to 10 weeks in the fixed group, but remained stable from 10 to 20 weeks. Vertebral body angle was significantly higher in the remobilized group (9.6º) compared to the fixed group (5.0º) at 20 weeks. Vertebral body angulation in the remobilized group was further evident on μCT, and led to shearing of the implanted eDAPS under physiologic compressive loading. In contrast, the eDAPS remained well aligned in the fixed group, resulting in uniform axial compression of the implanted construct similar to the native disc (Figure 3).

Discussion

These data suggest that long-term *in vivo* implantation of the eDAPS results in maintenance of construct composition and functional integration. While mechanical properties and MRI T2 values were not different between fixed and remobilized groups, remobilization had adverse effects on motion segment morphology, regardless of whether the external fixator was removed at 5 or 10 weeks post-implantation. It is likely that even after 10 weeks *in vivo*, eDAPS integration is not sufficient to fully support restoration of native loading, particularly in the hypermobile rat caudal spine, which lacks stabilizing posterior elements. Ongoing work is further investigating the

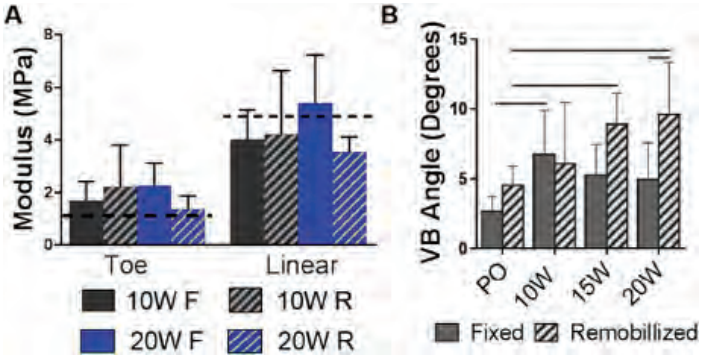

Figure 2. (A) Moduli for each experimental group. Dashed lines = native rat tail properties. **(B)** Vertebral body angle over time for fixed and remobilized groups. Bars denote significance.

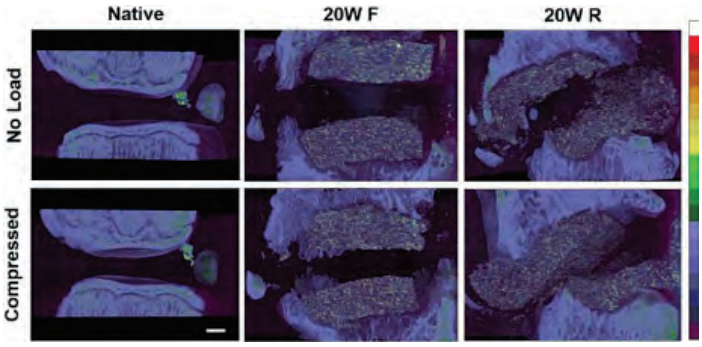

Figure 3. 3D reconstructions of μCT scans of motion segments from the fixed and remobilized groups, compared to the native rat tail disc, before and after application of 3N compression using the Scanco *in situ* compression device. Color scale represents bone mineral density.

biochemistry, histology and tensile properties of the 20 week implantation groups. Future work will evaluate the eDAPS in larger pre- clinical animal models, which have a more human-like morphology and motion.

Significance

Current surgical strategies for treating disc pathology do not restore native disc structure or function. A tissue-engineered disc replacement capable of integrating with the native environment, while maintaining composition and mechanical function, will significantly advance treatment options for patients with degenerative spinal pathology.

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TGF-b Improves Cell Viability in Human-Sized Disc-Like Angle Ply Structures (DAPS)

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Introduction

A number of whole-disc tissue engineering strategies have emerged for the replacement of pathologic discs[1,2], with some recent studies showing promise *in vivo*[3,4]. Our group recently developed disc-like angle ply structures (DAPS) sized for the rat tail (small, 1.5 mm height, 4 mm diameter) and showed that these constructs achieved near native composition[3, 5]. However, a major challenge remains in scaling these constructs to human size, where homogeneous matrix deposition will be required throughout a large expanse[6]. Transforming growth factor-beta (TGF-β) is one of the most widely utilized mediators for tissue engineering, as it can spur matrix formation[7]. However, our findings and those of others have shown that supplementation with active TGF-β results in heterogeneous matrix accumulation, concentrated near the periphery. To overcome this limitation, one recent publication described the provision of latent TGF-β alongside active TGF-β, and showed that this enhanced cell and matrix distribution in chondrocyte- based cartilage constructs[8]. In the present study, beginning with a chemically defined medium[5], we assessed the impact of latent TGF-β supplementation on nucleus pulposus (NP) cell matrix production and distribution in a 3D-hydrogel and DAPS culture system sized for human application.

Methods

NP cell-laden agarose hydrogel culture

NP cells were encapsulated in a 2% agarose hydrogel at a density of 20 million cells/mL. Constructs (diameter: 10 mm, thickness: 4 mm) were cultured for 5 weeks in one of three media conditions: chemically defined media (CDM) with 10 ng/ml TGF-β3 (Active TGF), CDM with 43 ng/ml latent TGF-β1 (Latent TGF), or Active + Latent TGF media (Active + Latent TGF).

Large sized DAPS fabrication and culture

Large sized DAPS (6 mm × 20 mm outer diameter, NP diameter = 10 mm) were next fabricated. Electrospun poly(ε-caprolactone) (PCL) aligned sheets (thickness: 250-300 μm) were used for developing the AF region of the DAPS by cutting sheets into strips at a 30 degree angle[3]. Bovine AF cells (3,333 cells/mm^2) were seeded onto the strips and cultured for 1 week in CDM containing active TGF-β. To form the circular AF region, with alternating fiber orientations in each layer, strips were coupled and wrapped concentrically using a custom mold[5]. To fabricate the NP region of the DAPS, bovine NP cells were encapsulated in 2% agarose (20 million cells/mL) and cultured for 2 weeks in chemically defined media containing active TGF alone, or active + latent TGF prior to combining with the AF region.

Viability, mechanical properties, histological assessment, and quantitative T2 MRI

Construct halves were stained with Live/Dead for cell viability. A custom MATLAB program was used to automate counting of cells in each region. Compression testing was carried out as in[5]. Additional samples were stained with Alcian blue and picrosirius red to visualize glycosaminoglycans (GAG) and collagen, respectively. Structure and NP hydration were also assessed by quantitative T2 MRI, as in[5].

Results

Regional assessment of viability at 5 weeks showed a depth-dependent decline in viability in Active and Latent TGF-supplemented NP agarose constructs, especially in the central region. In contrast, simultaneous Active + Latent TGF supplementation resulted in a more homogeneous distribution of living cells (Figure 1A). Histology also showed intense staining for GAGs though the tissue sections in this Active + Latent TGF supplemented construct (Figure. 1B). Next, large sized DAPS were successfully fabricated and cultured in media containing Active TGF with/or without Latent TGF for up to 10 weeks (Figure 2A). Active + Latent TGF-supplemented DAPS had a significantly higher cell viability in the center of NP region compared to those cultured in Active TGF alone (Figure 2B, C). The transition strain also significantly decreased in the Active + Latent TGF-supplemented DAPS at 10 weeks. However, there were no significant differences in the toe region modulus between Active TGF and Active + Latent TGF DAPS at this time point (Figure 2D). For both groups, histology showed intense staining for GAGs and collagen at the tissue periphery, but far less collagen staining in the

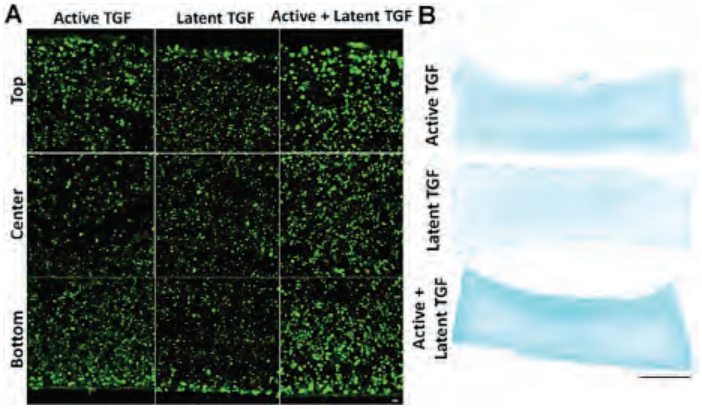

Figure 1. (A) Representative Live/Dead staining of NP cell-laden agarose gels cultured in three different media formulations for 5 weeks (Bar = 10 μm). **(B)** Alcian Blue staining of proteoglycans (Bar = 2mm).

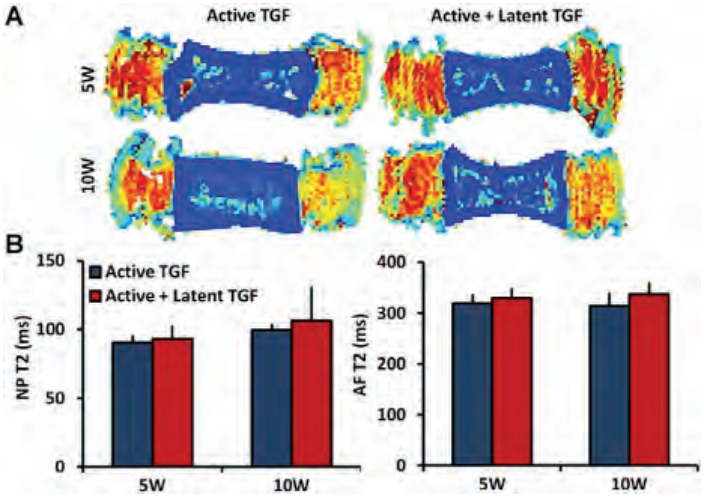

Figure 3. (A) Composite T2 maps for each experimental group. **(B)** NP and AF T2 values over 10 weeks culture (n = 3).

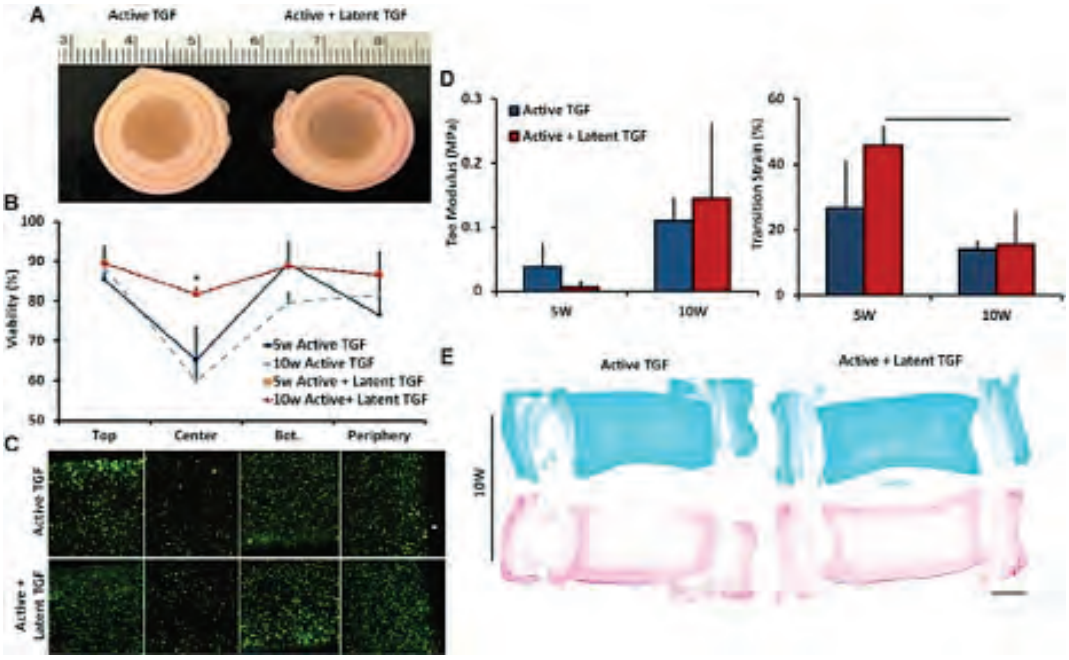

Figure 2. (A) Gross appearance of DAPS cultured for 10 weeks. **(B)** Quantification of viability (n = 3, *:$p < 0.05$ vs. 5w and 10w Active TGF) **(C)** Live/Dead viability staining. **(D)** Mechanical properties of DAPS (n = 3) E. Alcian blue (top) and picrosirius red (bottom) stained DAPS at 10 weeks (scale = 2 mm).

tissue interior (Figure 2E). NP and AF T2 values of Active + Latent TGF-supplemented DAPS were similar to that of Active TGF alone cultured DAPS (Figure 3A,B).

Discussion

This study explored the impact of Active TGF and Latent TGF supplementation on the homogeneous growth and maturation of large sized DAPS in vitro. Our findings demonstrate that combination of Active TGF with Latent TGF dramatically improves disc-like ECM content with homogeneous cell viability in these large NP cell-laden hydrogel constructs. Notably, despite the increased cellularity, Active TGF mixed with Latent TGF had no impact on construct properties. Furthermore, we noted persistent heterogeneity in matrix distribution under these conditions. These findings suggest that while provision of Latent TGF can improve cell viability in large constructs, additional work is required to optimize matrix deposition when the NP is coupled to an AF region.

Significance

Our findings suggest that the combination of Active TGF and Latent TGF can mitigate gradients in viability observed in large tissue constructs. Further optimization of this growth is needed for improving the human translation of tissue engineered discs.

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Nucleus Pulposus Cells have Epithelial Cell-Like Cytoskeleton and Highly Express N-Cadherin

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Introduction

Back pain related to intervertebral disc (IVD) degeneration is a common condition and is believed to initiate in the nucleus pulposus (NP). Understanding the characteristics of the NP cells may help design strategies to prevent and/or revert IVD degeneration. In this study, we aim to examine actin cytoskeleton organization by staining filamentous actin (F-actin) with fluorescently-tagged phalloidin and analyzing gene expression profiles.

Methods

All animal experimental procedures were approved by the Institutional Animal Care and Use Committee of the Corporal Michael J. Crescenz Veterans Affairs Medical Center in Philadelphia. For mouse tail injury model, twelve young adult (8 week old) female C57BL/6j mice (the Jackson Laboratory, Bar Harbor, ME, USA) were used in this study. Under anesthesia, the mouse tail IVDs were injured with a 26-G needle inserted under fluoroscopic guidance. Histological evaluation of Alcian Blue and Haematoxylin and Eosin (H&E) counter stained sections confirmed typical changes during injury. Tail IVDs with adjacent vertebral bodies were isolated, decalcified with 12.5% EDTA (Sigma), embedded in OCT compound (Tissue-Tek, Torrance, CA), and cryosectioned. Actin filaments were stained with Alexafluor 488 phalloidin (Thermo Fisher Scientific), covered with mounting medium containing DAPI (Vector Laboratories, Burlingame, CA, USA), and imaged with a confocal microscope (Nikon Eclipse Ti, Nikon, Japan). For gene expression analyses, the lumbar and coccygeal vertebrate of 4 mice were isolated with a scalpel under a dissecting microscope: the gelatinous NP was scraped off with a scalpel. Annulus fibrosis (AF) tissues, identified by their concentric rings, were shaved off the cartilaginous endplate with a scalpel. Total cellular RNAs were extracted and the Mouse Extracellular Matrix & Adhesion Molecules RT Profiler PCR Array (Qiagen, Gaithersburg, MD) was used to profile the expression of 84 genes important for cell-cell and cell-matrix interactions.

Results

In NP cells from intact IVDs, actin filaments are highly concentrated at the periphery of the cell, where they form a three-dimensional network beneath the plasma membrane (n=5; Figure 1A). This cell shape is reminiscent of that in the epithelium where cells exhibit cobblestone morphology. In injured IVDs, NP cells transition to a more oval shape and with a reduced cellular density (Figure 1B); actin filaments appear to have reorganized. Among the 84 genes examined, gene expression analyses showed cadherin 2 (cdh2; commonly known as neural (N)-cadherin) expressed higher in the NP than in AF, while secreted phosphoprotein 1 (spp1) was highly expressed in both the NP and AF. Thus, these genes were further examined by quantitative Real-Time PCR. NP, AF, and knee articular cartilage (AC) were isolated from a further 8 mice. The validated primer sets for cdh2, spp1 and b2m were purchased (QuantiTect Primer, Qiagen, Gaithersburg, MD). Relative expression was calculated using the $2^{-\Delta\Delta Ct}$ method, normalized to *b2m* as an endogenous loading control. Cdh2 gene expression was significantly higher in the NP compared to AF, which in turn was significantly higher than the AC. ($n = 8$ for NP and AF; $n = 4$ for AC, $p < 0.01$; Figure 2A). Spp1 was expressed at equally high levels in the NP, AF and AC ($n = 4, p > 0.05$; Figure 2B).

Discussion

We were surprised to find that the normal NP cells represented a cobblestone organization (epithelial cell-like), with cells becoming more oval shaped (considered chondrocyte-like) following injury. Cdh2 gene is expressed higher in the NP than AF or AC, which would be linked to the unique morphology of NP cells. Future studies will include examination of gene expression and protein distribution of Chd2 and other epithelial cell makers, to elucidate the role of this intriguing cell phenotype in IVD degeneration.

Significance

IVD degeneration is thought to initiate in the NP. NP cells reside in a high pressure and

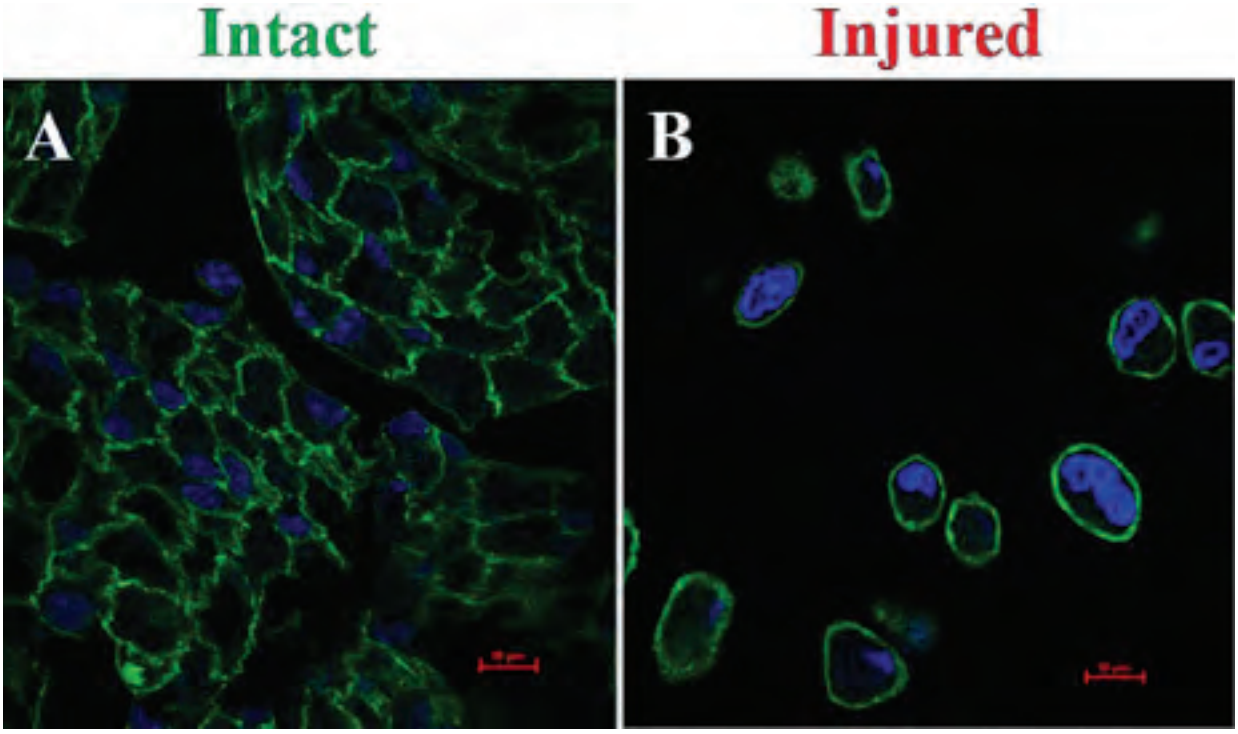

Figure 1. Injured tail nucleus pulposus cells proliferate. Green: F-actin cytoskeleton stained with phalloidin; Blue: cell nuclei stained with DAPI. Scale bar equals 10 um.

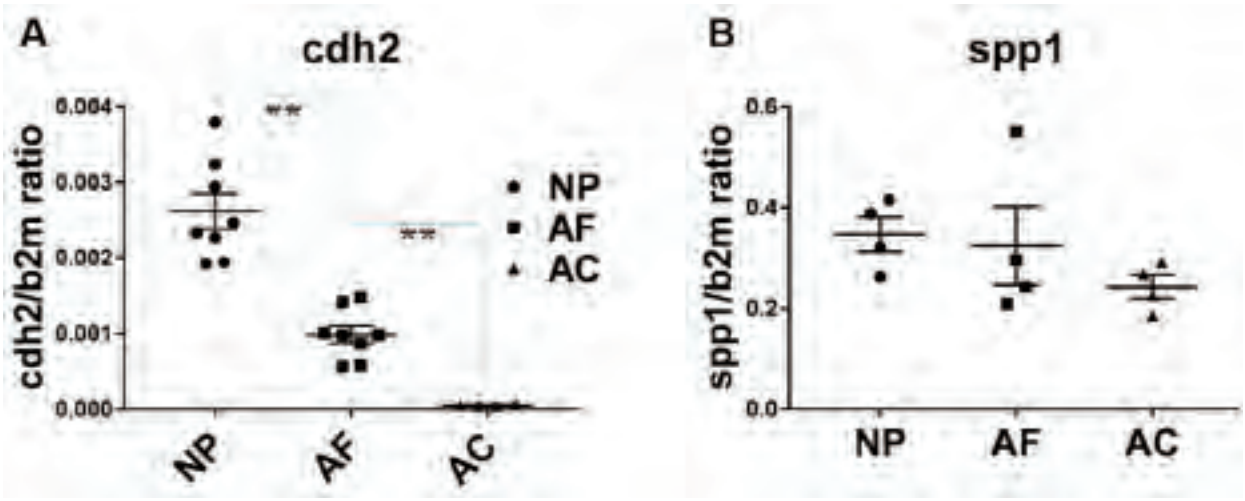

Figure 2. Gene expression by real time PCR in murine nucleus pulposus (NP), annulus fibrosis (AF) and articular cartilage (AC) tissue. Cdh2: cadherin 2; spp1: secreted phosphoprotein 1. Each point represents an individual animal; n = 4-8. **p < 0.01

low nutrient environment, and thus, require specialized physiological properties. A better understanding of the cytoskeleton and cell-cell interactions present in the normal NP, as well as the changes observed in response to injury may lead to better repair strategies for the degenerating disc.

Tips & Tricks: Concurrent Unicompartmental Knee Arthroplasty and Anterior Cruciate Ligament Reconstruction

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Background

Anterior cruciate ligament (ACL) deficiency has classically been considered a contraindication to unicompartmental knee arthroplasty (UKA).[1] In cadaveric studies of UKA, ACL-deficient knees exhibited increased femoral rollback at 0, 30, 90, and 120 degrees of flexion.[2] This may increase polyethylene wear on the posterior aspects of the tibial insert, which may contribute to tibial component aseptic loosening and UKA failures.[3,4] Other surgeons, however, delineate between ACL-deficient knees with instability and those without instability. Partial knee replacement is offered to the latter group; this group is often older and has less functional demands. This group may also exhibit ACL deficiency that is more likely related to large osteophytes that provide stability and will continue to do so as long as they are preserved during the UKA.[5,6]

In contrast, young and active patients who develop post-traumatic unicompartmental knee osteoarthritis from discrete ACL injuries have limited surgical options with regards to maintaining an active lifestyle.[7,8] In the population that is looking for pain-relief, increased stability, eventual return to high level of function, and a faster recovery from surgery, UKA with a concurrent ACL reconstruction is a viable surgical option. While uncommonly performed, studies show high short and medium-term survival rates, encouraging patient-reported outcomes, and biomechanics similar to UKAs in ACL-competent patients.[9-14] This article aims to describe the particulars associated with a single stage UKA and ACL replacement and the salient points of pre-operative evaluation and intra-operative technique.

Preoperative Assessment

Preoperative assessment includes a thorough history of past knee trauma, injuries, diagnosis of inflammatory arthropathy, non-operative therapies undertaken, and any previous surgeries. Prior (failed) ACL reconstructions are of particular importance. It is also essential to fully understand the location of pain and symptoms of instability, and to determine if the patient's primary complaint is instability or pain. A primarily unstable patient with a lesser degree of unicompartmental pain may benefit from ACL reconstruction alone, whereas a chief complaint of pain with instability may indicate UKA plus ACL reconstruction. On physical exam, overall alignment, a correctable coronal plane deformity, cruciate ligament integrity, and range-of-motion should all be assessed. As with isolated ACL reconstruction, pre-operative range-of-motion should be optimized with physical therapy prior to surgery. Three-view knee and standing radiographs should be obtained to assess all three compartments and overall mechanical axis alignment. All other indications for a UKA should be met.

Surgical Considerations

Pre-operative Collaboration

Collaboration between arthroplasty and sports medicine surgeons is essential for coordinating a surgical plan. Our protocol involves both surgeons being present at the beginning of the procedure to draw out their surgical incisions and ensuring that each surgeon's approach does not conflict with the other. We typically utilize standard incisions for the UKA, drawn prior to arthroscopy and confirm our arthroscopic portals accordingly.

First stage: Diagnostic Arthroscopy, Tunnel placement

The initial part of the procedure involves a diagnostic scope to evaluate the knee, assess the competency of the ACL, and to confirm there is no significant degeneration of the contralateral or patellofemoral compartments. This is done after the arthroplasty surgeon has delineated his or her planned surgical incisions. If there is significant degeneration of the contralateral compartment, the decision to convert to a TKA may be made.

After confirmation of appropriateness to proceed with a combined UKA and ACL reconstruction, the femoral and tibial tunnels are made. For medial UKA, both tibial and femoral tunnels are placed in standard locations. For lateral UKA, the tibial tunnel is placed in the standard location, but the femoral tunnel is modified due to removal of bone on the lateral condyle during lateral UKA. Given the insertion of the ACL on the lateral femoral condyle and the corresponding bony cuts, femoral tunnel placement would be slightly shallower and

anterior to ensure the tunnel is not violated by the femoral cuts for the UKA (Figure 1). Once the tibial and femoral tunnels are drilled, a 9.5cm graft passer is threaded through the tunnels.

Stage 2: Unicompartmental Knee Arthroplasty

Once the temporary ACL graft passer is in place, the unicompartmental arthroplasty is performed through the usual approach. Care is taken to protect the temporary graft during the procedure. UKA components are placed and trialed. The final components can be cemented in standard fashion at this time, or after the final ACL graft placement depending on surgeon preference.

After completion of the arthroplasty portion, the knee is evaluated through a full range of motion to determine if the graft passer is impinging on implants or the intercondylar notch.

Stage 3: Completion of ACL reconstruction

Once the UKA components have been cemented in place, a bone-patellar tendon-bone (BPTB) autograft is harvested. The graft passer is used to shuttle the BPTB autograft through the tibial and femoral tunnels. Of note, the graft selection is due to surgeon preference and may be autograft or allograft, BPTB, hamstring, or quadriceps tendon. The typical advantages and disadvantages of each graft apply per surgeon experience and preference.

Post-Operative Care

Post-operative care is guided by the Multicenter Orthopaedic Outcomes Network (MOON) ACL Protocol.[15] Patients are made weight bearing as tolerated with crutches immediately after surgery (no knee immobilizer if a femoral nerve block is not administered).

Unique Complications and other concerns

In theory, the tibial tunnel for the ACL reconstruction could serve as a stress riser, resulting in a higher risk of proximal tibia fracture. The risk may be mitigated if the tibial tunnel is aligned more vertically.[16] However, an actual case has yet to be reported in the literature. The risk of deep infection is not demonstrated in the literature, and the longer surgical episode and relation to deep infection remains theoretical.

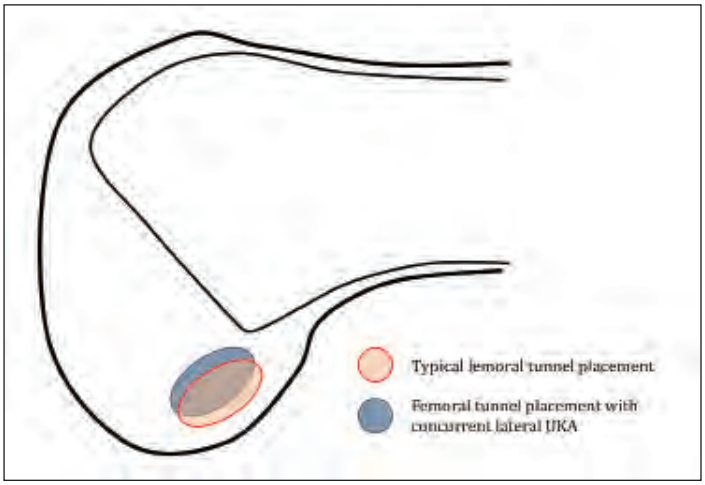

Figure 1. Location of femoral tunnel placement in the setting of concurrent lateral UKA..

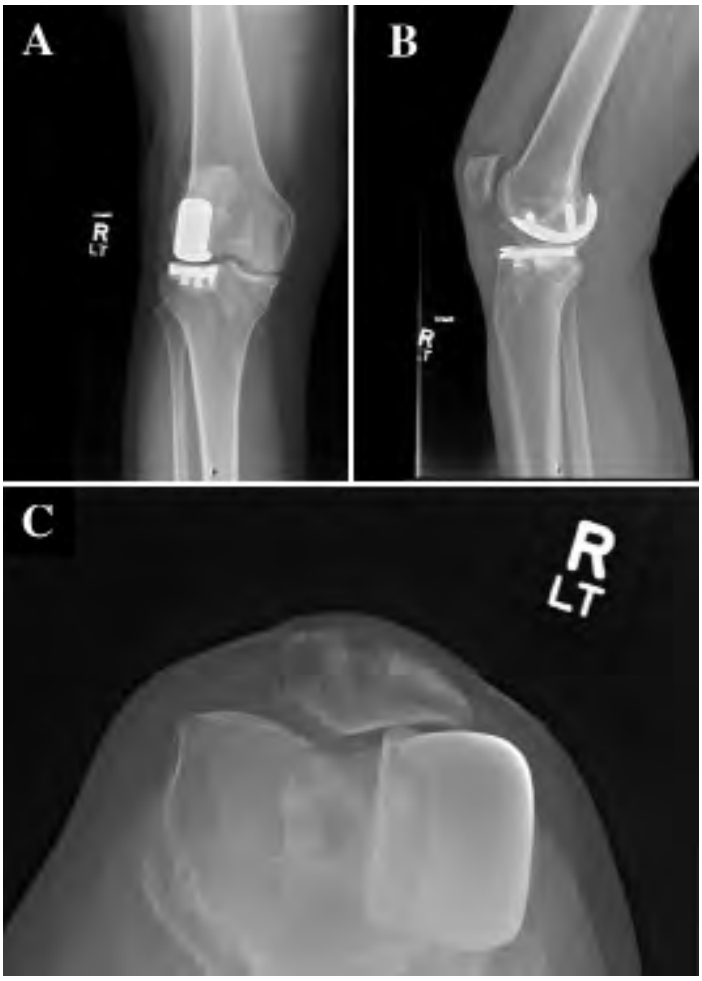

Figure 2. Post-operative radiographs of a 43-year-old female patient who underwent concurrent lateral UKA and ACL reconstruction. **(A)** AP radiographs. **(B)** Lateral radiographs. **(C)** Sunrise radiographs

Conclusion

Concurrent UKA and ACL reconstruction may be an appropriate option for unicompartmental osteoarthritis and ACL deficiency in the younger, more active patient whose goals are to return to a higher level of activity with less pain, more stability, and preservation of future surgical options. Communication and appropriate pre-operative planning between surgeons is essential for an optimal result.

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Computational Optimization of Graft Tension in Simulated Superior Capsule Reconstructions

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Introduction

Superior capsular reconstruction (SCR) has received increased attention as a surgical technique to address massive 'irreparable' rotator cuff tears, however, the graft loading mechanics during activities of daily living remain poorly understood. In addition, very little is known about the influence of initial graft positioning and tensioning with regard to implant performance and longevity. The goal of this study was to characterize the biomechanics of this repair by: 1) identifying activities of daily living that may overburden the graft, and 2) optimizing the graft placement used during implantation.

Methods

In Vitro Cadaveric Experiment

Six skeletonized cadaveric upper extremities from 5 donors (4M, 1F, mean 65.6 y.o) were used in this study. An SCR repair with a dermal graft (Allopatch HD, Arthrex, Naples Florida) was performed on by an experienced orthopaedic surgeon. Specimens were 3-D scanned (Einscan, Afinia, Chanhassen, MN), fitted with reflective markers for motion capture (Optitrack, Natural Point Inc., Corvallis, OR), and securely mounted to a universal test frame (TA Instruments 3550, New Castle, DE). A load to failure protocol was performed by translating the humerus superiorly (relative to the stationary scapula) at a rate of 0.5 mm/s[1] until rupture of graft fixation occurred at the anchor points on the glenoid. The 3D geometry and motion data were used to create 6 degree-of-freedom simulations of the experiment in OpenSim[2] and to calculate the 95% confidence interval of the ultimate graft strain before failure was calculated.

In Vivo Motion Analysis

With institutional review board approval, upper extremity kinematics of nine different ADLs (Table 1) were captured using motion analysis (Raptor Series, Motion Analysis Corp, Santa Rosa, CA) on eight subjects (4M, 4F, mean age 21.5 ± 1.4 y.o). Shoulder kinematics were calculated for each subject and then 95% confidence intervals for the three glenohumeral joint angles were calculated for each ADL.

Table 1. Activities of Daily Living Performed

1. Reach behind head
2. Comb hair behind head
3. Lift heavy object overhead
4. Lift heavy object to shoulder height
5. Lift light object overhead
6. Lift light object to shoulder height
7. Tuck in shirt behind back
8. Wash middle back
9. Wash opposite shoulder

In Silico Musculoskeletal Modeling

A validated OpenSim model of the upper extremity[3] was modified to include a virtual SCR repair (Figure 1A). The kinematic envelopes of glenohumeral motion were explored with simulations of the ADL motions captured with 3-D marker tracking. Maximum graft strains during these simulations were calculated and compared to the experimentally determined failure thresholds previously determined in the in vitro cadaveric experiment. A "safe" zone of operation was defined with as a lower bound of -5% strain and an upper bound of 14% strain, which was based on the 95% confidence interval for failure that was previously determined. Surgical techniques associated with graft tensioning were simulated by iteratively modifying shoulder position, ranging from 0 to 40° abduction, 0 to 40° of forward flexion, and −20° and 20° degrees of internal rotation in 1° increments for a total of 64,000 surgical placements with unique graft tensions.

Results

The cadaveric experiment indicated that the 95% confidence interval for graft ultimate strain was 14.0 – 23.8%. Activities involving ligament-lengthening posterior shoulder rotation (back washing and shirt tucking) were found to excessively strain the graft, which may cause graft failure and require surgical revision (Figure 1B,C). In general, graft elements typically did not exceed their failure strains while lifting objects overhead, lifting objects to shoulder height, hair combing, reaching behind the head, or washing the opposite shoulder. Surgical placement of

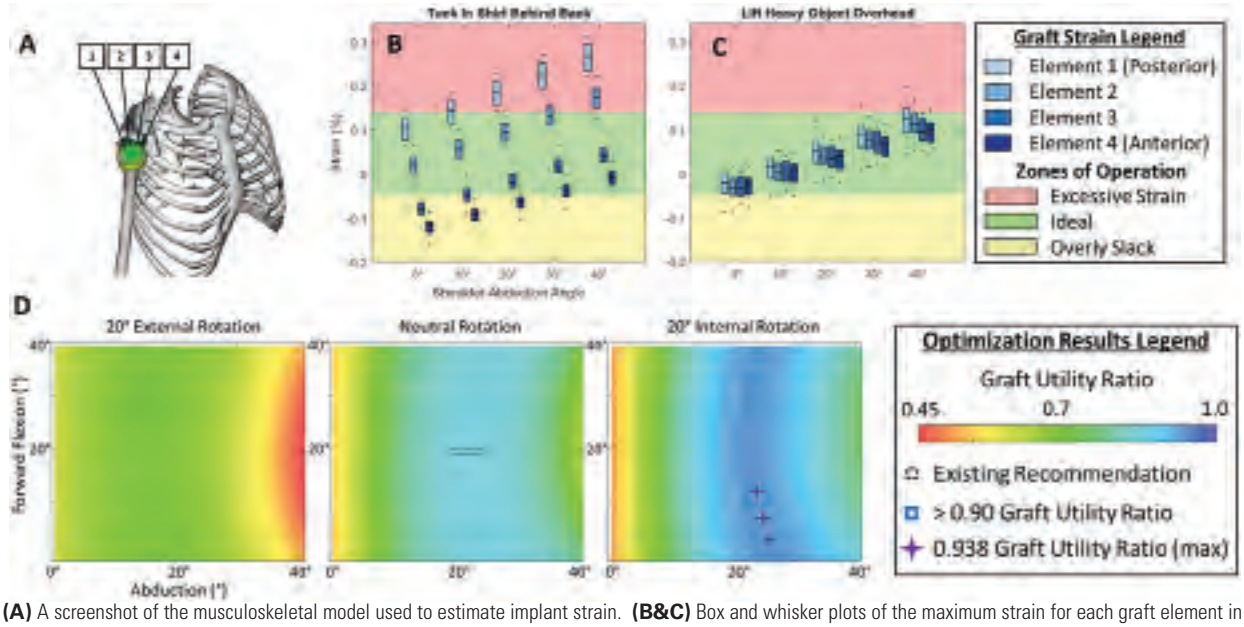

Figure 1: (A) A screenshot of the musculoskeletal model used to estimate implant strain. **(B&C)** Box and whisker plots of the maximum strain for each graft element in the model at four different humeral abduction angles during implantation (forward flexion and internal/external rotation were held constant at 0°). Posterior reaching activities, such as shirt tucking, induce a wide spectrum of strain across the length of the graft, and often lead to excessive strain or laxity. **(D)** Results of the optimization presented as heat maps for graft tensioning at three different internal/external rotations. Technique guides currently suggest that the arm should be placed in 20-25° abduction and 20° forward flexion (dashed box), but the results of the current study suggest that orienting the humerus in approximately 25° abduction, and 20° internal rotation during implantation will result in optimal graft performance. Forward flexion angulation does not play an important role in graft strain.

the grafts was sensitive to both humeral internal rotation and abduction (Figure 1C). Humeral orientations of approximately 25° abduction and 20° internal rotation were found to be the optimal pose to hold the arm in during implantation. Placing the humerus in extreme ranges of our test, such as 40° of abduction, and 20° external rotation resulted in scenarios in which excessive strains were applied to the grafts during ADLs. Similarly, poses such as 0° of abduction, and 20° internal rotation resulted in scenarios in which the grafts were consistently slack.

Discussion

This study represents the first biomechanical investigation of the relationships between surgically induced graft tension and simulated post-operative graft performance during ADLs. Activities that involved large amounts of humeral internal rotation tended to excessively strain the most posterior element into ranges associated with graft failure; thus, it is advised that extreme caution should be exercised when performing posterior-reaching activities. Our results indicate that graft utility is optimized by implanting the graft with the shoulder in approximately 25° of abduction and 20° of internal rotation. Previous recommendations, which lack biomechanical validation, suggest placing the shoulder in 20-30° of abduction and 20° of forward flexion[4,5]. While the recommended abduction orientation closely matches the current results, changes in forward flexion angle during implantation minimally affects graft performance. Finally, and perhaps most interestingly, internal/external rotation of the humerus was not included in the previous surgical guidelines. The current results suggest that 20° of internal rotation leads to improved implant performance.

Conclusion

This study implemented a multidisciplinary workflow that utilized *in vitro* biomechanical experimentation, *in vivo* 3-D motion capture, and *in silico* musculoskeletal modeling to identify post-SCR activity limitations and to investigate the relationships between surgically induced graft tension and post-operative graft performance during ADLs. This paradigm presents an additional tool, aside from clinical studies and cadaveric experimentation, to better predict and understand the strengths and limitations of superior capsular reconstruction. More broadly, this approach has potential to be translated to other soft tissue repairs with the goal of providing valuable information to clinicians and rehabilitative specialists to manage patient expectations and guide rehabilitation.

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U·P·O·J

Treatment of Focal Cartilage Defects of the Knee: An International Survey

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Introduction

A focal articular cartilage defect is a well-defined area of damage to the hyaline cartilage which comprises the articular surface of a joint.[4] These defects have numerous etiologies, including inflammation, trauma, vascular accidents, and joint instability.[15] They have limited healing potential and can contribute to premature osteoarthritis if untreated.[4]

Many techniques for cartilage restoration have been developed, popular options including debridement, microfracture, autologous chondrocyte implantation (ACI), osteochondral autograft transfer (OAT), and osteochondral allograft transplantation (OCA).[15] Debridement removes the damaged cartilage; microfracture breaches the subchondral bone to fill the defect with fibrocartilage.[15] OAT and OCA both utilize osteochondral plugs to fill the defect;[15] OCA uses cadaveric tissues, while OAT harvests from less critical areas of the joint.[15] ACI uses cultured chondrocytes derived from a patient's own cells.[15] Techniques like total (TKA) and partial knee arthroplasty (PKA) restore joint surfaces, but are not typically used to treat focal defects.[1,3]

Currently, there is no consensus regarding the best method to repair focal cartilage defects of the knee.[13] Surgeons addressing these defects must consider numerous surgical options and conservative measures (e.g., physical therapy).[7] A review of the literature yielded case series, randomized controlled trials, and reviews evaluating various techniques.[2,8,10,11,14,16] One review identified five controlled trials evaluating ACI, OAT, and microfracture; the authors concluded that no single technique consistently or significantly outperformed the others.[13] Recent prospective trials have concurred.[12]

This project aimed to examine the variation in selecting, settings for selecting, and regional preferences of treatments being used by orthopaedic surgeons around the world in hopes of guiding knowledge translation strategies for evidence-based management of these injuries. We hypothesized that management of focal cartilage defects of the knee will differ by geographical region.

Methods

We surveyed 33 internationally-based orthopaedic surgeons who were acquainted with the investigators. Surveys were distributed and collected electronically via REDCap (Research Electronic Data Capture); non-responders received automated reminders.

Surgeons were asked for demographic information and treatment preferences for two mock cases. We collected data regarding location of training/practice and years of experience. Both cases presented an 18 year-old male complaining of knee pain: Case 1 presented a small lesion (1 cm by 1 cm); Case 2 presented a large lesion (2 cm by 3 cm). Surgeons selected either physical therapy or surgery. Those who initially treated with surgery or selected surgery after conservative management failed were presented with seven techniques: debridement, microfracture, OAT, ACI, OCA, PKA, and TKA. Cases and treatment options were illustrated to ensure the surgeon could respond regardless of their proficiency in English (Figure 3).

Data collected from the survey was analyzed by grouped frequency analysis. Fisher's exact test was used to evaluate statistical significance.

Results

We received 18 completed surveys (54.5%); 1 survey was incomplete and discarded. All surgeons completed medical school and residency abroad. Fourteen countries were represented for medical school (5.5% North American, 16.7 % South American, 33.3% European, 16.7% Middle Eastern, 22.2% Asian, and 5.5% Oceanian). 14 countries were represented for residency with 16 surgeons training in the same country as their medical school. For fellowship, 10 surgeons (55.5%) trained abroad, 3 (16.7%) trained abroad and in the USA, and 5 (27.8%) trained in the USA. 50% practiced in an academic setting, 17% in a private setting, and 33% in a mixed setting. The average level of experience was 11.2 years of unsupervised practice (range 0 - 35).

For Case 1, 67% initially treated with surgery meanwhile 33% attempted physical therapy (Figure 1); all surgeons would treat with surgery if conservative management failed. 72% preferred microfracture, 17% preferred OAT, and 11% preferred ACI (Figure 2).

For Case 2, all but one surgeon (94%) initially treated with surgery (Figure 1); all surgeons would treat with surgery if conservative

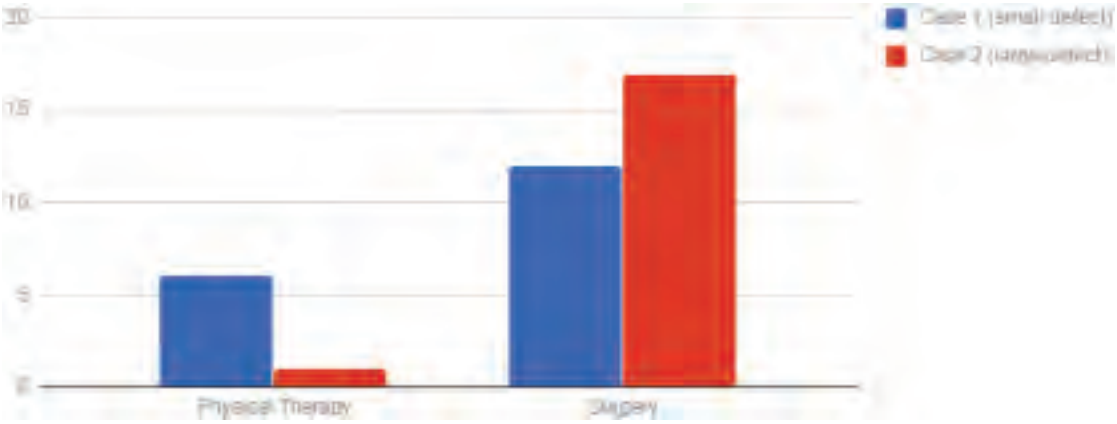

Figure 1. Conservative vs. Surgical Management of Focal Cartilage Defect.

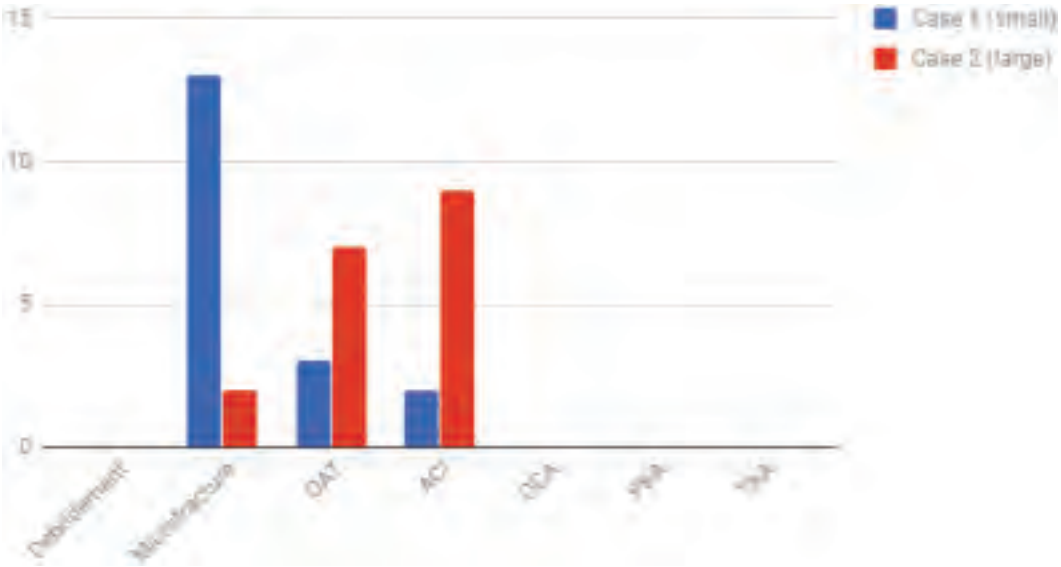

Figure 2. Surgical Management of Focal Cartilage Defects

management failed. 50% preferred ACI, 39% preferred OAT, and 11% preferred microfracture (Figure 3).

No statistically significant variations between geographic regions were observed in either case.

Discussion

We wanted to examine common treatment practices among orthopaedic surgeons worldwide for focal articular cartilage defects of the knee in skeletally mature individuals. A literature search identified similar efforts in medicine and orthopaedics.[5,6] However, none focused on focal articular cartilage defects.

The responses revealed surgeons were more likely to treat with surgery, especially if defects were large. Regardless of size, all surgeons who initially preferred conservative management chose to pursue a surgical option if no improvement occurred.

Microfracture was preferred for small defects. Far fewer preferred ACI or OAT, and none selected arthroplasty, which was expected for multiple reasons. Additionally, none chose debridement or OCA.

For large defects, we did not find a clear frontrunner. 50% selected ACI but almost as many selected OAT. Far fewer chose microfracture which is consistent with prior studies which observed poorer outcomes when using microfracture to treat defects larger than 2 to 4 cm^2.[8,11] Again, none selected debridement, OCA, or arthroplasty. We were surprised that none chose OCA but this may be due to unavailability of fresh osteochondral allograft in their regions.

We were not able to detect any significant variation in management by location of residency or fellowship training. It is possible that significant variation exists but was not captured due to small sample size.

Additional challenges we encountered included the high percentage who completed at least part of their fellowship in the USA. We presumed that fellowship would have the greatest impact on a surgeon's preferences. We had not fully considered the impact of a surgeon's current setting and location of practice on preference of technique and did not capture this data. In the future, we hope to have a larger survey pool and a higher response rate.

Conclusion

Surgeon preferences did not differ significantly worldwide. Microfracture was the preferred treatment for small defects, but most were split between ACI and OAT for large defects.

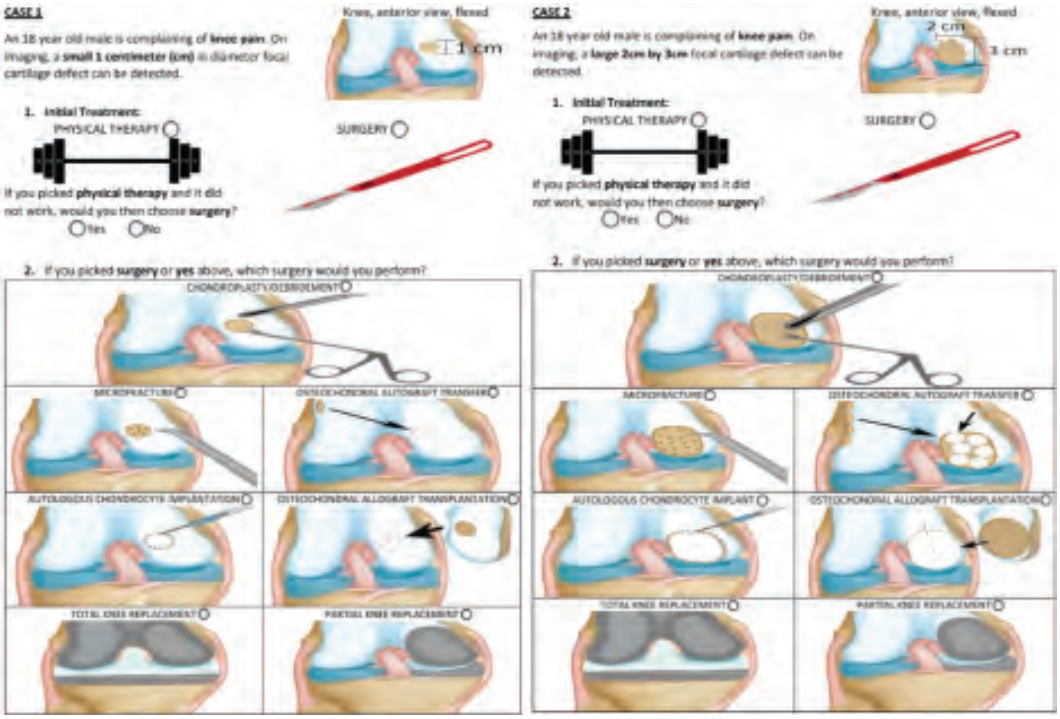

Figure 3. Cases and Treatment Options

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Loss of Tension Increases Meniscus Degradation in a Degradative Microenvironment

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Introduction

The menisci are semi-lunar shaped fibrocartilaginous wedges located between the femur and the tibial plateau and support the structure and mechanical function of the knee joint. Menisci are comprised primarily of circumferentially aligned type 1 collagen bundles, which function to convert compressive forces into tensile hoop stresses[1]. In addition to circumferential fibers, the meniscus contains radial tie fibers that originate at the meniscus periphery and interdigitate amongst the circumferential fiber population[2]. Understanding meniscus structure and function is particularly important given the high incidence of meniscal pathology, and its association with progressive joint degeneration[3]. In particular, radial tears are clinically correlated with an increased incidence of chondral lesions[4] and are considered to be irreparable. These tears interrupt circumferential fibers and, as a result, reduce tensile strain transmission in the vicinity of a tear. Of note, several studies on tendon and other dense connective tissues have reported that when collagen fibrils are under a moderate amount of pre-strain, collagenase-mediated degradation is inhibited[5,6], as was evidenced by a reduction in the loss of mechanical properties in the presence of matrix degrading enzymes. Here, we evaluated whether a radial tear in the meniscus would predispose the tissue to collagenase-mediated digestion in the vicinity of the defect. For this, we used second harmonic generation (SHG) imaging, in which signal intensity is positively correlated with organized and aligned collagen[7–9]. Using this method, we visualized local changes in collagen organization as a function of pre-strain and location relative to a radial defect in the context of exogenous collagenase, which is upregulated in the joint in the context of meniscal injury[10].

Methods

Medial menisci (n = 4) were harvested from adult (skeletally mature) cows. The top third of each sample was removed, as were both the anterior and posterior horns. Menisci were then sectioned to 350 mm thickness in the transverse plane. Four samples (25.4 mm width) from each meniscus were sutured to rubber backing using 3-0 TiCron sutures placed at the apex of the outer body and the anterior and posterior inner edges. After suturing, the tissue was placed in a tensioning device (Figure 1A) with a gauge length of 25.4 mm. Type I Bacterial Collagenase (Worthington) was reconstituted in Phosphate Buffered Saline supplemented with magnesium and calcium (PBS+) at a concentration of 60U/mL. Each sample was randomly assigned to one of four conditions: 0% strain in PBS+ (CTL), 0% strain in collagenase (no strain, NS), 4.5% strain in collagenase (S), and 4.5% strain in collagenase with an added half-width radial defect in the body of the tissue (SD). After 8 hours of collagenase digestion at 37^{O}C, samples were washed thoroughly in 4^{O}C PBS and imaged whole-mount in the transverse plane in eight regions of interest (ROIs) relative to the defect (Figure 2A) at 25X magnification using SHG (840 nm excitation). Maximum intensity projections spanning 142 ± 7.1 microns of the tissue depth were generated, and the mean signal intensity was quantified in FIJI. Signal intensity was normalized to the PBS control for each sample. Data were compared using a 2-way ANOVA across treatment groups and ROIs with Tukey's post-hoc tests.

Results

Visual inspection post digestion showed that PBS+ (CTL) incubated tissues maintained their pre-incubation structural characteristics and opacity. Conversely, in collagenase-incubated tissues, areas of degradation were readily apparent via changes in tissue opacity (Figure 1B). Quantification of mean SHG signal intensity indicated that strained (S) tissues had no significant differences from CTL tissues ($p = 0.064$), whereas non-strained, collagenase treated tissues (NS) had a lower intensity than CTL tissues ($p < 0.0001$). Interestingly, radially defected (SD) tissues revealed no differences in intensity compared to NS tissues ($p = 0.999$), but showed significant differences compared to intact, strained tissues (S) that were also incubated with collagenase ($p = 0.0002$) (Figure 2B). There was no clear pattern of SHG signal change as a function of location ($p = 0.870$) though within just the SD group, the inner center ROIs were shown to have reduced signal compared to outer edge ROIs ($p = 0.0524$).

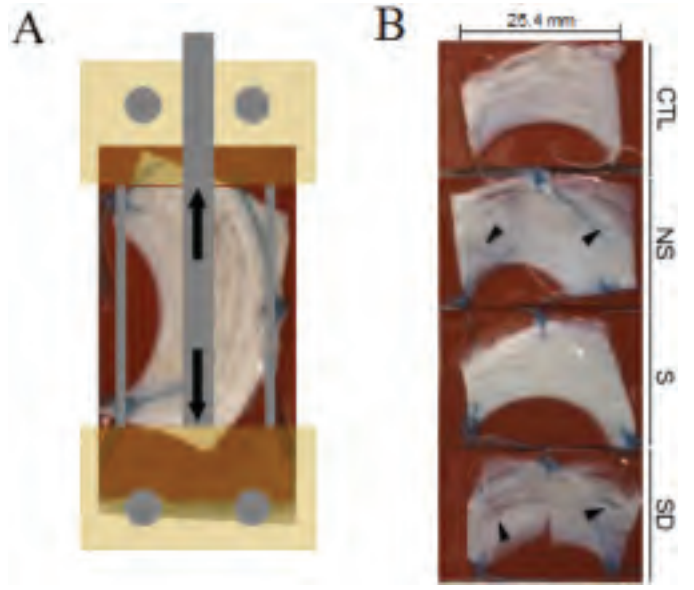

Figure 1. (A) Meniscus specimen sutured to backing with a schematic of the tension clamp device. Tension shown with black arrows. **(B)** Specimens from collagenase digestion groups and PBS control shown after digestion for 8 hours. Black arrowheads indicate regions of apparent digestion.

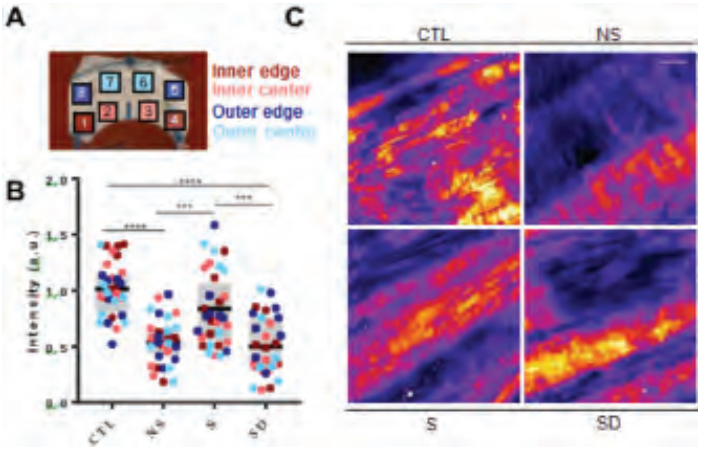

Figure 2. (A) Black boxes indicate regions of interest for imaging. **(B)** Quantification of SHG signal intensity normalized to CTL. Colors indicate ROI. **(C)** Representative images of the maximum projection of digested tissue from each treatment group. Images are from the same sample and ROI (inner edge). SB = 200 microns.

Discussion

This study establishes a platform to investigate structural reorganization and remodeling in the context of radial meniscus defects. The clamp system can be used to transmit variable amounts of strain to explant tissues that are either intact or contain a 'radial' defect to generate regions of reduced strain. The results of this study show that using this system, application of collagenase leads to a loss of SHG signal in the absence of pre-strain. When strain was applied in the context of added collagenase, greater SHG signal was retained compared to similarly collagenase treated unstrained controls. When the sample was defected, altering strain patterns in the tissue, collagenase treatment resulted in increased loss of SHG signal, indicating that a radial tear made the tissue susceptible to aberrant remodeling. These findings suggest that, like in other dense connective tissues, the application of strain can protect collagen from the action of local matrix degrading enzymes. The observation of increased local remodeling with loss of local strain may lead to aberrant cell mechanosensing in the vicinity of focal defects in the meniscus[11], which may exacerbate altered signaling and lead to a cascade of degeneration, ultimately compromising tissue function.

Significance

This study develops a model platform in which to investigate structural reorganization of meniscal explants in the context of loss of pre- strain in a degradative environment. Future studies using this platform will inform large animal studies of meniscal remodeling and degeneration after injury and provides a controlled setting in which to study how mechanical loading regulates the development of pathology after injury.

Acknowledgements

This work was supported by an OREF New Investigator Grant, the NIH, and the Department of Veterans Affairs.

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Single cell imaging of Col1/Col2 fluorescent reporters in the murine meniscus reveals marked spatial heterogeneity

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Introduction

The molecular composition and organization of the extracellular matrix (ECM) is essential for the function of load bearing tissues such as the knee meniscus. To better understand the mechanisms governing meniscus development, maturation, and remodeling, mouse models have become a prominent tools that provide a genetically tractable platform through which to both visualize and perturb molecular signaling and matrix formation [1][2]. Recently, a novel transgenic reporter mouse in which the expression of three distinct fluorescent reporter proteins is driven by promoters for the Col1a1, Col2a1, or Col10a1 genes [3] has been demonstrated as powerful system for studying spatiotemporal changes in expression of critical collagen types during tendon enthesis maturation [4]. Leveraging this mouse model, our goal is to investigate an important unanswered question of meniscus development and homeostasis. Namely, despite the fact that the meniscus is most often described as having a well-defined cartilaginous, Collagen II-rich 'inner' zone and fibrous, Collagen I-rich 'outer' zone, marked and emergent heterogeneity is observed in the ECM of both regions during aging [5] and pathologic remodeling following injury [6]. This is suggestive of multiple endogenous cell types with varying lineage capacities located within the tissue. To ultimately establish whether these cells are present and operative throughout development and maturation, the current study used the Col1/2/10 reporter mouse to assay expression profiles of individual meniscus fibrochondrocytes (MFCs) as a function of location within a juvenile meniscus.

Methods

Mouse model

This study utilized triple transgenic reporter mice with promoters for Col1a1, Col2a1, and Col10a1 driving CFP, YFP, and mCherry expression, respectively [2][3]. Animal use was approved by the University of Pennsylvania IACUC.

Sample preparation and staining

To characterize a time point prior to the ossification of the meniscal horns, knees from 2 week old mice (n = 4) were harvested, fixed, cryo embedded, sectioned with cryofilm [7], and their nuclei were counterstained with TO-PRO-3. Sections were taken from multiple cutting planes and levels throughout the menisci and imaged on an Axio Scan.Z1 microscope. To elucidate regional variation in expression profiles, both coronal and axial sections were imaged. Following fluorescent imaging, sections were stained with Alcian blue and Picrosirius red (for proteoglycans and collagen content, respectively) and imaged again to correlate matrix deposition with reporter expression.

Image quantification

Meniscus areas within coronal sections were segmented and defined as the regions of interest. Fluorescent intensity from the Col1 and Col2 channels was plotted from the inner margin to the outer boundary of the meniscus—with 0 marking the inner most and 1 the outermost boundary. In transverse sections, images were thresholded to segment individual nuclei. Reporter intensity for each cell was then measured and scatterplots were generated to correlate Col1 and Col2 expression in individual cells. Fluorescence intensities in both cases were scaled to the brightest cell detected within a slice. All image processing was performed using Fiji and custom written MATLAB scripts.

Results

High, uniform Col1 expression (Col1+) in cells located within the cruciate ligaments and high, uniform expression of Col2 (Col2+) in cells within the articular cartilage confirmed expected patterns of Col1/Col2 expression in the knee joint (data not shown). While Col10 positive cells (Col10+) were detected within the hypertrophic chondrocytes of the secondary ossification center, no Col10+ cells were detected within the meniscus at this time point. Cells within the meniscus did show a distinct zonal expression of Col1 and Col2 in the anterior horn, with Col1+ cells located in the outer region and a sharp transition to Col2+ cells in the center and inner zones (Figure 1a). This zonal distinction was much less evident, however, within the body and posterior horn of the meniscus. Rather than regions of uniform expression, Col1+ and/or Col2+ cells were

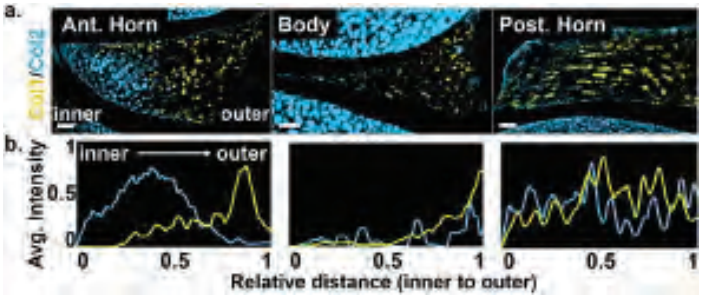

Figure 1. (A). Rep resentative coronal images of Coll (yellow) and Col2 (blue) expressing cells in the anterior hom, body and posterior hom of the meniscus. **(B)**. Fluorescence intensity plots for the corresponding images in **(C)**. Fluorescence intensity was scaled to the h ighest average valu e in the section. Distance scaled to total width of meniscus segment: O = inner-most, I = outer-most, Scale bars: 50µm.

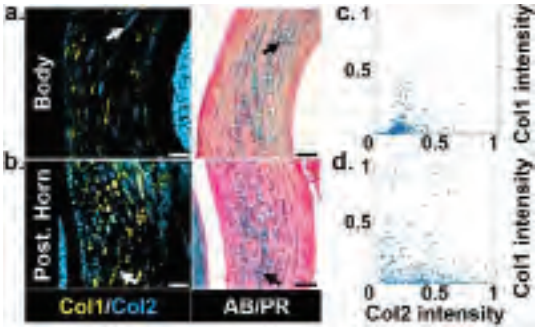

Figure 2) (A,B): Fluorescence and Alcian blue (AB)/ Picrosirius red (PR) images of the same section from the **(A)** body and **(B)** posterior hom region. Arrows point to the same cells in corresponding images. **(C,D):** Coll vs. Col2 fluorescence intensity in MFCs of the **(C)** body and **(D)** posterior horn images. Intensities scaled to the highest val ue meas ured in the section. Scale bar: 50µm.

interspersed throughout the inner and outer zones (Figure 1b,c). Indeed, transverse sections highlighted the presence of Col2+ MFCs within the body and posterior horn (Figure 2a,b), though much fewer cells within the body showed active Col1 or Col2 expression when compared to the posterior horn (Figure 2c,d). Interestingly, chromogenic staining of these same sections showed proteoglycan deposits in regions with either Col2 expressing or Col I expressing MFCs (Figure 2a,b arrows).

Discussion

Imaging the triple-reporter mouse meniscus through multiple planes of sectioning revealed that, while collagen expression within the anterior horn is consistent with the notion of distinct inner Col2-rich versus outer Col1-rich zones, the body and posterior horn portions display overlapping Col1/Col2 expression profiles. In fact, the clear zones observed in the anterior horn are likely due to the ongoing ossification process that will occur at a later age in these animals. In the body and posterior horn regions, numerous cells expressed Col1, Col2, or both simultaneously, and were interspersed with one another throughout the meniscus expanse (Figure 2c,d). This observation suggests that development emplaces cells of multiple and varying potentials throughout the meniscus as it forms, and this heterogeneity in cellular disposition may precipitate the accumulation of the proteoglycan-rich deposits seen in the outer regions during aging and degeneration.

Significance

This work evaluated the expression of key fibrocartilage associated collagens on an *individual* cell level within the developing meniscus. This provides a quantitative assessment of the distribution of Col1/2/10-expressing cells throughout the entire expanse of the tissue - establishing a baseline and validating a promising platform for future work involving cellular-level measurement of gene expression of ECM proteins in response to mechano- biologic perturbations in both *in vitro* and *in vivo* settings.

Acknowledgements

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Tips and Tricks: Semiextended Suprapatellar Intramedullary Nailing of the Tibia

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Background

The history of intramedullary nailing of long bone fractures is long and has evolved continuously for over 100 years. Initial treatments reported in German literature described the use of ivory pegs as intramedullary implants. During World War I, Hey Groves from England described placement of metallic rods for the treatment of gunshot wounds, but this technique did not gain popularity due to a high reported infection rate.[1] In 1931, Smith-Petersen described the use of stainless steel nails for treatment of femoral neck fractures.[2] During the same time, Gerhard Küntscher of Germany took the idea of the Smith-Petersen nail and developed the Küntscher nail which he popularized during World War II on many patients, including American soldiers. He later went on to develop flexible reamers allowing placement of larger nails, which helped advance fracture stability. Further advances came along in subsequent decades including interlocking screws and different nail designs. The 1990's signaled a major expansion with the indications of reamed and unreamed tibial nailing.[3]

Classically, placement of tibial nails was via an infrapatellar (IP) approach, either via a trans- or parapatellar exposure with the knee in flexion or hyper-flexion. This approach creates technical challenges for proximal third tibial fractures with the extensor mechanism complex extending the proximal fragment, resulting in a procurvatum deformity of the tibia. In addition, fluoroscopic intra-operative imaging can be challenging in visualizing the starting point with the knee in flexion. The semiextended technique, described by Tornetta *et al* in 1996, places the knee in approximately 15 degrees of flexion to combat these distracting forces.[4] This semi-extended technique evolved into a suprapatellar (SP) approach through the quadriceps tendon to access the proximal tibia, avoiding disruption of the patellar tendon and its retinaculum.

Initial concerns were raised about damage to the patellofemoral joint and possibility of septic arthritis of the knee. However, recent studies have mitigated these concerns. Cadaveric studies demonstrated nail insertion pressures below that for articular cartilage damage.[5] Clinical studies further showed some immediate cartilage changes on post-operative arthroscopy, but a normal MRI at 1 year with no clinical knee pain. Additionally, suprapatellar nailing has been shown to have a significantly decreased rate of distal tibia malalignment, improved reduction in the sagittal plane, less operative and fluoroscopic time, and decreased anterior knee pain.[6-9] With regards to concern for sepsis, a recent multi-center study demonstrated a very low (1.4%) but non-significant difference in the rate of septic arthritis of the knee with suprapatellar or infrapatellar approaches in open tibial fractures.[10]

This overview of suprapatellar intramedullary nail placement seeks to review tips and tricks to successful utilization of this technique to ensure good clinical outcomes.

Treatment Considerations

Preoperative Evaluation and Planning

Before deciding to proceed with semiextended SP nailing of the tibia, several factors need to be assessed. Preoperatively, radiographs of the knee should be reviewed with particular focus on the patellofemoral compartment to assess for any injury, arthritis, or other condition that may predispose to difficulty accessing this space. On clinical exam, adequate patellar mobility is essential in order to access the proximal tibia and accommodate the cannula and surgical instruments. Typically, two quadrants of patellar mobility are needed for adequate access to prevent iatrogenic damage and proper instrumentation.

Suprapatellar nailing of the tibia requires a specific set of instruments that is distinct from the IP set. Specifically required is the protective insertion sheath, made of PEEK or metal. A separate, specific jig is then utilized through the cannula underneath the patella to access the proximal tibia while preventing iatrogenic injury to the cartilage of the patellofemoral joint.

Operative Evaluation

Positioning

The patient is positioned supine on a radiolucent table with a bump under the ipsilateral hip to ensure the patella is facing upwards. Next, the injured extremity is positioned with the knee in approximately 10 to 20 degrees of flexion over radiolucent foam or a radiolucent bump. (Figure 1) This serves two purposes: to

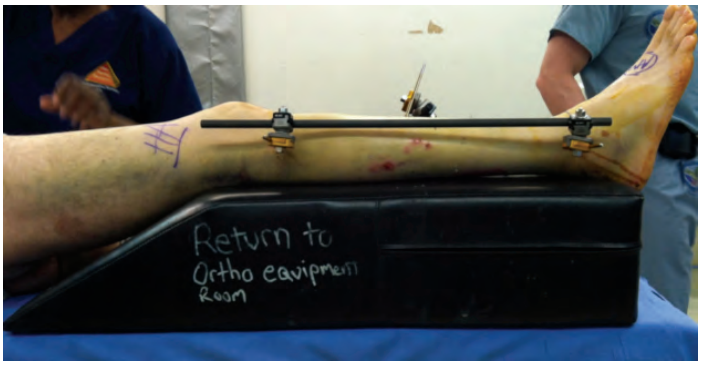

Figure 1. Semi-extended positioning of operative leg

keep the knee in flexion and to keep the leg elevated allowing lateral radiography of the extremity. Proper positioning allows easy access to the proximal tibia for instrumentation, easier imaging as compared to an IP approach, and less difficulty with reductions, particularly when using adjuvant techniques for distal or proximal injuries.

Imaging

After proper positioning, fluoroscopic imaging is significantly easier as compared to IP nailing. As the limb is parallel to the floor, fluoroscopy does not need to be rotated and can shoot directly downwards, allowing easier operative access to the limb and less operative and fluoroscopic time. (Figure 2) A lateral can also be obtained in a standard fashion.

Suprapatellar Nail Insertion

Starting one finger breadth from the superior pole of the patella and extending 2-4 cm proximally, an incision is carried down through the quadriceps tendon in line with the fibers and down to bone. The tendon is sharply incised and adhesions are freed in the suprapatellar pouch and intra-articularly to allow placement of the soft tissue guide. This step is key in allowing ease of passage of the soft tissue guide for proper starting point. Next, the soft tissue guide is inserted retropatellar above the trochlea, followed by a guidewire. A perfect AP and lateral of the knee is needed to ensure proper placement of the guidewire. (Figure 3) The guidewire should placed slightly medial to the lateral tibial spine on the AP, and at the junction of the anterior cortex and articular surface in line with the anterior cortex on the lateral x-ray. Keeping in line with the anterior cortex is key to prevent posterior cortex violation and to ensure the nail will be centered down the shaft of the tibia. (Figure 4) If the starting point is too anterior, there is risk for an iatrogenic fracture of the tibial tubercle. The guidewire is then provisionally advanced past the level of the tibial tubercle. Some systems allow placement of a separate guide pin through the jig and into the femur providing further stabilization of the jig and soft tissue guide thereby preventing it from backing out. This is an important step to prevent injury to the patellofemoral joint. After finding the proper starting point, the opening reamer used to open the proximal tibial cortex. (Figure 5) At this point, the ball tipped guide wire is introduced through the soft tissue guide in the jig. The fracture must now be reduced. If the fracture is an isthmus fracture, the ball tipped guide wire can simply be passed down the tibia. However, if the fracture is distal or proximal where the diameter of the intramedullary device will not "fill" the canal, then a near anatomic reduction utilizing closed, percutaneous, or open techniques is necessary. SP

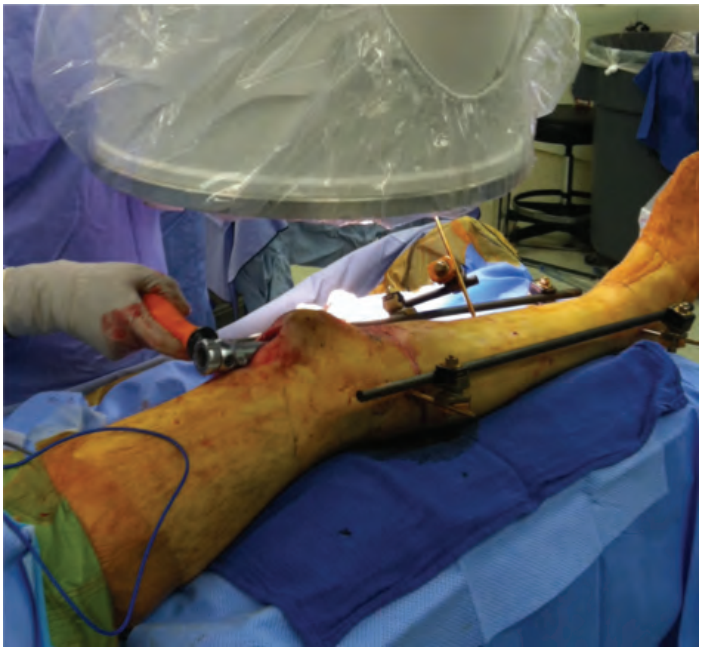

Figure 2. Positioning of fluoroscopy.

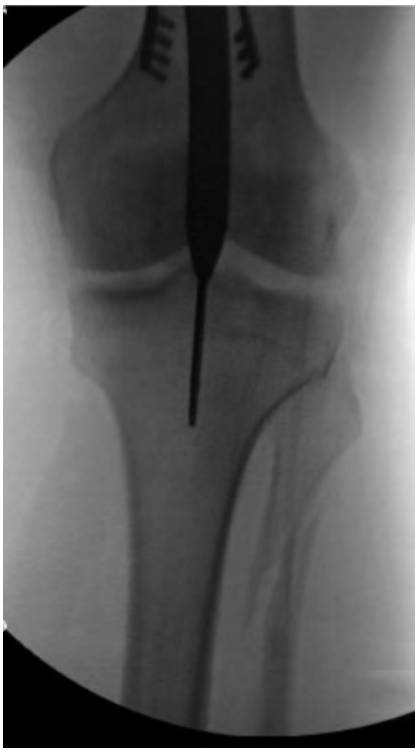

Figure 3. AP X-ray of the knee demonstrating proper starting point through soft tissue sleeve.

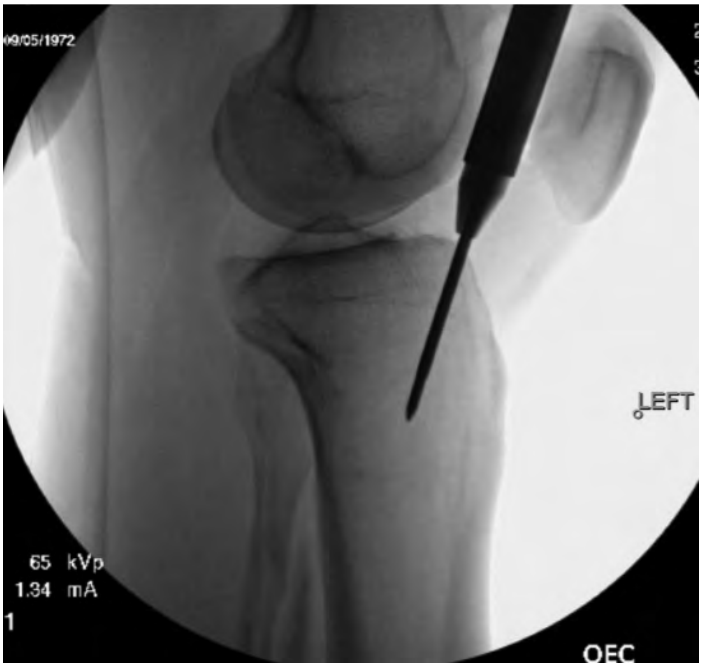

Figure 4. Lateral X-ray of the knee demonstrating suprapatellar approach through soft tissue sleeve.

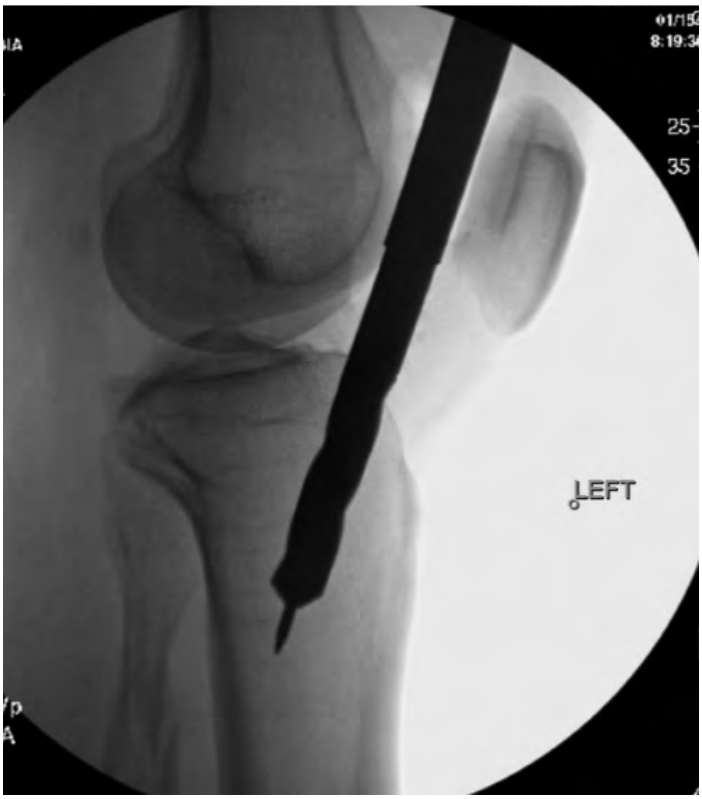

Figure 5. Passage of opening reamer through soft tissue sleeve.

nailing facilitates fracture reduction, especially in proximal third tibia fractures.As the leg is flat on the operating table and not in hyperflexion, distracting muscular forces and gravity are neutralized allowing the fracture to be easily reduced and held. The guide wire is then passed and nail placement proceeds in a standard fashion with sequential reaming, nail placement, and interlocking screw fixation.

Conclusion

In summary, semiextended suprapatellar intramedullary nailing of the tibia is a safe and often advantageous approach to a common problem. SP nailing of the tibia has been shown to have decreased anterior knee pain, decreased operative and fluoroscopic time, improved sagittal alignment, and decreased malalignment in distal tibia fractures as compared to infrapatellar tibial nailing. Near term studies have demonstrated no clinical differences in knee outcomes. Further studies are needed to assess this approach long term. With focus on several key steps of the procedure, semiextended suprapatellar intramedullary nailing of the tibia can be a successful technique surgeons can use for treatment of these fractures.

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Additional Screw Use in Olecranon Fracture Reconstruction Changes Failure Mode During Fatigue Testing

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Introduction

Olecranon fractures account for 10% of all upper-extremity fractures in adults[1] and are often caused in the elderly population by a fall from standing height. Plate fixation (Fig 1A) has become an accepted method for stabilization of olecranon fractures[2], but the presence of osteoporotic bone can lead to construct failure when the forearm is subjected to external loads.[3] However, it has also been shown that effective post-operative rehabilitation protocols require the patient to perform early range of motion exercises to limit stiffness and facilitate the ultimate performance of activities of daily living.[4] These protocols routinely increase the ranges of motion and the external loads applied to the affected joint over a prescribed course of time, which may ultimately lead to premature implant failure. Anecdotal clinical experience has led us to believe that a novel technique in which an additional non-locking screw, targeted from distal to proximal through the plate and aimed towards the tip of the olecranon (Fig 1B), may improve implant performance. It is currently unknown if the use of an additional screw improves the load bearing capacity of the implant. Therefore, the goal of this study was to assess the biomechanical efficacy of this technique by applying an accelerated fatigue test consisting of elbow flexion/extension motion under increasing loads. We hypothesized that the additional screw would improve the stability and fatigue life of the construct in comparison to a control group that did not use the extra screw.

Methods

Nine matched pairs of fresh-frozen, cadaveric upper extremity specimens were used for this study (3M, 6F, average age: 81.2). Specimens underwent trans-humeral and trans-forearm amputations at the midpoints of the bones, making sure to keep the radioulnar interosseous ligament, elbow capsule, and triceps intact. The implants (DePuy Synthes 3.5 mm VA-LCP Olecranon Plates, West Chester, PA) were first properly positioned on intact bones and held into place with Kirschner wires. An oscillating saw was then used to create a 3 mm transverse osteotomy at the center of the sigmoid notch of each specimen. Nine randomly selected arms were reconstructed using the standard surgical technique (CTRL), while the contralateral limbs were reconstructed with the previously described extra screw technique (EXPT). An accelerated fatigue protocol consisting of loaded elbow extensions was simulated by applying controlled displacements to the triceps tendon, similar to previously published protocols.[5] Retroreflective marker clusters were placed on the proximal and distal ulnar bone fragments so that relative motion between fragments was tracked in 3-D space (Optitrack Motive). Prepared specimens were secured to a test frame (TA ElectroForce 3550) and triceps tendons were gripped with a custom-built clamp. A flexible steel cable was routed through a set of pulleys to connect the tendon clamp, actuator, and grounded load cell of the test frame. To create the extension/flexion motion of the elbow, the actuator displaced the triceps tendon 20 mm in a sinusoidal pattern at 0.2 Hz. This tendon excursion corresponded to a range of motion between 90° and approximately 55° of flexion (Fig 2). Arms were initially cycled 30 times at 0.2 Hz with an empty fixture attached to the distal forearm. Additional masses were hung in 0.5 kg increments every 30 cycles until failure occurred. Failure was defined by (1) permanent relative displacement of ulnar bone fragments exceeding 3 mm, or (2) catastrophic failure of the bone or implant. The total number of cycles, maximum torque, and total work performed against gravity were calculated for each specimen. Paired one-tail t-tests were performed for measures of total cycles and total work. The level of significance was set at $p<0.05$.

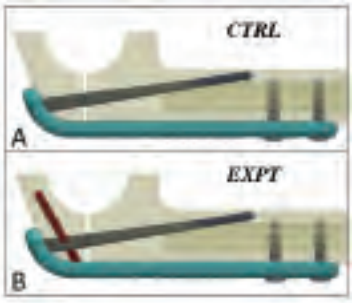

Figure 1. Computer aided drawing representations of the **(A)** control group and **(B)** experimental group.

Results

Modes of failure were different between the CTRL and EXPT groups. Permanent displacement

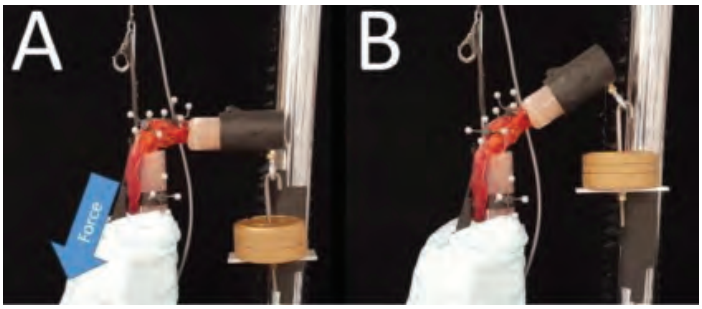

Figure 2. Photographs depicting the testing protocol. **(A)** Displacement of a cable attached to the triceps tendon results in a downward force. **(B)** The displacement of the tendon results in approximately 35° of loaded elbow extension.

exceeding 3 mm (i.e. loosening (Fig 3A)) occurred in seven out of nine cases for the CTRL group. Instantaneous catastrophic failure (Figure 3B) prior to 3 mm of fragment displacement occurred once, and there was one instance where the specimen completed the loading protocol and did not fail. Out of the nine specimens tested in the EXPT group, seven specimens failed via catastrophic failure, where the bone sheared through the screws. Two specimens failed due to fragment displacement exceeding 3 mm.

There were no significant differences in terms of number of survived cycles, maximum torque sustained, or work performed. The CTRL group sustained an average of 200 (±167) cycles before failure, while the EXPT group sustained an average of 192 (±131) cycles ($p = 0.33$). The CTRL group sustained an average maximum torque of 8.60 (±6.55) Nm before failure, while the EXPT group sustained an average maximum torque of 8.56 (±5.24) Nm ($p = 0.825$). Finally, the CTRL group experienced an average of 1123.4 (±1746.6) J of work against gravity before failure, while the EXPT group sustained an average of 1063.6 (±1246.4) J before failure ($p = 1.00$).

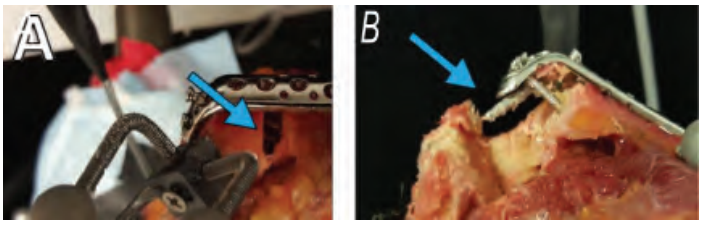

Figure 3. Photographic representations of the two failure modes that occurred during testing. **(A)** Fragment migration that exceeds 3mm in width (77% rate for CTRL group). **(B)** Catastrophic failure where the proximal bone fragment fractures and construct stability is lost (77% rate for EXPT group).

Discussion

Addition of a supplemental oblique retrograde non-locking screw does not provide improved fatigue life to a non-locking plate olecranon implant; however, the failure mechanisms suggest that the use of the additional screw enhances the stability of the repair construct, as it effectively reduced relative motions of the ulnar segments during loading. Reduction of the cross sectional area of the additional screw may reduce stress riser intensity and provide improved fatigue life.

Significance

There may be value in an additional screw in the proximal segment; however, biomechanical studies that analyze the effect of reducing the cross sectional area of the retrograde screw are required.

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Reconstructing Proximal Humerus Fractures with Locking Plates: Don't Miss High?

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Introduction

Upper extremity fractures account for one-third of the total incidence of fractures in the elderly [1] and the incidence of proximal humeral fractures significantly increases in osteoporotic bone.[1,2] Current rates of clinical failure are unacceptably high, with humeral head collapse, fixation failure, and hardware-related complications leading to revision rates between 27% and 59.2% in some studies.[3,4] Previous research has indicated that utilizing the calcar as an anchor point for screws is an effective method to provide medial column support (Fig 1).[5,6] These studies make comparisons of groups that either utilize a calcar screw as an anchoring point or do not; however, they do not characterize the clinically relevant consequence of "missing" the calcar with screw placement during surgery. This study sought to elucidate the mechanisms associated with proximal and distal placement of locking plates in two-part proximal humeral fractures. We hypothesized that neutral placement of the plate would provide the best fixation, while distal and proximal plate locations would exhibit significant reductions in fixation strength.

Methods

This study was first performed with 9 left osteoporotic humerus Sawbones models (Pacific Research). Specimens were assigned either neutral calcar screw insertion (SN; n =3), 8 mm distal calcar screw insertion (SD; n = 3), or 8 mm proximal calcar screw insertion (SP; n = 3) (Fig 1). The study was repeated and expanded with nine matched pairs of cadaveric specimens (4 M, 5 F, average age 81.2) in the following groups: CN, n = 6; CD, n = 6; CP, n = 6. All specimens received a two-part 30° wedge osteotomy at the surgical neck of the humerus. Fractures were stabilized using locking proximal humerus plates (LCP Proximal Humerus, DePuy Synthes) with six locking screws. Quasi-static torsional stiffness tests were performed, and quasi-static axial compression tests at 0, +20, -20 degrees of ab/adduction were conducted for all specimens. Cadaveric specimens underwent an additional cyclic fatigue protocol consisting of axial compressive loads between 50-250 N for 5000 cycles at a rate of 1 Hz. A ramp to failure at a rate of 0.1 mm/s was performed after completion of the fatigue test. Maximum humeral head displacement during fatigue loading was measured with optical 3-D motion tracking techniques (OptiTrack), and ultimate load was recorded. One-way ANOVAs with alpha = 0.05 were performed to determine differences within the Sawbones and cadaveric groups.

Results

In the Sawbones experiment, distal placement provided significantly improved construct stiffness over proximal placement in 3 out of 5 assays (Fig 2 and 3). In two cases, distal placement of the implant improved construct stiffness when compared to neutral placement. There were no significant biomechanical differences in angular or axial stiffness between the cadaveric groups. No significant differences were found for maximum displacement or ultimate load. In general, the Sawbones constructs were much more compliant than the cadaveric constructs.

Discussion

Contrary to our overall hypothesis, the results from the Sawbones experiment suggest that distal implant placement is either equal to or stronger than neutral placement while proximal implant placement seems to decrease construct stiffness. However, the results from the cadaveric experiment did not provide similar significant results, as plate placement did not have a significant effect on torsional stiffness, axial stiffness, humeral head displacement, or ultimate load. Variations in human anatomy and bone mineral density led to variations in experimental data and future studies should include higher sample sizes. When comparing between the

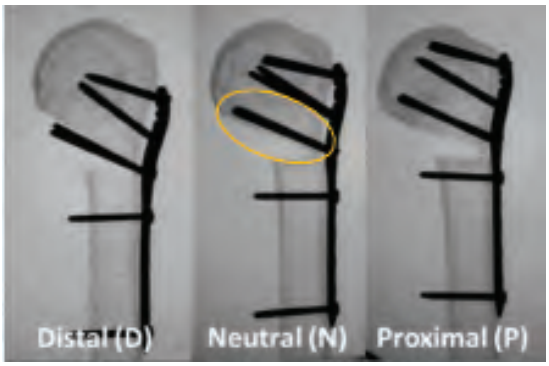

Figure 1: Fluoroscopic images of the 3 groups tested in the experiment. The screws circled in yellow are inserted into the calcar.

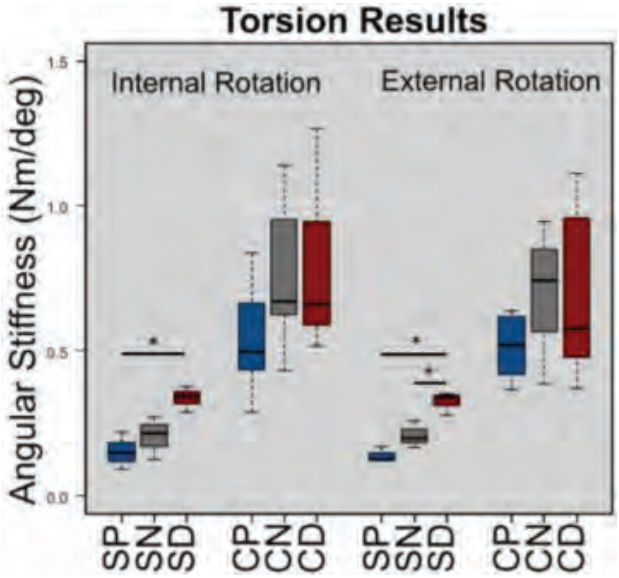

Figure 2: Plots of angular stiffnesses for Sawbones and cadaveric specimens. Significant differences between groups are marked with a *.

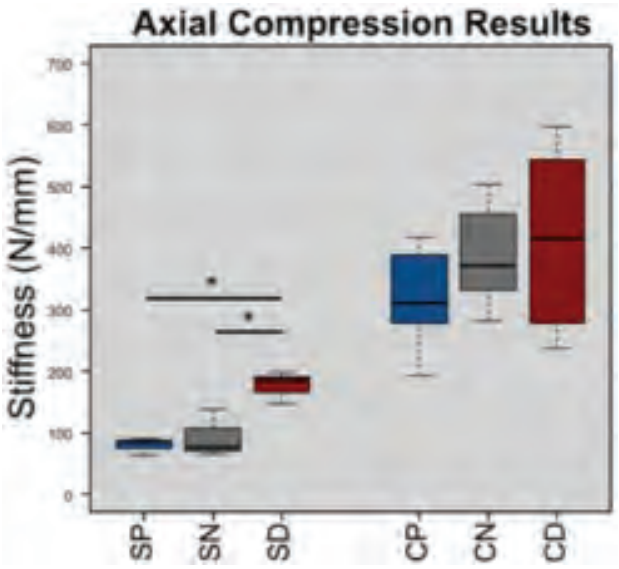

Figure 3: Plots of stiffnesses for Sawbones and cadaveric specimens during the 0° axial test. Significant differences between groups are marked with a *.

Sawbones and cadaveric models, it is clear that this surrogate for osteoporotic bones do not provide the same mechanical properties as the human condition. However, it is our belief that a Sawbones model, which includes realistic geometry, thinned cortical walls, and soft cancellous bone, provides a useful surrogate for biomechanical testing, despite the large decrease in mechanical strength.

Clinical Relevance

The purpose of this study was to provide guidance for surgeons who may not achieve idealized screw placement during a proximal humerus reconstruction. Results suggest that screws inserted below the calcar may act as an effective buttress to provide support to the medial column of the humerus, whereas "missing high" results in decreased construct stiffness.

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Prior Focal Radiation Causes Atrophic Nonunion Fracture in Mice

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Introduction

Unlike many other tissues that healing with a scar, bone is a unique one that can regenerate completely after injury. However, up to 5-10% of bone fractures have delayed or nonunion healing. Among them, atrophic nonunion is especially challenging for the physician and thus is a major clinical burden in skeletal trauma treatment. Patients treated with radiotherapy (e.g. cancer, heterotopic ossification) are less likely to regenerate bone and more prone to develop fracture nonunion within the irradiated area even after several years of treatment. To better understand the relationship between radiation and fracture nonuion, we investigated the fracture healing process in mouse long bones with prior focal radiation.

Methods

All procedures were approved by our institution's Animal Care and Use Committee.

Animals

Two-month-old male WT (C57BL/6) mice or Col2- Cre Rosa-Tomato mice in a C57BL/6J background received radiation (8 Gy twice, day 1 and day 3) at the midshaft of right tibiae (5 mm in diameter) from a focal irradiator (SARRP, Xstrahl). Two weeks later, closed transverse fractures were made within the irradiated area and the same area in the contralateral legs via a blunt guillotine with a pre-inserted intramedullary pin.

μCT- Bilateral tibiae were harvested at scheduled time points and scanned by vivaCT 40 (Scanco Medical AG) at a resolution of 10.5 μm for measuring callus volume (CV), bone volume (BV), and bone volume fraction (BV/CV).

Histology and Immunohistochemistry (IHC)

Tibiae were fixed in 4% PFA, decalcified in 10% EDTA, and processed for paraffin or frozen sections followed by Safranin- O/fast green staining or IHC. For EdU staining, mice received 1.6 mg/kg EdU at 3 h before sacrifice.

Mechanical testing

Tibiae harvested at 6 weeks after fracture were placed on a 3-point bending fixture and loaded with mechanical force at the previously fractured site using an Instron 5542. The force to failure curve was recorded for analyzing peak load, stiffness, and energy to failure.

Periosteal mesenchymal progenitor isolation

Mice long bones were dissected free of surrounding tissues and digested in 2 mg/mL collagenase A and 2.5 mg/mL trypsin. The first 5 min digested cells were discarded. Periosteal mesenchymal progenitors were released by a subsequent 20 min digest and cultured in 15% αMEM for standard osteogenic and chondrogenic differrentiation.

Statistics

Data are expressed as means±SEM and analyzed by paired, two-tailed Student's t-test.

Results

At two weeks after radiation and right before fracture, bone marrow hematopoietic components in the irradiated region had already recovered but the periosteal cellularity was significantly lower compared to non-irradiated bone. Three days after fracture, compared to that in control, the periosteum layer in irradiated bones expanded much less at the proximal side of fracture, the region close to the growth plate, and did not expand at all at the distal side of fracture, the region close to the ankle (Figure 1A). Consistently, EdU staining indicated less proliferation within the prior irradiated periosteum at the proximal site and almost no proliferation at the distal side compared to non-irradiated bone (Figure 1B). Consequently, at 1 and 2 weeks after fracture, CV and BV were drastically decreased in irradiated bones at the proximal side with virtually no bone detected distal to the fracture line (Figure 2). Histology uncovered that, while the irradiated bones attempted to heal through endochondral and intramembranous ossifications at the proximal side albeit at much less robust level compared to control, only cells with fibrotic morphology and type 1 collagen matrix were detected at the distal side (Figure 3). Those cells did not stain for osteogenic (osterix and osteocalcin) or chondrogenic (Sox9 and type 2 Collagen) markers (data not shown). They did not express VEGF, leading to no vessel infiltration (Figure 4) and no osteoclasts in the area (data not shown). Lineage tracing using Col2-Cre Rosa-Td Tomato

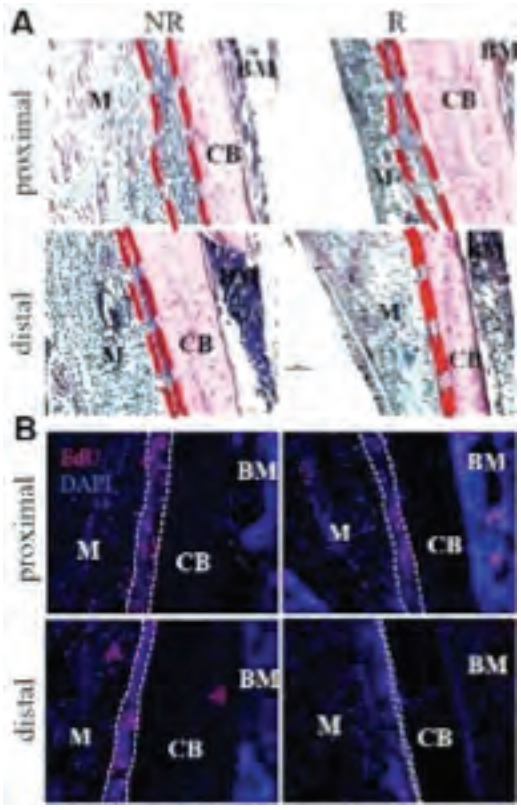

Figure 1. Prior radiation reduces periosteum responses toward fracture. HE **(A)** and EdU **(B)** stainings of fractured bones at 3 days post fracture. Dash lines depict periosteum. NR: non-irradiated; R: irradiated; CB: cortical bone; M: muscle; BM: bone marrow.

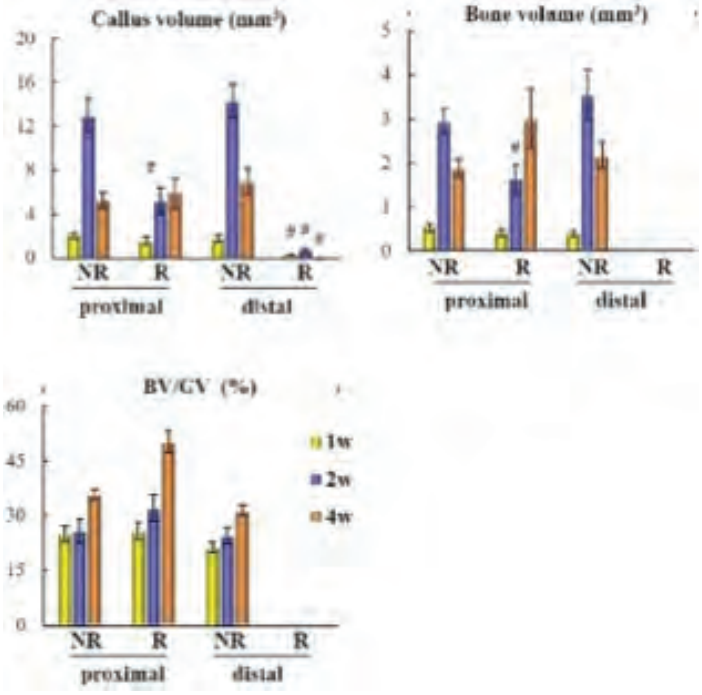

Figure 2. Prior radiation has distinct effects on callus formation at two ends of the fracture line. MicroCT analysis of callus volume (CV) and bone volume (BV) within the callus at 1, 2, and 4 weeks after fracture. n= 6 mice/group. #: $p<0.05$ R vs NR.

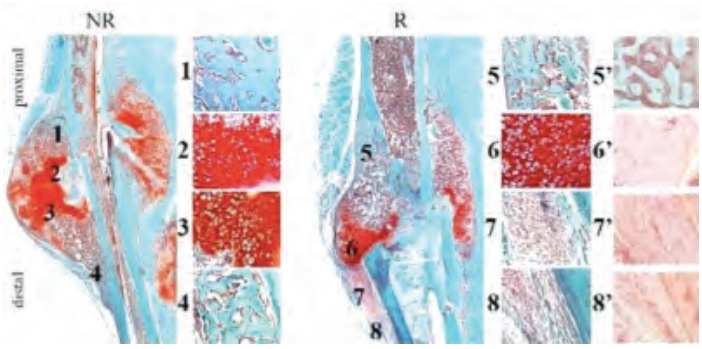

Figure 3. Fibrous tissue (images 7 and 8) is formed at the fracture distal end in prior irradiated bone at 2 weeks after fracture as shown by Safranin-O/fast green staining. Images 1-8 are magnified images for areas shown on the left panel. Images 5'-8' are Picro-Sirius red staining of the same sites as images 5-8.

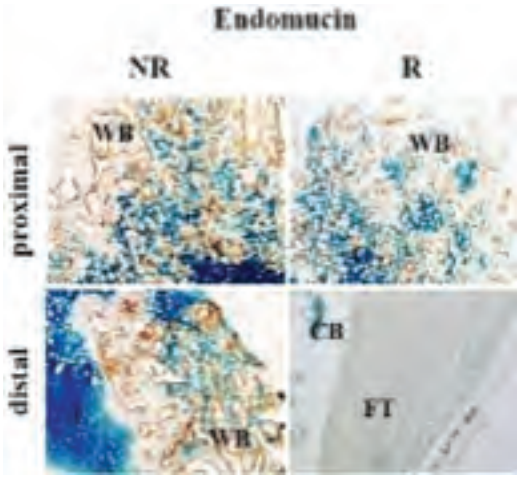

Figure 4. Fibrous tissues formed at 2 weeks after fracture at the distal end in prior irradiated bone are devoid of vessel invasion as shown by IHC of endomucin (a marker for endothelial cells, brown). CB: cortical bone, C: cartilage, WB: woven bone, FT: fibrous tissue.

mice that specifically label bone mesenchymal lineage cells, including periosteal progenitors [1], revealed that these fibrotic cells are not originated from periosteal progenitors (Figure 5). At 4 and 6 weeks after fracture, the bony callus at the proximal side appeared to drape over the fibrous tissue of the distal side but without consolidation (Figure 6, arrows). This resulted in a nonunion in the entire irradiated cohort (n = 11 mice). Mechanical testing confirmed a drastically decreased peak load (−86%), stiffness (−75%), and energy to failure (−73%). Culturing periosteal mesenchymal progenitors under hypoxia conditions (0.1% oxygen) showed that radiation suppresses cell proliferation and inhibits osteogenic differentiation but not chondrogenic differentiation (data not shown).

Discussion

This location-dependent healing in prior irradiated bones demonstrates that both periosteum insult and a lack of surrounding vasculature are critical elements leading to fracture nonunion.This partially explains why fracture healing is difficult to achieve in patients who have been treated with radiotherapy. In our animal model, fibrous tissue instead of

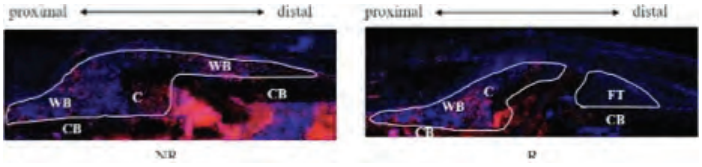

Figure 5. The fibrous tissue at 2 weeks post fracture in prior irradiated Col2-Cre Rosa-Tomato mice contains no Tomato positive cells. CB: cortical bone, C: cartilage, WB: woven bone, FT: fibrous tissue.

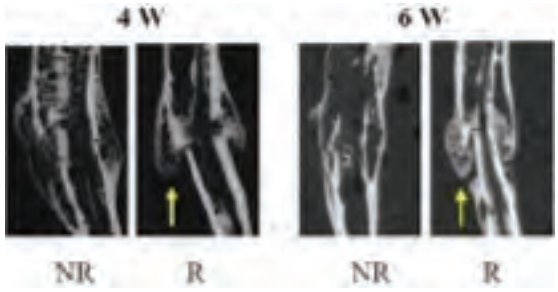

Figure 6. Representative microCT images of nonirradiated and irradiated fracture callus at 4 and 6 weeks post fracture.

bone/cartilage is formed at the distal end of fracture after radiation, and these fibrous cells lack chondrogenic and osteogenic differentiation ability. These changes mimic clinical atrophic nonunion in which primarily fibrous tissue is detected at the fracture ends. Although the origin of this fibrous tissue is currently unknown, our data indicated that they do not come from periosteum. One possible source could be the surrounding muscle resident cells.

Significance

We establish a highly reliable, nonsurgical, and clinically relevant atrophic nonunion fracture model in mice for future investigations that will be relevant to patients undergoing radiotherapy but more broadly for those with atrophic nonunion. Particularly, identifying the source and characteristics of fibrous tissue may pave a way to resolve this clinically challenging disease.

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Delirium Reduced with Intravenous Acetaminophen in Geriatric Hip Fracture Patients

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Introduction

Post-operative delirium is associated with opioid use in the elderly and is a common complication of geriatric hip fractures with reported incidences from 16-70%. Intravenous (IV) acetaminophen is a safe and efficacious medication in elderly patients and has been shown to reduce use of opioids after hip fracture. At our institution, IV acetaminophen was administered in the first twenty-four hours post-operatively as part of a multi-modal pain control regimen for geriatric hip fractures patients. We hypothesized that this intervention may reduce the rate of delirium through decreased opioid consumption.

Methods

A retrospective review of 123 hip fragility fracture patients over age 60 from January 2016 to December 2016 was performed. Patients were compared in terms of age, sex, pertinent baseline medical characteristics, pre-admission functional status and American Society of Anesthesiologists (ASA) classification. The protocols for pre-operative assessment, post-operative mobility, and geriatric co-management were consistent throughout the study period. Type of anesthesia administered, admitting service, fellowship training of attending surgeon, and number of opioid doses pre-operatively were also compared. Delirium was identified using a validated chart-based review tool. The rate of delirium, as well length of stay, pain scores, opioid administration, need for one-to-one supervision, and readmissions were compared.

Results

Sixty-five patients (52.8%) received IV acetaminophen during this period. There were no significant differences in baseline characteristics between groups. Ten out of 65 patients receiving IV acetaminophen post-operatively experienced delirium compared to 19 out of 58 who did not receive the medication (15.4% vs 32.8%, $p = 0.024$). The IV acetaminophen group also required fewer doses of IV opioids on post-operative day 1 (0.37 vs 1.19 doses, $p = 0.008$), were less likely to require one-to-one supervision (9.2% vs 24.1%, $p = 0.025$), and had shorter lengths of hospital stay (6.37 vs 8.47 days, $p = 0.037$). Groups had similar surgical and anesthetic treatment, pre-operative opioid doses, and times from admission to the operating room. Patients were more likely to receive IV acetaminophen when admitted to the orthopaedic service compared to other services (57.7% vs 34.6%, $p = 0.036$). Readmission rates and discharge dispositions did not vary with significance between the two groups.

Discussion

The results of this study indicate that IV acetaminophen can appropriately supplement opioid medication in providing adequate post-operative pain control as evidenced by significantly lower use of intravenous opioids on post-operative day one. As IV acetaminophen was only prescribed for 24 hours post-operatively, it follows that opioid utilization was not different on post-operative days two and three. The pain scores also show a non-inferiority compared to opioids in controlling surgical pain. The reduced use of opioids immediately after surgery may have been a large factor in reducing the rate of delirium in patients receiving IV acetaminophen. The rate of delirium in patients that did not receive IV acetaminophen is consistent with that cited in previous literature. Additional factors which could have predisposed patients to delirium including age, pre-existing medical conditions and pre-surgical opioid administration, amongst others, were compared and not found to be different between the two groups. A greater proportion of patients that were admitted to the orthopaedic service received IV acetaminophen. We believe this is a result of increased familiarity of this medication availability for hip fracture patients amongst the orthopaedic providers compared to other services.

The standard practice at our institution for patients presenting with a geriatric hip fracture is admission to the orthopaedic service with co-management by a geriatric consult team. Deviations from our standard pathway are medically indicated in select cases and accounted for only 17% of patients in this series. An analysis of only patients admitted to the orthopaedics service was performed. The analysis showed a nearly identical reduction of more than 50% in the rate of delirium. This subgroup analysis, along with no other differences in patient

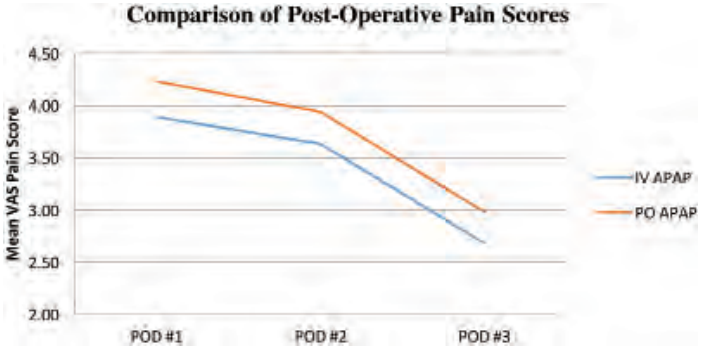


Figure 1. Comparison of Post-Operative Pain Scores. VAS—Visual Analog Scale. POD – Post-Operative Day.

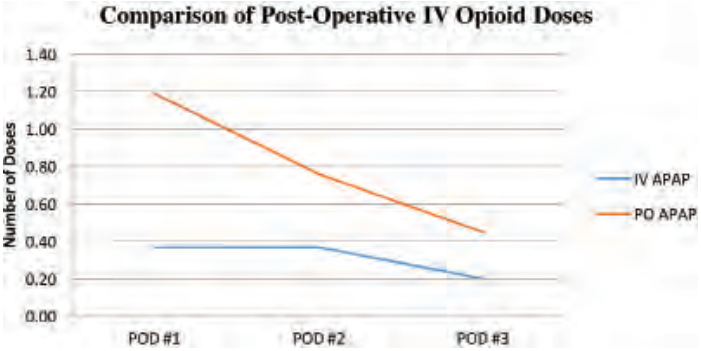
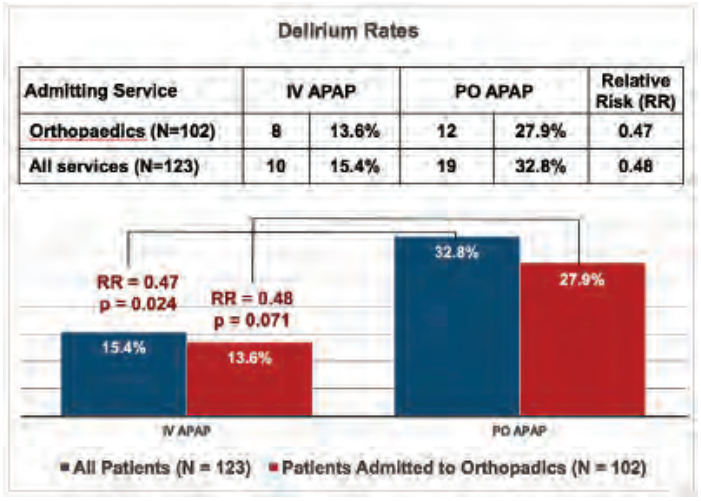


Figure 2. Comparison of Post-Operative Opioid Use. VAS – Visual Analog Scale. POD—Post-Operative Day.



Admitting Service	IV APAP		PO APAP		Relative Risk (RR)
Orthopaedics (N=102)	8	13.6%	12	27.9%	0.47
All services (N=123)	10	15.4%	19	32.8%	0.48

Figure 3. Delirium Rates and Relatively Risk of Delirium with IV Acetaminophen in Patients Admitted to the Orthopaedic Service and All Patients.

characteristics between the two groups, leads the authors to conclude that the effect observed in this study was largely are result of the IV acetaminophen administration.

The difference in secondary outcomes implies that the use of IV acetaminophen may lead to a cost savings, despite a higher medication cost per dose, through reduced need for one-to-one supervision and shorter hospital stays. In our review, patients who became delirious had hospital stays that were nearly 2.5 times longer than those that did not. Other studies have also shown that delirium independently leads to increased mortality in hip fracture patients.

Conclusion

Delirium is a prevalent complication in geriatric hip fractures and has a detrimental effect on patient recovery. Prevention requires a skilled medical and surgical team and use of appropriate treatment modalities. The inclusion of IV acetaminophen in a post-operative opioid-sparing pain protocol can lead to less use of opioid medication after surgery and subsequently lower rates of delirium in the geriatric hip fracture population. This effect may reduce the utilization of inpatient resources for direct patient supervision and provide for shorter hospital stays.

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Notch Signaling in Osteoclasts is Essential for Resorption, but Dispensable for Osteoblast Coupling

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Introduction

Bone loss due to excessive osteoclast resorptive activity is a major source of patient morbidity and mortality. In addition to their role as bone resorbing cells, osteoclasts promote the differentiation of bone-forming osteoblasts. This coupling role is apparent in both genetic and pharmacologic suppression of the osteoclast numbers, both of which result in a concomitant decrease in the number of osteoblasts. Conversely, approaches that inhibit osteoclast activity while preserving the osteoclast number preserve osteoblast function. Notch signaling plays a crucial role in osteoclast maturation and function. Our lab has previously demonstrated that stimulating the Notch pathway in committed osteoclasts precursors results in large multinuclear cells with increased resorptive activity whereas chemical inhibition of the same caused smaller osteoclasts with impaired resorption. Herein, we investigated osteoclast resorptive and coupling functions in the context of genetically inhibited Notch signaling.

Methods

Notch activation requires cleavage of its intracellular domain NICD to translocate into the nucleus and interact with co-activators such as Mastermind-like1 (MAML) for transcriptional activation. Wild type (WT) [LysM-Cre/− dnMAML−/−] and dnMAML [LysM-Cre/−dnMAMLMye+/−] mice were utilized in this study. dnMAML mice express a dominant negative form of MAML that inhibits the transcriptional complex. Furthermore, this dnMAML expression is restricted to myeloid lineage cells, which include osteoclasts and their precursors. Cells from tibial and femoral bone marrow of both wild type and dnMAML+ mice were isolated and cultured for osteoclast differentiation with Monocyte/Macrophage Colony-Stimulating factor (MCSF) and mouse Receptor Activator of Nuclear Factor kβ Ligand (RANKL). The osteoclasts were later used for tartrate-resistant acid phosphatase (TRAP) staining, gene expression analysis using quantitative PCR (q-PCR) and functional assays such as bovine cortical bone resorption and osteoblast stimulation. Osteoblast precursors from wild type mice were cultured in presence of condition media obtained from both wild type and dnMAML osteoclasts separately. Both alkaline phosphatase activity and mineralization content were determined in the osteoblasts. All mice were maintained as per the guidelines issued by Institutional animal care and use Committee (IACUC) of the University of Pennsylvania.

Results

Using the dnMAML+ osteoclasts we observed that inhibition of Notch signaling results in osteoclasts precursors that fail to mature and function without significant alterations in early osteoclastic gene expression. Osteoclasts from the dnMAML group showed defect in maturation process and were smaller in size and fewer in number compared to the wild type (Figure 1A). The functionality of dnMAML+ cells upon stimulation with Notch signaling by Jagged-1 showed down-regulation of Hes1 (marker for Notch activation) compared with the wild type which is consistent with suppressed Notch

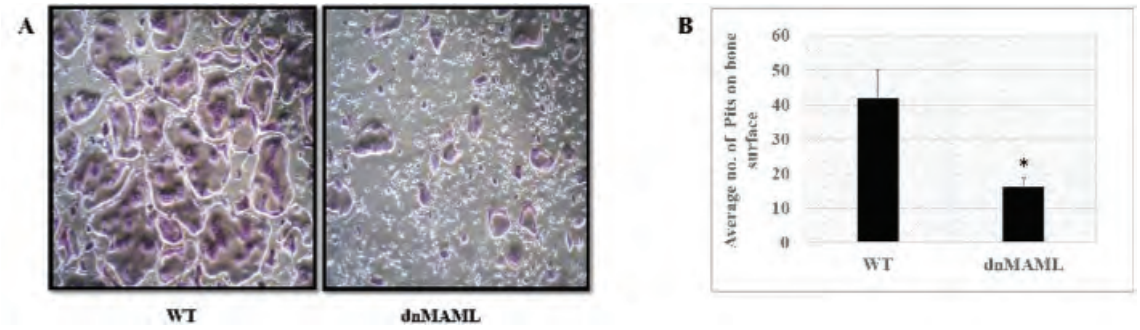

Figure 1. Reduced osteoclast maturation and resorptive function by dnMAML expressing osteoclasts. **(A)** Osteoclasts from the WT are giant and fully mature while the osteoclasts from Notch defective mice (dnMAML) fail to fuse effectively and remain immature using TRAP stain (purple). **(B)** The osteoclast precursors from both WT and dnMAML mice were differentiated on bone slices, stained using toluidine blue and quantified. dnMAML osteoclasts shows significant lesser number of resorption pits (*p<0.05).

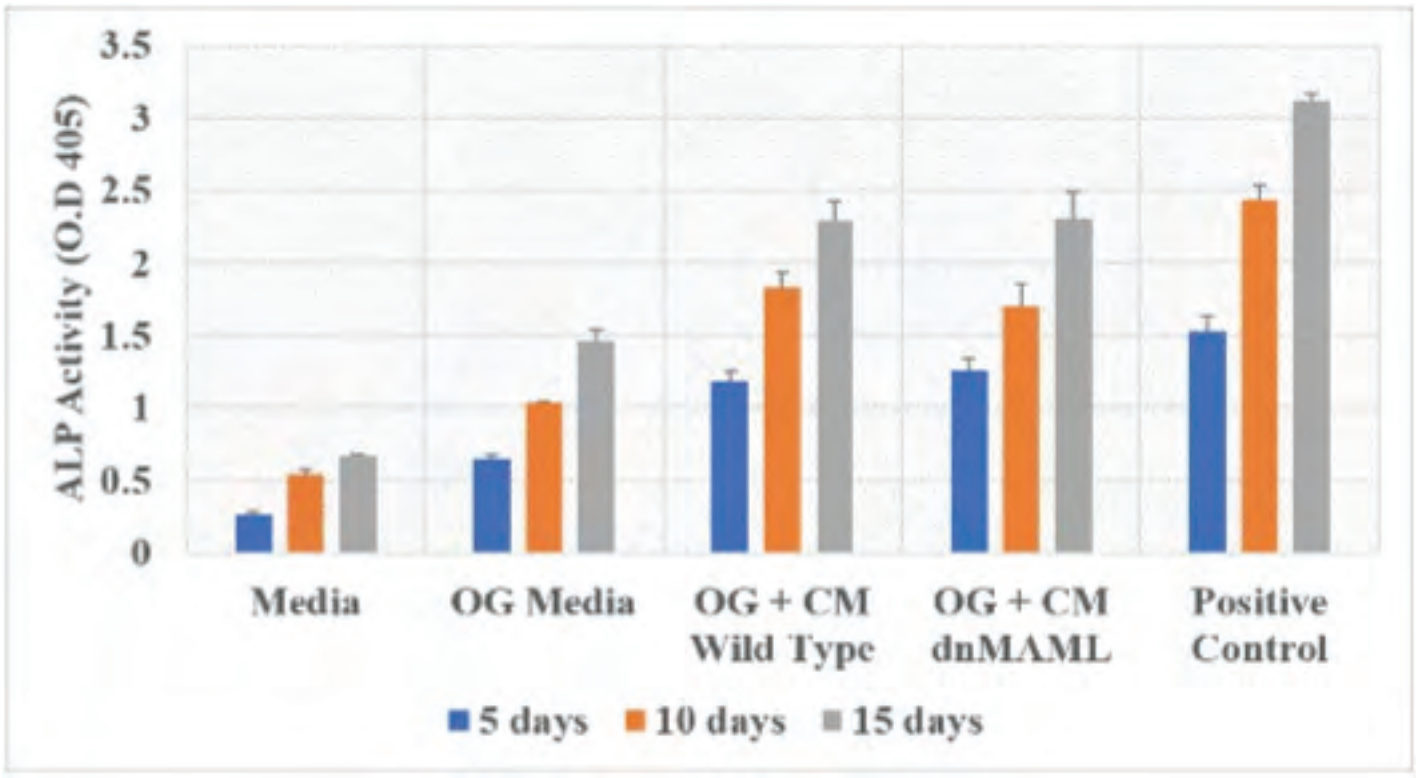

Figure 2. dnMAML osteoclasts retain their osteoblast stimulating ability. Cultured osteoblast precursors were cultured under osteogenic conditions in the presence of unconditioned medium or medium conditioned by WT or dnMAML osteoclasts. WT and dnMAML osteoclast conditioned medium similarly enhanced osteogenesis. OG media is osteogenic media while positive control is OG media + bone morphogenetic protein.

signaling. Next, functional characterization of genetically modified osteoclasts (dnMAML+) was performed using bone slices. dnMAML expressing osteoclasts showed significantly lower resorption and formed fewer resorption pits compared to the wild type (Figure 1B). dnMAML+ showed lesser TRAP positivity using the bone slices and were found to be smaller and immature. TRAP activity in the condition media collected at regular intervals from osteoclasts seeded over bone slices showed marked reduction in the enzymatic activity due to lesser bone resorption by dnMAML+ osteoclasts. Lastly, no significant difference was observed in alkaline phosphatase activity (Figure 2) and mineralization ability of wild type osteoblasts stimulated with either WT or dnMAML osteoclast conditioned medium.

Discussion

In our present work, we have demonstrated that osteoclasts derived from dnMAML mice showed no significant differences in early osteoclastic gene expression compared to wildtype. However, osteoclasts with defective notch signaling had decreased TRAP production and decreased bone resorption. Lastly, dnMAML+ osteoclasts preserved osteoblast function and activity. These observations suggest that inhibition of Notch signaling impairs osteoclast maturation rather than early commitment and gene expression. Importantly, this suggests that the regulation of Notch signaling could allow for the persistence of immature, weakly resorbing osteoclasts that retain their osteoblast-stimulating activity.

Significance

The current work provides a mechanistic insight into osteoclast function and important pre-clinical data informing potential use of Notch signaling inhibition in osteoclasts to improve bone mass.

Osteoprogenitor YAP and TAZ Promote Bone Fracture Repair

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Introduction

Bone fracture healing requires progenitor cell mobilization, differentiation, and matrix deposition, but the molecular mechanisms remain incompletely understood. Recently, we found that yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) promote bone matrix development through regulation of collagen expression and organization[1]; however, the roles of YAP and TAZ in osteogenesis remain controversial. Separately, we have found in endothelial cells that YAP and TAZ regulate feedback control of cytoskeletal dynamics to control acto-myosin equilibrium and enable motility[2]. In osteoprogenitor cells, cytoskeletal remodeling regulates activation of the osteogenic transcriptional program[3], potentially through YAP/TAZ. Here, we tested the hypothesis that osteoprogenitor YAP and TAZ promote bone fracture healing and regulate cytoskeletal reorganization to control osteogenic differentiation.

Methods

We generated two mouse models: 1) constitutive allele dosage-dependent YAP/TAZ conditional knockout mice and 2) adult-induced double homozygous conditional knockout mice (YAPfl/fl;TAZfl/fl;TetOff-Osx-Cre, hereafter cDKOi), by ablating YAP and/or TAZ by Cre-recombination under control of the Osterix1 promoter. All animal experiments were approved by the IACUC. In inducible knockouts, Cre expression was repressed by doxycycline (dox) administration from conception to 14 weeks of age, while constitutive knockouts were bred and raised without exposure to dox. Unilateral femoral fractures were created at 16 weeks of age. Bone marrow stromal cells (MSCs) were isolated from both WT and Osterix conditional YAP/TAZ- deficient mice. MSCs were cultured in osteogenic media prior to either RNA isolation or staining for filamentous actin. Comparisons were made using Student's t-tests. Non-parametric Mann-Whitney tests were used if necessary. A p-value less than 0.05 was considered significant.

Results

In vivo, both WT and cDKOi mice exhibited callus formation in response to bone fracture (Fig.1 A). Compared to WT littermates, cDKOi mice had significantly lower bone volumes, at both one and two weeks post-fracture ($p < 0.05$), but had equivalent total callus volumes (Fig.1 B-C, $N = 6 - 12$). In vitro, cDKOi MSCs had increased filamentous actin intensity and increased stress fiber formation after 7 days in osteogenic media, which persisted to 14 days (Fig.2 A-B). Expression of YAP, TAZ, Osterix, and collagen1a1 (Col1a1) were not different prior to Osterix induction (day 0; Fig. 3A); however, Osterix-mediated Cre-recombination reduced

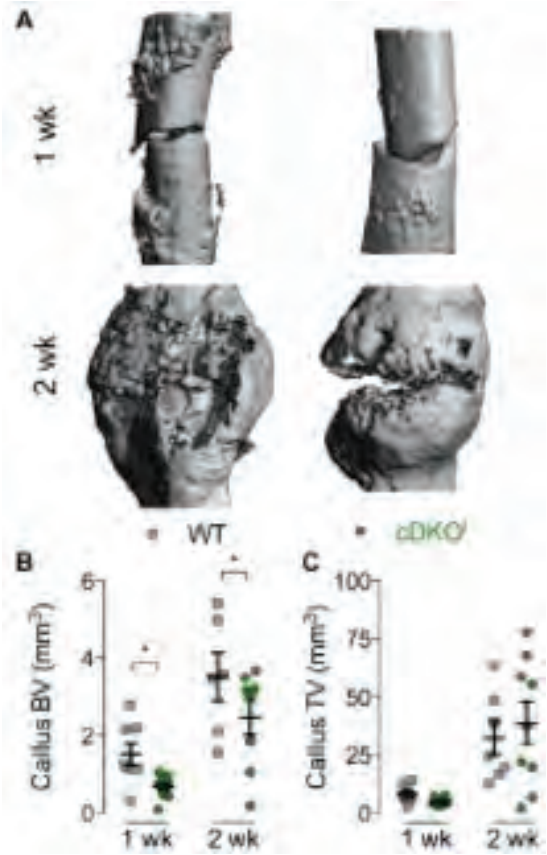

Figure 1. Inducible dual homozygous YAP/TAZ deletion impaired *in vivo* fracture healing. **(A)** representative 3D CT reconstructions. Quantification of calus **(B)** and **(C)** total bone volume.

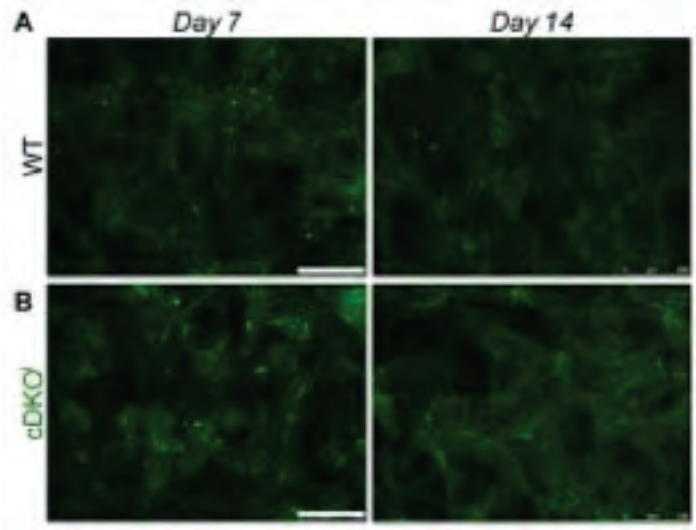

Figure 2. Increased stress fiber formation *in vitro* following Osteriz-induced YAP/TAZ deletion. **(A)** WT and **(B)** cDKO MSCs in osteogenic induction media for 7 and 14 days. Scale bar = 250μM.

TAZ mRNA expression levels after seven days in osteogenic media while differences in YAP expression did not reach significance (Fig. 3B). At day 7, Osterix-conditional YAP/TAZ deletion reduced Col1a1, osteocalcin (Ocn), alkaline phosphatase (Alp), and bone sialoprotein (Bsp) expression, while Runx2 and Osterix mRNA levels were not significantly altered (Fig.3 B-C).

Discussion

YAP/TAZ deletion from osteoprogenitor cells reduced fracture callus ossification, but did not impair cartilaginous anlage formation, consistent with our prior observations in developmental endochondral ossification[1]. In osteoprogenitor cells, YAP/TAZ deletion upon Osterix induction increased actin stress fiber formation, suggesting conservation of the cytoskeletal feedback mechanism observed in endothelial cells[2]. In addition to stress fiber persistence,YAP/TAZ deletion reduced osteogenic gene expression. Together, these data implicate YAP/TAZ in cytoskeleton-dependent control of osteogenesis during endochondral fracture repair.

Significance

A mechanistic understanding of how these proteins combinatorically regulate osteogenesis could guide future therapeutic strategies for bone regeneration.

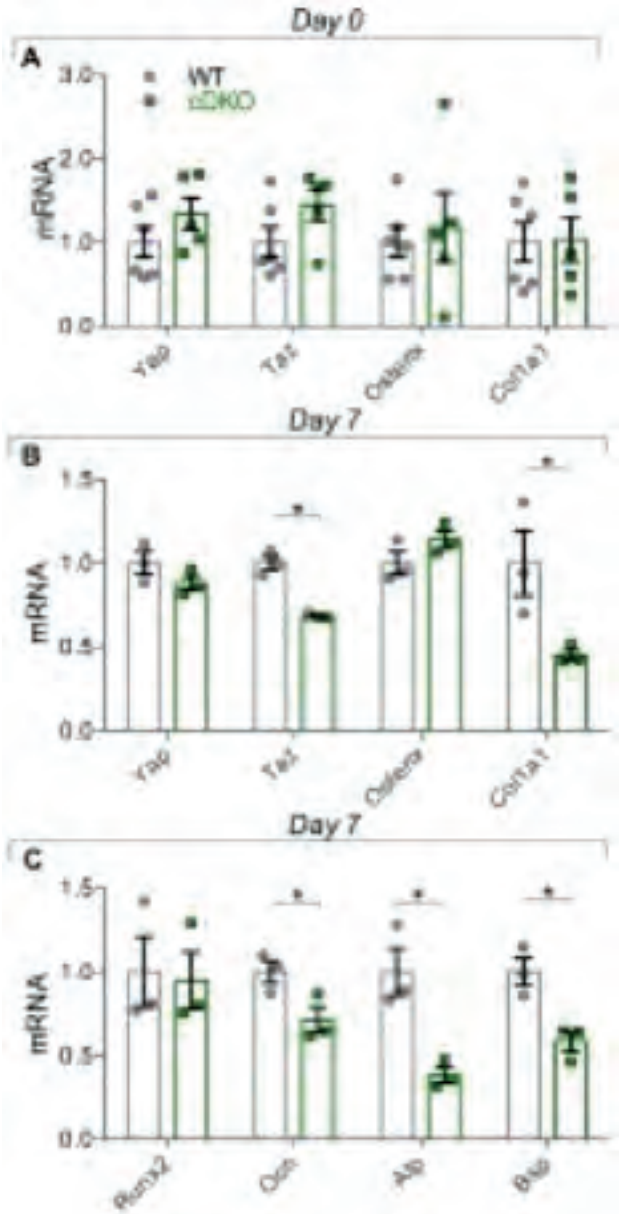

Figure 3. Decreased osteogenic gene expression following Osterix-mediated YAP/TAZ ablation *in vitro.* **(A)** mRNA expression levels of YAP, TAZ, Osterix, and collagen 1a1 (Col1a1) prior to Osteoinduction (Day 0), **(B)** mRNA expression levels of YAP, TAZ, Osterix and col1a1 following Osterix-induction (Day 7) **(C)** mRNA expression levels of Runx2. Ossification (Ocn), alkaline phosphatase (Alp) and bone sialoprotein (Bsp) at day 7.

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Microarchitectural Adaptations in Rat Maternal Bone Induced by Pregnancy and Lactation Exert Protective Effects against Future Estrogen Deficiency

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Introduction

Pregnancy and lactation induce dramatic maternal bone loss, which recovers partially post-weaning[1]. Although reproductive history does not increase the risk of developing postmenopausal osteoporosis[1], recent studies utilizing high-resolution computed tomography (CT) found that the effects of reproduction on maternal bone microstructure persist long after weaning[2-4], forming a paradox. We hypothesized that reproduction may induce changes in the bone structural and/or cellular response to future estrogen deficiency, resulting in an altered pattern of postmenopausal bone loss. To test this hypothesis, we investigated the skeletal effects of ovariectomy (OVX) surgery in rats with and without a history of pregnancy and lactation.

Methods

Animal Experiments

All experiments were IACUC approved. Female, SD rats were divided into two groups: Reproductive and Virgin. Starting at age 3 months, reproductive rats underwent 3 cycles of pregnancy and lactation, with a 6-week post-weaning recovery period between each cycle. At age 12 months, all rats underwent OVX surgery to induce estrogen deficiency.

Microstructural Analysis

17 rats (9 reproductive, 8 virgin) underwent in vivo μCT imaging of the proximal tibia prior to OVX, as well as 4, 8, and 12 weeks post-OVX (10.5μm, vivaCT 40, Scanco Medical) for the evaluation of trabecular and cortical bone microstructure. Whole-bone stiffness was estimated through finite element analysis (FEA).

Cell Activities

17 rats (9 reproductive, 8 virgin) were euthanized at 4 weeks post-OVX. Tibiae were harvested and processed for MMA embedding. Longitudinal sections were stained with Goldner's Trichrome, and the numbers and surfaces of osteoblasts and osteoclasts (N.Ob/BS, N.Oc/BS, Ob.S/BS, Oc.S/BS) were quantified within the secondary spongiosa.

Effects of Baseline Microstructure on Bone Loss

Stepwise multiple linear regression was performed to identify the baseline trabecular parameters that were most predictive of the degree of post-OVX bone loss. To further evaluate the role of trabecular thickness, individual trabecular dynamics (ITD) analysis[5] was performed. A trabecular volume of interest (VOI) was identified within the registered μCT scans made prior to and 4-weeks post-OVX, and was subjected to individual trabecular segmentation (ITS), to isolate individual trabecular elements. The extent of bone loss and changes in connectivity were tracked for each trabecula, and the baseline characteristics associated with connectivity deterioration were identified.

Results

Over 12 weeks post-OVX, virgin rats underwent 76%, 87%, 52%, and 22% decreases in bone volume fraction (BV/TV), connectivity density (Conn.D), trabecular number (Tb.N), and whole-bone stiffness, respectively ($p<0.05$), with no change in trabecular thickness (Tb.Th, Fig 1). In contrast, reproductive rats showed

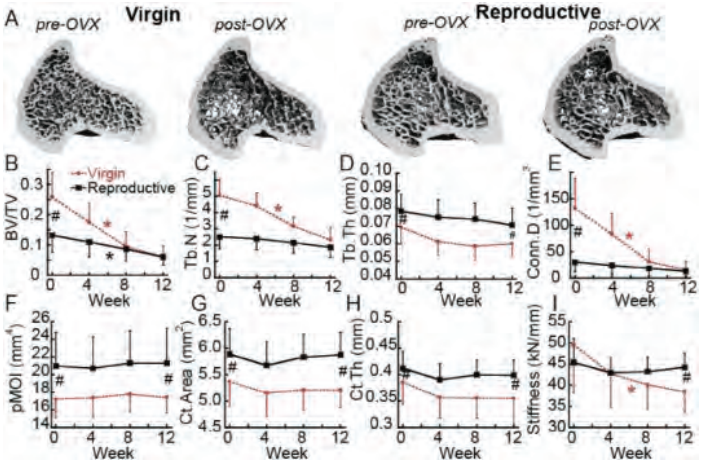

Figure 1. (A) 3D renderings of virgin and reproductive tibiae pre- and 12 weeks post-OVX. **(B-E)** Post-OVX changes in trabecular microstructure **(F-H)** Post-OVX changes in cortical bone structure **(I)** changes in whole bone stiffness after OVX.

a 53% decrease in BV/TV, with no changes in Conn.D, Tb.N, Tb.Th, or whole-bone stiffness. Prior to surgery, reproductive rats had 49%, 77%, and 50% lower BV/TV, Conn.D, and Tb.N, respectively, than virgins ($p<0.05$), but by 12 weeks post-OVX, these parameters were not different between the two groups. Reproductive rats had 13-17% greater Tb.Th, as well as 22%, 10-13%, and 7-12% greater polar moment of inertia(pMOI), cortical area (Ct.Area), and cortical thickness (Ct.Th) than virgins throughout the study ($p<0.05$). Because of the differential post-OVX reductions in whole-bone stiffness between the two groups, virgin rats had 13% lower whole-bone stiffness than the reproductive group by 12 weeks post-OVX. Histomorphometry indicated that virgin and reproductive rats had highly similar osteoblast and osteoclast numbers and surfaces at 4 weeks post-OVX (Fig 2). Multiple linear regression showed that the combination of baseline Tb.N and Tb.Th was most strongly associated with the percent decrease in BV/TV, with an adjusted r2 = 0.69. ITD analysis (Fig 3) showed that virgin rats underwent a 125-179% greater rate of rod disconnection and plate perforation than the reproductive group. Furthermore, the trabeculae that underwent connectivity deterioration were significantly less thick than those that remained intact after OVX ($p<0.05$). Analysis of the overall distribution of trabecular thicknesses demonstrated a greater mean and variance of trabecular thicknesses in the reproductive group, as compared to virgins. However, isolation of the subset of trabeculae that underwent connectivity deterioration indicated that, for both groups of rats, a highly similar population of trabeculae, with a reduced thickness, underwent microstructural decay.

Figure 2. Cell activities 4 weeks post-OVX in virgin and reproductive rats.

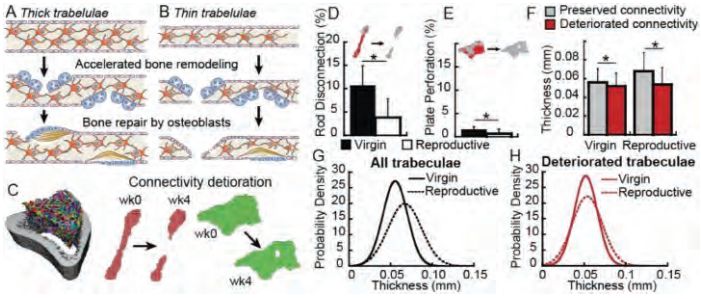

Figure 3. (A-B) Schematics of estrogen-deficiency-induced bone resorption, followed by osteoblast repair in **(A)** thick and **(B)** thin trabeculae. **(C)** Schematics of ITD analysis. Rate of **(D)** rod disconnection and **(E)** plate perforation. **(F)** Mean thickness of deteriorated and intact trabeculae post-OVX. **(G-H)** Probability density distribution of thickness of **(G)** all trabeculae and **(H)** deteriorated trabeculae. *$p<0.05$.

Discussion

Results from this study confirm the long-lasting effects of reproduction on maternal bone, as prior to OVX, reproductive rats showed inferior trabecular microarchitecture compared to virgins. After OVX, reproductive history resulted in a reduced bone loss rate, such that, by 12 weeks post-OVX, baseline differences in trabecular microstructure between reproductive and virgin rats were eliminated. In addition, reproductive rats showed elevated robustness of cortical bone throughout the experiment, and by 12-weeks post-OVX, reproductive rats had greater whole-bone stiffness than virgins, suggesting that reproductive history may have a protective effect on postmenopausal bone strength. Taken together, histology and ITD results indicate that reproductive-history-induced differences in OVX response did not result from alterations in bone cell activities, but instead were likely due to differences in baseline trabecular microstructure, and, in particular, trabecular thickness. The thicknesses of trabeculae undergoing structural decay were highly similar between reproductive and virgin rats, demonstrating that, regardless of reproductive history, the same population of thinner trabeculae, was responsible for the post-OVX connectivity deterioration. This is likely due to the increased susceptibility of thin trabeculae to undergo perforation or separation as a result of elevated bone remodeling[6]. The larger proportion of thick trabeculae in the reproductive group may explain the protective effect on post-OVX bone loss.

Significance

The effects of reproduction on bone health are unclear: pregnancy and lactation have long-lasting effects, but do not increase long-term fracture risk. This study shows that the unique microstructure of post-reproductive bone confers protective effects against postmenopausal bone loss.

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Scleraxis Targeted Collagen V Deletion Affects Bone Morphology with Altered Skeletal Loading

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Introduction

Classic Ehlers-Danlos syndrome (EDS) is characterized by abnormalities in connective tissue due to mutations in collagen V, with the most common mutation being haploinsufficiency in COL5A1. This syndrome is characterized by hypermobility, instability, hyperextensible skin, and abnormal wound healing [1,2]. Scleraxis-driven collagen V null (Col5a1Δten/Δten) mice have been developed to determine the role of collagen V in tendon [3,4]. In addition to differences in tendon, Col5a1Δten/Δten mice demonstrate decreased body size and exhibit reduced cortical bone polar moment of inertia (pMOI) [5,6], even though the role of collagen V in bone is believed to be limited [7]. The cause of this change in pMOI in these mice is unlikely, given the specificity of scleraxis, and as such, the cause of alterations in cortical bone morphology is unknown. Therefore, the objective of this study was to determine whether the observed bone morphological changes could be due to reduced skeletal loading. We hypothesized that any changes in bone morphology in the Col5a1Δten/Δten would be due to decreased skeletal loading.

Methods

Humeri from day 60 Col5a1+/+ (WT, n=8) and Col5a1Δten/Δten (NULL, n=13) mice, and ribs from day 120 Col5a1+/+ (WT, n=10) and Col5a1Δten/Δten (NULL, n=8) mice (IACUC approved) were prepared for high-resolution micro-computed tomography (μCT). Rib bone was chosen as a skeletal structure that is relatively load-independent and therefore its structure would not be affected by decreased mechanical loading. High-Resolution micro-CT. All samples were scanned using a μCT 35 (Scanco Medical AG). The epiphyseal and metaphyseal regions of the humeri, defined as proximal and distal to the growth plate, respectively, as well as the ribs at the cortical midshaft, were scanned at an isotropic resolution of 6μm. Standard cortical and trabecular morphometry parameters (trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular spacing (Tb.Sp)), were measured for all humeri, while ribs only underwent cortical evaluation. Samples were kept hydrated with phosphate buffered saline (PBS) during scanning.

Data Analysis

The maximum pMOI for the cortical regions was calculated using custom code (MATLAB) and standard cortical and trabecular evaluations provided by Scanco were used to obtain all other parameters. Statistics Unpaired t-tests ($p<0.05$) were used to compare between WT and NULL mice for both humeri and ribs.

Results

Body weight was significantly decreased in the NULL mice when compared to the WT mice for both the day 60 and day 120 mice (Fig.1A-B).

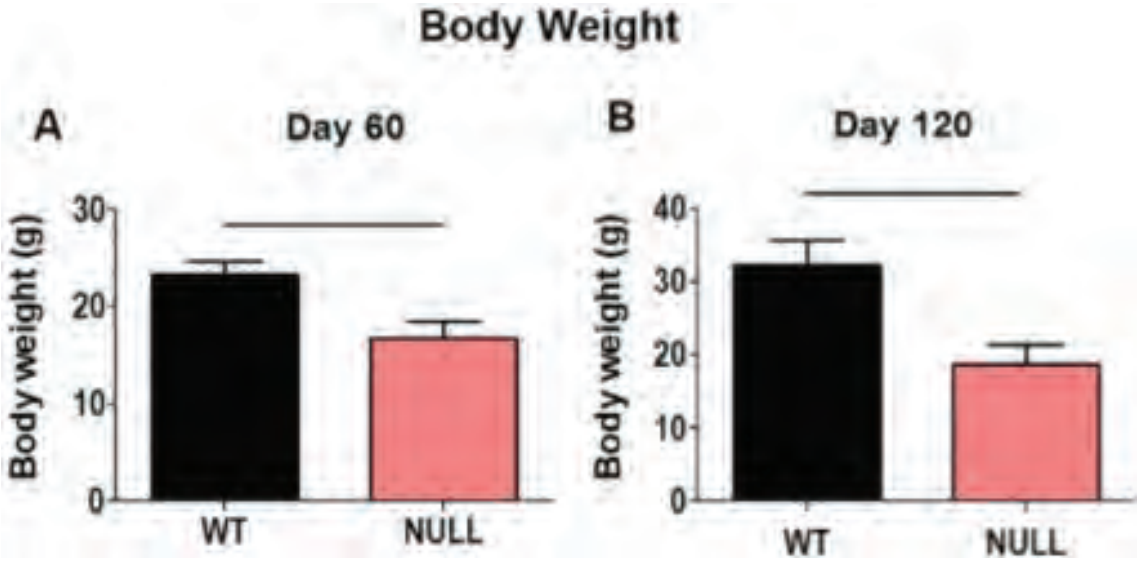

Figure 1. Body weight in WT was significantly greater than NULL at **(A)** day 60 and **(B)** day 120

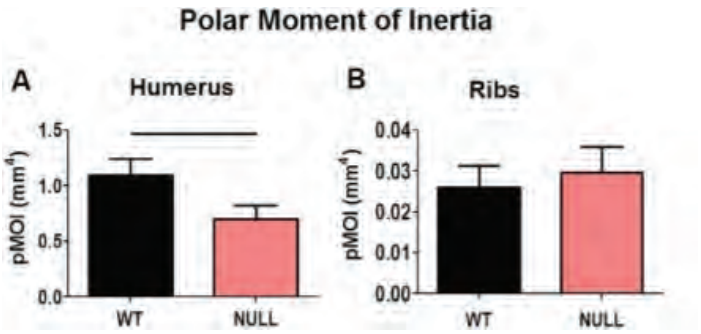

Figure 2. (A) pMOI was greater in the WT than the NULL for the humeri but **(B)** no changes were shown in the ribs.

Cortical regions. pMOI in the WT mice was significantly greater than in the NULL mice for the humeri (Fig.2A); however no changes were detected in pMOI in the ribs between groups (Fig.2B). There were no changes found for the other cortical parameters (data not shown). Trabecular regions. Tb.N was greater in the WT mice than the NULL mice in the epiphyseal region, (Fig.3A), and greater in WT mice than NULL mice in the metaphyseal region (Fig.3B). Tb.Th was greater in WT mice than the NULL mice in the epiphyseal region (Fig.3C) and in the metaphyseal region (Fig.3D). Tb.Sp in WT was decreased compared to NULL in both the epiphyseal region (Fig.3E) and metaphyseal region (Fig.3F).

Discussion

This study investigated whether changes in bone morphology in Col5a1Δten/Δten were caused by reduced loading due to body weight. The WT mice had greater body weight than the NULL mice and therefore exhibited greater mechanical loading on load-bearing skeletal structures resulting in more numerous, thicker trabeculae in WT mice when compared to NULL mice. The only differences in cortical bone were observed in pMOI in the humeri, but not in the ribs. This indicates that altered skeletal loading due to a decrease in body weight is a strong contributing factor to the differences observed between the WT and NULL mice. In addition to reduced body weight, these mice exhibit altered mobility and diminished activity [7], which may also contribute to reduced mechanical loading. These results are also in agreement with previous studies demonstrating that increased volume of mineralized tissue is induced by increased loading, and that mechanical unloading leads to trabecular bone loss [8,9]. Previous research in EDS patients has shown a reduction in bone mineral density (BMD) and lower trabecular bone scores (TBS) [10]. Although we found no differences in BMD, we did observe reduction in trabecular morphological parameters. In conclusion, results indicate that bone loss consistent with EDS may be due to mechanical unloading of load-bearing skeletal

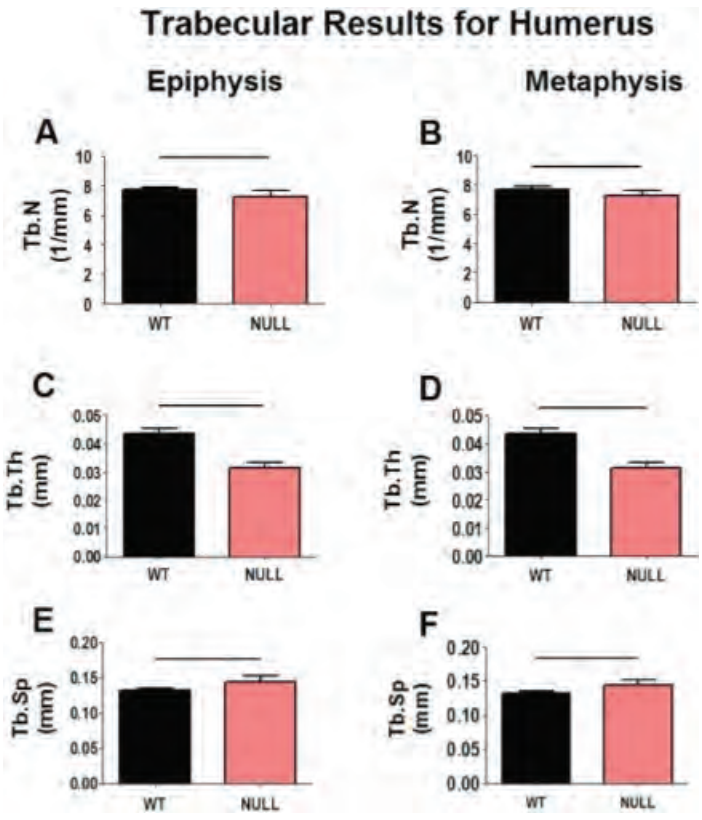

Figure 3. Tb.N was significantly greater in WT than NULL in both the **(A)** epiphysis and **(B)** metaphysis. Tb.Th was significantly greater in WT than NULL in both the **(C)** epiphysis and **(D)** metaphysis. Tb.Sp. was decreased in WT compared to NULL in both the **(E)** epiphysis and **(F)** metaphysis.

structures. However, other influences such as level of physical activity or aging might also contribute to this bone loss and future studies will investigate these potential influences further.

Significance

This study highlights the importance of monitoring bone integrity in patients suffering from classic EDS especially with reduction in physical activity and body weight during aging.

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Alternating Parathyroid Hormone (PTH) and Alendronate Treatment Regimens Further Improve the Efficacy of Daily and Cyclic PTH Regimens in Osteoporosis Therapy

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Introduction

As the only FDA-approved anabolic agent for treating osteoporosis, intermittent PTH can only be used 18-24 months in clinical practice. However, bone mineral density rapidly decreases upon withdrawal from PTH treatment despite its potent effect of promoting new bone formation[1]. In our previous study, μCT results showed a continuous anabolic window during the first week of PTH discontinuation in ovariectomized (OVX) rats[2]. During this anabolic window, no change occurs in osteoblast and osteoclast number while bone mass and microarchitecture continue to improve.

However, after a 2-week discontinuation of PTH, osteoblast number starts to decline and osteoclast number increases significantly.To fully utilize this anabolic window, a cyclic treatment regimen with repeated cycles of on and off daily injection of PTH may be able to maximize the efficacy of PTH and extend treatment duration[3]. Furthermore, adding the anti-resorptive treatment during the off-PTH period may prevent the increased osteoclast activities and further improve the treatment. Therefore, the objective of this study is to test the effect of cyclic and sequential treatment regimens alternating PTH and alendronate (ALN, an anti-resorptive agent) on bone microarchitecture and mechanical competence.

Methods

Animals

29 female SD rats received bilateral OVX surgery at age 4 months and developed osteopenia for 4 weeks.These rats were assigned to VEH (n=6, saline for 18 weeks), PTH-VEH (n=6, PTH 40μg/kg 5x/wk for 9 weeks followed by saline for 9 weeks), cyclic PTH-VEH (n=7, PTH for 3 weeks followed by saline for 3 weeks, repeat for 3 cycles), cyclic PTH-ALN (n=5, PTH for 3 weeks followed by ALN 20mg/kg 2x/wk for 3 weeks, 3 cycles) and cyclic ALN-PTH (n=5, ALN for 3 weeks followed by PTH for 3 weeks, 3 cycles).

In vivo μCT Imaging

Sequential scans of the proximal tibiae were performed by in vivo μCT (Scanco Medical) at 10.5 μm voxel size at week-4 (OVX surgery),0, 3, 6, 9, 12, 15 and 18. The same volume of interest (VOI, Fig 1A) was identified by 3D image registration[4] in all scans and subjected to trabecular bone microstructural analysis.

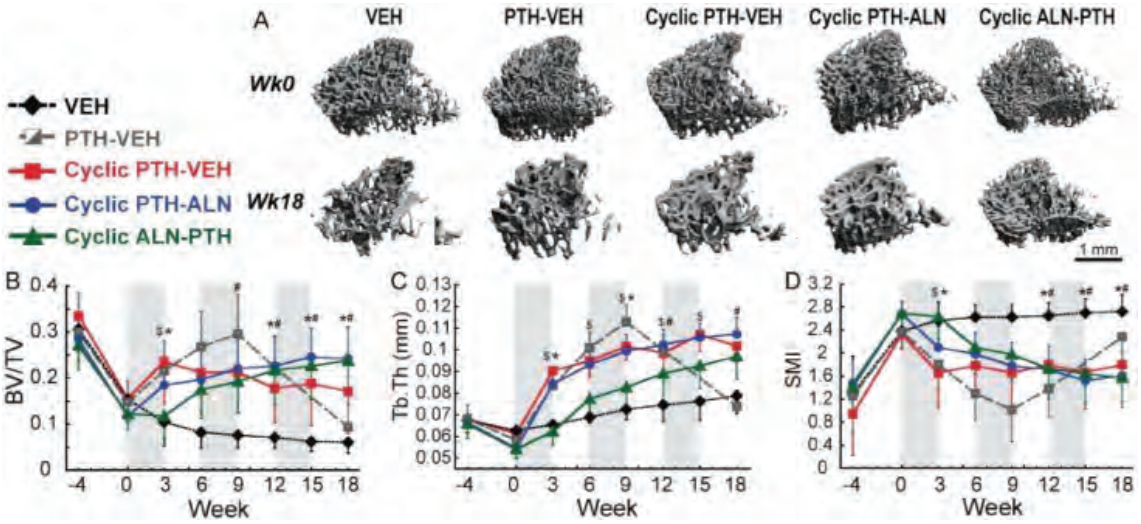

Figure 1. (A) Representative 3D images of trabecular bone microarchitecture of the proximal tibia at the baseline and end of different treatment regimes. Changes in tibial trabecular bone **(B)** BV/TV, **(C)** Tb, Th, **(D)** SMI in different treatment groups.

Ex vivo μCT Imaging

The center 2 mm of the vertebral body of lumbar vertebra L2 was imaged by μCT at 10.5 μm voxel size, and cross-sectional area (CSA) and trabecular bone microstructure were assessed. Uniaxial compression test of L2: A 4-mm-thick section of the vertebral body with processes was excised[5] and compressed to failure at a displacement rate of 1.8 mm/minute by using Instron 5542. Load-displacement curves were used to calculate peak load, stiffness, and energy to failure. Apparent-level properties, including ultimate stress, elastic modulus, and toughness, were estimated by normalizing extrinsic properties by μCT- derived total CSA, as described in[6].

Statistics

Longitudinal comparisons were made using a 2-way, repeated-measures ANOVA, adjusted for baseline values, and cross-sectional comparisons were made using 1-way ANOVA. Bonferroni corrections were applied to all post hoc tests.

Results

4-week osteopenia development in tibiae caused 51% and 11% decrease in bone volume fraction (BV/TV) and trabecular thickness (Tb.Th) respectively, and a 105% increase in structure model index (SMI, Fig 1 B-D). Bone microarchitecture deterioration continued in VEH rats for 18 weeks. Meanwhile, in PTH-VEH group, 9-week PTH treatment led to greater BV/TV, Tb.Th and lower SMI than all the other groups. However, these improvements were no longer present after the 9-week discontinuation from PTH treatment. On the other hand, cyclic PTH treatment efficiently maintained the benefit of 3-week PTH treatment in BV/TV and SMI from the 1st cycle of treatment, and further increased Tb.Th over the next 2 cycles of PTH on and off treatment. Furthermore, both alternating PTH-ALN and ALN-PTH regimens further improved the benefit of PTH treatment in BV/TV and SMI when compared to cyclic PTH-VEH regimen (Fig 1B and D). Interestingly, only the cyclic PTH-ALN regimen led to greater Tb.Th than the cyclic PTH-VEH group. Results of lumbar vertebra L2 suggested greater BV/TV and Tb.Th in both cyclic PTH-ALN and ALN-PTH groups than all the other groups (Fig 2 A-C). Additionally, peak load, energy to failure, and apparent-level toughness were 29%, 45%, and 43% greater in the cyclic PTH-ALN than the cyclic PTH-VEH group (Fig 2 D, E and H), and 29%, 48%, and 46% greater in the cyclic ALN-PTH than the cyclic PTH-VEH group, respectively. In contrast, there were no difference in any of the L2 mechanical properties among VEH, PTH-VEH, and cyclic PTH-VEH groups (Fig 2 D-I).

Discussion

Similar to previous clinical findings[1], this study showed that significant bone loss and bone microarchitecture deterioration occurred in OVX animals after discontinuation of PTH treatment. The cyclic PTH-VEH treatment regimen alleviated bone deterioration and extended the total duration of treatment. However, despite continuous increases in Tb.Th, the cyclic PTH-VEH regimen did not further improve BV/TV or SMI during the 2nd and 3rd cycles of treatment; neither did it improve any of the L2 mechanical properties by the end of the 3rd cycle. By adding antiresorptives (ALN) during the off-PTH period, both cyclic PTH-ALN and ALN-PTH regimens showed greater improvement in bone microarchitecture at the proximal tibia and lumbar vertebra when compared to cyclic PTH treatment regimen. Furthermore, cyclic treatment regimen with alternating PTH and ALN injections led to greater bone strength at both whole bone and apparent levels. In conclusion, cyclic and sequential treatment of PTH and anti-resorptive agent can further improve the treatment efficacy of daily and cyclic PTH treatment regimen and extend PTH treatment duration.

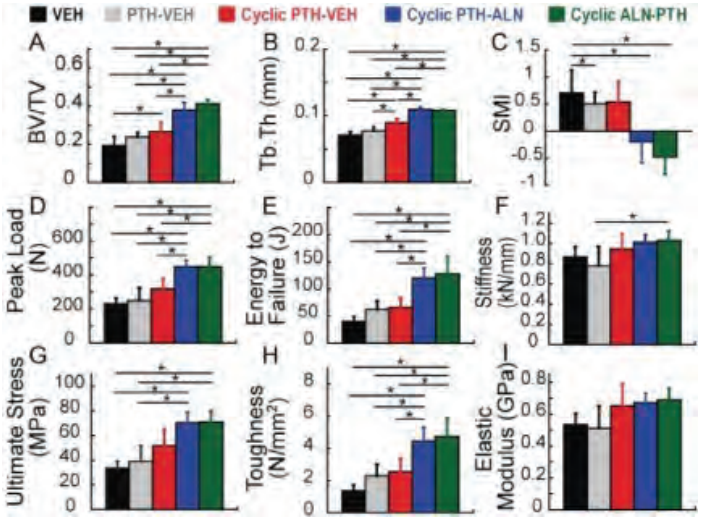

Figure 2. (A-C) Lumbar vertebra L4 trabecular bone microstructure: **(D-F)** Extrinsic mechanical properties of L4l **(G-I)** Apparent level properties, derived by normalizing extrinsic properties by total corss-sectional area * $p<0.05$

Significance

By testing various cyclic and sequential treatment regimens alternating PTH and anti-resorptive agents, this study provided important insight into the clinical design and optimization of pharmacological treatment strategies to maximize the duration and efficacy of osteoporosis treatment.

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Roles of Collagen V in the Structure and Mechanics of TMJ Condyle Cartilage: A Fibro-Hyaline Hybrid

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Introduction

The mandibular condyle cartilage in the temporomandibular joint (TMJ) has a unique bi-layered layout of a collagen I-dominated fibrocartilage layer covering a collagen II and aggrecan-dominated hyaline cartilage layer[1]. This distinctive hybrid structure endows the mandibular cartilage with its specialized biomechanical functions for the high frequency loading of the TMJ during daily speaking and chewing activities[2]. Similar to knee osteoarthritis (OA), degeneration of mandibular cartilage is a hallmark of TMJ OA[3], affecting 10-16% of the US population[4]. Currently, there is very limited understanding of the molecular mechanisms governing the formation of this hybrid tissue extracellular matrix (ECM)[5]. Such knowledge is critical for documenting TMJ OA progression and for designing tissue repair strategies. The initial ECM fibrillogenesis of collagens I and II are regulated by collagens V and XI, respectively[6], and the importance of collagen XI in TMJ function has been highlighted by the phenotype of *Col11a1*$^{+/-}$ (*Cho/+*) murine TMJ[7]. Thus, this study aims to reveal the roles of collagen V in TMJ condyle cartilage structure and function. We also will provide new insights into the high prevalence of TMJ disorder[8] in classical Ehlers-Danlos Syndrome (EDS), a human genetic disorder due to collagen V deficiency[9].

Methods

TMJs were harvested from 3-month old wild-type (WT) and *Col5a1*$^{+/-}$ C57BL/6J mice. The null mice (*Col5a1*$^{-/-}$) were not included as they are embryonic lethal[10]. We applied histology and immunofluorescence (IF) imaging to quantify the TMJ morphology and sulfated glycosaminoglycans (sGAG) staining and the presence of collagen V. We performed SEM imaging on the mandibular condyle surface[11] to quantify collagen fibril diameter. To quantify the modulus of the surface fibrocartilage layer, AFM-based nanoindentation was performed with a microspherical tip ($R \approx 5$ μm, $k \approx 2$ N/m, μMasch) on the central region of a freshly dissected condyle following our established procedure[12].To quantify the mechanical properties of the hyaline layer, we performed nanoindentation on 5-μm thick, unfixed cryosections of the TMJ condyle using Kawamoto's tape method[13]. Hyaline cartilage has two disctinct domains of pericellular and territorial/interterritorial matrices (PCM versus ECM).To delineate these two regions, we applied perlecan IF- image-guided AFM-nanomechanical mapping in PBS. In brief,AFM was performed on each 20 × 20 μm^2 region with ring-shaped PCM terrains using a microspherical tip ($R \approx 2.25$ μm, $k \approx 1$ N/m, μMasch) and a MFP3D (Asylum Research). Effective indentation modulus, E_{ind}, was calculated via finite thickness-corrected Hertz model[14]. The Mann-Whitney U test was used to detect the significance between WT and *Col5a1*$^{+/-}$ cartilage at $\alpha = 0.05$.

Results

In comparison to the WT control, the *Col5a1*$^{+/-}$ mandibular condyle exhibits altered gross-level morphology,and substantial reduction in sGAG staining in histology (Fig. 1). Meanwhile, IF-imaging of collagen V confirms the presence of collagen V in the WT condyle cartilage, and its reduction in *Col5a1*$^{+/-}$ mice (Fig 1). On the mandibular surface, *Col5a1*$^{+/-}$ cartilage exhibits significantly larger fibril diameters (30 ± 6 nm versus 25 ± 7 nm, mean ± std, ≥

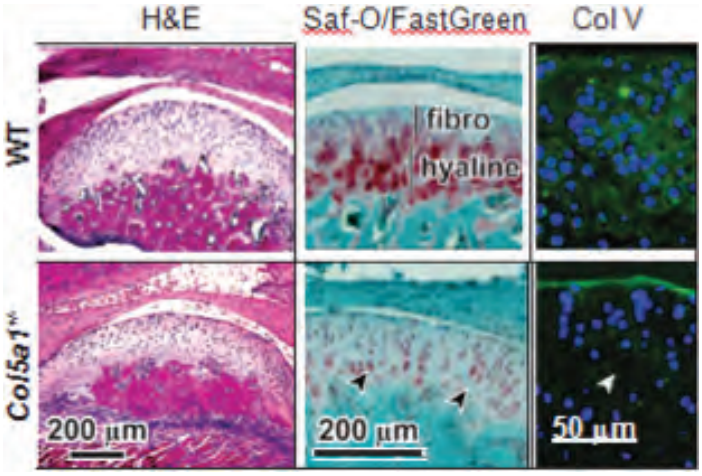

Figure 1 Histological and immunofluorescence imaging of wild-type (WT) and *Col5a1*$^{+/-}$ murine TMJ condyle. H&E shows overall condyle morphology, and Saf-O staining shows reduced sGAGs (black arrowhead) in *Col5a1*$^{+/-}$ condyle cartilage. IF imaging of col V confirms the reduction of collagen V in *Col5a1*$^{+/-}$ cartilage (while arrowhead).

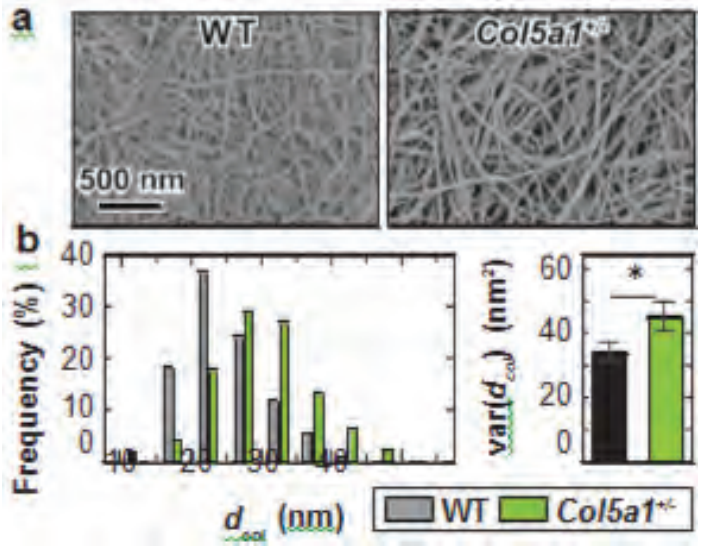

Figure 2 (A) Representative SEM images of TMJ condyle cartilage surfaces. **(B)** Quantitative analysis shows increased collagen fibril diameter and increased heterogeneity (variance) on *Col5a1*$^{+/-}$ condyle surface (mean ± 95% CI, *: $p < 0.05$ from $n > 300$ fibrils on 3 animals).

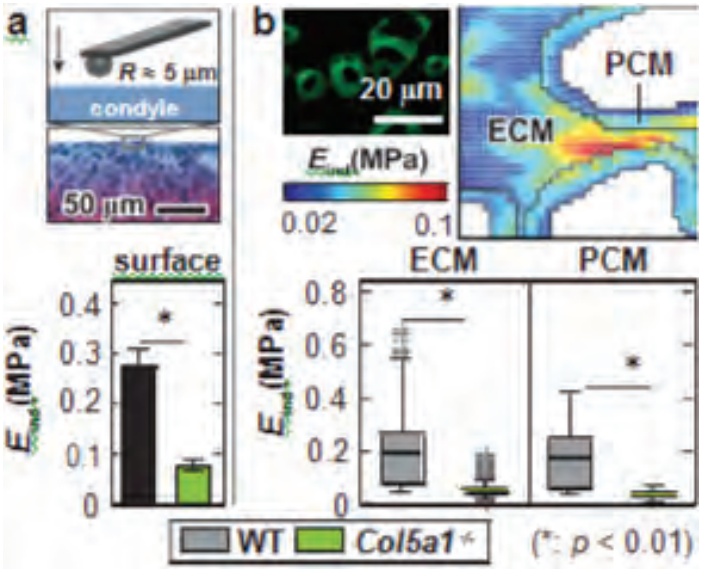

Figure 3 (A) The superficial fibrous layer of *Col5a1*$^{+/-}$ cartilage shows reduced modulus than the WT (mean mean ± 95% CI, ≥ 45 locations of 3 animals). **(B)** Perlecan IF-guided AFM on the cryo-section of secondary hyaline layer shows reduced modulus in both ECM and PCM in *Col5a1*$^{+/-}$ cartilage ($n = 3$).

700 fibrils from $n = 3$ animals) and increased heterogeneity (variance) (Fig 2a, b). Under AFM, both the fibrous and hyaline layers show significant reduction of E_{ind} in *Col5a1*$^{+/-}$ mice (Fig. 3a,b). Notably, in the hyaline layer, the reduction of E_{ind} was significant in both the PCM and ECM (Fig. 3b).

Discussion

This study illustrates the importance of collagen V in regulating the formation of both the fibrocartilage layer, and unexpectedly, the secondary hyaline layer of the mandibular condyle cartilage. In the fibrocartilage layer, the fibril thickening in *Col5a1*$^{+/-}$ mice is in agreement with the known roles of collagen V. During collagen I fibrillogenesis, collagen V co-assembles with collagen I to initiate fibril nucleation[10]. The reduction of collagen V thus leads to increased fibril diameter and heterogeneity (Fig. 2). These structural defects contribute to the loss of tissue integrity, as manifested by the reduction of surface modulus (Fig. 3a).

The reduction of sGAG staining (Fig. 1) and modulus (Fig. 3b) of the hyaline layer, which is unexpected, suggests that collagen V is also critical to the assembly of hyaline cartilage. The mandibular cartilage is an integrated unit of fibrous and hyaline layers (Fig. 1). Therefore, collagen V can influence the hyaline layer possibly through governing the growth of the fibrous layer, or through directly regulating the assembly of hyaline layer. It is possible that the lateral over-growth of collagen I fibrils could influence collagen II fibril assembly in the hyaline layer, resulting in reduced inter-fibril spacing and aggrecan. Meanwhile, it is also possible for collagen V to directly regulate collagen II fibril structure, since we observed salient defects in the hyaline cartilage PCM, the region where cell-mediated initial fibril assembly takes place[15]. This possibility is also supported by the fact that collagen V is more abundant in mature articular cartilage in the form of collagen V/XI heterotypic chains[16]. Therefore, our ongoing studies are developing collagen V/XI compound inducible knockout mice to elucidate their coordinated activities in regulating the formation of this uniquely structured, fibro-hyaline hybrid cartilage.

Significance

The newly discovered role of collagen V in regulating hyaline cartilage has the potential to provide new paths for understanding disease progression and regeneration of TMJ tissues.

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Meniscus Cell Migration Through Dense Fibrous Networks Is Regulated By Nuclear Mechanics

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Introduction

Cell migration to a wound site is required for tissue repair[1]. However, the small pores of dense connective tissue extracellular matrix (ECM) present an obstacle to migration.This is primarily the result of the cell nucleus, the largest and stiffest organelle in the cell[2]. Modulating nuclear stiffness is, therefore, one potential strategy for enhancing cell mobility that could be leveraged to improve repair of dense connective tissues. Previously, we showed that Trichostatin A (TSA, a histone deacetylase inhibitor) induced chromatin relaxation and decreased nuclear stiffness in adult meniscus cells (aMCs), enhancing their migration through micron- sized pores using a transwell assay[3]. Here, we extend this work to a physiologic context, and determine whether such chemically induced nuclear softening modulates migration through fiber networks of varying porosity and through native tissue.

Methods

To assess migration through nanofiber networks, a custom-PDMS chamber was implemented[3]. The system consisted of a top reservoir containing basal growth media (BM) and a bottom reservoir containing BM supplemented with 200 ng/mL PDGF (as a chemoattractant, Fig. 1A). Fluorescently labeled (Cell Tracker) poly(ε-caprolactone)/poly(ethylene oxide) (PCL/PEO) composite aligned fibrous scaffolds (composed of 0%, 25% or 50% sacrificial PEO fibers, Fig. 1B) were interposed between the two reservoirs (Fig. 1A).Adult meniscus cells (aMCs), passage were seeded on the top of each scaffold and cultured in BM with/without TSA (200 ng/ml) for an additional 2 days (Fig. 1A). After a total of 3 days, 3D reconstructions of cell and scaffolds were obtained from confocal z-stacks to quantify infiltration3. Additionally, a cell/ECM model was developed in which the nucleus was taken to be a compressible neo-Hookean solid and the critical force required to pull the nucleus through these fiber networks was predicted (COMSOL Inc., Stockholm). To assess the impact of nuclear softening in the longer term, aMCs were seeded onto PCL/PEO 25% aligned scaffolds and cultured in TGF-β3 containing chondrogenic media for 4 weeks. TSA was applied once a week for 1 day (Fig. 2A). At 4 weeks, cryosections were obtained and stained with Picrosirius Red and DAPI. To quantify cell infiltration into the constructs, cell nuclei through the scaffold depth were counted using Image J. Finally, to investigate the role of nuclear softening on migration in native tissue, meniscus tissue explants (6 mm diameter, 6 mm height, Fig. 3A) were devitalized at their periphery and re-colonization was evaluated over time. For this, cells along the periphery of the explants were selectively lysed via a 2-cycle freeze-thaw process (-20°C for 30 min followed by thawing at room temperature for 30 min, repeated twice on Day -2, Fig. 3A). Freeze-thawed explants were treated with TSA for 1 day (Day -1, Fig. 3A) and the explants were then cultured in fresh BM for an additional 3 days.At day 3, LIVE/DEAD staining was used to assess the number of live cells within 1 mm of the periphery in 8

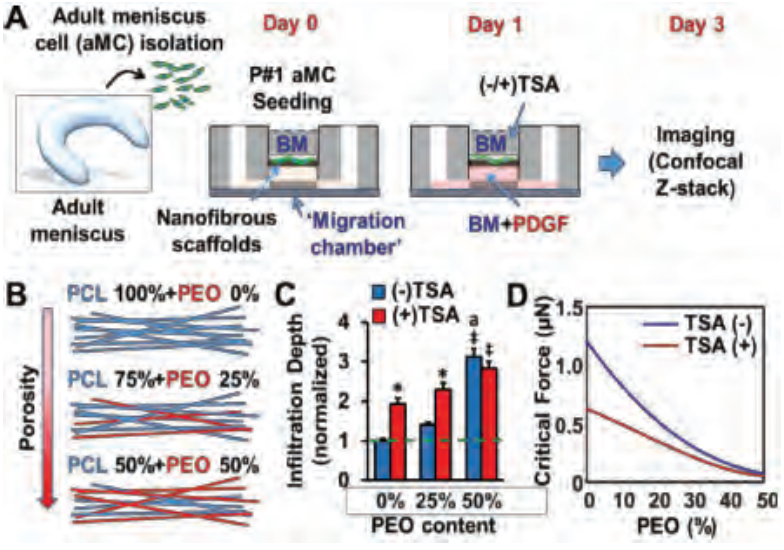

Figure 1. Schematics of **(A)** study design and **(B)** removal of sacrificial PEO fibers to increase porosity. **(C)** Quantification of cell infiltration [n = ~30, *p<0.05 vs (−) TSA, ‡p<0.05 vs 0% PEO, [a]p<0.05 vs 25% PEO, mean ± SEM, normalized to the control 0% PEO group]. **(D)** Predicted force required for nuclear entry into the scaffold as a function of PEO content.

regions of the cutting plane using Image J. Statistical analysis was carried out in Graphpad Prism; sample number for each assay is as indicated in the figure legends.

Results

Cell infiltration depth increased as a function of PEO content in the absence of TSA [(−)TSA, Fig. 1C] and TSA treatment [(+) TSA] enhanced this infiltration into scaffolds of lower porosity (lower % PEO groups, <25%) (Fig. 1C). The cell model predicted a decrease in critical force for nuclear entry into the scaffold as the PEO content (and so porosity[4]) increased (Fig. 1D). Consistent with the experimental data, the model predicted no effect of nuclear softening at higher PEO percentages (~50%). Taken together, these findings suggest that decreasing nuclear mechanics and/or increasing scaffold porosity enhance interstitial cell infiltration into dense fiber networks. In longer term cultures, control groups [(-)TSA], showed collagen deposition only at the border of the constructs (Fig. 2B). With TSA treatment [(+)TSA, 1x per week], the deposition and distribution of collagen was increased (Fig. 2B). Similarly, DAPI-stained cross-sections revealed a greater depth of aMC infiltration into scaffolds treated with TSA [Fig. 2C, D]. In native tissue, the 2-cycle freeze-thaw process effectively eliminated live cells at the explant periphery (Day -2, Fig. 3B, D), while preserving viability in the center (Fig. 3B). A greater number of these viable cells migrated into the previously devitalized border region over three days of TSA treatment, compared to untreated control groups (Fig. 3C and D).

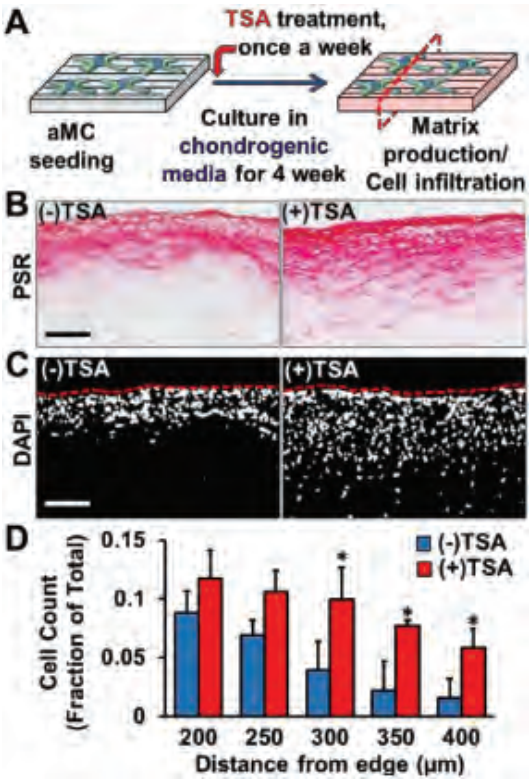

Figure 2. (A) Schematic of study design. Representative cross-sections of aMC-laden nanofibrous constructs at week 4 stained for collagen (PSR: picrosirus red staining, **(B)**) and cell nuclei (DAPI, **(C)**), bar = 100 μm. **(D)** quantification of MFC infiltration with/ without TSA treatment [n = 3 images].

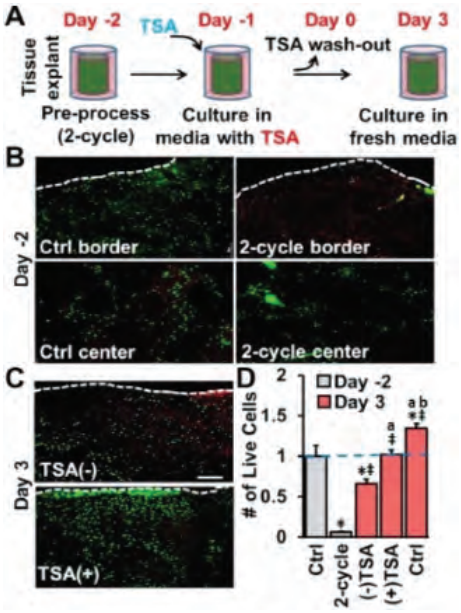

Figure 3. (A) Study design. **(B)** Representative Live (green)/Dead (red) images at the periphery or center of control explants (Ctrl) and freeze- thawed explants (2-cycle) at day -2. **(C)** Live/Dead staining 3 days post TSA treatment. **(D)** Quantification of live cells at the periphery [n = 24~32 images from 3~4 explants, normalized to cell number in ctrl groups at day -2 (dashed line), mean ± SEM, *p<0.05 vs. Ctrl, ‡p<0.05 vs. 2- cycle, [a]p<0.05 vs.(−)TSA, [b]p<0.05 vs. (+)TSA.

Discussion

This work shows that both decreasing meniscus cell nuclear mechanics (via chromatin decondensation) and increasing scaffold porosity (via removal of sacrificial fibers) enhances adult meniscus cell interstitial migration in dense fibrous networks. The finding of increased collagen deposition in scaffolds subjected to repeated TSA treatment also suggests that de-condensation does not permanently interrupt cellular phenotype or matrix forming capacity. Notably, nuclear softening enhanced migration even in the context of dense, adult, meniscus ECM, suggesting that mobility of cells can be increased while preserving the loadbearing structure of the native tissue. Ongoing studies are reducing this finding to practice via the programmed release of de-condensing agents from implanted nanofibrous scaffolds and testing this as a therapeutic in a large animal (ovine) model of endogenous meniscus repair.

Significance

Our findings support the concept that decreasing physical impediments to migration through nuclear softening can improve dense connective tissue repair by enabling more cells to migrate to and colonize the wound site after injury. This will have widespread application in the promotion of endogenous repair in all poorly healing dense connective tissues.

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Biocompatibility and Bioactivity of an FGF-Loaded Microsphere-Based Bilayer Delivery System

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Introduction

Biodegradable micro-particle systems have attracted increasing interest for use as delivery vehicles for drugs, proteins, and other factors[1-2]. Several new strategies have been developed to improve protein stability within such biodegradable polymer matrices[3]. For instance, sustained release of basic fibroblast growth factor (bFGF) from microspheres can promote proliferation and differentiation processes in a wide range of cells[4]. Albumin is commonly included in such formulations, both as a model protein to monitor release and as a carrier to preserve growth factor activity and prolong shelf-time[5]. In this study, we developed microspheres (MS) containing both Alexa-tagged BSA and bFGF and incorporated them into a Bilayer Delivery System (BiLDS)[6]. This system was designed to sequester MS in a defined pocket between two nanofibrous scaffolds, where the scaffold provides a template for new tissue formation while enabling independent and local release from the co-delivered MS. The objective of this study was to evaluate the biocompatibility and bioactivity of an FGF-loaded BiLDS system in vitro and in vivo.

Methods

Microsphere and BiLDS fabrication

Microspheres were produced by combining 75:25 PLGA (0.15 g/mL, Mw=70 kDa) with/without 200 μg recombinant human bFGF and Alexa-BSA in dichloromethane. The external phase of the emulsion consisted of 5 mL of aqueous 1% poly(vinyl alcohol). To generate the bilayered delivery system (BiLDS), each MS formulation (Alexa-BSA MS and Alexa-BSA/bFGF MS) was suspended in 50 μl of PBS and placed onto the center of an aligned poly(ε-caprolactone) nanofibrous scaffold (6×8 mm)[6]. A second layer was placed on top and the two layers were sealed together by heat-annealing in a circular pattern around the microspheres using a custom heating device.

Direct/indirect tenocyte culture

For direct culture, rat tenocytes (5000 cells/BiLDS) were seeded onto the BiLDS and cultured for 18 days in 1% FBS containing DMEM. For indirect culture, each BiLDS was incubated in basal media for 1 week at 37°C. Tenocytes were seeded (3×10^3 cells/well) into a 24-well plate and the conditioned media from each BiLDS was added. At regular intervals, cell viability (via MTT assay, n=4-5) and MS and cell morphology (via actin staining and SEM, n=3) was evaluated.

BiLDS release in-vivo: BiLDS containing no MS, Alexa-BSA-MS, and Alexa-BSA/bFGF-MS (n=4/group) were fabricated and implanted into the rat's dorsal subcutaneous space. At 1, 2, and 4 weeks, samples were recovered and fluorescence images were taken to identify MS within the BiLDS and frozen sections were processed for hematoxylin and eosin (H&E) staining. Statistical analysis was performed by 2-way ANOVA with Tukey's post-hoc test.

Results

SEM images demonstrated that MS were spherical with a smooth surface. Alexa-BSA and Alexa-BSA/bFGF MS ranged in diameter from 1.5-3 μm and 1.5-4.5 μm, respectively (not shown) (Fig. 1A, B). SEM images also showed a seal along the margin that effectively localized MS within the BiLDS (Fig. 1C) and cross-sectional views of the BiLDS showed large quantities of MS within the BiLDS (Fig. 1D). In direct culture, cell viability and proliferation of Alexa-BSA and Alexa- BSA/bFGF BiLDS increased during culture and were significantly higher than control at day 18 (Fig. 2A). Cells attached and spread along the BiLDS (Fig. 2B). SEM images confirmed this finding, and cross-sectional views showed that MS remained entrapped after 18 days (Fig. 2C). In indirect culture, after 4 and 7 days, proliferation in media from Alexa-BSA/bFGF BiLDS was higher than from no MS and Alexa-BSA BiLDS (Fig. 2D, E). After implantation, fluorescent images showed that MS remained within the BiLDS (Fig. 3A) and H&E staining revealed increased cellularity at the periphery with greater infiltration into nanofiber layers of the Alexa- BSA/bFGF BiLDS (Fig. 3B).

Discussion

In this study, we developed a bilayered delivery system to deliver bFGF in a local manner using a clinically relevant and previously validated scaffold system. We previously showed

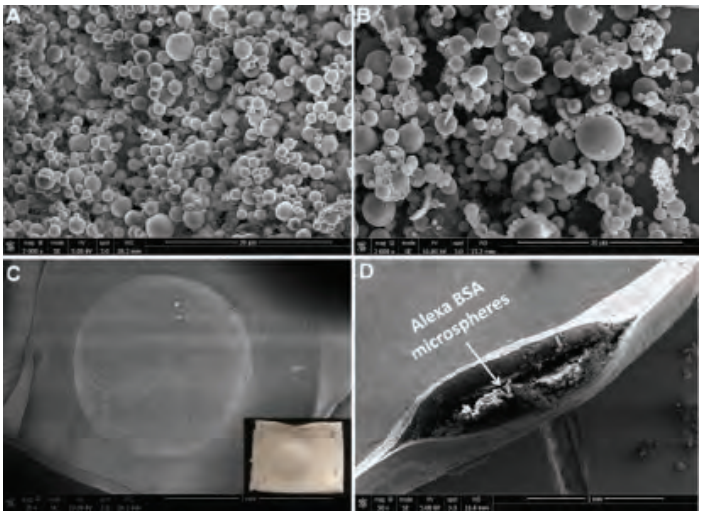

Figure 1. SEM of **(A)** Alexa-BSA and **(B)** Alexa-BSA/bFGF MS. **(C)** Top view and **(D)** cross-section showing MS within BiLDS (scale = 1mm).

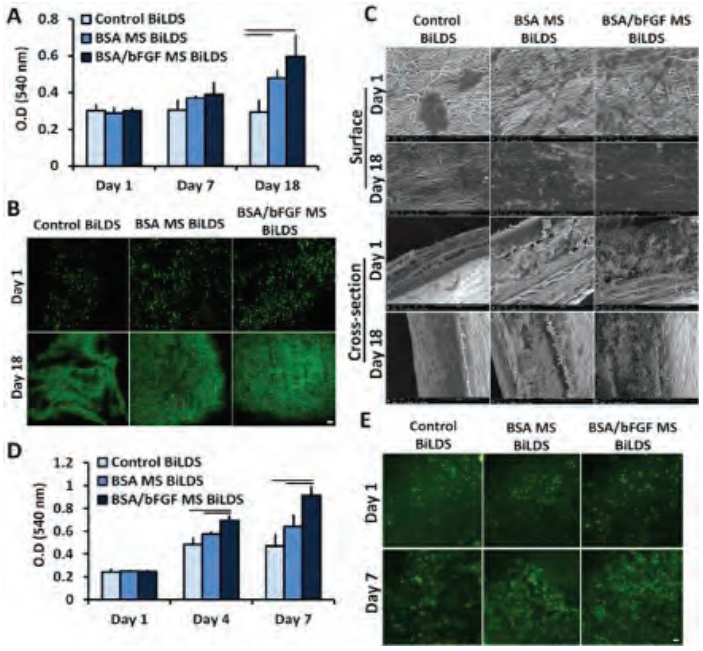

Figure 2. (A) Viability, **(B)** actin staining, and **(C)** SEM over 18 days with direct culture of tenocytes on BiLDS. **(D)** Viability and **(E)** actin staining over 7 days with indirect culture of tenocytes in media from BiLDS (Scale = 10 μm).

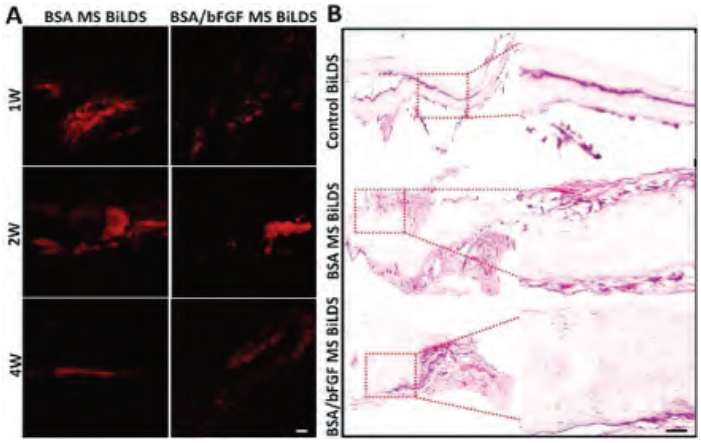

Figure 3. (A) Fluorescent images of Alexa tagged MS in BiLDS after implantation. **(B)** H&E staining after 4 weeks in vivo (scale = 200 μm).

that MS entrapped within the BiLDS system showed a somewhat attenuated release profile compared to free MS, and that protein release was sustained and continuous for up to 30 days[6]. Importantly, our new data show that cell viability and proliferation were enhanced in the context of Alexa-BSA/bFGF BiLDS, both in vitro and in vivo. MS delivered via the BiLDS system persisted in a localized area after implantation for at least 4 weeks, and bFGF release increased colonization of the implant. These data establish the BiLDS technology as a sustained in vivo drug delivery platform that can localize protein and other growth factor release to a surgical site. In future studies, we will explore the ability of this BiLDS technology to deliver growth factors to promote repair in a small animal model of rotator cuff injury.

Significance

This work establishes the biocompatibility and bioactivity of a MS- loaded bilayered delivery system (BiLDS) for sustained release in a localized and clinically relevant fashion for tissue repair and regeneration.

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In Vivo Translation of an Injectable Chondrocyte-Laden Micro-Scale 'Noodle' to Promote Cartilage Repair

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Introduction

Microfracture (MFx) is one of the most common surgical procedures used to promote cartilage repair. In this process, bone marrow is released into a defect site through mm-sized drill holes into the subchondral bone. Mesenchymal stem cells (MSCs) within this marrow colonize the defect and form a fibrocartilaginous tissue over time. While common, outcomes for MFx are suboptimal in terms of restoration of native tissue structure, function and durability, and the procedure is contraindicated in older persons whose MSC population has dwindled. To address this limitation, co-culture systems have been developed for in vitro culture in which factors released from a small fraction (<20%) of co-localized chondrocytes (CH) are used to promote the chondrogenesis of MSCs from older donors. Our recent work showed that the intercellular communication that occurs between CHs and MSCs in co-culture is mediated by extracellular vesicles (EV)[1]. EVs from CHs promoted MSC chondrogenesis, proliferation and matrix formation in 3D culture, while at the same time reducing MSC apoptosis, inflammatory signaling, and osteo/adipogenic differentiation. Of note, the distance over which this intercellular communication occurred was very small, and thus close proximity of the two cell types is critical for successful outcomes[2-4]. To take advantage of this co- culture effect, and to translate these findings towards clinical application, we introduced a CH-laden micro-scale 'noodle' ('micro-noodles'; Ø250μm) that provides 10 times greater surface area across which encapsulated cells can communicate compared to a conventional cylindrical construct (Ø4×2.25mm) of the same volume. Within these micro-noodles, CHs readily take up nutrients and secrete factors over a small path length. Here, we investigated the chondro-inductive capacity of these micro-noodles in vitro in a marrow-mimicking environment, and then tested their impact in a large animal model of cartilage repair, where the recipient MSCs in this in vivo co-culture system were those present in the defect after a MFx procedure.

Methods

Study 1

Adult porcine CHs and MSCs were obtained from articular cartilage and bone marrow, respectively, and were expanded through passage[1-2]. CHs were labeled with CellTracker and suspended at 20 or 60 × 10^6 cells in 1% w/v methacrylated hyaluronic acid (MeHA) (Lifecore Biomedical)[3]. Micro-noodles were fabricated by UV crosslinking using a custom-built micro-bore tubing system[5]. Formed micro-noodles (Ø 0.25 × 70 mm) were cultured in a defined medium with TGF (CM+; 10ng/mL) for 2 weeks. To investigate the chondro-inductivity of CH-laden micro-noodles on MSCs in a bone marrow-like environment, pre-cultured micro-noodles were mixed with MSCs (CH:MSC ratio = 1:4) in fibrin gel (Tisseel) for an additional 2 weeks.

Study 2

To enable tracing of micro-noodles after implantation, MeHA was mixed with methacrylated rhodamine B and/or radiodense zirconium (IV) oxide nanoparticles. Micro-noodles loaded with methacrylated rhodamine B and/or zirconium nanoparticles were visualized on a fluorescent/confocal microscope or via microCT (Fig 1C-D). For the in vivo study, three adult Yucatan mini-pigs (18 mos.) were used, with the surgical protocol as previously described[6]. Four chondral defects (Ø4 mm) were created in the trochlear groove in a unilateral procedure. After MFx, micro-noodles with or without cells were loaded into the defects. Animals were euthanized after 1 week, the trochlear groove was grossly inspected and imaged, and individual cartilage defects (including the underlying bone) were isolated for histology/immunohistochemistry and infrared imaging. Significance was determined by two-way ANOVA with Tukey's post hoc ($p<0.05$).

Results

Study 1

In vitro, CH-laden micro-noodles promoted MSC chondrogenesis in fibrin at sites adjacent to noodles, while constructs with only MSCs showed little matrix formation, primarily in the periphery (Fig 1A-B). Constructs with micro-noodles showed dense proteoglycan, Collagen I and II deposition (not shown).

Study 2

When micro-noodles were injected into the in vivo defect, they remained in place and

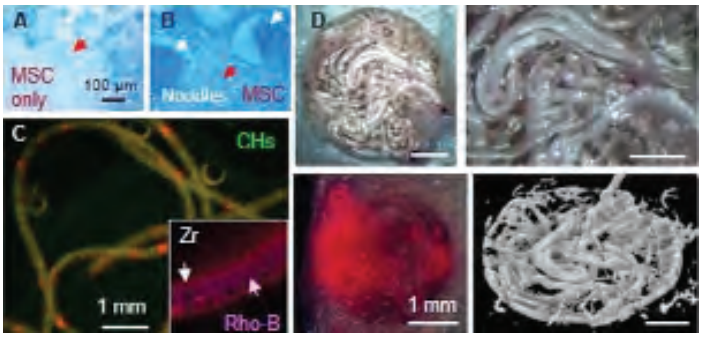

Figure 1. Fabrication and validation of micro-noodles *in vitro.* **(A-B)** Influence of CH-laden micro-noodles on MSC chondrgeneis in fibrin gel. Aldan blue staining for PGs **(A)** MSC only (red arrows), **(B)** micro-noodles (white arrows)} (2w culture+2w pre-culture of micro-noodles in CM+) **(C)** Rhodamine B and Zr nanoparticle-labeled micronoodles. (Inset=micro-noodle; Zr nanoparticle=black. speckles). **(D)** Osteochondral Unit with Zr nanoparlicle-modified micro-noodles **(Top left)**, Zoomed view **(Top right)**, Micro-noodles detected by fluorescent scope **(Bottom left)**, μCT imaging of Zr nanoparticle-modified micro-noodles **(Bottom right)**.

retained their fluorescent characteristics after one week, as was visualized by fluorescent/confocal microscopy (Fig 2A-C). CHs remained within the micro-noodles and maintained their rounded cell morphology. Histological analysis showed that injected micro-noodles were randomly distributed throughout the defect and promoted matrix deposition. Matrix staining was greatest in regions in which micro-noodles and bone marrow were in close contact with one another, while regions filled only with marrow resulted in little cartilage-like matrix production (Fig 2D-F).

Discussion

In this study, we developed a 'micro-noodle' system to harness the chondro-inductivity of CH-secreted factors on MSCs both in vitro as well as in a large animal model of cartilage repair. MSCs in fibrin gel that were adjacent to micro-noodles at the center of the construct produced robust proteoglycans whereas those cultured alone produced little matrix. After confirming the potential for tracking rhodamine B- and zirconium nanoparticle-modified micro- noodles using various imaging modalities, we demonstrated that CH-laden micro-noodles remained in place for at least 1-week post-implantation in a large animal cartilage defect model. Histological analysis showed that these CH-laden micro-noodles interdigitated into the bone marrow and fibrous tissue

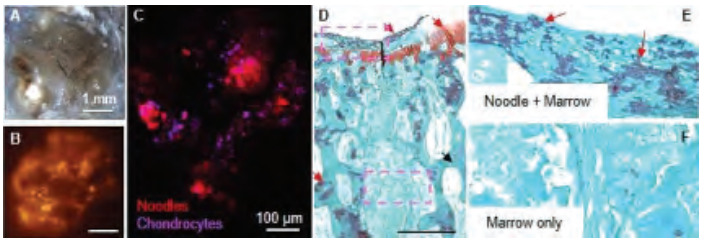

Figure 2. Retention of micro-noodles in a large animal cartilage defect model *in vivo.* **(A)** Gross image of defect filled with micro-noodles, **(B)** Micro-noodles detected by fluorescent scope, **(C)** Micro-noodles remained in the defect after 1 week post surgery , **(D)** Cell-laden micro-noodles combined with microfracture (Safi-O slaining Red/dark red staining (red arrow) indicate PGs, **(E)** Zoomed view: Matrix deposition shown in dark red on the wound site (red arrow}, where micro-noodles and bone marrows were mixed in, **(F)** Microfracture mediated defect area at the bottom, where bone marrows were mostly present.

filling the defect after MFx, and that a greater amount of matrix was formed in these regions. Despite the promise of these early findings, some micro-noodles were dislodged from some defects, potentially due to their low stiffness and the presence of synovial fluid. Ongoing studies are focused on enhancing the delivery and adhesion of these micro-noodles within the defect as well as designing a fully arthroscopic system for delivery of autologous chondrocyte-seeded micronoodles in a one-step, minimally invasive procedure. If successful, this technology has the potential to dramatically improve cartilage repair therapeutics.

Clinical Relevance

This novel micro-noodle system provides an efficient means by which to promote intercellular communication between chondrocytes and bone marrow MSCs in the context of microfracture. If successful, this in vivo co-culture approach will enhance functional cartilage formation with microfracture procedure and expand its indications into older patient populations.

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Resorbable Pins Enhance Retention of Nanofibrous Scaffolds in a Porcine Focal Chondral Defect Model

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Introduction

The repair of focal cartilage lesions remains a challenging issue in orthopaedics. Left untreated, large focal lesions may progress to osteoarthritis, ultimately requiring total joint replacement[1]. Current interventions, such as microfracture, result in the formation of fibrocartilage and have poor long-term outcomes[2]. Emerging technologies that involve scaffold placement for cell delivery, such as matrix-induced autologous chondrocyte implantation (MACI), have recently been reported to have superior outcomes[3]. Indeed, the success of early scaffold-based approaches has encouraged considerable innovation in the field of cartilage tissue engineering. As these new scaffolds and constructs emerge, one important consideration is the need for a reliable fixation technique for these various formulations. Previous work by our group evaluated the ability of a subchondral bone anchor (Mitek Microfix, Depuy) to support the retention of a 3D woven poly(ε-caprolactone) (PCL) scaffold in a full-thickness chondral defect in a large animal model[4]. While this fixation method provided adequate retention, it may not be suitable for all scaffold materials and resulted in notable disruption of the subchondral trabecular bone. Thus, the objective of this study was to evaluate additional fixation techniques that could be applied to multiple scaffold compositions in various defect geometries in a large animal model.

Methods

Full-thickness chondral defects were created unilaterally in the trochlear groove of 6 adult male Yucatan mini-pigs following a minimally invasive arthrotomy[5]. In 3 pigs, four 4mm-diameter defects (n=12 defects total) were created, with 10 receiving an electrospun nanofibrous hyaluronic acid (HA) scaffold. Scaffolds were fixed with press-fitting (n=2), fibrin glue (Tisseel, Baxter, n=2), or resorbable pin (Aesculap AG, n=6). In the other 3 pigs, two 8mmx4mm oblong defects were created (n=6 defects total), with five of the defects receiving nanofibrous

PCL scaffolds fixed with two resorbable pins. All defects were subject to bone marrow stimulation via microfracture. The remaining two circular and one oblong defects served as microfracture controls. Animals were allowed to weight-bear immediately after surgery and were euthanized after 2 weeks. Gross evaluation, micro-computed tomography (micro- CT), and histology were used to assess scaffold retention, quality of adjacent and opposing cartilage surfaces, and bone morphometry. Additional biomechanical tests were performed to assess the failure load of the pin in ex vivo osteochondral samples. Pins were inserted into osteochondral explants with a loop of 4-0 vicryl suture around the head. The suture was tensioned at a rate of 0.05mm/s with an Instron mechanical tester until pin failure occurred (n=3). Fisher's exact test was used to compare retention rates between scaffolds fixed with pin to non-pin fixed scaffolds.

Results

Press-fitting and fibrin fixation resulted in no retention of HA scaffolds in the 4mm defects (PF: 0/2, Fib: 0/2). Pin fixation resulted in complete retention of HA scaffolds in the 4mm defects (6/6) and almost complete retention of PCL in the 8mm oblong defects (4/5). The overall retention rate for pin fixed scaffolds was significantly greater than non- pin fixed scaffolds (91% vs. 0%; $p<0.05$). Gross observation of the adjacent cartilage revealed no damage and India ink staining of the patella confirmed that no patterns of abnormal wear had occurred from the head of the pin. (Fig. 1). Micro-CT confirmed gross evaluation of scaffold retention and demonstrated normal trabecular architecture surrounding the pin (Fig. 2). Histological analysis revealed normal safranin O staining of the adjacent cartilage and very little staining of the repair tissue, which was fibrous and hypercellular at this early time point (Fig 3). Ex vivo mechanical testing of the pin showed that the failure strength was 7.4 +/− 1.8N, with pin failure occurring at the mid-substance.

Discussion

Our results conclusively show that bioresorbable polylactide pins provide reliable fixation of multiple scaffold materials in various defect geometries in a mini-pig chondral defect model. All adjacent and opposing cartilage surfaces were healthy and intact, indicating that

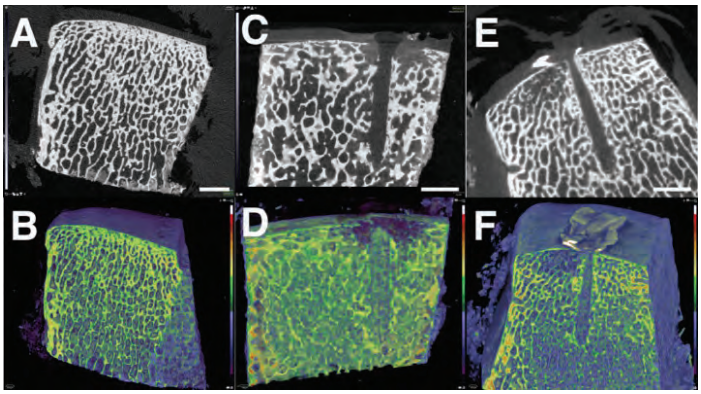

Figure 1. Micro-CT images and heat-mapped volume renderings (warmer colors indicate increased BMD). **(A,B)** Control sample from a non-operative limb showing healthy cartilage and normal trabecular architecture and bone mineral density for an adult mini-pig. **(C)** Image showing intact pin and HA scaffold within a 4mm defect. **(D)** Volume rendering shows normal trabecular architecture and bone mineral density. **(E)** Slice through 8mm oblong defect showing pin and radio-opaque PCL scaffold retained in the same plane as the surrounding.

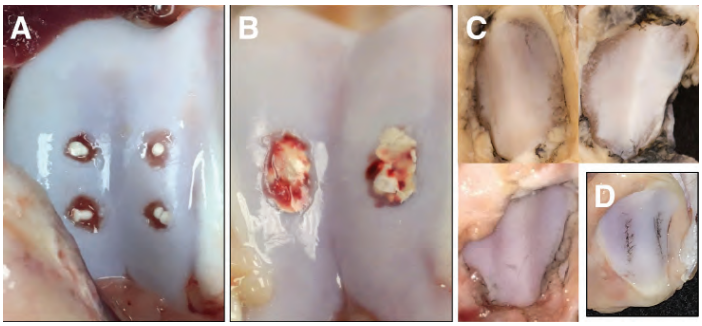

Figure 2. Post-mortem gross images. **(A)** HA scaffolds fixed with single pins in 4mm defects. **(B)** PCL scaffolds fixed with 2 pins in 8mm defects. **(C)** India ink-stained patellae demonstrating a lack of abrasions from pin implantation. **(D)** Control patella stained with India ink after ex vivo abrasion with scalpel (positive control for staining).

these pins did not cause any detrimental mechanical wear during joint motion. Unlike the bone anchor we previously evaluated[4], this pin did not cause major disruption or incur remodeling of the subchondral bone. While histological analysis revealed proteoglycan- deficient, fibrous repair-tissue, we did not expect extensive repair at this early time-point. The ability of this pin to retain nanofibrous cartilage repair

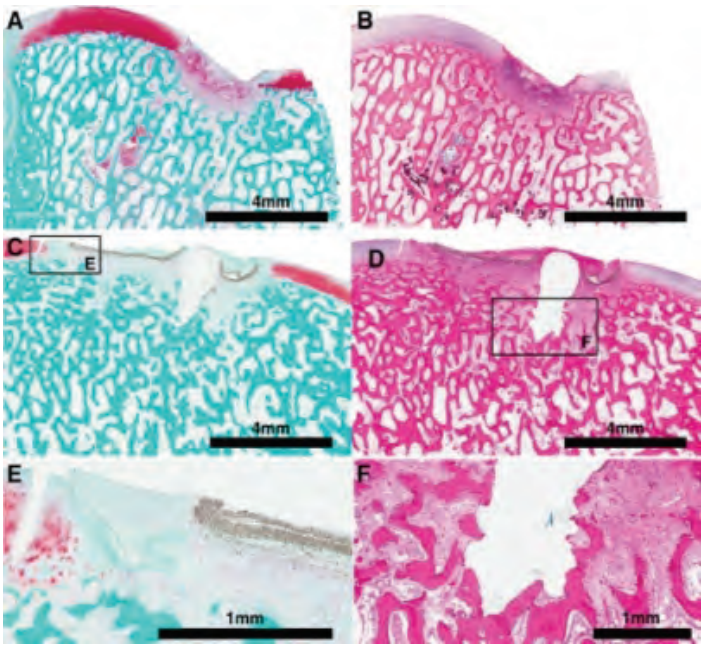

Figure 3. Histology of 4mm and 8mm defects. **(A&B)** SafO/FG and H&E staining of 4mm defect show HA scaffold retained above the subchondral plate. **(C&D)** Pin-fixed PCL scaffold retained above the subchondral plate. **(E)** Edge of scaffold and fibrous tissue at defect border. **(F)** Normal trabecular architecture surrounding site of pin insertion.

scaffolds in a focal chondral defect with no associated damage to surrounding cartilage or disruption to subchondral bone make it a promising fixation technique for long-term cartilage repair studies using advanced scaffold formulations.

Significance

These findings demonstrate a reliable fixation technique that will enable long-term studies of cartilage repair scaffolds in a clinically-relevant large animal model.

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Induced Deletion of Biglycan in Mature Tendon Reveals a Surprising Role during Adulthood

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Introduction

Tendon is a highly organized tissue composed of a collagen network linked via small leucine-rich proteoglycans (SLRPs). Biglycan (Bgn) is a SLRP present in the extracellular matrix, is a regulator of collagen fibrillogenesis, and is highly expressed during tendon development [1]. Further, reduction in *Bgn* expression has been shown to alter tendon fibril diameter and viscoelastic properties [2]. However, the role of Bgn on tendon homeostasis has yet to be determined, independent of its influence on development. Therefore, the purpose of this study was to determine the effect of acute, conditional deletion of biglycan on mature, uninjured tendon. Due to its minimal presence in normal adult tendon, we hypothesized that deletion of biglycan expression in mature, uninjured tendon would have no effect on tendon mechanics or structure.

Methods

Female $Bgn^{+/+}$ control (WT, n=16) and bitransgenic conditional $Bgn^{flox/flox}$ mice with a tamoxifen (TM) inducible Cre, (B6.129-Gt(ROSA)26Sortm1(cre/ERT2)Tyj/J, Jackson Labs) were utilized ($I\text{-}Bgn^{-/-}$, n=16) [3] (IACUC approved). Cre excision of the conditional alleles was induced in mature (120 day) [3] mice via three consecutive daily IP injections of tamoxifen (4.5mg/40g body weight). WT mice received TM injections to control for any potential side effects. Mice were euthanized at 150 days of age. The patellar tendon-bone complex from one limb of each animal was dissected and prepared for biomechanical testing [4]. Tendons (n=16) were subjected to a viscoelastic testing protocol containing three stress relaxations, each followed by frequency sweeps, with the test culminating in a ramp-to-failure. Dynamic collagen fiber realignment was quantified using cross- polarization imaging [4]. Percent relaxation was quantified for each stress-relaxation. Dynamic modulus and phase angle delta were computed for each frequency sweep at multiple strain levels. Fiber realignment and failure stress were computed during the ramp-to-failure. Samples for transmission electron microscopy (TEM) analysis of fibril structure (n=4) were fixed *in situ* [5]. Cross sections through the midsubstance of the patellar tendon were examined at 80 kV. Fibril diameter was measured using images from the center of the tendon. Student's t-test was used to compare groups for mechanical properties. A two-way ANOVA with post-hoc Bonferroni corrections was used to compare across groups and strains for collagen realignment.

Results

Induced deletion of *Bgn* showed decreased elastic modulus (Fig. 1A) at the tibial insertion and decreased max stress (Fig. 1B) when compared to WT. No differences were seen in

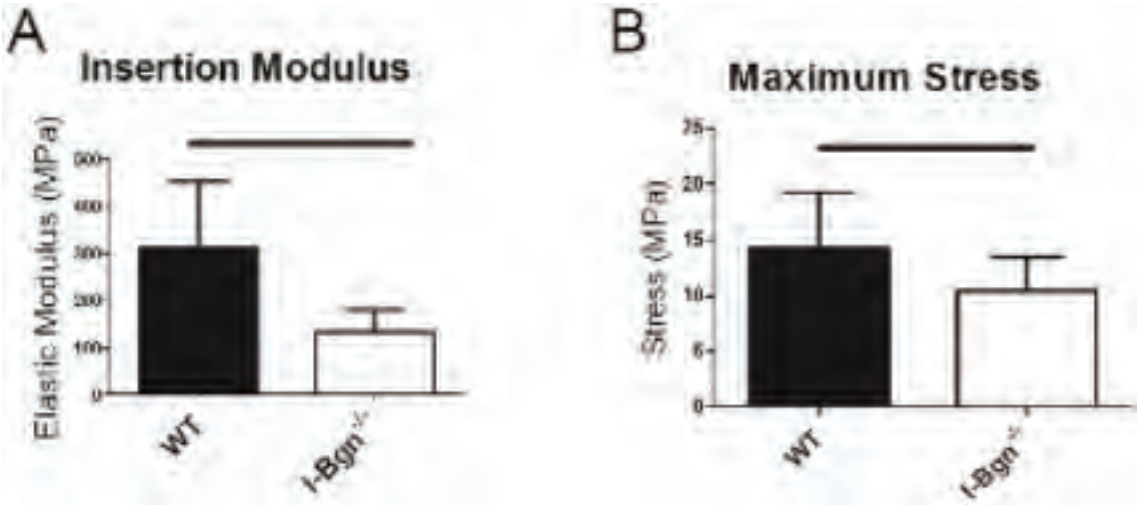

Figure 1. Quasi-static properties of WT and I-$Bgn^{-/-}$ patellar tendons.

midsubstance modulus or transition strain between groups. I-*Bgn*$^{-/-}$ showed decreased dynamic modulus at 3, 4 and 5% strain across all frequencies (Fig. 2). No changes were seen in tan(δ) or percent relaxation. I-*Bgn*$^{-/-}$ tendons exhibited an increase in realignment earlier in the insertion compared to WT (Fig. 3A). I-*Bgn*$^{-/-}$ tendons also displayed increased realignment between the toe and linear regions and greater linear region realignment in the insertion and midsubstance (B) compared to WT (Fig. 3). I-*gn*$^{-/-}$ mice exhibited greater heterogeneity in fibril diameter and larger diameter fibrils compared to WT mice (Fig. 4).

Discussion

Contrary to our hypothesis, acute deletion of *Bgn* expression in mature mice had a surprisingly large impact on tendon mechanics and structure 30 days after knockdown of *Bgn* gene expression. I-*Bgn*$^{-/-}$ tendons showed inferior material properties during quasi-static and dynamic loading in the toe, transition, and linear regions across different rates of loading. I-*Bgn*$^{-/-}$ tendons also displayed an early initiation of realignment in the insertion, a greater magnitude of realignment throughout the linear region, and the ability to continue fiber realignment later into the ramp-to-failure than WT tendons. TEM revealed changes in structure at the fibril level, where I-*Bgn*$^{-/-}$ tendons displayed an increase in fibril heterogeneity and overall diameter, indicating a dysregulation of fibrillogenesis. These results demonstrate a role for Bgn in maintaining tendon mechanical response across a diverse set of loading conditions, and structure across multiple scales. While Bgn is known to play major roles during tendon development and healing, it has been thought to play a relatively minor role in tendon homeostasis in adulthood. This is in contrast to decorin, another class I SLRP that comprises ~90% of tendon proteoglycans in the adult [6], which was hypothesized to have a large effect on tendon properties after knockout in mature tendons. Interestingly, and in direct contrast to the current findings, conditional knockout of decorin in a mature mouse in a similar study resulted in minimal changes in structure and function compared to WT [7]. One possible explanation could lie in the interaction these SLRPs have with each other and with the rest of the tendon matrix. While Bgn and decorin are thought to play similar roles in fibril crosslinking, they likely play different roles in collagen I fibrillogenesis, where decorin inhibits fibrillogenesis via binding of collagen molecules, while

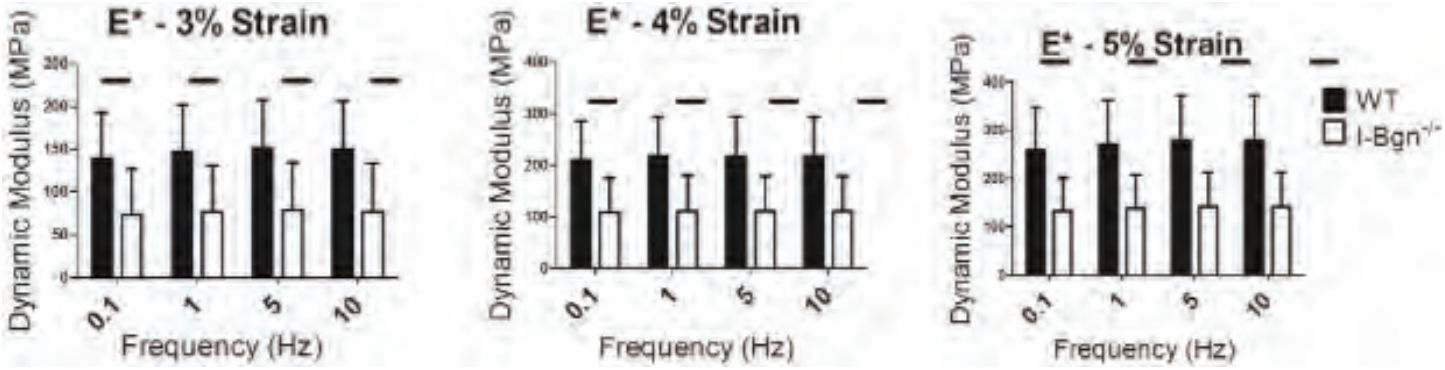

Figure 2. Viscoelastic properties of WT and I-*Bgn*$^{-/-}$ patellar tendons.

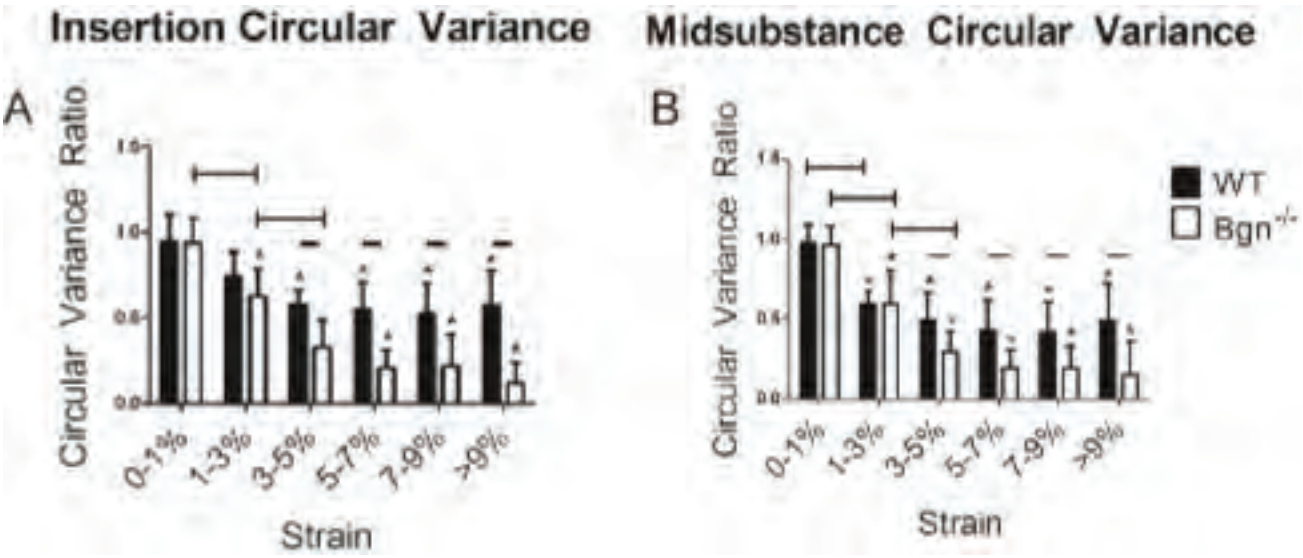

Figure 3. Realignment of WT and I-*Bgn*$^{-/-}$ patellar tendons.

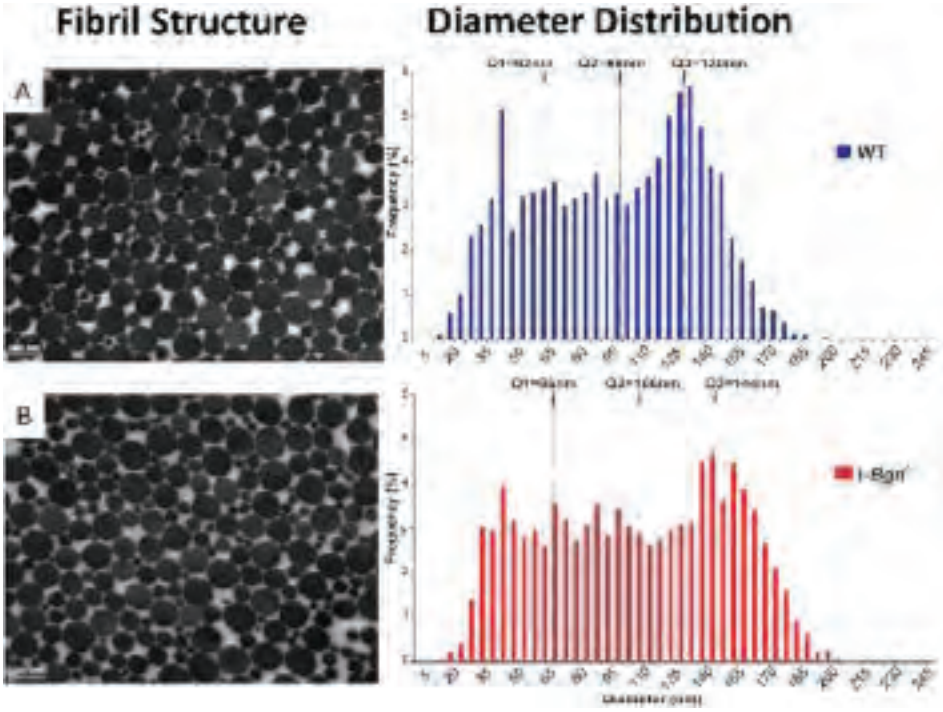

Figure 4. Transmission of electron microscopy analysis of WT and I-*Bgn*$^{-/-}$ patellar tendons.

Bgn does not [8]. Regardless, any compensatory changes that occur in these conditional mice will need to be evaluated in further studies to determine the mechanisms governing the changes demonstrated in this study. Overall, this study provides surprising evidence that Bgn plays an important role in tendon homeostasis.

Significance

This study demonstrates that biglycan plays an important role in mature tendon homeostasis. This knowledge will be used to better understand tendon matrix protein interactions throughout adulthood and aging.

Acknowledgements

We acknowledge financial support from NIH/NIAMS R01AR068057, P30AR0696919, T32AR007132, and the NSF GRFP.

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Gender Dependent Alterations in the Mechanical Response of Collagen V Haploinsufficient Murine Tendons

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Introduction

Classic Ehlers-Danlos syndrome (EDS) patients, who commonly have mutations in the *COL5A1* gene, suffer from connective tissue hyperelasticity, joint instability, and skin hyperextensibility. The role of collagen V in fibrillogenesis in tissues such as skin, cornea, and tendon has been firmly established [1], wherein collagen V haploinsufficiency leads to abnormal tissue development and altered collagen assembly. Recent basic science studies suggest that differences in hormone physiology between sexes may be a factor influencing tendon health [2-4]. Given the joint laxity and tissue hyperelasticity in classic EDS patients, gender-specific changes in hormone levels, the different hormones produced, and their effect on body structure and composition, may further exacerbate the detrimental changes present in pathological tendons. Therefore, the objective of this study was to eva luate the role of gender in the mechanical response of normal and *classic* EDS tendons. We hypothesized that female *classic* EDS mice will have inferior tendon mechanical properties compared to male *classic* EDS mice, but there will only be differences in structural properties due to gender in wild type tendons.

Methods

Adult male and female WT C57/BL6 and HET ***Col5a1***$^{+/-}$ EDS mice (n=60) at 150 days of age were used (IACUC approved). Uninjured patellar tendons were assessed to determine mechanical properties for both genders and genotypes. *Mechanics*. The patella-patellar tendon-tibia complexes were dissected and prepared for mechanical testing [5]. Tendons were subjected to a viscoelastic testing protocol [5,6] consisting of 1) preconditioning, 2) stress relaxation at strain levels of 2%, 3% and 4%, 3) a sinusoidal frequency sweep (10 cycles at 0.1, 1, 5, and 10 Hz) at each strain level, 4) return to gauge length, and 5) ramp to failure. Tendon length was measured at nominal load prior to test initiation. Statistics. Two-way ANOVAs with post-hoc Tukey tests were used to assess the effects of genotype, gender, and their interaction on mechanical properties. Two-way repeated measures ANOVAs with post-hoc Tukey tests were used to assess the changes in viscoelastic properties. Significance was set at $p \leq 0.05$ and trends at $p \leq 0.1$.

Results

WT male patellar tendons had significantly higher failure load and tissue stiffness when compared with WT females (Fig. 1A,B). WT male tendons also had significantly higher failure stress and tissue modulus when compared with WT females (Fig. 2A,B). The viscoelastic response followed similarly with WT males exhibiting significantly elevated dynamic modulus at 10Hz and across all strains when compared to WT females and trending increases at 0.1 Hz and 1 Hz (Fig. 3, only 3% data shown). HET male tendons had a significantly higher failure load when compared with HET females, with no difference observed in tissue stiffness (Fig 1A,B). WT males had significantly higher failure stress and a trending increase in modulus when compared with HET females (Fig 2A,B). HET male and female mice showed trending differences at 2% strain with frequencies of 0.1

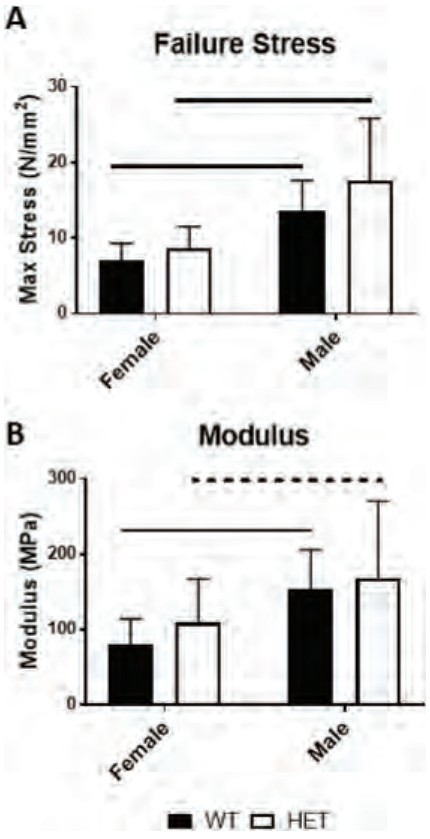

Figure 1. Structural properties of female and male WT and HET Col5a1$^{+/-}$ patellar tendons. WT male patellar tendons failed at higher loads **(A)** and had increased stiffness **(B)**. Solid lines denote significant $p \leq 0.05$ and dashed lines denote trends at $p \leq 0.1$.

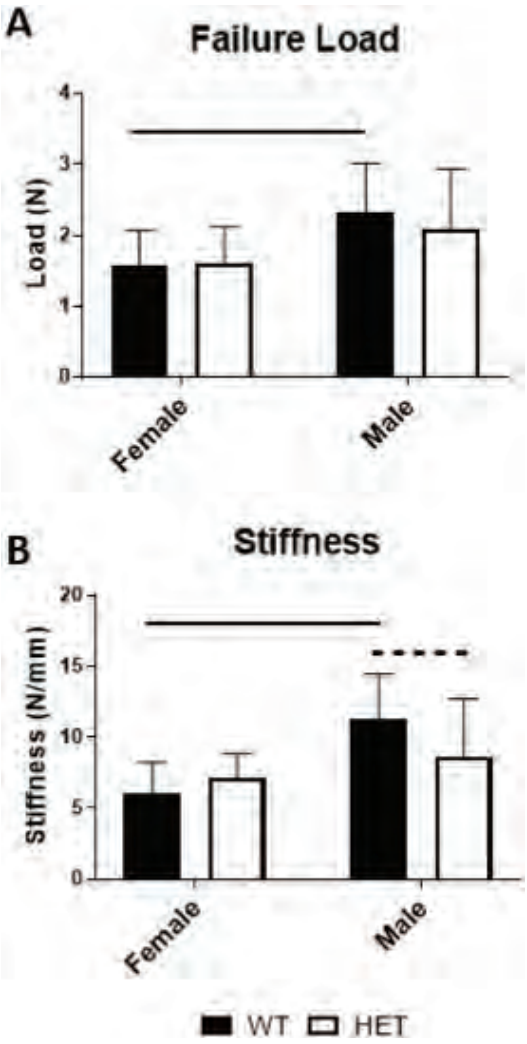

Figure 2. Material properties of female and male WT and HET Col5a1$^{+/-}$ patellar tendons. WT and HET male patellar tendons failed at higher stress **(A)** and WT male patellar tendons had an increased modulus **(B)**. Solid lines denote significant $p \leq 0.05$ and dashed lines denote trends at $p \leq 0.1$.

and 1 Hz, and at 4% strain, 1 Hz (data not shown). Male HET tendons trended towards a decrease in stiffness compared to WT tendons, with no other difference between genotypes. Male WT and HET tendons had a significantly larger area than female mice of the same genotypes (data not shown).

Discussion

WT male patellar tendons demonstrate superior material and structural properties compared to WT female patellar tendons. As female patellar tendons were significantly smaller than male patellar tendons, it is not surprising that their properties would be decreased. Conversely, it is surprising that although HET male patellar tendons were significantly larger in cross-sectional area than female patellar tendons, the same differences in structural properties seen in WT tendons were not present. This contrasting finding indicates that the structural properties of HET male tendons were affected by the reduction of type V collagen to a greater degree than the structural properties of HET female tendons, after

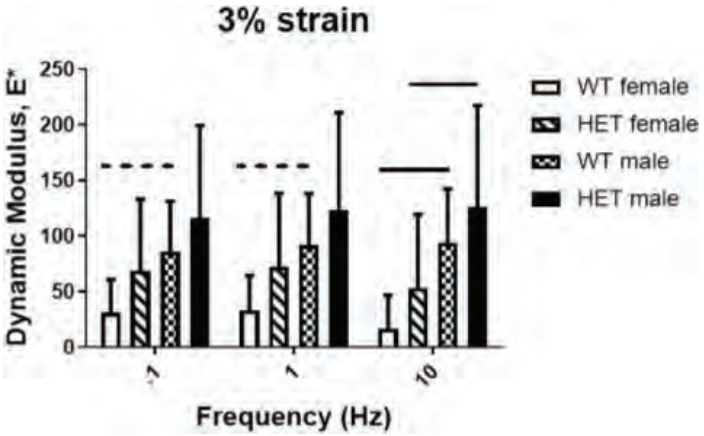

Figure 3. Viscoelastic properties of female and male WT and HET Col5a1$^{+/-}$ patellar tendons. At a frequency of 10 Hz and strain of 3%, WT and HET male patellar tendons dynamic moduli were significantly increased when compared to WT and HET female patellar tendons. Similar findings were seen at 2% and 4% strains across all frequencies.

considering the inherent gender-differences. We hypothesized a negative effect of female sex hormones on patellar tendon health, yet our results indicate the opposite. This finding is extremely interesting as previous studies have reported an influence of sex hormones on tendon health [2-4], without a clear determination of how hormones would affect tendon function. Furthermore, although HET ***Col5a1***$^{+/-}$ EDS mice have a 50% reduction in fibril number [1], this did not result in significant differences between HET and WT material, structural or viscoelastic properties. However, a trend toward a significant difference in stiffness between male WT and HET mice supports our conclusion that a reduction in type V collagen content affects male tendon mechanical properties to a greater degree than female properties. This indicates a gender specificity of the effects of collagen V on patellar tendon mechanical properties. Future work may include histological analysis of HET male and female patellar tendons to understand the cellular differences that could explain these mechanical differences.

Significance

This study demonstrates that sex hormones and gender-specific effects of hormone expression play a tendon-specific role in tendon health, and can influence the degree to which tendon properties of *classic* EDS mice are affected.

Acknowledgements

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Predicting Multiscale Strain Transfer and ECM Stress Transmission during Healing and Dynamic Loading in Tendon

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Introduction

The extracellular matrix (ECM) is a major component of the biomechanical environment with which tendon cells (tenocytes) interact (Fig.1). Dynamic reciprocity between ECM and cell forces can affect many cell responses (e.g., inflammation, migration, proliferation, and differentiation), cell-cell communication, and tissue patterning/re-arrangement [1]. Although loading induced changes in gene and protein expression have been studied in tendon [2], appreciation for how applied strains result in nuclear shape changes that may drive these downstream responses remains limited. The ability or hindrance of cells to deform under applied strain may have important physiological consequences and may be a potential therapeutic target. Therefore, the objectives of this study were to (1) predict nuclear strain transfer in tendon from multiscale mechanical, structural, and compositional properties during healing and after perturbations of dynamic loading using multiple regression models and (2) apply a constitutive model to elucidate the role of dynamic mechanical loading and tendon healing on the ability for tenocytes to sense stress over long distances. We hypothesized that the nuclear aspect ratio (nAR) and ΔnAR would be predicted by strain stiffening, collagen disorganization, and cellularity and that healing and high dynamic loading would decrease ECM stress transmission.

Methods

Study Design

Female C57BL/6 mice at 150 days of age were randomized into uninjured controls (n=75 mice) and those that received bilateral excisional injuries (n=88 mice) to their patellar tendons (IACUC approved). Injured animals were randomized into groups euthanized at 2 or 6 weeks post-injury.

Ex vivo Assays

Tendons were harvested immediately and prepared for mechanical testing under aseptic conditions to maintain cell viability. Tendons (n=10-13/group) were preconditioned, randomized into zero, low, or high magnitude loading protocols (corresponding to the toe or linear regions of the force-displacement curve) for 1000 cycles at 1Hz prior to dynamic mechanical analysis, and ramped at constant strain rate to 1% or 10% strain. Force and displacement data were used to compute several mechanical properties (|E*|, tanδ equilibrium stress σeq). The same tendons were snap frozen at 1% or 10% strain and cryosectioned for multiphoton imaging to evaluate collagen fiber disorganization (circular standard deviation (CSD)), cellularity, F-actin, nuclear aspect ratio (nAR), and nuclear disorganization (nCSD).

Multiple Regression

Assumptions for linear analysis were satisfied. Pearson's correlations were calculated between independent variables. Backward linear regression was performed (F to enter: 0.05, removed: 0.10) to predict nAR and ΔnAR.

Constitutive Modeling

A constitutive law for fibrous matrices was applied to model stress transmission in tendon using experimental inputs. Finite- element simulations of this constitutive law were used to study the effect of material properties of the isotropic (Eb) and fibrous (Ef) components of the matrix, the shape of cells, and the polarization of cell contractile forces on force transmission in fibrous matrices in response to dynamic loading and healing. Briefly, two distinct groups of aligned and isotropic fibers were incorporated: (1) Isotropic fibers were modeled as neo-Hookean hyperelastic and (2) energy functions describing

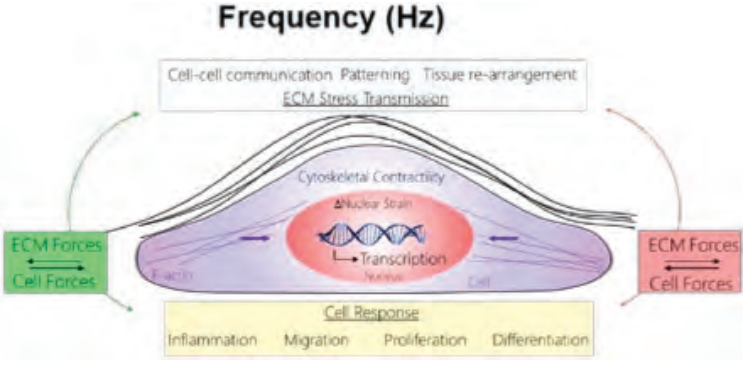

Figure 1. ECM and cell forces can have important physiological consequences.

Table 1: Correlations to nAR

		σeq	|E*|	Cellularity	F-actin	CSD	nCSD	Heal
nAR	R-Value	0.40	0.33	−0.74	−0.83	−0.85	−0.81	−0.89
	Sig. (2-tail)	<0.001	<0.001	<0.001	<0.001	<0.0001	<0.001	<0.001
	N	91	172	176	170	178	175	181

aligned fibers were chosen so that the tendon matrix increases in stiffness under tensile loading [3]. A 3D 1-element model was constructed with tendon-specific geometries in Abaqus/CAE to determine the model parameters. A 3D axi-symmetric model was used (Mesh size: 1-6μm) to evaluate ECM stress transmission. Cells contracted up to 5% of their volume along their principal axis. During cell contraction, the maximum principal stresses, nodal displacements, and nodal coordinates were output and analyzed in MATLAB (v2012a; Mathworks; Natick, MA).

Results

Bivariate correlation revealed that σeq, |E*|, cellularity, F-actin staining, CSD, nCSD, and healing correlated with nAR, with correlation coefficient magnitudes ranging from r=0.33 to r=0.85 (Table 1). Using these parameters, backward linear regression determined that cellularity, nuclear disorganization, and healing were significant predictors of nAR (R^2=0.85, $p<0.001$). Bivariate correlation determined that Δeq, tanδ, cellularity, F-actin, Δ nCSD, healing, and high magnitude loading were significantly correlated with ΔnAR (indicates the capacity for nuclei to deform under applied loading). The categorical variables healing and fatigue loading were the strongest predictors of ΔnAR (R^2=0.39, $p<0.001$). In the constitutive model, healing tendon demonstrated decreased displacement transmission profiles compared to uninjured intact tendon (Fig.2). Additionally, fatigue loaded tendon displacement profiles decayed rapidly within short distances from the cell surface.

Discussion

This study determined that multiscale mechanical, structural, and compositional properties could predict nuclear strain transfer and investigated the effects of healing and dynamic loading on tendon cell stress transmission through the ECM. nAR was strongly correlated with several macroscale and microscale properties, highlighting its relationship to multiscale tendon properties. nAR was most correlated to nCSD and F-actin staining. Interestingly, the ΔnAR in healing tendon was primarily correlated to matrix mechanical properties and cellular properties, whereas the ΔnAR in dynamically loaded tendon was primarily correlated to macroscale mechanical properties and nuclear organization. Therefore, it is likely that the mechanisms of nuclear strain transfer are inherently fundamentally different between these groups. Additionally,

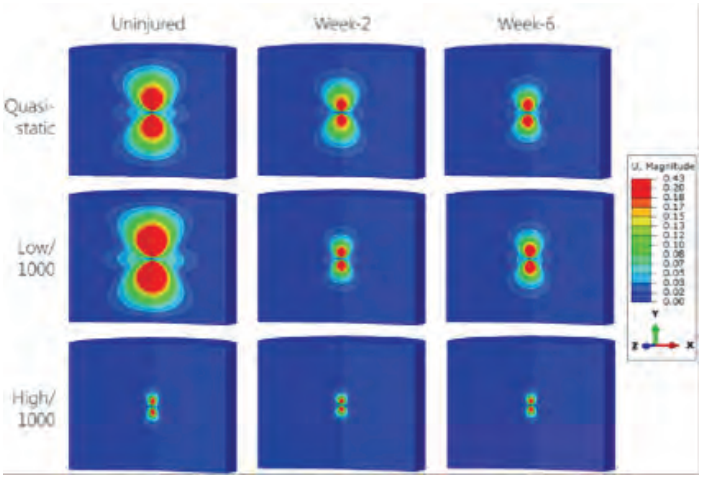

Figure 2. Displacement profiles comparing the effect of healing and cyclic loading ECM stress transmission]

tendon healing and fatigue loading drastically decreased simulated stress transmission compared to uninjured control tendons. These large differences are likely due to an elongated toe-region resulting from fatigue loading. Knowledge gained from these models may advance our understanding for cell-ECM and cell-cell communication within tendon throughout healing and in response to dynamic loading, and will provide further insight into the role of rehabilitation on tendon following injury.

Significance

Combined experimental and modeling approaches showed that tendon healing and dynamic loading affect stress transmission in tendon. This work predicts the mechanical, structural, and compositional properties that contribute to the dynamic capacity of tendon nuclei to respond to loading.

Acknowledgement

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Collagen GFP Reporter Mice Reveal Unique Subsets Of Cells Within The Tendon Midsubstance

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Introduction

Heterogeneity within tendons and ligaments has traditionally been defined at the tissue level. Although, cells residing within the tendon fascicle, known as internal tendon fibroblasts or tenocytes, have classically been regarded as a homogenous population. Recent work has suggested that cells at multiple stages of the lineage exist within the internal population [1]. *In vivo* tools are needed to identify the progenitors and more mature cell types to better understand this lineage. To this end, our lab has identified lineage tracing and GFP reporter mouse lines that map to certain subset of cells within the tenocyte population. We previously reported that Col1a1(3.6kb)-CFP mice containing a 3.6kb fragment of the Col1a1 promoter display similar expression to Scx-GFP within multiple tendons and ligaments [2]. In addition, we demonstrated that Col1a1(2.3kb)-GFP, with a truncated 2.3kb region of the Col1a1 promoter, and Col6a1-GFP transgenic mice display expression in only a subset of cells within the tendon fascicle. The objectives of the current study are 1) to quantify the number of Col1a1(2.3kb)-GFP+ and Col6a1-GFP+ cells within multiple tendons and ligaments at different stages of growth and 2) to measure endogenous gene expression profiles of laser captured GFP+ cells using a microfluidic qPCR array to further define the level of cellular heterogeneity.

Methods

Transgenic Mice

All animals and procedures were approved by UPenn's IACUC. Two transgenic mouse lines were used in this study: 1) **Col2.3GFP** - Col1a1(2.3kb)-GFP mice contain 2.3kb of the Col1a1 promoter driving GFP expression [3] and 2) **Col6GFP** – BAC containing Col6a1 promoter driving GFP expression (acquired from MMRRC).

Experimental Design

Fore- and hindlimbs were isolated from P4, P14, and P28 mice for cryohistological analysis while knees from P14 mice were isolated for LCM and qPCR. The patellar tendon (**PT**), cruciate ligaments (**ACL/PCL**), Achilles tendon (**AT**), and supraspinatus tendon (**ST**) were analyzed for histology (n=4-5/group). For LCM, **Col2.3+** and **Col6+** cells were isolated from the PT and compared to **ACL/PCL**, articular cartilage (**AC**), and *whole* PT midsubstance controls from Col2.3GFP (**Col2.3PT**) and Col6GFP (**Col6PT**) sections (n=4/group).

Cryohistology

Limbs were fixed in formalin, embedded, counterstained with DAPI, and imaged on the Zeiss Axio Scan.Z1.

Laser capture microscopy (LCM)

Knees were fixed in 4% PFA, embedded, and sectioned using CryoJane system. Slides were dehydrated and GFP+ cells or larger regions of tissue were isolated using the ArcturusXT laser capture microscope.

Microfluidic qPCR Array

RNA was extracted from LCM samples, converted to cDNA, and preamplified for 93 targets and 3 housekeeping genes. qPCR reactions for 96 samples and 96 genes were run on Fluidigm's 96.96 Dynamic Array IFC yielding 9,216 individual Ct reactions.

Image Quantification

The GFP intensity was recorded for each cell within the tendon/ligament midsubstance. An equivalent minimum threshold was applied and the percentage of GFP+ cells was computed.

Statistics

One-way ANOVAs with either tissue type or age as fixed factors were used to analyze the number of GFP+ cells in the histological sections. Principal component analysis and hierarchical clustering were used to summarize the qPCR data.

Results

Age and tissue dependence of fluorescent reporters

Both tissue type and age had an effect on Col2.3GFP and Col6GFP expression (Fig. 1; $p<0.05$). Col2.3GFP expression increased in both the AT and PT with age (Fig. 1A). Conversely, Col2.3GFP was higher in the ACL/PCL and ST at P4 and P14 but significantly dropped at P28 ($p<0.05$). Col6GFP expression was highest in

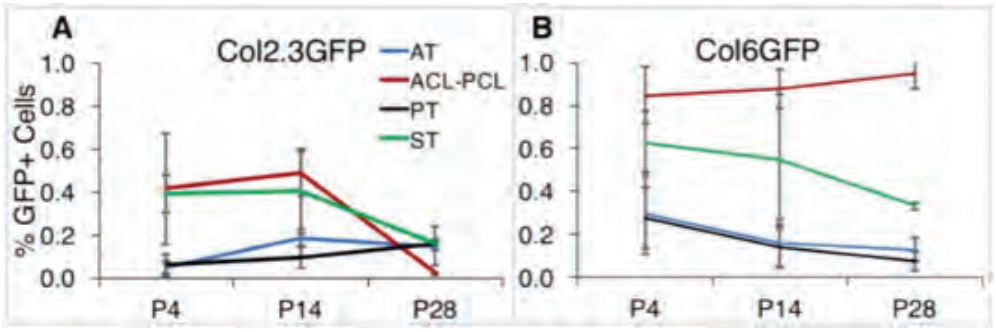

Figure 1. Percentage of Col2.3GFP+ **(A)** and Col6GFP+ **(B)** cells in AT, ACL=PCL, PT, and ST at postnatal days 4, 14 and 28.

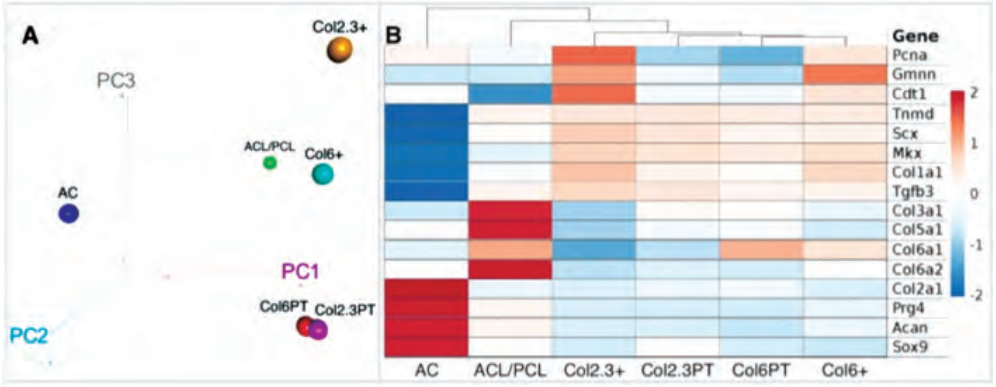

Figure 2. Principal component scores **(A)** of 6 tissue/cell groups and hierarchical clustering of groups **(B)** for subset of genes from dCt values of Fluidigm 96.96 dynamic assay.

the cruciate ligaments (ACL/PCL) at all three ages (Fig. 2B). There was an increasing trend in Col6GFP expression in the ACL/PCL with age while the three tendons all decreased with age. Interestingly, the AT showed a regional variation in both reporter lines (data not shown). The region of the AT midsubstance proximal to the enthesis but adjacent to the calcaneus displayed elevated Col2.3GFP expression at P4 and P14 with a significant drop at P28, similar to the ACL/PCL. Additionally, this region of the AT had the highest Col6GFP expression at all time points.

Endogenous gene expression indicates Col2.3GFP+ cells are more unique than Col6GFP+ cells in the PT

Principal component analysis of the 93 target genes and 6 cell/tissue types (Col2.3+, Col6+, Col2.3PT, Col6PT, ACL/PCL, and AC) revealed that 92% (57+26+9%) of the total variance was accounted for in the first 3 principal components. PC scores indicated that AC was the most different (Fig. 2A). However, Col2.3+ cells were more unique from *whole* PT samples than Col6+ cells (Fig. 2A). In fact, Col2.3+ cells expressed higher levels of cell cycle genes (Pcna, Gmnn, Cdt1) (Fig. 2B). The tendon samples expressed higher levels of tenogenic markers (Tnmd, Scx, Mkx, Col1a1, Tgfb3) while the ACL/PCL expressed higher levels of other collagens (Col3a1, Col5a1, Col6a1, Col6a2). Finally, the AC samples had the highest levels of cartilage-related genes (Col2a1, Prg4, Acan, Sox9).

Discussion

In order to better understand tendon pathologies and to develop improved repair strategies, we must first improve our understanding of the tendon lineage, including markers that define cells at multiple stages of the lineage and signaling pathways that regulate the differentiation of progenitors into mature tenocytes. We utilized two GFP reporter strains in this study to demonstrate a level of cellular heterogeneity within the internal tendon fibroblast (i.e., tenocyte) population that has not been appreciated previously. The Col2.3+ cells may be of particular interest as they display significant changes in expression with age (Fig. 1A) as well as larger differences in endogenous gene expression compared to *whole* PT controls than the Col6+ population (Fig. 2). Col2.3GFP's age-related expression changes correlate with changes in mineral apposition rate in these tissues during growth [4]. In addition, these cells also express higher levels of cell cycle genes. Therefore, we hypothesize that Col2.3GFP is a marker of an actively growing cell phenotype with increased proliferation, metabolic activity, and ECM production. A hypothesis that we will test in future studies.

Significance

An improved understanding of the cellular markers and signaling pathways that define and regulate the tendon lineage will be crucial to developing new therapies to attenuate the progression of pathologies and improve repair outcomes following injury. The anatomical and temporal differences in GFP expression found in this study indicate that cells within the tendon midsubstance are not as homogeneous as previously thought. Using these model systems, we aim to identify the phenotype and function of these cells during normal processes of growth, homeostasis, and repair.

Acknowledgements

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RNAseq-based Analysis of Differential Gene Expression Associated with Tendon Injury in the Mouse Achilles Injury Model

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Introduction

Incomplete tendon healing leads to significant mobility restriction, pain and substantial health care costs. Understanding the molecular mechanisms responsible for tendon healing will provide important insights to help develop a focused therapeutic modality to stimulate tendon repair.The goal of this study is to identify the differentially expressed genes associated with tendon injury. We aim to determine the biological pathways that alter in response to tendon injury using the mouse Achilles tendon injury model.

Methods

All animal experiment procedures were approved by the Institutional Animal Care and Use Committee of the Children's Hospital of Philadelphia and University of Maryland.

Tendon surgery

A complete transverse incision was made at the midpoint of the right Achilles tendon in 8-week- old female C57/BL6 mice and the gap was left open[1]. Animals were returned to cage activity and euthanized 1 or 3 weeks after surgery, representing the inflammation/proliferation and repair phases, respectively. Harvested tendons were snap-frozen in liquid nitrogen for RNA preparation.

RNA-seq and analysis

Total RNAs were prepared from uninjured tendons (8 tendons/sample, n=3) and injured tendons (2 tendons/sample, n=3-4) by RNeasy Fibrous Tissue Mini Kit (Qiagen). Stranded RNAseq libraries was generated and indexed by TruSeq RNA library prep kit v2. RNA integrity, cDNA amplification, cDNA fragmentation and barcode ligation were confirmed by Agilent BioAnalyzer.The RNA-seq and data analysis were performed in the Next Generation Sequencing Core at the University of Pennsylvania (Illumina Hiseq 4000, ~40 million reads/lane). After alignment to the mouse genome, mapping to the exons of each gene, and then quantile normalization, differentially expressed genes were identified and analyzed by Ingenuity pathway analysis (IPA) and Gene set enrichment analysis (GSEA).

Results

Comparison of 1-week injury tendon to the uninjured tendon

4537 and 5029 genes were differentially up- and down-regulated, respectively in injured tendons (more than 2-fold, $p<0.01$). GSEA analysis with C2-CP (curated gene sets-canonical pathways) databases showed negative regulation of the gene sets involved in respiratory electron transport and ATP synthesis and positive regulation of the gene sets with O-glycan biosynthesis and mitotic activity (Fig. 1A).

Comparison of 3-weeks injury tendon to the uninjured tendon

3722 and 4240 genes were differentially up- and down-regulated, respectively (more than 2-fold, $p<0.01$). GSEA analysis also showed similar enrichment plot profiles in the gene sets of the respiratory electron transport, TCA cycle and ATP synthesis (Fig. 1B).

Comparison of 1-week injury group to 3-weeks injury group

920 and 739 genes were differentially up- and down-regulated, respectively in 3-week injury group compared to 1-week injury group (more than 2-fold, $p<0.01$). GSEA analysis revealed negative regulation of the gene sets involved in cell cycle regulation and DNA damage, and positive regulation of the gene sets involved in peptide elongation and cytochrome p450 in drug metabolism. The gene sets involved in the respiratory electron transport were up-regulated in the 3-weeks injury group by GSEA analysis (Fig. 1C). The IPA analysis showed consistent results with those by the GSEA analysis: The oxidative phosphorylation, mitochondrial dysfunction and TCA cycle pathways were ranked in top 3 in comparison between 1- or 3-weeks injury and the uninjured group; The cell cycle (chromosomal replication and DNA damage check point) pathways were highly ranked in comparison between 1-week and 3-weeks injury groups.

Discussion

The global gene expression analysis demonstrated strong down regulation of the respiratory electron transfer and ATP synthesis

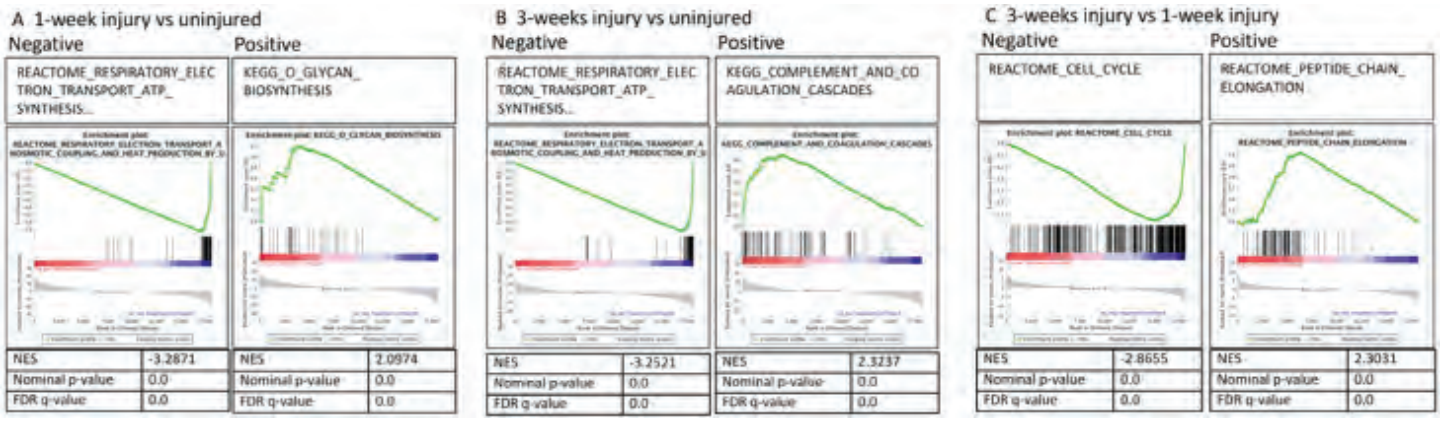

Figure 1

pathways (oxidative phosphorylation pathway) in the early phase of the tendon healing process in mice compared to the normal uninjured tendons. Results may be linked to our findings that mouse injured tendons stimulated lactate synthesis pathway and that the contents of metabolites of the TCA cycle were reduced after injury[2]. Further investigation of energy metabolism in injured tendons is required. Comparison of the gene expression profile between 1-week injury and 3-weeks injury indicate a decrease in cell proliferation, an increase in protein synthesis and a recovery of respiratory electron transfer pathway in the early phase of tendon repair. Reduction in gene expression involved in sensing and protection of DNA damage in the 3-week injury tendon may give negative impact on tendon repair.

Significance & Clinical Relevance

While a large number of clinical and preclinical approaches have been attempted, none result in complete recovery of the mechanical structure and function in injured tendons. This study provides important information to develop a targeted therapeutic modality for tendon repair.

Acknowledgements

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Prolonged Release of Ibuprofen from a Nanofibrous Delivery System Under Physiological Conditions

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Introduction

Using non-steroidal anti-inflammatory drugs (NSAIDS) to mitigate inflammation may represent a promising approach to modulate the tendon healing environment. In particular, biodegradable nanofibrous delivery systems offer an optimized architecture and surface area for cellular attachment, proliferation, and infiltration while releasing soluble factors to promote tendon regeneration [1–3]. Previous work confirmed the sustained release of ibuprofen (IBP) from Labrafil-modified poly(lactic-co-glycolic) acid (PLGA) microspheres *in vitro* in PBS and characterized a bilayer delivery system (BiLDS) incorporating these microspheres for localized delivery of therapeutics [4]. Nonetheless, the behavior of ibuprofen-releasing BiLDS in more physiologically relevant conditions and their influence on tenocytes *in vitro* is unknown. Therefore, the objective of this study was to evaluate the release profile of IBP from both PLGA microspheres alone and within BiLDS in serum and to elucidate their effect on primary tenocytes. We hypothesized that IBP would release at a faster rate from both the free microspheres and the BiLDS in serum than in PBS and the direct and indirect delivery of IBP *in vitro* would not have an adverse effect on cellular viability or morphology.

Methods

Microsphere and BiLDS Fabrication

PLGA microspheres with varying concentrations of Labrafil® M1944CS oil ranging from 0 to 600 μL (P0, P30, P300 and P600) and 30mg/mL of IBP were created using an oil-in-water emulsion technique with an external phase of 1% poly(vinyl alcohol). The microsphere solution was stirred for 4 hours at room temperature. The BiLDS were created by entrapping 10mg of the P300 microspheres, without and with IBP (BiLDS_MS and BiLDS_IBP), between two sintered 6 x 8mm electrospun poly(ε-capalactone) (PCL) scaffolds. The microspheres and BiLDS were then SEM imaged for morphological analysis.

In Vitro Release Studies

In the first release study, 20 mg of free microspheres were submerged in 5mL of normal rat serum or PBS and incubated at 37°C. The quantity of total IBP released (μg/mL) was measured over 14 days using a competitive ELISA assay and UV spectrophotometer (λ= 223nm). In the second release study, BiLDS_MS and BiLDS_IBP were incubated on a shaker at 37°C in 5mL serum up to 14 days. In the one group, BiLDS_IBP and BiLDS_MS, the total 5mL of serum was collected at 0.5, 3, 7, 14 days and in the 'continuous' groups (BiLDS_MS_C and BiLDS_IBP_C), 2mL of serum was collected at the same time points and replaced with fresh serum to assess the effect fresh serum had on the release of IBP from the BiLDS over time.

In Vitro Cell Study: Primary Achilles tenocytes were isolated from Sprague-Dawley rats and cultured in DMEM with 10% FBS and 2X penicillin-streptomycin (P/S) for one week. The tenocytes (passage 1) were seeded at 5 x 10^3 per construct on empty BiLDS (BiLDS), BiLDS_MS and BiLDS_IBP for the direct cell study. The cells were maintained in media with 1% FBS. For the indirect study, the same BiLDS groups were submerged in culture media for one week and the conditioned media was then added to cells cultured on TCP at 5 x 10^3 cells per well.

Tenocytes were cultured with normal culture media as the control. MTT cell proliferation assay and Alexa Fluor 488 phalloidin fluorescence staining for actin were used to quantify metabolic activity and visualize cell morphology over 14 days for both studies.

Statistics: Comparisons between groups at each time point were assessed using two-way ANOVAs with post-hoc Bonferroni tests. Significance of differences was set at $p<0.05$.

Results

Qualitatively, the microspheres in each group were consistent in morphology and similar to the representative image of P300 microspheres in Figure 1A. SEM images of the BiLDS confirmed the presence of microspheres between the two nanofibrous scaffolds (Fig. 1B). The IBP released in a linear manner from all the microsphere groups in serum (Fig. 2A), whereas there was an initial burst in release in PBS (Fig. 2B).

Furthermore, the P0 microspheres released 74% more IBP than the P600 microspheres through Day 14, indicating the total amount of IBP released was inversely related to the

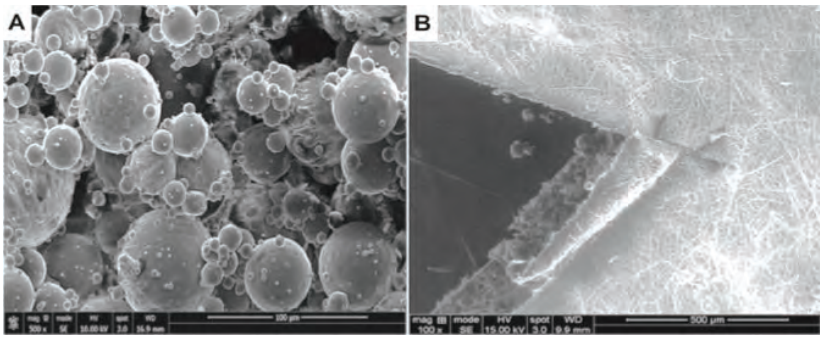

Figure 1. SEM images of **(A)** P300 microspheres at 500× and **(B)** the cross-section of a BiLDS at 100×

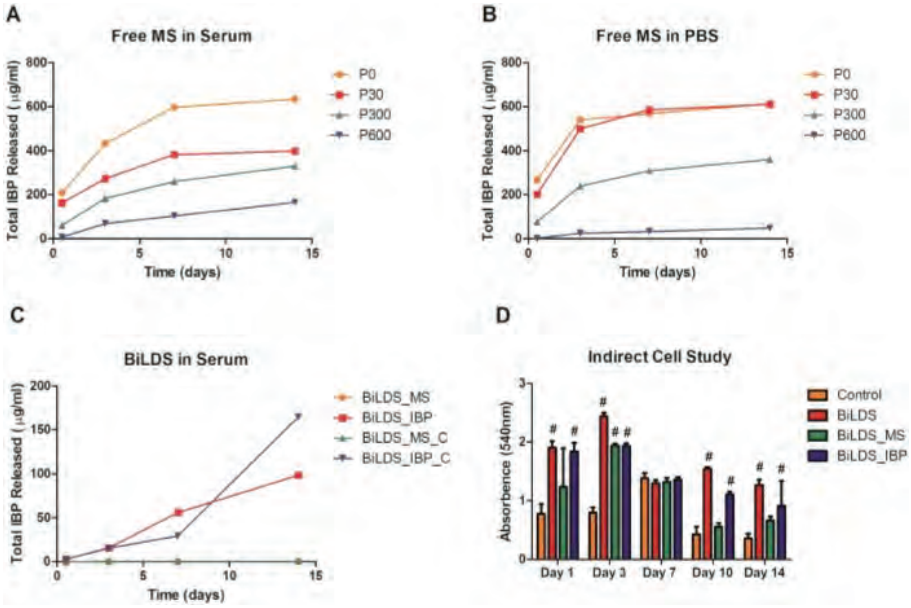

Figure 2. Release of IBP from free microspheres in **(A)** serum and **(B)** PBS over 14 days **(C)** Release of IBP from the BiLDS in serum over 14 days. **(D)** MTT cell proliferation assay results of primary Achilles tenocytes cultured in conditioned medium from control (TCP), BiLDS alone, and BiLDS with and without IBP.

concentration of Labrafil oil used to create the microspheres. At Day 14, 165 μg/ml of total IBP was released from the BiLDS in serum, which was about 70% less than the free P300 microspheres in serum. The BiLDS with IBP in the continuous group, BiLDS_IBP_C, had a significant increase in total IBP released from Day 7 to Day 14 (Fig. 2C). There were no differences in cell viability over 14 days for all the BiLDS groups in the direct cell study (data not shown). However, when the cells were cultured in conditioned media for the indirect cell study, there was a significant increase in cellular viability at Day 1, 10 and 14 for the BiLDS and BiLDS_IBP groups and at Day 3 for all the groups in comparison to the cells cultured in control media (Fig. 2D).

Discussion

Similar to previous studies, the addition of Labrafil oil slowed the release of IBP over time. The release of the ibuprofen was delayed and sustained from the P300 microspheres enclosed in the bilayer scaffold design in serum, confirming the prolonged behavior of the microspheres in physiologically relevant conditions. This is a desirable characteristic in modulating inflammation during the tendon healing phase *in vivo*. Also, the addition of fresh serum over time, resembling *in vivo* conditions of exchange of serum, increased the release of IBP from the BiLDS. This could be due to the frequent pH changes in the environment affecting the scaffold degradation or release kinetics [5]. *In vitro* biological assessment proved that all the components of the BiLDS were biocompatible. Furthermore, the concentration of IBP released did not have any detrimental effects on cellular viability or morphology. Future studies will investigate the regenerative effects of the BiLDS using an *in vitro* inflammation model. **SIGNIFICANCE:** This study identifies the therapeutic potential of a biocompatible nanofibrous bilayer delivery system for prolonged and continued released of ibuprofen to mitigate inflammation during tendon healing.

Acknowledgements

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